Best Pharmaceutical Practices in a Nutrition Support Team

An in-depth scientific analysis with focus on parenteral nutrition in an established nutritional team in a Swiss university hospital

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Dekan

Dedicated to my family

Table of Contents

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Abbreviations

AiO	All-in-one
ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	Body Mass Index
COPD	Chronic obstructive pulmonary disease
CVC	Central venous catheter
DHA	Docosahexaenoic acid
DLS	Dynamic light scattering
DRM	Disease-related malnutrition
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
ESPEN	The European Society for Clinical Nutrition and Metabolism
GIT	Gastrointestinal tract
GMP	Good Manufacturing Practice
HPN	Home parenteral nutrition
LC	Liquid chromatography
LCT	Long-chain-triglycerides
LLD	Largest lipid droplet
LOS	Length of hospital stay
MCT	Medium-chain-triglycerides
MLLD	Mean of the largest lipid droplet
MNA	Mini Nutritional Assessment
MS	Mass spectrometry
MUFA	Monounsaturated fatty acids
MUST	Malnutrition Universal-Screening Tool
NRS 2002	Nutritional Risk Screening 2002
NST	Nutrition support team
ONS	Oral nutritional supplements
O/W	Oil in water
PCS	Photon correlation spectroscopy
PICC	Peripherally inserted central catheter
PN	Parenteral nutrition
PNALD	Parenteral nutrition-associated liver disease
PUFA	Polyunsaturated fatty acids
QoL	Quality of life
RDA	Recommended daily allowances
RFS	Refeeding syndrome
SGA	Subjective Global Assessment

List of Figures

List of Tables

1 Aim

Malnutrition in hospitalised patients is a serious and often underestimated problem. It is well established that the recognition and adequate treatment of malnutrition upon hospitalisation is of highest importance for a successful patient outcome. Nevertheless, the knowledge level for most health care professionals insofar as nutritional assessment and appropriate nutritional support is still low and training inadequate, especially that of the attending physicians who have first contact with patients. Errors in medication and nutritional therapy lead to increased morbidity and mortality, as well as prolonged treatment. Prevention of these oversights enables optimised and safe clinical nutritional therapy and also medication treatment. An interdisciplinary nutrition support team (NST) comprising a physician, dietitian, nurse and pharmacist is necessary for the good nutritional management of a patient from admission until discharge as well as further care at home. Their function includes nutritional assessment, evaluation and determination of individual nutritional requirements, recommendations for nutritional therapy and management of the nutritional care plan. There are different forms of clinical nutrition therapy to prevent and treat malnutrition when physiological feeding is not possible or insufficient. In particular, patients who are to receive home parenteral nutrition (HPN) require continuous monitoring by a well-educated NST. From the outset, the patient will be in steady contact with the hospital due to the need for long-term follow-up and mandatory monitoring for this complex and challenging treatment.[1,2]

The pharmacy profession is undergoing major transformations, therefore additional skills and knowledge are required to achieve best pharmaceutical practice and care. Many changes have occurred and thus, interdisciplinary cooperation becomes more important and HPN is used more and more, increasing the challenges of the pharmacist with these complex parenteral nutrition (PN) formulations. Technical and pharmaceutical developments have helped to establish safe, convenient and effective HPN. The pharmacist, as a member of an NST, can contribute by defining and evaluating best practices and efficiency to prevent medication errors, thus ensuring an increased quality of life (QoL). The role of the pharmacist as part of an NST depends on specific pharmaceutical expertise, including knowledge, experience and skills in the field of clinical nutrition, particularly in PN. Nutritional therapy as part of a patient's overall treatment plan and therefore embedded in the medication therapy, requires the involvement of the pharmacy.[3]

This thesis investigates pharmaceutical aspects in the field of clinical nutrition, focusing on aspects of PN in particular. The main objective of this thesis is to illustrate the various pharmaceutical activities in an NST throughout the clinical nutrition process with a focus on PN. To clarify, the research aims are:

- What role should the pharmacist play in an NST?

- Is he/she prepared for the professional challenges?
- Which best practices can the pharmacist provide to increase the quality of treatment, safety and QoL for a patient?

To this end, four independent projects were defined in order to reach the aims:

(I) What is the importance and role of the pharmacist?

- Identification of malnourished patients or patients at nutritional risk, where the pharmacist can make an important contribution.
- Responsibility for maintenance of professional competence in nutrition support management by providing education and skills training.

(II a +b) Which contributions can the pharmacist give to provide a safe and effective drug and nutritional therapy and therefore an improved QoL?

- Monitoring and optimisation of nutrition support therapies including care for HPN patients and management of good nutritional supply, providing safe and effective treatment and therefore improving the patient's QoL. Specific focus was given to the so far not prospectively analysed situation in Swiss adult HPN patients and benefit of HPN on QoL in patients with specific disease.

(III) Which compounding related questions arise and which stability and compatibility assessments have to be done to ensure medication safety?

- Patients with long-term PN or critically ill patients especially need additional components or medications added to a PN admixture, requiring strict aseptic compounding and previous stability and compatibility assessments.

These different aspects of pharmaceutical expertise are part of the thesis as shown in the four presented studies in Chapter 4 and highlight how a pharmacist with appropriate training and experience can contribute to the activities in an NST and therefore improve a patient's outcome and QoL.

2 Introduction

2.1 Disease-related malnutrition

Malnutrition in hospitalised patients is a serious problem, also in industrialised countries. A consent definition for malnutrition is often lacking due to different screening systems and assessment methods. Therefore, there is a wide range of prevalence of hospital malnutrition.

2.1.1 Definition and prevalence of disease-related malnutrition

Although malnutrition is a common subject, different definitions for malnutrition, for the appropriate nutritional screening method and for the assessment of the nutritional status exist. The European Society of Clinical Nutrition and Metabolism (ESPEN) has developed a consensus for the definition of undernutrition: *"A state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass and body cell mass) leading to diminished physical and mental function and impaired clinical outcome from disease*".[4] The most frequent reason for malnutrition in developed countries is disease associated with increased requirements for nutrients because of stress-induced, altered metabolism and which will be referred to as disease-related malnutrition (DRM). The causes of DRM are multifactorial and are principally associated with insufficient food or nutrient intake and impaired nutrient digestion or absorption. DRM and disease interfere with each other. Chronic diseases, including cancer, AIDS, chronic obstructive pulmonary disease (COPD) or acute diseases such as infection, burns or trauma can lead to reduced intake with anorexia, malabsorption and finally cachexia. Drug-related side effects can also cause anorexia or interfere with the insufficient intake/absorption of nutrients, e.g. chemotherapies, antibiotics, morphine, neuroleptics, proton-pump-inhibitors, etc. Furthermore, social and psychological factors can also contribute to decreased food intake, including problems with shopping or cooking, living alone, depression and poverty.[5]

DRM among hospital patients is a serious, widely prevalent and often underestimated problem. Many studies have been performed in hospitals and found a prevalence of 20-50% of DRM. The wide range of prevalence of malnutrition is due to the lack of a definition of malnutrition, non-existence of a uniform screening method, different medical settings and different patient groups.[6] Several studies indicate that morbidity (more fractures, infections, decubiti and impaired wound healing), mortality, length of hospital stay (LOS), complication rate (mainly infections) and thereby the health care costs, increase in malnourished patients or patients at nutritional risk. This patient group also shows a diminished QoL with physical and mental problems.[7,8,9,10] Therefore, it is very important to start early with nutritional support including oral nutritional supplements (ONS), enteral nutrition (EN) or even PN to treat and prevent DRM.

2.1.2 Nutritional screening

DRM is a treatable comorbidity. Therefore, rapid and simple identification of patients at risk and effective nutritional management are essential. Optimised nutritional management including rapid identification and treatment of DRM should be available in each hospital and patients should be supported by an interdisciplinary NST. Clinical nutrition and particularly PN needs the support of an NST. Their tasks include the identification, assessment, prevention and treatment of malnutrition, increasing the efficiency and safety of the nutritional management.[2,11] The guidelines suggest that a patient should be screened as part of the admission procedure, assessed and nutritional support should be commenced immediately. Nutritional screening should be conducted in all patients upon admission to the hospital and within 24-48 hours. Additionally, the outcome should be monitored and a patient care plan created.[12] Different standardised, reliable, rapid and simple screening methods exist and these validated tests support staff to identify patients at nutritional risk early and to start nutritional therapy without loss of time. The Nutritional Risk Screening (NRS 2002), the Mini Nutritional Assessment (MNA), the Subjective Global Assessment (SGA) and the Malnutrition Universal-Screening Tool (MUST) are the most common screening tools.[13] The NRS 2002 is recommended in hospitals and allows for identification of patients at nutritional risk within a few minutes.[14]

2.1.3 Education and training in clinical nutrition

DRM is often not detected when a patient is admitted to hospital because of insufficient knowledge and experience of the medical staff. In 2001, the Dutch Diabetes Association conducted a national screening for DRM in 6150 hospital patients, the results indicating that approximately 25% of them were undernourished. Unfortunately, not even half of these patients were identified properly by the nursing and medical staff. Therefore, the awareness of DRM among medical staff should be increased. Often, the nutritional status of patients worsens during the hospital stay due to the lack of nutritional support, the disease itself, the therapy or other interventions which can further increase the risk of complications, LOS and overall costs.[15] A study conducted in Denmark showed that almost 40% of patients in hospital were at nutritional risk, however, only a portion of these patients received nutritional intervention. No more than 33% of patients had a prescription for a nutritional intervention and merely 18% of the patients reached the given goals.[16] Another questionnaire-based study with doctors and nurses in Denmark showed that only 20% of them conducted a nutritional screening or assessment. Neither the body weight nor the dietary intake was recorded. The most common reasons for inadequate nutritional practice are insufficient knowledge, low priority, unclear responsibility, lack of time, material, techniques and guidelines.[17,18] This was also shown in our study (see Chapter 4, Publications).[19] A study conducted in Brazil in an intensive care unit confirmed that education in nutritional management alone is inadequate for medical students, doctors and nursing staff. Therefore,

it is very important to implement educational programs to improve the nutritional management in hospitals. Tools such as bedside teaching, short conferences incorporating active participation, discussion rounds, use of educational media and the participation of a multi-professional NST are proposed.[20]

2.2 Clinical nutrition

The term 'clinical nutrition' includes all nutritional measures provided to people under medical or nursing care and involves preventive and therapeutic aspects. Four criteria determine nutritional support: expected duration of inadequate oral intake, nutritional status of the patient, severity of disease, specific conditions and stress factors, e.g. burns, sepsis, etc. The goals of clinical nutritional support are the improvement of body mass and composition, wellbeing and QoL, the reduction of complications, morbidity, mortality and faster recovery from illness. Nutritional support should be individually implemented in patients with malnutrition or at nutritional risk.[21] There are different types of nutritional support: ONS, EN and PN but in this thesis, the focus will be on PN.

2.2.1 Enteral nutrition

The term EN includes feeding via nasogastric/enteral or percutaneous tube (tube feeding) and ONS. Consequently, EN comprises all forms of nutritional support that indicate the use of "dietary foods for special medical purposes" as defined in the European legal regulation of the commission directive 1999/21/EC of 25 March 1999.[22]

2.2.1.1 Oral nutritional supplements

If the patient is able to eat, nutritional support should be started using this most physiological oral route. When the food intake of a patient is <75% of required intake over a period of five days, oral supplementation must be started.[23,24] Upon diagnosis of DRM ONS containing macro- and micronutrients are used. These contain different enrichments/fortifications with protein, carbohydrate powders or fat, come in a variety of flavors (vanilla, cappuccino, strawberry, etc.), with various energy and protein contents, e.g. low (1 kcal/mL) to high (2.5 kcal/mL) caloric value, or enriched with proteins (15-20%) or without proteins. There are also ONS with or without dietary fibres and with disease specific compositions, e.g. immune enhancing products, products based on short-chain peptides or diabetes specific products. ONS can enable patients to cover their nutritional requirements when normal food intake is insufficient. To encourage the compliance of ONS intake, the ONS can be prescribed like other medications and they can also be diluted or combined with ice cream, juices or fruits.[25,26]

2.2.1.2 Tube feeding

When normal eating and ONS are insufficient to cover the nutritional requirement, EN with tube feeding is indicated, provided that the gastrointestinal function is sufficient. The principal indication for EN is a (partly) functional and accessible gastrointestinal tract (GIT) and the incapability or unwillingness to cover the nutritional need orally. Possible indications for EN are disorientation, e.g. coma, depression,

apoplexy; mechanical impairment when eating or swallowing, e.g. tumor in ear, nose and throat or GIT area; neuromuscular impairment, e.g. dysphagia; increased nutritional need, e.g. sepsis, anorexia; and inflammation processes, e.g. stomatitis, esophagitis.[27]

The indication for EN should be regularly controlled and continually assessed. Compared to PN, enteral tube feeding shows several advantages[28]:

- Lower complication rates
- More cost-effective
- Increased patient safety and easy practicability
- High acceptance by the patients
- Structural and functional maintenance of gastrointestinal function (prevention of mucosal atrophy and mucosal barrier against pathogens; intestinal immune system)

When the gastrointestinal function is insufficient or not accessible, or the patient has severe metabolic and circulatory instability, EN should not be used or should be stopped.[29]

2.2.2 (Home) Parenteral nutrition

PN is indicated when the gut is not functioning or accessible. The American Society of Parenteral and Enteral Nutrition (ASPEN) defines PN as: the intravenous administration of nutrients, either delivered through a central vein, usually the superior vena cava, or through a peripheral vein. Thus, water, nutrients such as amino acids, glucose, lipids, electrolytes, vitamins and trace elements are administered intravenously.[24,30]

Comparing EN with PN, PN provides standardised administration of substrates ready for intermediate metabolism into the blood stream in gastrointestinal dysfunction (digestion, absorption). However, this intravenous nutrition is less physiological than EN and there is a higher complication rate due to the parenteral administration. Last but not least, PN is more expensive and requires a higher level of instruction and monitoring.[31,32] Advances in (H)PN regarding nutritional products and their delivery (catheters), monitoring and care enable many patients to live at home and to have a good or almost reasonable QoL in their normal environment instead of prolonged hospital stays. (H)PN can be a lifesaving or life extending therapy.[33]

2.2.2.1 Prevalence of home parenteral nutrition

It is difficult to estimate the prevalence of HPN patients, because there are global differences in the organisation of care, the inclusion and management of the patients. A European survey reported a

prevalence of 2-40 HPN patients per million inhabitants and an incidence of 4-6 per million per year for HPN patients with benign underlying diseases.[34,35] Since its beginning in the 1970's, the prevalence and incidence of HPN usage in Europe has been continually increasing and is approaching US values. This is mainly due to shorter HPN in patients with terminal diseases, e.g. cancer.[33,36] A recent study conducted in Switzerland showed a prevalence of four HPN patients per one million inhabitants in Switzerland and is therefore comparable with other European countries.[37]

2.2.2.2 Indications for (home) parenteral nutrition in adults

PN is indicated when oral and/or EN is not possible for more than three days or contraindicated because of a partial or totally non-functional GIT. Consequently, it is not possible or insufficient to cover the nutritional requirements by the enteral route and to treat or prevent malnutrition.[38] If the patient can cover <75% of his energy requirement through EN, the commencement of PN should be evaluated.[24] For example, in patients with intestinal failure and an impaired liquid, electrolytes or micronutrients balance, who are not able to cover their protein-energy requirement by enteral intake, total or partial PN is indicated. Reasons for an intestinal failure are obstruction, dysmotility, surgical resection (Short Bowel Syndrome), a congenital defect or disease associated with impaired absorption.[39] Indications are severe diarrhea or vomiting, high-output fistula, perforation or obstruction of the GIT, after surgical interventions (e.g. after bariatric surgery), patients with cancer, inflammatory bowel diseases like Crohn`s disease or severe neurological disorders. In particular, a further increase in cases following bariatric surgery are expected in the future.[37] On the other hand, indications such as AIDS will disappear because of the improved treatment possibilities in the recent years.

HPN support is indicated in patients who cannot meet their nutritional requirement by oral or enteral intake but are able to receive their therapy outside the hospital.[11] The indication for HPN should be checked monthly in the first three months and thereafter quarterly.[3]

2.2.2.3 Contraindications for parenteral nutrition

When a functioning GIT can absorb adequate macro- and micronutrients, PN is not allowed. Another contraindication for PN is impossible venous access (technical problems) or when the risks exceed the benefits of PN. Absolute contraindications are life threatening situations where survival measures have priority over nutritional needs, e.g. state of shock, severe acidosis pH <7.2, hypercapnia pO_2 >75 mmHg, hypoxia - pO_2 <50 mmHg, ethical considerations or refusal by the patient.[21]

2.2.2.4 Parenteral nutrition substrates and requirements

Depending upon the patient's additional food intake (oral and/or enteral), the correct and individualised PN formulation has to be chosen: total or complete PN including all nutrient requirements in the absence of significant oral or enteral intake or partial PN, in which only the absent portions are administered parenterally to meet optimal requirements. Complete PN is composed of amino acids, carbohydrates, fat, water, electrolytes, vitamins and trace elements. The exact nutritional requirements of a patient have to be determined, taking into consideration the metabolic situation (stress situation) and the nutritional status. The following subchapters refer to general recommendations of substrates and their requirements in adults.

2.2.2.4.1 Carbohydrates

Carbohydrates are a vital substrate improving the nitrogen balance through an anabolic and protein-saving effect. In most PN for adults, they cover 50-60% of the non-protein-energy during artificial nutrition, comparable to normal food. Four kcal, resp. 16 kJ are obtained per gram of carbohydrates. In general, high concentrated, hypertonic glucose solutions (up to 50%, respectively 500 g/L) are used to provide the physiological substrate and are now the only form used in PN. The energy requirement for an adult depends upon his specific metabolic situation, disease-specific aspects and activity level and amounts to 25-35 kcal/kg of body weight per day (basal energy requirement). The basal metabolic rate is then multiplied by an activity or stress factor. The energy expenditure must be considered in relation to the parenteral administration of glucose, because there are limits of glucose oxidation. Carbohydrates can be stored only in limited amounts as glycogen in the liver or in the musculature.[40]

The gluconeogenesis is elevated in stress situations, e.g. critically ill patients. The initial ebb phase of post-aggression metabolism with hyperinflammation and high glucose energy consumption is characterised by catabolic processes (proteolysis) caused by the massive increase of catecholamine release and other stress factors. During the post-aggression phase (parenteral) nutrition is mainly indicated as protein-saving measure. In the following anabolic phase (flow phase), the needed synthesis process is increased and the exogenous glucose recovery is used again. In adults, the recommended max. daily glucose dose is 3-4 g/kg body weight infused over 24 hours or max. 5-7 mg/kg body weight per minute. Accordingly, the glucose dose in PN determines the administration rate or the duration of daily PN. Greater amounts of exogenously administered glucose are metabolised into fat, resulting in a fatty liver because the high administration of glucose is too high. The administration of carbohydrates together with amino acids (and lipid emulsion) is the most effective way to enhance protein saving. This mixed infusion is the most common type in hospitals.[40]

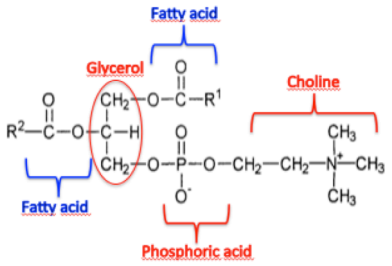
2.2.2.4.2 Lipids

Lipids, administered as lipid emulsions in PN admixtures, are an energy source contributing 20-40% to the non-protein-energy requirement. They are also essential nutrients as components of cell membranes (phospholipids, glycolipids and cholesterol as the main structural components of cell membranes), precursors for hormone build-up and for eicosanoids and their kinin derivatives. Parenteral lipid emulsions are 10-20% oil in water (O/W) emulsions containing a different fatty acids profile. Quantitatively, the most important fatty acids compound in EN and PN are triglycerides, which are stabilised with lecithin emulsifiers (important phosphate source of ca. 15 mM in commercial lipid emulsions). The phosphoric acid and the choline build the polar part of lecithin, which is hydrophilic and serves to increase the solubility of the lipids and thus guarantees the emulsification of the fatty acids (Table 1).[41]

Table 1: Lecithin

Phosphatidylcholine

(Lecithin)



→ in egg yolk, soya beans

→ antioxidative, emulsifying

→ component of the cell membranes

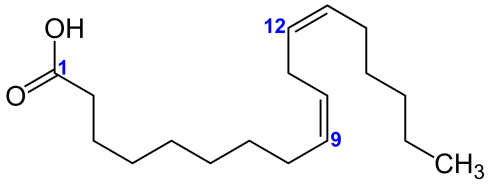
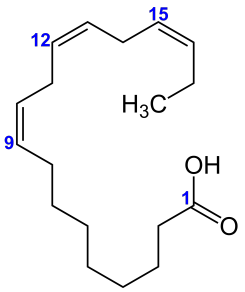
→ amphiphilic

In contrast to the glucose solutions, lipid emulsions have a high energy density (9 kcal/g lipid) and a low osmolarity (ca. 300 mosm/L), are almost pH neutral, and can therefore also be administered peripherally. As a consequence, high infusion rates of glucose can be avoided and hyperglycemia and hepatic steatosis can be prevented. Moreover, these are important for the provision of essential fatty acids as PN without lipids can lead to subnormal serum levels of essential fatty acids within one week. The recommended daily dose for parenteral lipid emulsions in adults is 0.7-1.3 g triglycerides/kg body weight (max. 1.5 g/kg body weight in post-aggression metabolism with impaired glucose tolerance). An excessive lipid intake can lead to fat overload syndrome, accompanied by fever, icterus, hepatosplenomegaly, thrombocytopenia, metabolic acidosis and hypoalbuminemia. Therefore, the concentration of triglycerides should be monitored and controlled at <400 mg/dL (4.6 mmol/L).[41]

There are various types of fatty acids emulsions, such as long-chain-triglycerides (LCT; 16 carbons or more), medium-chain-triglycerides (MCT; 8-14 carbons), structured lipids, olive oil or mixed emulsions. Saturated, monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids are distinguished by their metabolic behavior and physiologic effects. Saturated fatty acids contribute as energy source, while PUFAs are part of structural lipids. Omega-6-fatty acids and Ω-3-fatty acids, belong to the essential fatty acids and cannot or can only minimally be synthesised in humans (Table 2).[41] With the parenteral

administration of lipid emulsions containing oleic acid (Ω-9-MUFA), a high administration of Ω-6-fatty acids (and the related risk of an increased lipid peroxidation) can be reduced and the PUFA profile can be modulated. Oleic acid is present in high concentrations in olive oil. Olive oil and soya oil emulsions contain biologically active vitamin E (α-tocopherol) as an anti-oxidative protection. An additional need for vitamin E is necessary to protect the lipids (principally PUFAs) from lipid peroxidation and to deliver supplementary vitamin E. According to dietary guidelines 0.5 mg α-tocopherol is needed to protect 1 g of PUFA from peroxidation.[42] More about the lipid peroxidation is detailed in Chapter 2.3.1.1.

Table 2: Characteristics of Ω-6- and Ω-3-PUFAs

Ω-6-PUFA	**Ω-3-PUFA**
linoleic acid (C_{18-2})	α-linolenic-acids (C_{18-3})
	
→ mostly in sunflower, rape, and soya oils	→ mostly in rape, soya, linseed, and fish oils
→ arachidonic acid (C_{20-4})	→ eicosapentaenoic acid (EPA; C_{20-5})
→ proinflammatory	→ anti-inflammatory
→ prostaglandins and thromboxanes (n-2-serie) leukotrienes (n-4-serie)	→ prostaglandins and thromboxanes (n-3-serie) leukotrienes (n-5-serie)
→e.g. vascular tone ↑, platelet aggregation ↑	→ e.g. vascular tone ↓, platelet aggregation ↓

LCT emulsions are manufactured on a base of soya oil and contain a high ratio of pro-inflammatory Ω-6-fatty acids. The ratio of Ω-6-PUFA to Ω-3-PUFA is 8:1. MCTs are better tolerated in patients because they do not serve as a source for the synthesis of pro-inflammatory mediators and also because they can be oxidised directly in the mitochondria, independent from carnitine. Often, MCTs and soya oil are mixed (MCT/LCT emulsions). The available olive oil-based lipid emulsions contain olive oil and soya oil (ration 4:1) and show a high ratio of MUFA. The ratio of Ω-6-PUFA to Ω-3-PUFA is 9:1. Additionally, there are fish oil-based emulsions, containing Ω-3-PUFA, mainly as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[41] Omega-3-PUFAs are part of the cellular membrane and can influence the membrane fluidity, regulate ion channels, modulate hormonal activity, have immunologic effects and influence the gene expression.[43] Apart from these physical admixtures, there are also structured lipid emulsions, containing mixed triglycerides with Ω-6 and Ω-3 LCTs and MCTs. For example, SMOFlipid®

containing **S**oya oil (30%), **M**CT (30%), **O**live oil (25%) and **F**ish oil (15%), resulting in an optimal ratio of Ω-6-PUFA to Ω-3-PUFA of 2.5:1. The addition of EPA and DHA to lipid emulsions has positive effects on the cell membrane and inflammatory processes. It is also likely that fish oil enriched lipid emulsions decrease LOS in critically ill patients.[44]

2.2.2.4.3 Amino acids

Amino acids can be divided into essential, unessential and semi-essential amino acids (Table 3). Solutions of crystalline amino acids are difficult to handle because of the bad solubility of some amino acids, e.g. tyrosine, cysteine, or the instability in aqueous solutions.

Table 3: Classification of amino acids[45]

Essential amino acids	Unessential amino acids	Semi-essential amino acids
Isoleucine		
Leucine	Alanine	Arginine
Lysine	Aspartic acid	Cysteine
Methionine	Asparagine	Glutamine
Phenylalanine	Glutamic acid	Histidine
Threonine	Glycine	Serine
Tryptophan	Proline	Tyrosine
Valine		

In adult patients with normal organ function and a balanced metabolism 0.8-1.0 g protein/kg body weight is recommended daily; and in an altered metabolic situation 1.2-1.5 g/kg body weight, resp. 15-23 mg N (nitrogen)/kg body weight per day (100 g amino acids ≈ 6.4 g N). Patients with chronic renal insufficiency (without hemodialysis) should receive more than 0.6 g/kg body weight of amino acids per day. In a normal anabolic metabolic situation, a nitrogen-energy-ratio of 1:130 to 1:170 (g N/kcal) resp. 1:20 to 1:27 (g amino acids/kcal) is recommended. In PN admixtures, the proportion of amino acids is around 20-150 g/L.[45] The protein turnover in stress situations (trauma, burns, infections) is increased (10-30%), indicating an increased protein breakdown and synthesis, but resulting in a negative protein balance.[46]

2.2.2.4.4 Water and electrolytes

The water-electrolyte balance includes the physiological system of absorption and release of water and the closely related regulation of electrolytes. The calculation of the appropriate requirements is important and their provision should be adjusted to the clinical situation. Calculation of the

administration of fluids in patients with PN should include the PN itself, oral and enteral administered fluids as well as other infusions and fluid loss from diarrhea, severe vomiting, fistula, severe burns, etc. The normal fluid requirement of adults amounts to about 30-40 mL/kg body weight per day, but is higher in the case of extrarenal or renal fluid losses or in fever (10 mL/kg body weight per 1 °C increase of temperature >37 °C). Daily weighing is the only way to monitor the external water balance; and examination of the patient for evidence of dehydration, oedema, etc. can support it.[47]

In multichamber bags, electrolytes are already included at standard doses in the amino acid solution of a PN admixture. Before starting PN, the serum-electrolyte-concentration of sodium, potassium, calcium, magnesium and phosphate must be determined.[47] A patient with a normal fluid and electrolyte balance receives standardised amounts of electrolytes in PN[48]:

- 60-150 mmol sodium
- 40-100 mmol potassium
- 4-12 mmol magnesium
- 2.5-7.5 mmol calcium
- 10-30 mmol phosphate

In special indications, e.g. renal insufficiency, electrolyte-free solutions are required. Higher need of specific electrolytes has to be discussed with the pharmacist and stability and compatibility related questions have to be considered (see Chapter 2.3.1.2). Additional venous access (as separate infusions) would make sense. Multivalent cations, e.g. calcium, can precipitate in the presence of a high amount of anorganic phosphate. Organic salts can prevent such complications (more details in Chapter 2.3.1.2). Certain amino acids can chelate multivalent cations, reducing chemical reaction.[47]

2.2.2.4.5 Vitamins and trace elements

All lipid and water-soluble vitamins and trace elements have to be substituted parenterally in a total PN therapy (duration >1 week). The recommended daily allowance (RDA) has to be reconsidered when adjusting the dosage, except in special risk situations, in which an increased demand is needed, e.g. in patients with trauma, burns, liver diseases, etc.[47] Ready-made vitamin products (with lipid or water-soluble vitamins) like Soluvit®, Vitalipid® or Cernevit® or trace elements products such as Addaven® are available. The estimated daily requirement for adults is shown in Table 4.

Table 4: Daily requirement of vitamins and trace elements[47,48] and doses of ready-made products

Vitamins	**Estimated daily requirement**	**Soluvit®**	**Vitalipid®**	**Cernevit®**
Vitamin B_1 Thiamin	6 mg	3.1 mg	-	3.51 mg
Vitamin B_2 Riboflavin	3.6 mg	4.9 mg	-	4.14 mg
Vitamin B_6 Pyridoxin	6 mg	4.9 mg	-	4.53 mg
Vitamin B_{12} Cobolamin	5 µg	5 µg	-	6 µg
Pantothenic acid	15 mg	16.5 mg	-	17.25 mg
Niacin	40 mg	40 mg	-	46 mg
Biotin	60 µg	60 µg	-	69 µg
Folic acid	600 µg	400 µg	-	414 µg
Vitamin C	200 mg	113 mg	-	125 mg
*Vitamin A Retinol	3300 IU	-	3300 IU	3500 IU
*Vitamin D Calciferol	200 IU	-	200 IU	220 IU
*Vitamin E Tocopherol	10 IU	-	10 IU	11.2 IU
*Vitamin K	150 µg	-	150 IU	-
Trace elements	**Estimated daily requirement**	**Addaven®**		
Chromium	10-20 µg	10 µg		
Copper	0.3-1.2 mg	0.38 mg		
Iodine	70-140 µg	130 mg		
Iron	1-1.5 mg	1.1 mg		
Manganese	0.2-0.8 mg	0.05 mg		
Selenium	20-80 µg	79 µg		
Zinc	2.5-4 mg	5 mg		

2.2.2.5 Methods for administration of parenteral nutrition

The composition of the PN admixture (osmolarity) defines the central venous or the peripheral access. PN can also be administered via an arteriovenous shunt, as used for haemodialysis. Complete (total), long-term PN requires central venous access because of the high osmolarity (≥800 mosmol/L); a commercialised total PN admixture has an osmolarity of about 1500 mosmol/L (Smofkabiven®). The right internal jugular vein or the right subclavian vein are the most frequently chosen access points; subclavian access being preferred. Mostly, the catheter tip is located in the lower third of the superior vena cava, at the atriocaval junction or in the upper third of the right atrium. The catheter tip has to be

located under fluoroscopic or ultrasound guidance or the position has to be checked by x-ray after insertion. This reduces the risk for local complications significantly.[49]

For short-term PN in the hospital, non-tunneled central venous catheters (CVCs) or peripherally inserted central catheters (PICCs) are used. A PICC is another type of catheter with a smaller diameter and has the advantage of the elimination of the risk of complications of direct jugular or subclavian catheterisation and the more facilitated insertion, but the patient's physical activity and self-management is limited. For long-term PN (>3 weeks) and especially for HPN patients, tunneled CVCs like Hickman or Broviac catheters or totally implanted ports are used. Port systems are often used for patients with chemotherapy and requiring PN simultaneously in order to increase the safety and comfort of the patient and for financial aspects. These are usually made of polyurethane or silicone. There are catheters with a single, double or triple lumen; for patients in the hospital, a double lumen catheter is often used in order to avoid mixing of PN admixtures and other infused medications.[49]

Indications for peripheral PN are short-term PN for less than seven days with low osmolar preparations (600(-800) mosmol/L). Hypertonic solutions are irritants to the veins resulting in phlebitis and thrombosis. Addition of fat emulsions increases the volume and reduces the osmolarity. Furthermore, isotonic fat emulsions have a protective effect on the vascular endothelium.[50] Ideally, the cannula is inserted in a peripheral vein on the dorsum of the hand or at the forearm. Catheters with a caliber of 18 to 22 gauge are normally used in adults. Along with phlebitis, complications of peripheral PN also include thrombosis and infections.[51]

2.2.2.6 Complications of parenteral nutrition and prevention

PN is not only lifesaving, but can also be accompanied by different complications. Mechanical, technical, catheter-related or metabolic complications can occur. Furthermore, medication errors can also occur, which can be prevented by a pharmaceutical check. In this chapter, only catheter-related and metabolic complications with a pharmaceutical aspect will be discussed. Incompatibilities and instabilities of the PN admixture will be discussed in the next chapter.

Most of these complications arise from inadequate amounts of nutrients or from incorrect composition or administration of PN formulations. Individual monitoring and assessment of nutrient requirements and administration are inevitable to prevent such administration errors and complications. The pharmacist has an advisory function regarding the correct choice, composition, and administration of PN and the additives.

Catheter-related complications

Catheter-related complications are divided into early (local hematoma or abscess, catheter embolism, arrhythmias, pneumothorax central venous thrombosis), insertion-related (arterial puncture or injury) or late complications. Additionally, complications can also occur as a result of poor management or care. Technical complications include insertion problems, dislocation of the catheter or wrong position of the catheter tip.[52] Another complication with CVCs are intraluminal occlusions (0.07 episodes per catheter year),[53,54] which can occur because of lipid aggregates, precipitates of drugs/electrolytes or blood clotting and can be prevented by appropriate nursing measures. To prevent such mechanical complications, a CVC not in use should be flushed and blocked with isotonic sodium chloride solution. Heparin should not be used as a flushing or locking solution because of numerous incompatibilities. Should an occlusion occur, a first corrective measure is aspiration with 0.9% NaCl, followed by an injection. Where a suspected occlusion is caused by blood clots, urokinase is used, and in the case of lipid aggregates (developed slowly over days), sodium hydroxide (0.1 N NaOH) is used, always injected with a 10 mL syringe or bigger so there is not too much pressure.[49,55] Physicochemical precipitates, e.g. unsoluble crystals, caused by drugs or electrolytes such as calcium or phosphate, can be formed by incompatibilities between these components. Important are the calcium phosphate precipitates, which can be influenced by the amino acid composition of the PN admixture, relative calcium or phosphate content, temperature, pH, etc. In such instances, occlusions like this can try to be dissolved with pH-changes (using 0.1 N NaOH or 0.1 N HCl) (more details in Chapter 2.3.2.1).[56,57,58]

Catheter-related bloodstream infections are the most common and severe complications in patients with PN. In hospitalised patients, 0.45-1 infections/catheter year appear and HPN patients show 0.1-0.5 infections/catheter year.[59] In the case of a bacterial or fungal colonisation of the catheter, patients show clinical symptoms such as local redness, swelling, pain, fever, and/or an increase in serum-CRP. Most common infections are caused by gram-positive bacteria, primarily by staphylococcus epidermidis and staphylococcus aureus, also known as physiological skin bacteria.[60] The best prevention method is a strict asepsis, particularly regarding catheter management. Proper education and specific training of staff, an adequate hand washing procedure, choice of type of device and insertion site, aseptic handling, wearing of sterile gloves and coats, and correct local disinfection with 2% chlorhexidine have been shown to be effective in reducing the risk of catheter-related infections. The catheter exit site has to be dressed appropriately with sterile gauze or foil. Moreover, no blood sampling should be done using the CVC and neither in-line filters nor prophylactic antibiotics show positive effects on the infection rate. Flushing the CVC after each use with 0.9% NaCl is the best preventive measure against blood backflow and subsequent infections.[55]

Metabolic complications

These complications can be divided into three categories: deficiency states, acute and chronic metabolic complications. To prevent such complications, a detailed and regular lab assessment of the patient, e.g. glycemic control, and a balanced nutritional intake (composition of PN) are necessary. Deficiencies (electrolytes, vitamins, trace elements, essential fatty acids) have to be corrected prior to the prescription of PN in order to prevent more problematic and/or acute complications. Further acute or chronic metabolic complications are hyperglycemia, hypertriglyceridemia, liver steatosis, hepatic dysfunctions, cholestasis, cholecystitis or bone disease. The latter complications occur mainly in patients with long-term PN. For prophylaxis and therapy, calcium, phosphate and vitamin D dosages should be adjusted. Bisphosphonates can be given to patients with low bone density.[61] Hepatic complications occur in 15-40% of patients with PN. The risk for developing a **P**arenteral **N**utrition-**A**ssociated **L**iver **D**isease (PNALD) increases in patients with short bowel syndrome (small bowel <150 cm), absence of a continual colon, impaired bile circulation, frequent catheter infections, bacterial overgrowth of the small intestine, and lack of any EN or hypercaloric feeding.[11]

Another potentially life threatening metabolic complication is the refeeding syndrome (RFS). This syndrome occurs as a result of too fast or inadequate refeeding in patients at risk of malnutrition (catabolic). The most important clinical symptoms of a RFS are hypophosphatemia (<0.32 mmol/L), tachycardia, tachypnea and oedema.[24,62] Hypophosphatemia shows symptoms such as rhabdomyolysis, hemolysis, respiratory insufficiency and musculoskeletal and neurological impairments.[63] Risk constellations leading to a high risk for RFS at the beginning of refeeding are patients with anorexia nervosa, those who have gone on a hunger strike for several days, already malnourished patients with temporarily reduced nutritional intake, tumour patients (heavy weight loss), alcoholic and patients after bariatric surgery. An interdisciplinary and well-educated NST is inevitable for prevention, early identification and management of the RFS. Also in the sense of a safe treatment quality and maintenance of the patient safety.[64]

2.2.2.7 Systems for parenteral nutrition

At the beginning of PN, most nutrients including amino acids, glucose, electrolytes and lipids are given in parallel with or in sequence through a single intravenous line using different bottles. This method is called the **multiple bottle system**. The advantage of this system is the possibility and the flexibility of a dose adjustment for patients with rapidly changing needs. Disadvantages of the multiple bottle system are the numerous (6-8) bottle changes every day with different flow rates. As a consequence, solution compounding and administration errors are common, implying more frequent septic and metabolic

complications.[65] This system is no longer state of the art, indicating too many handling errors, inconvenience and not being appropriate for the home environment.

In the 1970's, Solassol introduced a new system to administer PN. This so called **all-in-one system** (**AiO**) showed improvements in safety, effectiveness, tolerance and convenience for PN. This system allows for administration of all nutrients (daily requirements), water, lipids, glucose, amino acids, electrolytes, trace elements and vitamins from one bag via one infusion line.[66] Advantages of this AiO system are listed below[67,68]:

- Cost-effective (reduced manpower costs in preparation, handling and delivery; reduced costs of material)
- Efficient and safe (simultaneous administration of all required nutrients, documented compounding, storage and administration)
- Regular and continuous administration (increased tolerance and stability, reduced risk of metabolic complications)
- Reduced risk of contamination (fewer manipulations, aseptic compounding, closed system)
- Only one intravenous access needed
- Simple and convenient administration (standardisation, clear instructions, suitable for HPN patients)
- Individual compounding is possible (patients with rapid changes of metabolic and energy requirements, e.g. intensive care, volume restriction or long-term HPN)

The advantage of a tailor-made compounded PN AiO admixture is that it can be adapted per the patient's need (energy, volume, substrates). This personalised regimen is based on an actual nutritional assessment and can be adapted according to the requirements of acute illness. These formulations are prepared aseptically in the hospital pharmacy and are ready to use. More about this aspect is discussed in Chapter 2.3 (Pharmaceutical tasks). Because of the limited stability, the shelf life is short (ca. one week) and requires cold storage (2-8 °C). Additionally these O/W emulsions are thermodynamically unstable, making a final sterilisation after preparation impossible. Therefore, AiO admixtures are susceptible to microbial risk. Furthermore, this system is not suitable as a drug vehicle, because of its complex formulation. Last but not least, AiO systems with their multiple components show many potential physicochemical instabilities (see Chapter 2.3.1). Regarding some pharmaceutical quality aspects, AiO formulations demonstrate a safe, effective, convenient and low-risk (microbial contamination) mode of PN and are now the standard for PN formulation. They are individually, aseptically compounded for immediate use or they are available as industrially manufactured, standardised multi-compartment containers or **multichamber bags** (Table 5). In the latter instance, the different components (glucose, amino acids and lipids) are contained in separate compartments and

mixed just before administration by mechanical pressing by hand on the PN container to break the individual seals. Industrial multichamber bags allow the admixing of stable components in a closed system (asepsis) directly before administration. The ready admixture is then homogenised by turning the bag several times. There are two-chamber bags without lipids and three-chamber with them.[67,68]

Table 5: Delivery systems for PN admixtures[67]

	Container with single components	Container with combined components	Two-in-one admixtures	All-in-one admixtures
Amino acids				
Glucose				
Lipids				
Ready-to-use	**(-)**	**(+)**	**+**	**++**

The special, multilayer plastic container and the cover wrapping, which also serve as light and air protection (oxygen) and guarantee heat sterilisation, extend the shelf life of these admixtures. The shelf life of these commercialised (unmixed) multichamber bags is more than 12 months and they can be stored at room temperature. Commercial multichamber bags are compounded without micronutrients and have almost only low electrolyte content because of high incompatibility risk and reduced stability. Therefore, vitamins, trace elements and additional electrolytes should be added to the AiO directly before the infusion or are infused separately at the end of the PN treatment. After mixing, the bag should be stored at 2-8 °C and administered within 24 hours. It is not possible to adapt these standardised PN admixtures to the specific individual requirements of patients but in most cases, patients needing PN can be treated initially (short-term) with such industrial multichamber bags. For long-term HPN, neonates or critically ill patients in particular, such standardised PN admixtures do not cover the correct requirements and the compounding of an individual AiO admixture is necessary.[69]

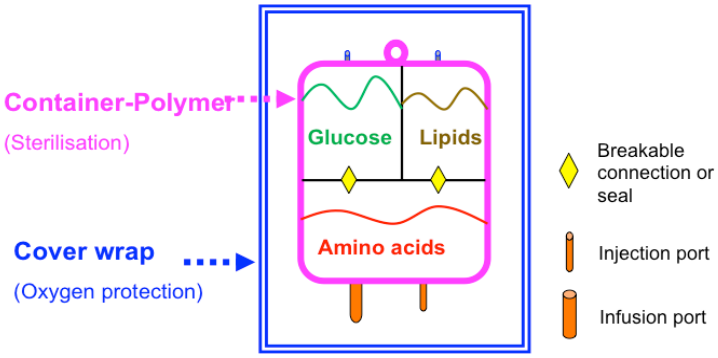


Figure 1: Industrial multichamber (3-chamber) bag

2.3 Pharmaceutical tasks in the nutrition team – with focus on PN admixtures

Total PN admixtures contain more than 50 individual dissolved and therefore, potentially reactive components, including glucose, amino acids, lipids, triglycerides with PUFAs, electrolytes, vitamins and trace elements. Therefore, the potential physicochemical interactions between the components, the container or admixes are numerous. The handling and preparation of this complex O/W emulsion requires pharmaceutical expertise to guarantee the quality of the product, but also the safe administration.[70]

According to the DGEM guidelines, the tasks of a pharmacist include the following[69]:

- Providing pharmaceutical advice for health care products, material and equipment for PN
- Checking and preventing potential interactions/incompatibilities between components and other additives, e.g. drugs
- Providing instructions on the stability and handling of PN admixtures (storage, light protection, administration, etc.)
- Checking and verifying the prescription of a PN admixture for individual patients, their preparation, distribution and final inclusion in the treatment protocol (drugs!)
- Documenting and checking of the individual preparation of AiO admixtures (and possible additives)
- Advising on the selection, composition and administration of PN
- Advising on drug-related aspects such as potential admixing, the stability, compatibility and bioavailability
- Maintaining quality assurance and increase of quality and drug safety
- Advising of adverse reactions and allergies due to drugs or nutritional components
- Providing education and training (health care professionals, patient, relatives)

Pharmaceutical expertise is necessary in an NST to guarantee the quality, safety and effectiveness of PN (Figure 2). A pharmacist's responsibilities and activities include: education of health care professionals, patients and their relatives; adherence to good pharmaceutical practice principles, as well as definition of standards and coordinative and administrative functions; quality control and documentation; research activities; selection and instruction of the safe handling of nutritional products; and last but not least, the formulation and compounding of PN admixtures including stability and compatibility assessments. Usually, PN product preparation takes place in a hospital pharmacy, ensuring the best possible aseptic conditions and pharmaceutical expertise.[70,71] Adequate training of an NST reduces catheter-related complications, e.g. sepsis, or other mechanical or metabolic complications and therefore also re-admission into hospital.[11] Pharmaceutical advice is also necessary to avoid incompatibilities and instabilities, especially in the compounding process, because they are seen as

preventable medication errors.[72] As an important example the correct dosing and administration of calcium and phosphate is shown in Chapter 2.3.1.2. Also errors in preparation (especially multiple step preparation) or administration occur and belong to preventable errors in intravenous drugs.[73]

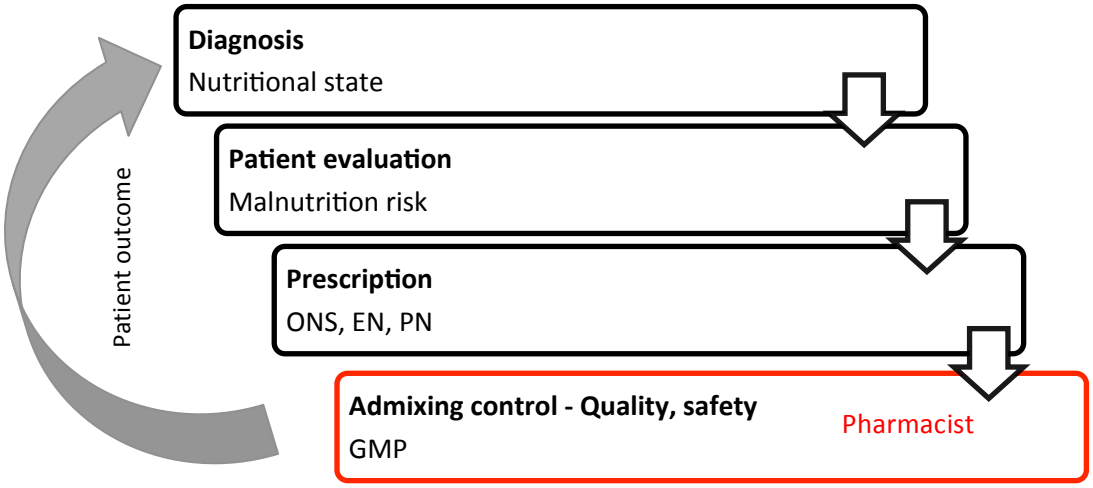


Figure 2: NST - Multiprofessional process

According to the guidelines, an AiO admixture must be[69]:

- "Therapeutically and pharmaceutically suitable for the patient"
- "Free of microbiological impurities and pyrogenes"
- "Correctly dosed and admixed (compatible)"
- "Correctly labelled, stored and administered"

Correct and complete labelling of a PN admixture is very important to prevent medication errors.[68]

- *Patient (name, date of birth, body weight)*
- *Administration date*
- *Product details*
  - *Composition (concentration, daily dosage)*
  - *Energy and protein content*
  - *Storage instructions*
  - *Administration instructions*
  - *Expiry date (storage and administration period)*
- *Manufacture identification*
  - *Date of manufacture*
  - *Lot number*
  - *Manufacturer*

Figure 3: Labelling of PN admixtures[68]

Appropriate (manufacturing) conditions, e.g. laminar air-flow, and a trained and skilled pharmaceutical staff are preconditions for a strict aseptic and correct compounding or ready-to-use preparation of PN admixtures. Good Manufacturing Practice (GMP) as a standard of quality is compulsory (materials, room and airflow conditions, equipment, employees (training), process definition, documentation, distribution) for manufacturing AiO admixtures. The manufacturing process needs to be validated regularly according to GMP and supplementary guidelines.[74] Furthermore, as AiO admixtures cannot be sterilised at the end of preparation, a strict aseptic technique and sterile and pyrogene-free infusions are mandatory as part of the compounding procedure. Additionally, the compounding of the AiO admixture after a defined admixture sequence should be carried out as close as possible to the administration time because of stability problems. Finally, pharmaceutical evaluation/documentation is required for the ready-to-use manufacture of a PN admixture. The most important factors are shown in Figure 4.[68]

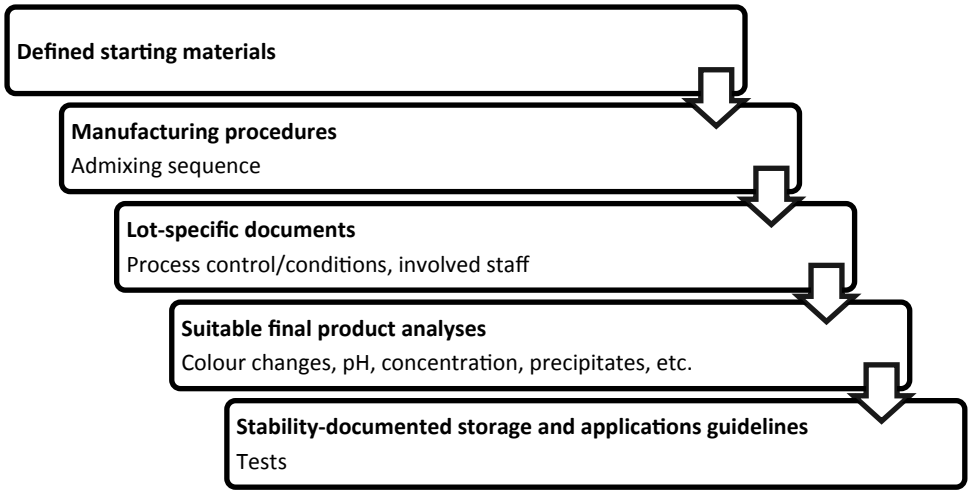


Figure 4: Important factors for the pharmaceutical assessment of a PN admixture[68]

2.3.1 Compatibility and stability of AiO admixtures

Compatibility and stability tests are part of the major duties of a pharmacist. Stability means that the ingredients in a PN admixture do not change in excess of given specs over a period of time. Compatibility indicates the circumstance in which the ingredients of a PN admixture do not interact together over a given period of time. To evaluate these reactions, specific knowledge and adequate methods are crucial.[72] Possible physicochemical reactions are shown in Table 6.[70]

Table 6: Physicochemical reactions[70]

Chemical reactions	Physical reactions
Oxidation and reduction (amino acids, PUFA, vitamins)	Precipitation (solubility product)
Hydrolysis (triglycerides)	Sorption, permeation, extraction phenomena (oxygen, lipophilic compounds)
Condensation and polymerisation (Maillard reaction)	Disruption of emulsion (divalent cations)
Elimination reactions (decarboxylation, water)	Thermal processes (oiling out)
Racemisation (optical active compounds)	Photo-induced processes (vitamin K_1)
Complex formation (trace elements)	

Physical interactions among PN components are often dependent on their solubility products or on the electrical interactions of charged solutes with the lipid emulsifier. These incompatibilities can be prevented by adequate dose administration because they are concentration dependent. Chemical reactions are influenced by co-factors, which have to be controlled. The different reactions can be influenced by the material of the bag, oxygen or light exposure, temperature, pH or other additives, e.g. catalysts. These reactions can end in a mechanical catheter occlusion, wherein modified bioavailabilities of drugs or nutrients can also induce adverse effects such as microvascular pulmonary emboli, etc. The most critical component in an AiO admixture is the lipid emulsion.[69]

2.3.1.1 Lipid emulsion stability

An O/W emulsion which mostly uses lecithin as the emulsifier is the primary factor leading to an unstable PN admixture. Lecithin as the amphoteric emulsifying agent is responsible for homogenous distribution of lipid droplets and the zeta potential. The non-polar fatty acid tails orient toward the oil phase, whereas the ionised polar phosphate groups extend into the aqueous phase. The mechanical and electrostatic repulsive forces prevent a coalescence of the small lipid droplets and a formation of large-diameter fat globules, coating each oil droplet with a layer of phospholipids, which provides a negative surface charge (zeta potential (ideal -30 to -50 mV)). The zeta potential is the electrical potential which acts on the shear plane of a particle and determines the strength of electrostatic interaction between particles. It is strongly pH dependent and in a pH of ca. 2.5 attains the value 0. The stability of an emulsion as a function of the pH can be predicted from the zeta potential. Using a lower pH value (standard pH of range between 6.0-9.0) reduces the zeta potential thus destabilising the emulsion.[75] Positively charged cations (divalent cations) impair this surface charge by modifying the zeta potential

by adsorbing to the negative charged droplet surface, neutralising the negative charge and allowing formation of larger droplets.[76] Commercially available lipid emulsions show a mean particle size of 0.25-0.5 μm, similar to natural chylomicrons. Fat globules bigger than 5 μm may occlude the microvasculature, e.g. pulmonary capillaries, leading to embolic syndrome or have pathological consequences to the reticuloendothelial system.[77]

Additives, electrolytes, trace elements and the surrounding pH are able to reduce the repulsive forces (zeta potential) between the lipid droplets by reducing the stabilising negative charge of the emulsifier (less ionised), leading to aggregation or even coalescence. The pH of a lipid emulsion decreases over time because of the hydrolysis of the triglycerides. Additionally, the addition of glucose (acidic) decreases the pH. A pH <5.0 implies an unstable lipid emulsion. Furthermore, amino acid solutions have a protective effect on the emulsion by enhancing the electrostatic barrier, the buffering capacity and electrolyte complexing. Therefore, an amino acid solution should always be added first to the AiO admixture, preserving the lipid stability. Positively charged cations (especially divalent cations like Mg^{2+} or Ca^{2+}) have a destabilising power on the repulsive forces. The zeta potential falls with increasing electrolyte concentrations (asymptotes to zero at high electrolyte concentrations). With falling zeta potential, the repulsive forces become weaker, until at a critical point they are no longer able to overcome the attractive Van der Waals force. At this point, the forces become mostly attractive, and flocculation occurs. The electrolyte concentration required to achieve this critical point is called critical flocculation concentration (→ zeta potential as a function of electrolyte concentration). Consequently the concentration of monovalent cations like Na^+ or K^+ should not exceed 130 mmol/L, and of divalent cations 8 mmol/L.[78]

Figure 5 shows the different phases of lipid emulsion instability. The first sign of destabilisation is **flocculation**, in which the emulsion droplets build coherent globules, retaining their individual forms. **Creaming** can occur without relevant change in particle size and is reversible by shaking. Thereby the electrical charge on the emulsion droplets is reduced, causing them to drift to the surface of the emulsion and alter its homogeneity. According to Stokes' law, the upward drift of these droplets occurs because the density is lower in the dispersed oil phase compared to the continuous water phase of the emulsion. The first irreversible phase of lipid instability is **coalescence**, in which the individual small droplets lose their mechanical and electrostatic barriers and form large droplets. Over time these growing lipid droplets can be measured using a light microscope. As this process continues, the growing lipid droplets expand until the oil begins to separate from the dispersed phase, or so called **oiling out.**[76,79] Methods to detect these instabilities are discussed in Chapter 2.3.1.3.

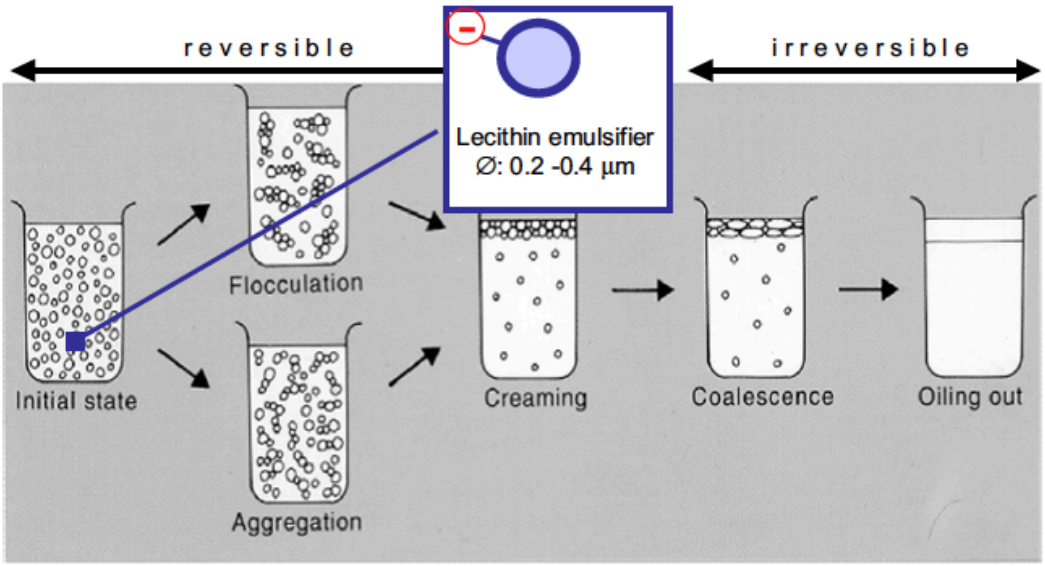


Figure 5: Phases of lipid emulsion instability[79]

It is prohibited to infuse AiO admixtures with signs of coalescence or oiling out to the patient!

Another important point to consider is lipid peroxidation. PUFAs are susceptible to oxidation in the presence of oxygen. They can form reactive radicals and aldehydes, leading to oxidative stress reactions and toxicity. Daylight, oxygen, temperature, trace elements and other additives can increase peroxidation. This is in contrast to correctly dosed anti-oxidative additives such as water-soluble vitamin C and the lipid soluble vitamin E which can reduce this risk. Measures to prevent peroxidation include more airtight and multilayered bags, light protection, storage in the fridge, addition of trace elements shortly before the infusion, and covering the bags including orange or yellow administration sets.[80,81,82]

2.3.1.2 Stability of other additives (electrolytes, vitamins, trace elements, calcium and phosphate)

The addition of additives such as electrolytes, trace elements and vitamins to PN admixtures can result in precipitation, leading to physical incompatibilities and chemical degradation. Therefore, simultaneous administration of trace elements and vitamins is not recommended; but must be administered shortly before the infusion. Monovalent electrolytes don't show any significant physical compatibility problems (high concentrations are generally well tolerated in PN admixtures). Di- or trivalent ions interactions (especially calcium and phosphate) can lead to precipitation. This is especially a problem when higher daily needs have to be administered (higher concentrated admixtures). When electrolytes are added to a lipid emulsion, the electrostatic field emanating from a negatively charged lipid droplet gives rise to a repulsive force on a neighboring droplet, and is partially screened. This allows Van der Waals attractive forces between the droplets to gain influence and form agglomerations. The reaction between calcium and phosphate is the most important aspect because they are a daily requirement (high requirement)

and indicate compatibility problems. Their instability depends on several factors including pH (high), low concentration of amino acids and glucose, nature of calcium and phosphate salts, temperature (high), high concentration of lipids and slow infusion rates, etc. The solubility of the two phosphate anions and their calcium salts is an important aspect of the safety of an intravenous therapy. Monobasic ($H_2PO_4^-$) and dibasic (HPO_4^{2-}) phosphate salts (inorganic) can form a salt with calcium, but the calcium dihydrogen phosphate is 60 times more soluble than the dibasic salt, the calcium monohydrogen phosphate (less dissociated). At a pH of 7.4 (physiological pH), approximately 60% of the phosphate is in the poorly soluble dibasic form (based on Henderson-Hasselbach equation), enhancing the possibility of calcium phosphate precipitation. The lower the pH, the more phosphate is in the monobasic form, which is more soluble. Therefore, the pH of the final PN admixture is an important factor regarding this aspect.[57] The concentrations of calcium (as gluconate salt) should be ≤2.5 mmol/L and phosphate (as the inorganic combination of sodium mono- and dibasic phosphate injection) ≤15 mmol/L. To prevent such precipitation, an organic salt of phosphate, e.g. glucose-1-phospahte, glycerol phosphate, should be used.[78]

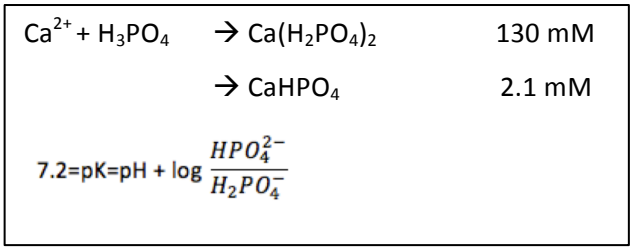


Figure 6: Influence of pH on the calcium x phosphate solubility product

The three most prevalent vitamin instabilities in PN are photodegradation, oxidation and interactions with the storage material. On the other side, solutions of trace elements have a very sour pH and contain di- or trivalent cations, e.g. iron, copper, selenium, chromium, zinc, which can influence the emulsion stability depending on the concentration. Manganese, zinc, ferric ions and especially copper catalyse the oxidation of ascorbic acid into dehydroascorbic acid and the production of oxalic acid and threonic acid. Vitamin C is oxidised with copper causing the concomitant reduction of copper from the cupric (II) to the cuprous (I) form. Cysteine in the amino acid solution can inhibit the catalytic effect of copper, slowing down the degradation of vitamin C. Also high temperature and a pH >4.0 can increase the degradation/oxidation of ascorbic acid. The products of ascorbic acid degradation (oxalic acid and threonic acid) can impair the stability of the emulsion by increasing the acidity. Additionally, oxalic acid interferes with free calcium, resulting in calcium oxalate precipitates which are dangerous for neonates.[83] Other vitamins are chemically unstable and are degraded by ultraviolet light (vitamin A and B_2) or diffuse into the semipermeable membrane of polyvinyl chloride containers (vitamin A). Another important chemical degradation is the reduction of thiamine. Lipid soluble vitamins (vitamin A, D, E, K) can be added to a lipid containing PE admixture and are therefore protected from ultraviolet light degradation. There are some pharmaceutical aspects that minimise interactions between nutrients and

the infusion bags: the effects of artificial or daylight can be reduced by protecting the bag or through the presence of a fat emulsion and use of multilayered or oxygen impermeable bags can lessen oxidation of vitamins.[57]

2.3.1.3 (Analytical) Methods to detect physical and chemical instabilities

Guidelines and regulatory requirements (production licence) recommend preparing AiO admixtures in specialised facilities, e.g. hospital pharmacy, under pharmaceutical supervision for parenteral product manufacturing or preparing, adhering to validated procedures for types and amounts of macro- and micronutrients, admixing order and the quality control (standard operating procedures, GMP). The PN admixtures should be inspected prior to and during infusion for signs of instability and incompatibility such as precipitation, discoloration, gas formation, aggregation, creaming and coalescence. A visual and instrumental inspection of the end product is inevitable to guarantee an effective, safe and high quality treatment to the patient.[3] Organoleptic, especially visual inspection, is a first, very important assessment in order to detect separations of phases or color changes. Further investigations are necessary to detect any changes in particle size, signs of lipid peroxidation or changes in concentration of glucose, amino acids and electrolytes (and to detect their degradation products).[84] The United States Pharmacopeia determined that the volume-weighted percent of fat greater than 5 µm ($PFAT_5$), has to be <0.05%.[85] It should be noted, that this monograph applies to manufacturers of lipid injectable emulsions. Given the anticipated changes in stability during the AiO compounding process, specifications have to be adjusted upwards to account for the qualitative difference in preparing emulsions for industry vs. clinicians. There are different methods to test the physical stability determined by the particle size, size distribution, surface potential or aggregation state. The coalescence of lipid globules indicates the instability of a lipid emulsion, therefore assessments of changes in the globule size distribution are essential. As part of a clinical routine, it is important that simple, fast and sensitive methods are available. They should be validated, e.g. indicate reproducibility, robustness, precision, etc., to provide an acceptable result. Two key parameters are required in a critical pharmaceutical assessment of an intravenous lipid emulsion to characterise the globule size distribution and to meet pharmacopeial standards: 1. Mean droplet size (statistical value) and 2. A large diameter (>5 µm) measurement for characterisation of the globule. Most important is the size limit of an individual particle as this has the greatest implications for safety issues (infusion safety).[86,87]

The United States Pharmacopeia recommends the dynamic light scattering (DLS) method, also called **photon correlation spectroscopy** (PCS) to determine the mean droplet size. Other methods to detect lipid particle size and distribution are called **laser diffraction** or **light obscuration**. The latter method uses a single-particle optical sensing technique to count a large number of particles and can measure

particles in the range of 1-150 µm. Therefore, a small number of large particles in the emulsions can be detected. A disadvantage is that the samples have to be diluted before measuring. The laser diffraction method can detect particles in the range of 0.05-3500 µm. Because the light beam illuminates the particles simultaneously, this method is not adapted to count the number of particles; it only provides the distribution of particle sizes. This method is not sensitive enough to determine small numbers of larger particles in a mass of smaller particles. Therefore, to detect unstable intravenous lipid emulsions, the light obscuration method is superior to the laser diffraction method.[75] The PCS method is based on the detection of a laser light scattered on a particle's bulk. Advantages of the PCS method are the simple and fast sample preparation and the statistical sample measurement. The PCS measuring range is 3-3000 nm. Disadvantages include the very small sample volume, the sample dilution and the impossibility to detect larger and therefore physiological more critical particles which are over the detection range. This method also doesn't allow a single particle statistic. Another method to test the emulsion is to use a **light microscope**. With light microscopy, 1000-fold magnification and oil immersion, particles of 1 µm are detectable. Larger lipid droplets or aggregates can be measured. Compared to the other methods, an advantage of the microscope method is that one can distinguish between solid particles (impurities, precipitation) and lipid droplets. Further advantages are that no sample predilution is necessary, that only small samples are used and also that particles up to 20 µm can be detected. Additionally, it is a validated, fast, simple and cost-effective method, applicable in the clinical routine, e.g. hospital pharmacy[88] The microscopic assessment form, including the specific procedure, is shown in Figure 7. Another important factor influencing the stability of the AiO admixture is the pH. Therefore, a supplementary method to test the stability of the formulation is a pH measurement. The pH of a lipid emulsion is in the range of 6-8. The pH of an AiO admixture (containing lipids) decreases because of additives like glucose, amino acids and electrolytes. The pH of a lipid emulsion also depends on the age of the emulsion (pH decreasing over time) because of the hydrolysis of fat triglycerides. A pH <5.0 indicates an unstable emulsion. The effect (zeta potential) responsible for this is described in Chapter 2.3.1.1.[78] Liquid chromatography (LC) is often used for pharmaceutical analyses and is frequently indicated in many official drug monographs.[86] A LC fractionates the substances on an analytical column and the detection of the substances is done by mass spectrometry (MS). A tandem MS (MS/MS) increases the selectivity. LC-MS/MS investigations are state of the art, representing a highly sensitive identification and quantification method. A drug (or vitamin) specific detection is possible and such an analysing instrument is nearly available in all bigger hospital medical labs (also for therapeutic drug monitoring). The analysis is possible in different biological matrixes such as blood, plasma or also lipid containing emulsions. A further advantage is the small sample preparation and the short pre-treatment of the samples.

Sample:_____ Date evaluation:_____

Lot:_____ Date preparation:_____

Storage temperature:_____ Storage duration:_____

Microscope:_____

All samples are turned upside down 2x. 10µl of the sample are transferred with a manual pipette to a microscope slide and covered with a coverslip, with oil immersion and a magnification of 1000x. Lens opening closed. Five visual fields of each of the three samples.

Visual evaluation: □ no changes □ creaming □ oil droplets

pH-value:_____

Specification	LLD_{max}	LLD >5µm	LLD≥2µm			Crystals	Aggregates
Visual field	[µm]	[n]	<20 [X]	20-50 [X]	>50 [X]	[µm]	[n]
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
1-15: LLD_{max}:_____µm $MLLD_{max}$:_____±_____µm LLD>5µm:_____							
Commentary:							

Figure 7: Microscope assessment form

2.3.2 Drugs and AiO admixtures

Critically ill patients or patients with a severe functional or anatomical failure of the GIT often use long-term PN. Quite often, simultaneous administration of one or more medications, or additives such as micronutrients, is necessary or convenient. On one hand, it is possible that the decreased intestinal absorption influences the bioavailability of orally administered drugs, which requires a parenteral drug administration to maintain an effective drug concentration in the body. Particularly the pharmacotherapy of patients in the intensive care unit, requires control of the efficacy of drug treatments. On the other hand, it is possible that a patient with PN has limited access to intravenous lines or difficult venous access, e.g. neonates, or a volume restriction to administer intravenous drugs, requiring PN admixtures as a drug vehicle. Additionally, fewer catheter manipulations decrease the infection risk, simplify the treatment and are more convenient, especially for patients with long-term HPN. However, such a situation can be problematic because sparse information is available about the compatibility and stability of drugs with AiO admixtures and the therapeutic outcome. When a drug or another additive is admixed to a commercialised PN formulation, a new formulation with changed properties is created and the associated manufacturer's quality can no longer be guaranteed. The PN formulation can influence the bioavailability of the drug or vice versa. Furthermore, there are many different drug, including generics, and PN formulations and different manufacturers, rendering it almost impossible to test and document all possibilities of mixing.[89]

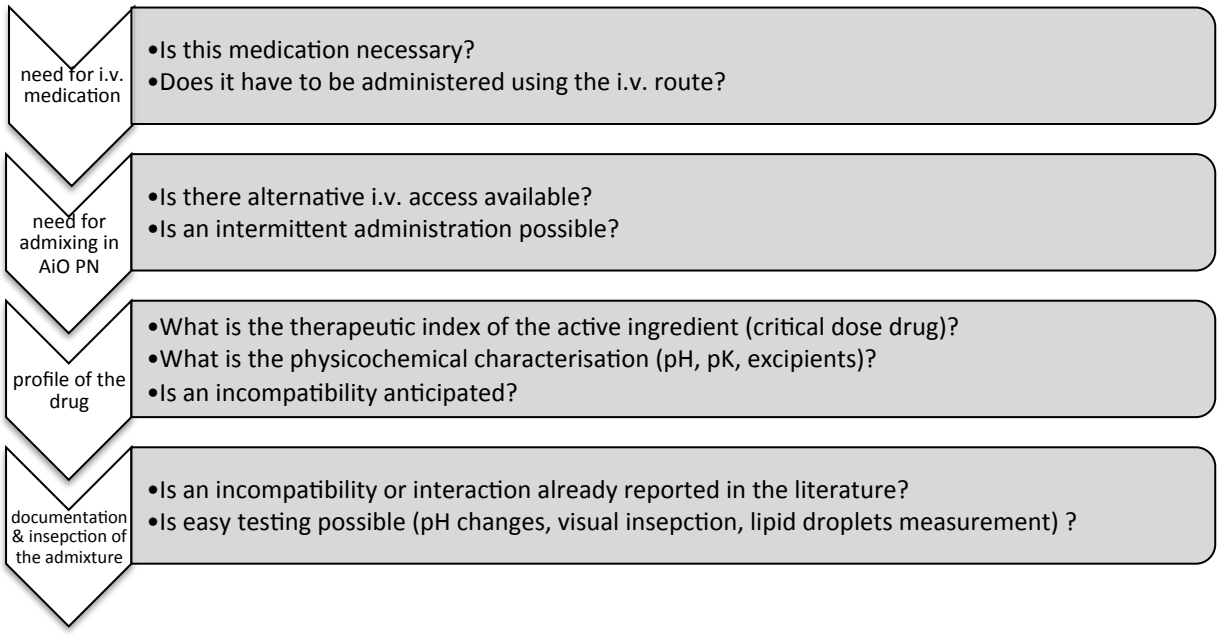


Figure 8: Algorithm for drugs and PN delivery

Before admixing a drug to a PN formulation, it is important to consider the algorithm in Figure 8. This requires pharmaceutical know-how, especially in the prescription and administration process, drug formulation and physicochemical characterisation of the drug. Regarding step one, alternative

formulations have to be used, e.g. sublingual tablets, if they are available. If it is possible, a multi-lumen catheter should be used in patients at the hospital. Otherwise, patients with cyclic HPN can administer intermittent intravenous medication after rinsing the catheter with sufficient rinsing fluid. In the last step of the algorithm, admixing can be considered if all the previous questions do not create an obstacle. An aseptic admixing in the appropriate sequence of admixing and dilution is inevitable. The assessment and documentation of compatibility and stability of a drug in an AiO admixture is a prerequisite for admixing it into a PN formulation. Appropriate methods and tests should be used by pharmacists in daily practice to prevent incorrect handling and medication errors and to guarantee a safe and efficient treatment (see also Chapter 2.3.1.3).[69,73]

Firstly, the emulsion character of the PN formulation can change when a drug is admixed to the AiO admixture. Drug formulations with a low pH (like midazolam or vancomycin) or a high pH (like acyclovir, metoclopramide, phenytoin or barbiturates) can reduce the repulsion forces between the lipid droplets in the PN formulation, leading to creaming or oiling out which is irreversible.[89] Drugs with a logP ≥3 (highly lipophilic), dissolved with the aid of cremophors or tweens, e.g. cyclosporine in Sandimmun®, can interact with the lipid emulsions resulting in an increased stability. Hence, the bioavailability of the drug and the triglycerides is changed.[90] Additionally, reactions of the drug with the container or administration material of the AiO admixture can occur. Lipophilic drugs like diazepam and nitroglycerin can be absorbed into the plastic of administration sets, which is mostly polyvinyl chloride. Other substances such as insulin, albumin or vitamin A can be absorbed on the container surface. An inactivation of drugs or PN components can also occur. Short acting drugs often show high chemical reactivity and therefore should not be added to a PN admixture because of the rapid inactivation. Trace elements (iron, copper, selenium) can catalyse oxidation or reduction of drugs or nutrients (epinephrine, vitamin C). The formation of precipitates can lead to potentially toxic reactions. This can be induced by drugs dissolved at pH <5 or >7. Weak acids or weak bases need a high resp. low pH to be dissolved. When these salts are added to a buffered PN formulation, precipitates can be built.[89]

In general, admixing with the AiO formulation is not allowed when:

- Solubilisers are present to dissolve lipophilic drugs
- Drugs are chemically instable
- Drugs have a narrow therapeutic range
- Drugs have short elimination half-lives

Only selected drugs with acceptable extended administration time, a large therapeutic index, and appropriate physico-chemical properties are candidates for admixing!

Figure 9: Candidates for admixing[90]

In the guidelines it is written that AiO admixtures should not be used as a drug vehicle because of the complex interaction potential. If it is possible, for therapeutic and practical reasons, stability and effectiveness must be examined and documented appropriately. The same is also relevant for medications infused into the same line via Y-connector. This situation can be eased by extrapolation from well-investigated to unknown drugs by defining their pharmaceutical profile (see Chapter 4.4 - the levetiracetam example). Nevertheless, a strict aseptic process according to the GMP protocol and pharmaceutical expertise should be adhered to.[69]

3 Overall summary of the thesis

The four different publications show the variety and also partly the new possibilities of activities of a pharmacist in an NST. Best pharmaceutical practice includes not only the responsibilities taking place in the pharmacy such as preparation, compounding, evaluation of the correct medication, treatment form, logistics, etc. but also the education and training of other health care professionals, the care and advising patients at home and monitoring of these patients; and last but not least, the handling of industrialised multichamber bags, checking of possible additives, strict aseptic handling and appropriate methods to test and ensure stability and compatibility. Though the role of the pharmacist in an NST is not well established, specific education and training in the field for these activities as part of the basic education of a pharmacist is necessary to promote and integrate the pharmacist as an important team member in the nutritional process.

The aim of this thesis was to provide insight into the different aspects of pharmaceutical expertise and the contributions of a pharmacist to improve the quality of treatment, safety and patients' QoL based on best pharmaceutical practice.

(I) The specific aim of this first prospective educational study was to improve malnutrition awareness and management in a tertiary hospital in the department of internal general medicine. The objectives included the identification of patients with a risk of malnutrition (using the NRS 2002) and whether an online educational intervention leads to an increase in basic knowledge, measured in the number of prescribed nutritional therapies. For this purpose, each of the 300 patients were screened in the pre- and post-intervention phase and the prescribed therapies were recorded. The intervention comprised an online education programme for the residents and a pocket card usable in the daily routine. The number of patients with a risk for malnutrition was remarkable at 54.1% resp. 61.7%. Despite these alarming statistics, the amount of nutritional prescriptions after the educational intervention did not increase (18.7% vs. 17%). The short (20-30 minutes) online educational intervention was not enough to change the awareness of medical staff and the subsequent management of this risk population. This study shows the necessity of education and postgraduate training in the field of clinical nutrition: early identification of patients at risk for malnutrition or with malnutrition, prescribing of adequate nutritional therapy and improvement of the nutritional knowledge. The pharmacist can play an important role in the education and skills training of health care professionals.

(II a) An optimal quality of treatment and a guarantee of patient's safety is a central element in patients at risk of malnutrition or depending on a nutritional device like HPN. There is very limited data on the specific characteristics in Swiss HPN patients, a prerequisite to evaluate efficiency and QoL of the

actual nutritional treatment. The second study aimed to collect representative nationwide data on current HPN patients in Switzerland for international comparability and benchmarking and to define and evaluate best practices. In this multicentre, nationwide, observational study, data were assessed at baseline and followed up after three months with a questionnaire with thirty-three adult HPN patients. The underlying disease and indication, as well as problems and risks influencing the outcome of HPN were identified. The most common underlying diseases were: cancer (42%), radiation enteritis (12%) and obesity (after bariatric surgery) (12%). The most common indication for HPN was short bowel syndrome (37%). HPN dependency and travel restrictions were of concern to most patients. Anthropometric parameters and QoL improved during the observational interval of three months. As a result of the Swiss HPN trial, for the first time there is the possibility to evaluate and compare HPN recommendations, professional care instructions, related to quality of treatment and patient safety, thus supporting the introduction of a Swiss HPN registry. A registry would allow for profound knowledge about therapy recommendations, care instructions and ensure better treatment quality and respectively greater patient safety. Monitoring and appropriate care and advice for patients, especially with HPN, are part of the pharmaceutical activities in an NST.

(II b) To focus more on the QoL of patients with HPN, a further study was conducted with patients with systemic sclerosis and gastrointestinal dysfunction. Because the deterioration of the nutritional and functional status has a severe impact on the prognosis of the underlying disease as well as on QoL, concerned patients require adequate and early nutritional therapy including partial HPN. The purpose of this study was to show the benefit of HPN on clinical outcome in terms of improvement of nutritional state and QoL during one year of observation and to motivate physicians to consider this palliative care with patients at later stages of systemic sclerosis. Five patients were included in this retrospective, single-centre pilot study. The data show that nutritional support by HPN is a feasible and safe method leading to a health benefit in terms of improved anthropometric parameters and QoL in patients severely affected by systemic sclerosis and late stage GIT dysfunction. Mean BMI increased from 19.1 kg/m^2 (range 17.4-20.3) to 21.0 kg/m^2 (range 18.3-23.4). QoL improved in all patients receiving HPN over 12 months as indicated by the summary of physical components (33.99 vs. 56.52) and the summary of mental components (49.66 vs. 88.26). HPN should be considered for malnourished, catabolic patients unable to maintain their nutritional state by other means. Monitoring of these patients, and thereby providing safe and effective nutritional therapy with improved QoL, are contributions that the pharmacist can provide.

(III) A third aspect of the pharmaceutical tasks investigated was the assessment of compatibility and stability of ready-to-use, compounded/prepared AiO PN admixtures and the potential as a drug carrier

for selected drugs with useful and rapid tests. The aim of the completing study was to assess the physicochemical stability and compatibility of the frequently used levetiracetam in commercialised ready-to-use PN admixtures under conditions of practice using validated tools. The study showed that levetiracetam was stable up to seven days in two different commercially available PN admixtures and at usual handling/storage temperatures (4 °, 22 ° and 37 °C). The stability of lipid emulsion was observed by light microscope and by visual inspection. No changes in pH occurred and no microscopic out-of-the-specs ($MLLD_{max}$ 2.4 ± 0.08 µm) or visual changes were observed. Moreover, the concentrations of levetiracetam were checked by LC-MS/MS and ranged 100 ± 15% of the theoretical value over seven days. The results show a valuable approach how to determine pharmaceutical stability and compatibility of drugs with PN in daily practice to support complex therapeutic schemes. This timely and cost-effective pharmaceutical support to document quality of complex therapeutic regimes increases convenience and avoids medical errors in the clinical setting. Levetiracetam is hydrophil (logP -0.6), neutral, has a wide therapeutic window and linear kinetics, therefore indicating a drug candidate for admixing. Physicochemical characterisation of drugs and PN admixtures, assessment of stability and compatibility, compounding and recommendations for possible additives, correct administration and right product are essential aspects of the pharmaceutical activities in an NST.

4 Publications (in peer-reviewed journals)

4.1 Disease-related malnutrition and physicians` education

Simple training tool is insufficient for appropriate diagnosis and treatment of malnutrition: A pre-post intervention study in a tertiary center

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Applied nutritional investigation

Simple training tool is insufficient for appropriate diagnosis and treatment of malnutrition: A pre-post intervention study in a tertiary center

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ABSTRACT

Objectives: To improve malnutrition awareness and management in our department of general internal medicine; to assess patients' nutritional risk; and to evaluate whether an online educational program leads to an increase in basic knowledge and more frequent nutritional therapies.
Methods: A prospective pre-post intervention study at a university department of general internal medicine was conducted. Nutritional screening using Nutritional Risk Score 2002 (NRS 2002) was performed, and prescriptions of nutritional therapies were assessed. The intervention included an online learning program and a pocket card for all residents, who had to fill in a multiple-choice questions (MCQ) test about basic nutritional knowledge before and after the intervention.
Results: A total of 342 patients were included in the preintervention phase, and 300 were in the postintervention phase. In the preintervention phase, 54.1% were at nutritional risk (NRS 2002 $\geq$3) compared with 61.7% in the postintervention phase. There was no increase in the prescription of nutritional therapies (18.7% versus 17.0%). Forty-nine and 41 residents (response rate 58% and 48%) filled in the MCQ test before and after the intervention, respectively. The mean percentage of correct answers was 55.6% and 59.43%, respectively (which was not significant). Fifty of 84 residents completed the online program. The residents who participated in the whole program scored higher on the second MCQ test (63% versus 55% correct answers, $P = 0.031$).
Conclusions: Despite a high ratio of malnourished patients, the nutritional intervention, as assessed by nutritional prescriptions, is insufficient. However, the simple educational program via Internet and usage of NRS 2002 pocket cards did not improve either malnutrition awareness or nutritional treatment. More sophisticated educational systems to fight malnutrition are necessary.

Introduction

Disease-related malnutrition (DRM) is defined by the European Society of Clinical Nutrition and Metabolism (ESPEN) as a condition that results from a lack of uptake or intake of energy and nutrients, which leads to an altered body composition with diminished function and a negative clinical outcome [1]. Many studies have been performed in hospitals and have found a high prevalence of DRM [2–4]. A multicenter survey conducted between 2003 and 2006, which included 32,837 newly admitted internal medicine patients of non-university Swiss hospitals, indicated that 18.2% of the inpatients were either malnourished or at severe nutritional risk [5].

DRM among hospital patients is a serious problem [6]. DRM negatively influences the immune system and muscle strength and is an independent risk factor for increased complication rates (mainly infections) and extended length of hospital stay, which results in a lower quality of life and higher healthcare costs [7,8]. DRM is a largely treatable co-morbidity, which makes rapid and simple identification as well as effective management essential. If nutritional risk is recognized early,

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then many patients with DRM can be treated uneventfully or even the disease can be prevented [9–11]. The ESPEN guidelines for good clinical nutrition management implied the screening of patients on admission, examination of malnourished patients, and implementation of nutritional support [12].

According to a Swiss study, patients with a Nutritional Risk Score 2002 (NRS 2002) of ≥3 should receive nutritional therapy that consists of oral nutritional support (dietary fortification, snacks, and oral nutritional supplements) or artificial nutrition (enteral or parenteral nutrition) [5,13].

Over the past decade, many surveys have evaluated the knowledge about the management of DRM among hospital physicians of different specialties. All of the surveys concluded that the knowledge concerning DRM management among physicians was poor, and consequently nutritional practice was insufficient; this circumstance results in a high prevalence of undetected DRM within hospitals [14–16]. Physicians and also medical students need more education and training in nutritional assessment and intervention [17].

To date, no study has sequentially tested the potential improvement of physicians' nutritional management knowledge and consequently increased the treatment of DRM after an online educational program. The specific aims of this prospective pre-post intervention study were to assess whether such a targeted educational intervention (online learning program) leads to an increase in basic knowledge in clinical nutrition and behavioral changes toward better malnutrition management and therefore to more frequent adequate nutritional therapies (measured by an aimed 10% more prescriptions).

Materials and methods

Study design

We conducted a prospective pre-post intervention study with a follow-up period. The study was conducted at the University Hospital of Bern from April 1, 2013, to July 31, 2014. The study was performed on three wards of the Department of General Internal Medicine (GIM). The study flow diagram and duration are illustrated in Figure 1.

Residents and patient selection

All of the residents (n = 84 [100%]) working at the GIM department were included in the study. The majority (42.9% in the first questionnaire and 53.7%

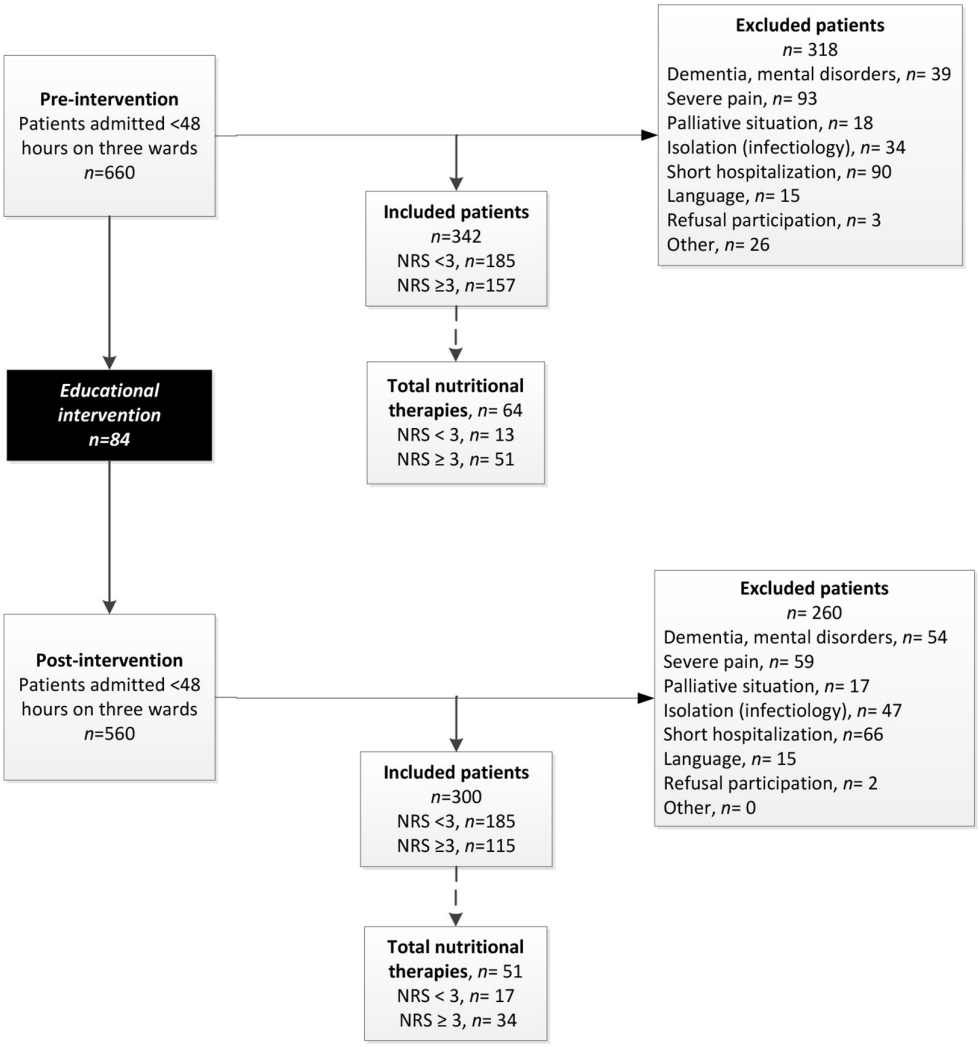

Fig. 1. Study flow chart. NRS, Nutritional Risk Score 2002.

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in the second questionnaire) were third- or fourth-year residents. Only a few were more experienced (6.1% and 7.3% with more than six years' experience) or first- and second-year residents (16.3% and 19.5%). To prevent losing participating residents because of the high changing and rotating number at the GIM department, all of the new residents entering during the study phase were included in the study, and all of the departing residents had to finish the intervention program. The participation of the residents was voluntary, and their data were encoded in such a way that the participants could not be identified from the documents presented. Demographic and professional characteristics of the physicians were collected.

Newly admitted (<48 h) adult patients (>18 y old) on the three wards were selected to participate in this study. The principal investigator (C.A.), a pharmacy PhD student, evaluated and included the patients in the study if the inclusion criteria were met. In the pre- and postintervention phase, an identical patient recruitment process was conducted, always by C.A. The exclusion criteria were as follows: a palliative situation and/or life expectancy less than 30 d; foreign language (except German, French, Italian, and English); isolated patients for infection reasons, uncontrolled pain, or reduced level of consciousness; patients with dementia or mental disorders; and patients who refused or were not able to sign the informed consent. Participation was voluntary. The participants could not be identified from the collected material, and no plausible harm to the participating individuals was identified.

Data collection

The included patients were screened with NRS 2002 by C A. [12,18]. The international validated screening tool NRS 2002 is a fast and simple screening method that is based on four variables—weight loss, body mass index (BMI), general condition, and amount of food intake in the preceding week—in addition to the patient's age and the severity of the underlying disease. The total score was calculated from the impaired nutritional status section (score 0 to 3), the score for the severity of the disease (an indicator of stress metabolism and increased nutritional requirements; score 0 to 3), and age adjustment (score + 1 for >70 y), and the total score ranged from 0 to 7. Patients are classified as being malnourished (score ≥3) or not (score <3), according to the total score obtained [18]. The length of stay and nutritional prescriptions were collected from the electronic medical records.

Preintervention phase and online multiple-choice questions test

The patients' data were collected on the GIM wards without the residents knowing about the conducted study. In a further step, the baseline knowledge of the residents on the nutritional management was tested using an online multiple-choice questions (MCQ) test, which was created by three experienced physicians and specialists in clinical nutrition and sent to all residents of the GIM department by internal hospital e-mail. The test contained 16 multiple-choice questions about the basics of clinical nutrition, nutritional management, recognition of malnutrition, NRS 2002 scoring, and nutritional therapies. Additionally, in a closed question, the residents were asked about their attitude/barriers toward nutritional therapy ("Why do physicians pay little attention to nutritional issues?").

Educational intervention phase

The online educational program (easyLEARN) was based on the MCQ test (the same topics in the MCQ test as in the online program) and contained basic details about (clinical) nutrition; a detailed definition of DRM; its prevalence, causes, and consequences; screening tool (NRS 2002); and treatment and management of patients at nutritional risk. Information and online access to easyLEARN were provided by internal e-mail to all of the residents (duration of the program: 20 to 30 min). The educational objectives included identification of the causes and consequences of malnutrition, the use of a nutritional screening tool for identification of malnourished patients, options and implementation of an adequate nutritional therapy, and the correct monitoring. There were no interactive case studies. The easyLEARN program was developed by the authors in collaboration with the Institute of Medical Education of the University of Bern. Furthermore, a pocket card that contained the NRS 2002 and nutritional therapy options was created and handed out to all of the residents.

Postintervention phase

Two months after the intervention (education), a new evaluation of the patient data was performed in the postintervention phase using the same method as in the preintervention phase. Additionally, the residents were asked to participate in the online MCQ test again, using the same questions as in the preintervention period.

Statistical analysis

All statistical analysis was performed with the software IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., released 2012). Some of the data were assessed using descriptive statistics only. Pearson two-sided chi-square test and paired *t* test were conducted, and *P* values <0.05 were considered to be statistically significant.

Ethics approval

This study was conducted in accordance with the ethics guidelines of the 1957 Declaration of Helsinki. Ethics approval for the study was obtained from the local ethics committee (Ethic Board Canton of Bern: Kantonale Ethikkommission Bern KEK Study No. 029/13). The participants provided written informed consent; the standard form of which was available on the file for each.

Results

Patient characteristics

When comparing the patients in the pre- and postintervention phase, no significant differences were found in the patients' characteristics (Table 1). On average, patients who were at nutritional risk were significantly older, with a mean age ± SD of 70.5 ± 15.65 y compared with patients without risk, with a mean age ± SD of 63.9 ± 16.52 y. Overall, the patients with NRS 2002 ≥3 stayed longer at the hospital, by 8.9 ± 6.07 d (range 0–36), compared with patients with NRS 2002 <3, by 7.0 ± 5.79 d (range 0–61). The mean BMI of the patients at risk was 23.5 ± 5.67 kg/m^2 (range 10.62–48.79, n = 262), whereas patients with NRS 2002 <3 had an average BMI of 28.0 ± 5.45 kg/m^2 (range 18.25–57.8,

Table 1
Comparison of characteristics between patient groups (pre- and postintervention)

Characteristic	Preintervention	Postintervention	*P*
Total, n (%)	342 (100)	300 (100)	
Sex, n (%)			0.625
Male	206 (60.23)	175 (58.33)	
Female	136 (39.77)	125 (41.67)	
Age (years; mean ± SD)	66.45 ± 16.91	66.92 ± 15.97	0.717
Age groups, n (%)			0.668
<45	39 (11.40)	29 (9.66)	
45 to 64	102 (29.82)	83 (27.67)	
65 to 84	157 (45.91)	152 (50.67)	
≥85	44 (12.87)	36 (12.00)	
BMI (kg/m^2; mean ± SD)	26.49 ± 6.64*	25.66 ± 5.07†	0.079
BMI groups, n (%)			0.053
<18.5	29 (8.68)*	21 (7.12)†	
18.5 to 24.9	116 (34.73)	121 (41.02)	
25 to 29.9	111 (33.23)	104 (35.25)	
≥30	78 (23.35)	49 (16.61)	
NRS 2002 (mean ± SD)	2.51 ± 1.36	2.41 ± 1.23	0.339
NRS 2002 groups, n (%)			0.053
NRS 2002 <3	185 (45.91)	185 (38.33)	
NRS 2002 ≥3	157 (54.09)	115 (61.67)	
Length of stay (days; mean ± SD)	7.78 ± 6.39	7.86 ± 5.49	0.478
Length of stay groups, n (%)			0.224
0 to <5	115 (34.80)	83 (27.76)‡	
5 to <10	136 (39.77)	136 (45.48)	
10 to <15	48 (14.06)	50 (16.72)	
15 to <20	21 (6.14)	13 (4.35)	
20 to <25	8 (2.34)	11 (3.68)	
≥25	10 (2.92)	6 (2.01)	
Reduced nutritional intake, n (%)	130 (38.01)	98 (32.67)	0.059
Weight loss, n (%)	132 (43.42)*	102 (35.79)†	0.158

BMI, body mass index; NRS 2002, Nutritional Risk Score 2002
Pearson chi-square 2-sided test
* n = 304.
† n = 285.
‡ n = 299.

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n = 367). The percentage of the patients at nutritional risk (NRS 2002 ≥3) with overweight was 8.6% and obesity 4.9%, versus 25.6% overweight and 15.3% obesity in patients with NRS 2002 <3. Remarkably, looking at patients with nutritional risk only, one-third were overweight (20.6%) or obese (11.8%).

Nutritional therapy

Three-hundred forty-two patients were included in the preintervention phase and 300 in the postintervention phase (n = 642 [100%]). In the preintervention phase, 54.1% (n = 157) were at nutritional risk (NRS 2002 ≥3) versus 61.7% (n = 115) in the postintervention phase (χ^2[1, n = 642] = 3.75, P = 0.053). A nutritional intervention was performed on 18.7% (n = 64) in the preintervention phase and 17.0% (n = 51) in the postintervention phase. Figure 2 shows the prescribed nutritional therapies in both phases. No significant difference regarding the number of nutritional prescriptions between the pre- and postintervention phases (χ^2[1, n = 642] = 0.319, P = 0.572) was observed; thus, the goal of 10% more prescriptions was not reached. Focusing on the NRS 2002, 32.5% with NRS 2002 ≥3 had a nutritional intervention in the preintervention phase and 29.6% in the postintervention phase (χ^2[1, n = 272] = 0.263, P = 0.691). Furthermore, 7% with NRS 2002 <3 received a nutritional therapy in the preintervention phase and 9.2% in the postintervention phase (χ^2[1, n = 370] = 0.580, P = 0.568).

Intervention and knowledge test

The first MCQ test was completed by 49 of the 84 residents (response rate 58%). The mean percentage of correct answers was 55.6 ± 9.38 (min, 35.7%; max, 78.6%). Additionally, the residents were asked, "Why do physicians pay little attention to nutritional issues?" The two most frequently mentioned barriers were that the manifest malnutrition of the individual patient was not noticed and that there was insufficient knowledge about malnutrition in general (see Fig. 3). In the intervention phase, 50 residents (response rate 60%) completed the easyLEARN program. Forty-one residents filled in the postintervention MCQ test (response rate 48%). The mean percentage of correct answers was 59.4 ± 16.35 (min, 42.9%; max, 73.6%). There was no significant difference in the percentage of correct answers between the pre- and postintervention MCQ test (χ^2[323, n = 42] = 326.04, P = 0.442). Only 26 residents completed the total intervention procedure (first MCQ test, easyLEARN program, and second MCQ test; response rate 31%) (see Fig. 4). These participants demonstrated improved results in the postintervention MCQ test compared with the preintervention MCQ test (mean percentage of correct answers 63.0 ± 10.43 versus 55.3 ± 9.39) (t [23] = −2.30, P = 0.031).

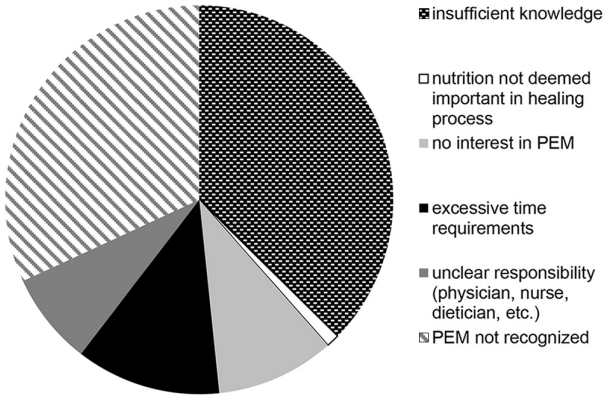

Fig. 3. Question of the multiple-choice questions (MCQ) test: "Why do physicians pay little attention to nutritional issues?" PEM, protein-energy-malnutrition.

Discussion

This prospective pre-post intervention study aimed to assess patients' nutritional risks and whether an online learning

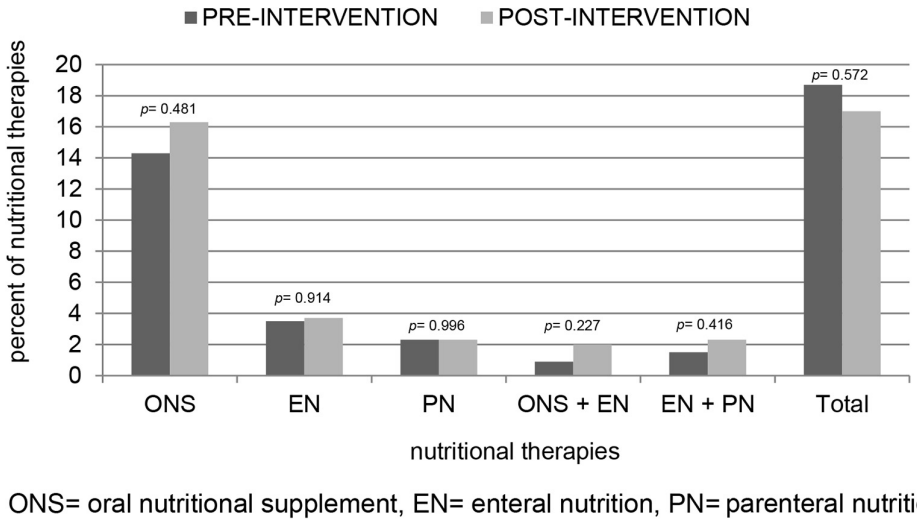

Fig. 2. Comparison of nutritional therapies given to patient groups (pre- and postintervention). EN, enteral nutrition; ONS, oral nutritional supplement; PN, parenteral nutrition.

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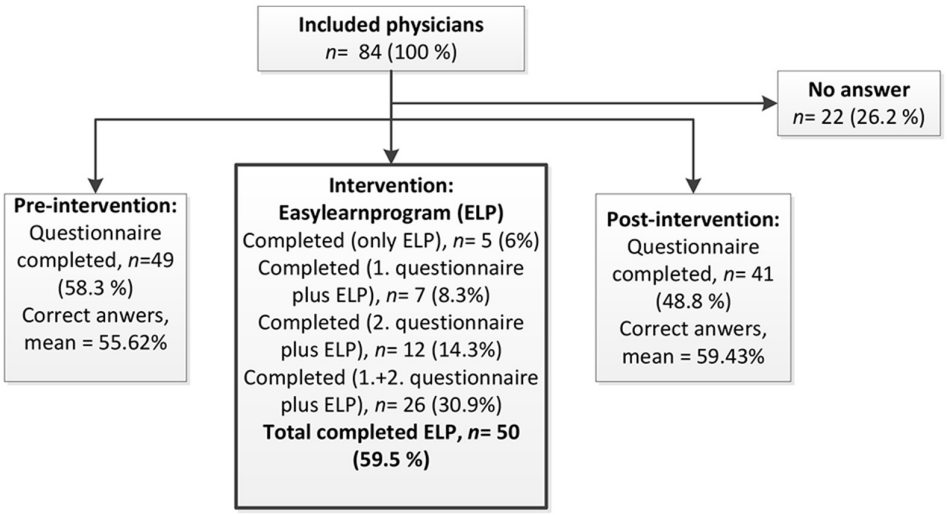

Fig. 4. Physicians' intervention flow chart and results of the multiple-choice questions (MCQ) test.

program, together with a ready-to-use pocket card, for residents enables an increase in their basic knowledge of nutritional management and would lead to more prescriptions for nutritional therapies for malnourished patients. The main finding was that this intervention had no significant effect on the number of prescribed nutritional therapies. We had two almost comparable patient groups in the pre- and postintervention phases, and we found a high percentage of malnourished patients in both groups. However, the percentage of prescribed nutritional support for these patients was remarkably low.

In teaching hospitals, 30% to 50% of GIM patients have been found to be at risk for DRM [19–22]. This study confirmed this high prevalence in elderly people in a Swiss GIM referral center along with the increased hospital stay of malnourished patients. To fight against DRM, the Public Health Committee of the Council of Europe adopted a resolution for preventing and treating DRM in hospitals [23], which outlined the importance of awareness of DRM. Nutritional knowledge at all levels of physicians is insufficient, and therefore DRM is not treated, as several studies have demonstrated [24–28]. Our data showed that a very high proportion, 42.4% of the patients (pre- and postintervention), suffered from DRM. The awareness of DRM in patients with overweight and obesity, a population per se at high risk of sarcopenia, is very low. We found a large portion of malnourished patients with normal body weight and malnourishment presenting even in overweight (20.61%) or obesity (11.84%). Considering that palliative patients and the patients with strong, uncontrolled pain—who are even more prone to DRM—were excluded, the number of malnourished patients could well be much higher. Furthermore, malnourished patients showed a longer length of hospital stay, which was statistically significant. Imoberdorf et al. [5] found only 18.2% of newly admitted internal medicine patients to be malnourished, probably because the included hospitals were to a great extent peripheral hospitals and not tertiary referral centers, such as the university hospital of Berne in this case. Such referral hospitals usually have higher rates of polymorbid patients with complex pathologies and complications, which could explain the higher prevalence of DRM found in our study.

Despite the high rates of malnourished patients, there is no universal screening program for nutritional assessment in our hospital that has been established to the extent necessary as indicated by other international findings, which implies that 21% to 73% of the hospital wards screen patients for nutritional risk on admission to the hospital on a standard-of-care basis [29]. This finding confirms the necessity of a routinely performed nutritional risk screening upon admittance of the patients, to not delay the necessary intervention.

The outcome in our study was measured with the prescribed nutritional therapies: only 18.7% and 17%, respectively, of malnourished patients (NRS 2002 $\geq$3) received nutritional support in the pre- and postintervention phases. The number of nutritional prescriptions as a marker for malnutrition management might be challenged, but the use of nutritional products correlates with the nutritional support actions in the hospital that influence the subsequent NRS 2002 monitoring of the patient. This low level of nutritional therapies correlates with the poor awareness of the treating residents. They lack the basic training of clinical nutrition during their medical traineeships, which is again not specific to Switzerland [20,30,31]. The lack of nutritional support measures was strengthened by the poor results in the nutrition knowledge test, even after the educational intervention with online education and pocket cards (55.6% versus 59.4% correct answers).

In our preintervention test, the residents were asked for the reason "why physicians pay little attention to nutritional issues." The two most reported reasons were insufficient knowledge and that the manifest malnutrition of the patient was overlooked or not recognized. The same reasons were also identified by a Danish research group [32]. Interestingly, a survey of Mowe et al. [33] in Scandinavia described that nearly 40% of the medical staff lacked techniques for identifying malnourished patients, and more than 50% found it difficult to prescribe adequate nutritional therapy. Those who assumed their nutritional knowledge to be good also showed better nutritional management practice. Furthermore, Mowe et al. [33] found that low knowledge was associated with difficulties in performing nutritional risk screening and nutritional assessments and in prescribing adequate nutritional therapies. Clinical nutrition or nutrition in general is usually neglected in medical schools. This finding was also confirmed by Adams et al. [17], who called for more and better training in nutritional

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assessment and intervention options for physicians, residents, and medical students.

The same authors reported on a new initiative that offers a free online education program for residents and other physicians. The lessons are practice-based and can be completed in 15 min or less. The modules contain detailed recommendations for nutritional assessments and appropriate therapies as well as practical applications and interactive case studies to reinforce the instructions and allow the residents to apply the newly learned skills immediately with patients [17]. Our study found that an online intervention of 20 to 30 min with an easyLEARN educational program did not cause a significant increase in correct answers in the MCQ knowledge test and in prescriptions of nutritional therapies. The residents who completed the whole program showed better scores in the second MCQ test, but this finding was not followed by an increase in nutritional prescriptions. Only offering training through a recommended e-learning tool and the distribution of a memo card was not successful in significantly changing the behavior of the young residents to the point of resulting in better malnutrition management.

An interdisciplinary nutrition team and different educational strategies are needed for better education in clinical nutrition, detection, and management [34]. A call for a multimodal and more compulsory educational intervention arises. Rasmussen et al. [35] conducted a study with a comprehensive nutritional action plan in two internal medicine departments (e.g., introduction of a screening system, nutrition sheet for physicians, nutrition record for nurses, and implementation of guidelines), which was able to increase the screening for nutritional risk from 3% to 50%, while 26% more patients (20%–46%) received a nutrition intervention within 1 week [35]. A study conducted in Brazil on the ICU concluded that a multifaceted educational nutritional intervention improved the quality of nutritional therapies. The intervention included nutritional therapy protocols, workshops for the physicians, and bedside clinical case discussion [36].

To our knowledge, this study is the first prospective pre-post intervention study that uses the validated NRS 2002 as a screening instrument. The study group of GIM residents from a large tertiary hospital center represents also the national educational status for this physician group. The study was conducted in a university hospital and addressed complex and multimorbid patients. All of the patients were screened. Another strength of this study is the use of a multifaceted intervention program: an online learning tool, which was created on purpose by experts in clinical nutrition and medical education, included a pre- and postintervention knowledge test, and printed material was distributed (a pocket card).

There are limitations to the study. Only half of the residents completed the whole program (first and second questionnaires and the easyLEARN program), because of the high turnover of the medical staff in a tertiary resident trainee center. Moreover, the main clinical decision maker (the attending physician) was not involved in the program. In addition, it was not possible to correlate the prescribed nutritional therapies with the prescribing physicians to obtain more information at the individual physician level.

Conclusions

This study found that a recommended educational online program together with the distribution of printed “pocket” materials alone was not effective at increasing the nutritional knowledge that should be accompanied by improved malnutrition management in a large university GIM clinic despite the high rate of malnourished patients. Our simple online educational intervention via Internet combined with a ready-to-use pocket card of the NRS 2002 with information on malnutrition management showed improvement in nutritional knowledge in the subgroup of residents who participated in the whole program. Nevertheless, there was no increase in the number of nutritional interventions, as assessed by nutritional prescriptions, which confirms the insufficient awareness and behavioral changes of the involved physicians. More sophisticated educational systems to fight malnutrition are necessary. Certainly, a compulsory multimodal training approach for residents in clinical nutrition is mandatory to successfully identify and manage malnourished patients and to create awareness and responsibility of the treating physicians. Further research is needed to explore the specifics of the multifaceted educational activities, including the format of the well-structured educational program, targeted at local circumstances, and interdisciplinary efforts to significantly improve knowledge in nutritional basics and malnutrition management skills of physicians and other healthcare professionals.

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4.2 Swiss adult HPN study

Management of Home Parenteral Nutrition: A Prospective Multicenter Observational Study

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Management of Home Parenteral Nutrition: A Prospective Multicenter Observational Study

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Key Words
Home parenteral nutrition · Patient characteristics · Underlying disease · Quality of life · Complications

Abstract
Background: There are no specific Swiss home parenteral nutrition (HPN) data showing patient characteristics, quality of life (QoL) and complications. The goal of this study was to collect representative nationwide data on current adult HPN patients in Switzerland for international comparability and benchmarking. ***Methods:*** This was a multicenter, nationwide, observational study. We conducted interviews for demographics, PN characteristics, QoL and complications. The data were assessed at baseline and after a follow-up of 3 months using a questionnaire. ***Results:*** Thirty-three adult patients were included. The most common underlying diseases were cancer, radiation enteritis and state after bariatric surgery, and the most prevalent indication was short bowel syndrome. During the 3-month observation period, significant increase or stabilization of body weight occurred in the patients, physical activity scores improved from 34.0 to 39.4 and mental scores improved from 41.9 to 46.4. HPN dependency and traveling restrictions were of the greatest concern. Diarrhea, xerostomia and/or thirst were frequent complaints. ***Conclusion:*** Anthropometric parameters and QoL improved during the observational period in this HPN cohort. These Swiss HPN data are prerequisite for evaluation and comparison of HPN recommendations and best clinical practice, status of professional care instructions related to HPN effectiveness, quality of treatment and patient safety.

Introduction

Parenteral nutrition (PN) is life saving and indicated when the gut is not functioning and due to oral or enteral intake not being sufficient to reach appropriate requirement target. Advances in home parenteral nutrition (HPN) enable many patients to survive, to live at home and to have good or reasonably good quality of life (QoL) in their normal environment instead of prolonged hospital stays. Today it represents an established and commonly used procedure [1]. Even in elderly patients with cancer, HPN has been shown to benefit nutritional status and QoL [2]. Patients can be treated in an outpatient setting, resulting in reduced healthcare costs [3].

Since the introduction of HPN in the 1970s, HPN prevalence and incidence have been steadily increasing in

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Europe, with a large multicentric survey showing an annual incidence of 4–6 per 10^6 inhabitants and a prevalence of 2–40 per 10^6 inhabitants [4–6]. The most common indications for long-term HPN in Europe are Crohn's disease, mesenteric vascular disease, cancer and radiation enteritis [7]. Other more recent studies confirm that malignancy is the single most common indication for HPN [8, 9].

PN causes important restrictions in personal life, particularly, in social life, mainly due to the cyclic nocturnal HPN administration. These patients show reduced QoL, with physical problems, HPN dependency, social restrictions, sleeping problems and financial problems [10].

Shaw et al. [8] performed a first retrospective epidemiological analysis of patients with home artificial nutrition in Switzerland, based on data provided by the leading national insurance provider. Over the 5-year analysis period, from 2005 to 2009, 433 HPN patients were recorded, showing increasing frequency of HPN.

Data on HPN patients' characteristics and living conditions are scarce, and little is known about the challenges and problems these patients face. The goal of this prospective study was to collect representative nationwide data on the current Swiss adult HPN patient group for international comparability and benchmarking.

Material and Methods

Study Design and Patient Selection

This multicenter, nationwide, observational study started in April 2013 and ended in March 2014. General practitioners and hospital physicians taking care of HPN patients were contacted. Their names were accessible through the Swiss Association for Common Tasks of Health Insurers (SVK). The physicians addressed were requested to obtain written consent from their patients to participate in the study. Inclusion criteria were the following: age >18 years, receiving HPN, life expectancy >30 days and signed written consent. Patients fulfilling the inclusion criteria were either visited at home for an interview or interviewed in their hospital's outpatient clinic.

Data Collection

Data were collected using an entry questionnaire and a follow-up questionnaire 3 months later. Patients included in the study either filled out the questionnaire together with their interviewer or on their own. The mean interview duration was about 45 min. The following data were collected: personal and demographic data, social aspects, detailed nutrition regimes and QoL according to the validated Short Form 36 Health Survey version 2 (SF-36v2)™ questionnaire, anthropometric data over time, indications for PN, medical history and prevalence of complications. The documents were available in three languages: German, French and Italian.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). To assess the effects of HPN on personal life, behavior and emotions, patients were interviewed about the effects of HPN and asked to check all applicable responses. HPN-related complaints could be evaluated by the patients in the questionnaire by choosing from 3 options: 'a little', 'medium' or 'strong'. To assess physical performance and mental health status at different time points (before disease, just before starting HPN and during HPN), the patients could choose between 4 different options ('very good', 'good', 'bad' and 'very bad'). The QoL of the patients on HPN was assessed using the SF-36v2™ questionnaire at the time of entry in the study and at the time point when the patients had to answer the follow-up questionnaires.

The SF-36v2™ is a multipurpose health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures and a preference-based health utility index [11]. These 8 scales are reduced to a physical component summary (PCS = physical functioning + physical role + bodily pain + general health) and to a mental component summary (MCS = vitality + social functioning + emotional role + mental health) [12].

Statistical Analysis

The statistical assessment was performed with IBM SPSS statistics for Windows, version 19.0 (IBM Corp., Released 2010, Armonk, N.Y., USA). The Wilcoxon test was used for continuous, non-parametric data. Results are reported as means with SD or as numbers and percentages. A p value of <0.05 was considered statistically significant.

Ethical Approval

This study was conducted in accordance with the ethical guidelines of the 1957 Declaration of Helsinki, and written informed consent was obtained from all participants. Ethical approval for the study was obtained from the Bernese Cantonal Ethics committee (KEK Bern, study no. 068/13), Bern, Switzerland.

Results

Forty-one patients were recorded during the 1-year investigation (fig. 1). Eight of the patients who were comparable to the study population did not consent to participate, while 33 participated (n = 100%) and filled in the entry questionnaire. The follow-up questionnaire was filled in by 24 patients. In 3 patients, the loss of follow-up was because they died during the study period due to the underlying disease (cancer), 4 patients ceased HPN and 2 patients had no more interest in the further participation of the study. This corresponds to about 4 patients per 1 million inhabitants in Switzerland and is comparable with other European countries. All tertiary university hospitals and all important referral centers of different regions of Switzerland, as well as namely physicians, who

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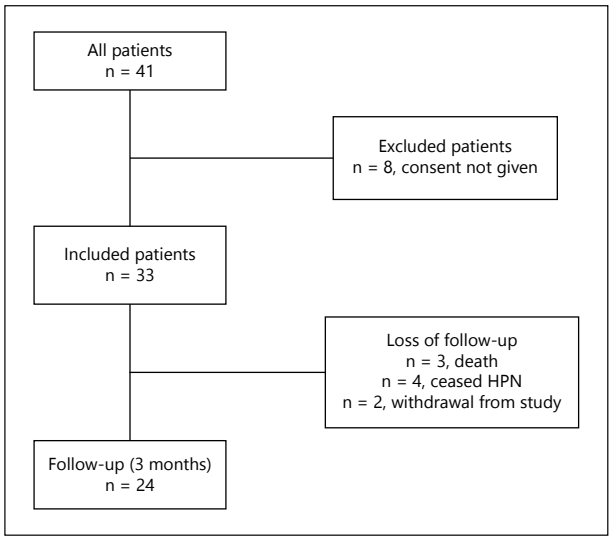

Fig. 1. Study flow diagram.

Table 1. Patient characteristics

Data	Results
Patients, gender, n (%)	
Male	12 (36)
Female	21 (64)
Age at start of HPN, years	
Age, mean ± SD	53.76±17.75
Age, median	59
Age, n (%), (f:m)	
<40	8 (24), (5:3)
41–60	11 (33), (9:2)
61–70	10 (30), (5:5)
≥71	4 (12), (2:2)
Geographical distribution (Switzerland), n (%)	
East part	1 (3)
North part	2 (6)
South part	3 (9)
Central part	5 (15)
West part	10 (30)
Region of Berne	12 (36)
Marital status	
Married	15 (45)
Single	9 (27)
Divorced	7 (21)
Widowed	2 (6)
Living situation, n (%)	
Partner	15 (45)
With children <18 years or with the parents	3 (9)
Alone	8 (24)
Nursing home	4 (12)
Catheter types, n (%)	
Hickman	18 (55)
Port-a-cath	14 (42)
Dialysis fistula	1 (3)

are familiar with HPN therapies, were contacted but not all of them had patients to contribute. The patients' characteristics are listed in table 1. The mean age on starting HPN was 53.8 ± 17.8 years. At the time of the initial interview, HPN treatment had been initiated on an average of 3.44 years previously, with a wide range from 2 days to 30.75 years. The mean BMI before disease was 28.5 ± 11.4 kg/m^2 and decreased significantly before starting HPN to a BMI value of 19.6 ± 6.7 kg/m^2 ($p < 0.001$). At the time point of the first interview, the mean BMI had increased significantly with HPN treatment to 22.0 ± 6.1 kg/m^2 ($p < 0.001$). The BMI could be kept stable at 21.5 ± 3.2 until the follow-up interview (fig. 2).

Underlying Diseases and Indications for HPN

The underlying diseases and the indications for HPN of the 33 patients are reported in table 2. As underlying disease cancer was predominant (n = 14, 42%), followed by post-bariatric surgery and post-radiation enteritis (n = 4 each, 12%). In 13 (39%) of the cases, a short bowel syndrome (SBS) was the indication for HPN.

Central Venous Catheter-Related Complications

Most patients (n = 32, 97%) used tunneled catheter systems like the Hickman or the Port-a-cath. Only 1 patient was fed through a dialysis arteriovenous fistula. In 45% of the patients (n = 15), there was at least one central venous catheter (CVC) replacement during the nutritional treatment, primarily due to infections, CVC occlusions or displacement. Eleven patients (33%) reported at least one infection during the HPN period. Intervention-related CVC complications (e.g. arterial lesions, fixation problems) occurred in 5 patients (15%) and CVC occlusions in 5 patients (15%). During the present observational period (follow-up questionnaire after 3 months from baseline), 6 patients (18%) had to have the CVC replaced due to infectious complications.

Effects of HPN on QoL

Regarding the employment, 85% (n = 28) of the HPN patients were no longer employed, either because of physical impairment or because they had already retired (n = 13). Nine percent (n = 3) had an employment with medium physical activity or were students. Less than half of the patients (39%, n = 13) were able to do the housekeeping themselves; 58% (n = 19) were dependent on family help. Personal care was performed themselves by 88% (n = 29). For attaching and removing the PN, 76% (n = 25) relied on external help, such as a homecare service or a nurse.

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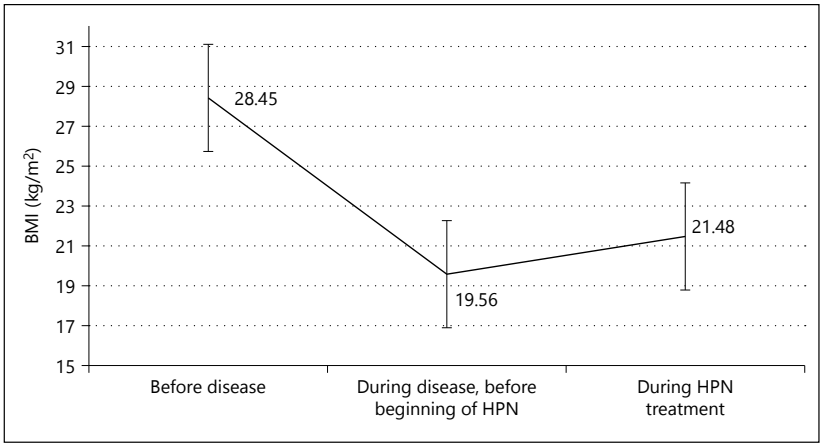

Fig. 2. The time course of BMI (mean ± SD).

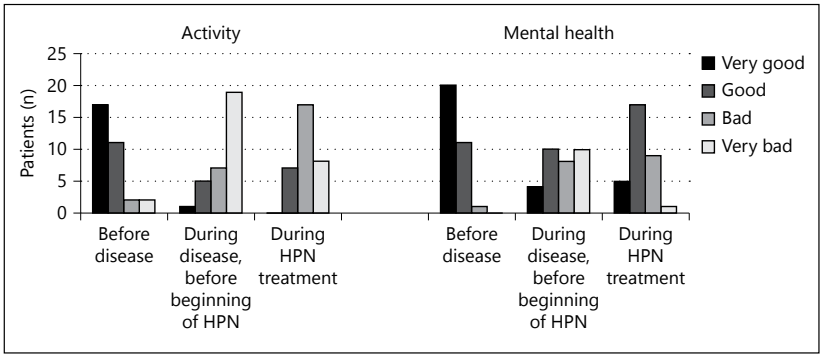

Fig. 3. Activity and mental health follow-up.

Performance level and mental health status are shown in figure 3. Before the disease, 52% (n = 17) of patients were very active. During the disease, but just before beginning HPN, 58% (n = 19) were not active at all. This improved during treatment with HPN, with 52% (n = 17) of patients reporting they were a little active. The mental health status was rated very bad in 30% (n = 10) during the disease, just before starting HPN. During HPN treatment, only 3% (n = 1) described their mental status as very bad. Almost all patients showed improved physical and mental QoL after 3 months (PCS 34.02 vs. 39.37; MCS 41.91 vs. 46.35), as shown in figure 4. Only 2 patients (6%) considered themselves healthy, while 7 (21%) described themselves as fairly healthy. Most patients reported in the QoL questionnaire that their health was not excellent at all (n = 12, 36%).

Aspects of HPN treatment that were reported as most disturbing were the restricted ability to travel and the impossibility to participate in social events (n = 21, 64%) and the dependency on the treatment (n = 19, 58%). Sleep

Table 2. Underlying diseases and indication for HPN

Diagnosis	n (%)
Cancer	14 (42)
Complications of surgery	5 (15)
Post-bariatric	4 (12)
Others	1 (3)
Radiation enteritis	4 (12)
Crohn's disease	3 (9)
Systemic sclerosis	2 (6)
Congenital bowel disease (Hirschsprung disease)	1 (3)
Motility disorders	1 (3)
Caecum perforation	1 (3)
Mesenteric infarction	1 (3)
Glycogenosis type Ia (–> severe inappetence)	1 (3)
Indication for HPN	**n (%)**
SBS	13 (37)
Malabsorption	10 (29)
Fistula	4 (11)
Obstruction	3 (9)
Severe malnutrition prior to surgery	1 (3)
Other	4 (11)

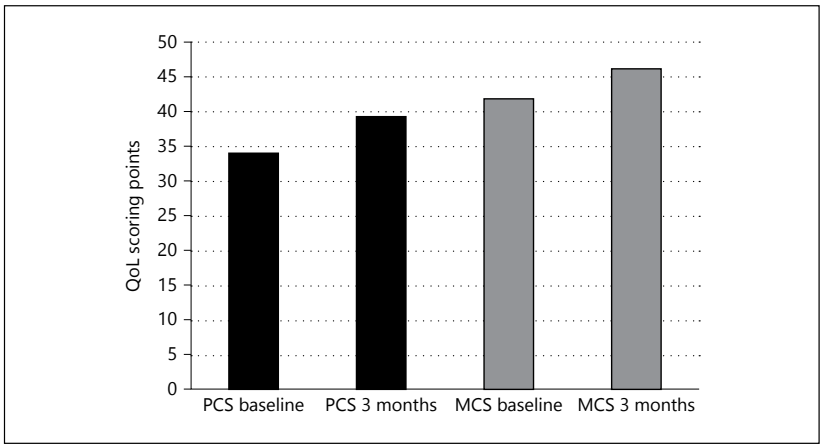

Fig. 4. QoL follow-up.

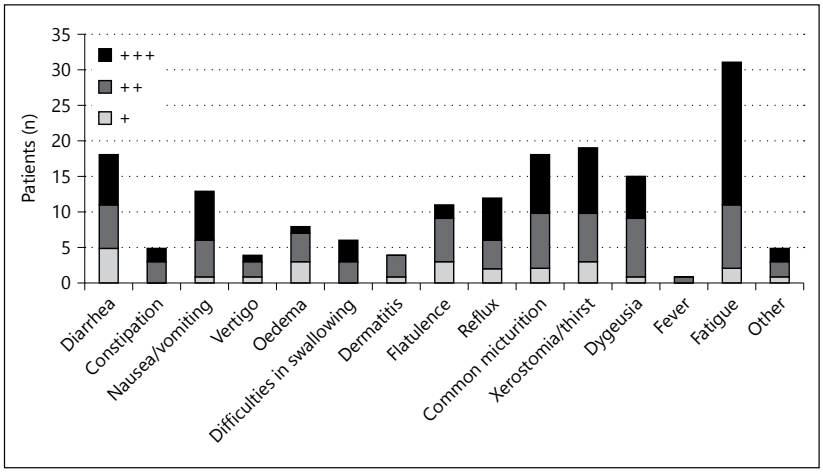

Fig. 5. HPN-related complaints.

disturbances because of noise generated by the mechanical infusion pump were mentioned 8 times (n = 8, 24%). Fear of further health complications (n = 5, 15%) and problems in partnership/family life (n = 3, 9%) were also listed. The HPN-related complaints are shown in the figure 5. The complaint cited most often was by far fatigue (n = 31, 94%). Rarely occurring complaints were pains, spasms, difficulty in controlling blood sugar level, night sweats and post-prandial health problems.

Discussion

The present prospective study is the first detailed analysis of HPN patients in Switzerland. We consider this survey as representative for the population of HPN patients in our country. Of the 41 HPN patients identified, 33 were included. The University Hospital of Berne provided 36% of the recruited patients, far more than any other site, which may be due to the long lasting clinical experience with this population. HPN is prescribed not only by important referral centers, but also by general practitioners taking care of these patients. There are no regular follow-ups, aspects or guidelines for HPN prescriptions and care in Switzerland.

The age and gender distribution in our study are comparable to those of other surveys, which also showed a much higher rate of female HPN patients [4, 13–15]. This is influenced by the underlying diseases, for example, post-radiation enteritis occurring in patients with gynecological malignancies. SBS may also be more likely to occur in women due to the shorter length of their small

intestine [16]. A final reason is the increasing number of bariatric patients in Switzerland, of which 75% are women [17].

Compared to other studies, the mean duration of HPN in our cohort is slightly lower (mean 3.44 years), but with a broader range (0.1–31 years) [10, 18]. There was also greater variation in our study due to the inclusion of a patient with Hirschsprung disease requiring HPN since birth and due to the inclusion of a patient with SBS since more than 30 years, corresponding to almost 9 times the mean duration of HPN.

Approximately, half of our patients have had at least one CVC replacement during HPN treatment. The complication mentioned most often was CVC infection. This corresponds with the results of previous studies: 28.6% had at least one catheter sepsis and 50% had at least one catheter change. CVC infection rate ranged between 0.38 and 4.58 episodes per 1,000 catheter days [19, 20]. To prevent infections and other catheter-related complications, good clinical practice and an experienced multidisciplinary team are mandatory [21]. Six patients (18%) needed a catheter replacement because of infectious complications in the 3 months of follow-up. This rate has to be interpreted with caution, because of the short follow-up period and because many patients just had started with the HPN therapy. The procedure in case of suspected CVC-related infection and subsequent removal is managed in a similar way throughout Switzerland. When a catheter infection is suspected, peripheral blood culture samples and culture samples from each catheter lumen are taken. If there is a definitive sign of local infection, for example, purulent secretion at the exit site, or a catheter-induced sepsis, the CVC is removed immediately and an antibiotic therapy is started [22].

In a European multicenter study, Van Gossum et al. [4] showed almost the same distribution of underlying diseases (cancer 42%, Crohn's disease 15%, vascular diseases 13%). Recently, the ESPEN HPN-Chronic Intestinal Failure Special Interest Group (European Society of Clinical Nutrition and Metabolism) created a survey to describe the use of HPN in post-bariatric surgery, including the indications and outcome. An interesting finding in our study is that 4 patients (nearly 15%) of our study population need HPN after bariatric surgery. Patients undergoing malabsorptive procedures are at risk of developing nutritional deficiencies and protein-energy malnutrition (PEM). A small number of patients will develop PEM and will therefore require HPN months to years after bariatric surgery. Bariatric surgery has increased significantly in the last years in Switzerland, with 750 bariatric interventions in 2001 compared with 4,000 in 2013 [17]. Not much is known about this group of patients requiring HPN to compensate for complications or side effects after bariatric surgery [23, 24]. Given the proportion of morbidly obese people in the Swiss population (in 2012: 11% men and 9% women) [25], post-bariatric PEM will be an emerging problem in the future.

On the other hand, other indications have dramatically decreased, noticeably, the 4% proportion of AIDS patients in earlier years, most of who died of wasting syndromes due to the lack of effective therapies [4, 26]. New treatments, better outcome and prevention strategies have increased survival and decreased the need for HPN in such patients [27]. This was also reflected in the fact that there were no AIDS patients in the current study. In the study of Van Gossum et al. [4], cancer was in first place (39%) at almost the same rate like in our survey. The proportion of HPN patients with oncological tumors has increased over the past years in Europe [28]. Previous Swiss data about the indications for home artificial nutrition demonstrated that neoplasms were the most frequent underlying disease (51%), diseases of the digestive system on the second place (10.4%) and diseases of the nervous system in third place (9.6%) [8]. In our study, there were no patients with underlying neurological disorders. This is probably due to the fact that patients with neurological disorders can mostly be treated with enteral nutrition, including PEG [29]. Another important fact is the change in official recommendations for HPN over the last years, repositioning HPN as a palliative treatment in cancer patients because of the relatively small proportion of PN-associated comorbidity risk factors [14, 30]. Regarding the indications for HPN, we found that SBS is the most frequent indication (37%), consistent with other published data [31, 32].

Our investigation also focused on the QoL of HPN patients. Both physical and mental QoL, assessed by the non–disease-specific SF-36v2, improved over time in our patients. Many other studies determined the QoL using the Karnofsky score, the SF-36 or a new specific questionnaire for HPN patients. Overall, patients with HPN have poorer QoL than healthy people or patients with chronic illnesses [13, 19, 32–34]. An earlier study with only 13 participants showed that none of those HPN patients had a regular employment, but 46% did most of the housekeeping [35]. Our data showed that 85% of patients had no employment, and only 39% were able to do the housekeeping on their own.

The additional subjective definition of physical performance and mental health status were also investigated by Winkler et al. [36], who achieved greater insight into the lives of HPN patients and their definition of QoL. In our study, most of the patients reported that they were 'very active' or 'active' before disease, comparable with healthy individuals. In the immediate period before starting HPN, most of the patients felt very tired, adynamic and 'not active'. Fortunately, after initiation of HPN, the performance level increased after weeks in most patients, showing the positive effects of HPN on well-being, body function and performance levels. The results concerning mental health were similar, with 'poor' mental health reported before starting HPN and 'good' mental health after initiation of HPN.

We conclude that our population profits by HPN from a better health status. Other studies confirm our findings showing improved QoL with HPN in both patients with benign and malignant underlying disease [37–39].

Restricted travel options, limited social interaction and activities as well as loss of independence were the most frequent complaints related to HPN. Other studies showed similar results, mostly evaluated in surveys: the lack of freedom, being dependent and limitations in social life [40, 41]. Moreover, Huisman-de Waal et al. [42] showed social and somatic impacts of HPN therapy on daily life, which are comparable with our data (e.g. fatigue, xerostomia, diarrhea; fig. 5).

Strengths and Limitations of the Study

This prospective study provides the first detailed analysis of HPN patients in Switzerland. It is intended to regularly follow-up (in longer time periods) this cohort. The presented data will form the basis for a national HPN registry, which is needed to evaluate the specific situation of this cohort in the national (healthcare) context.

The fact that the follow-up of the study was only 3 months, and 3 patients had just started HPN before inclusion in the study is a limitation. The short duration was chosen to minimize patients lost to follow-up. Second, it was difficult for most patients during the survey to distinguish between HPN-related side effects and side effects due to underlying disease, and it was very challenging to determine whether improved or worsened QoL was caused by the underlying disease or is a direct consequence of the HPN. A disadvantage of our study is that we do not have the information about how many patients were eligible for the present study, but did not give their consent to the physicians in charge.

Conclusion

We conclude that PN is life saving and shows physical and mental benefit for HPN patients, but there are also negative implications for QoL, especially in terms of social and emotional aspects and loss of autonomy. The number of patients after bariatric surgery seems to increase steadily, and PN is effective in this population. This first prospective analysis of Swiss HPN patients, focusing on anthropometric parameters and QoL, shows major improvements over the 3 months study period. These patients should be monitored over the long term to evaluate and compare outcomes and the impact of HPN on the underlying disease and HPN-associated complications. A national registry is a prerequisite for international comparability and benchmarking and can help to improve treatment quality and safety as well as to define best practices of HPN.

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Statement of Authorship

The authors declare that they have written the text themselves, and the work described herein is their own, unless otherwise acknowledged in the text. All sentences or passages quoted in this paper from other people's work have been specifically acknowledged by clear cross-referencing to author, work and page(s). All authors have participated sufficiently, intellectually or practically, in the present work and take public responsibility for the content of the article.

Disclosure Statement

None of the authors has a conflict of interest to declare.

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4.3 Quality of life in patients with systemic sclerosis and HPN

Home parenteral nutrition is beneficial in systemic sclerosis patients with gastrointestinal dysfunction

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Home parenteral nutrition is beneficial in systemic sclerosis patients with gastrointestinal dysfunction

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Objectives: To assess 12-month changes in nutritional status and quality of life (QoL) in systemic sclerosis (SSc) patients requiring home parenteral nutrition (HPN).
Method: We conducted a retrospective, single-centre database analysis of SSc patients regarding a 12-month period of HPN at an interdisciplinary University Unit/team for nutrition and rheumatic diseases. Nutritional status was analysed by nutritional risk screening (NRS) and body mass index (BMI). QoL was evaluated using Short-Form Health Survey (SF-36) questionnaires.
Results: Between 2008 and 2013, daily nocturnal HPN was initiated in five consecutive SSc patients (four females and one male, mean age 62.2 years) suffering severe malnutrition due to gastrointestinal tract (GIT) involvement. After 12 months of HPN, the mean NRS score decreased from 4.4 (range 4–5) to 1.4 (range 1–2), the mean BMI increased from 19.1 (range 17.4–20.3) to 21.0 kg/m^2 (range 18.3–23.4). QoL improved in all patients, reflected by the summary of physical components with 33.92 points before vs. 67.72 points after 12 months of HPN, and the summary of mental components with 49.66 points before vs. 89.27 points after 12 months of HPN. Two patients suffered one catheter-related infection each with subsequent surgical removal and reinsertion.
Conclusions: HPN is a feasible method for improving anthropometric parameters and QoL in SSc patients severely affected by GIT dysfunction. We recommend HPN in malnourished, catabolic SSc patients unable to otherwise maintain or improve their nutritional status.

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by increased fibroblast activity and resulting in multiple organ fibrosis (1). The gastrointestinal tract (GIT) can be affected in up to 90% of SSc patients. Nevertheless, GIT involvement is rarely reported, mostly because of other more prevalent organ complications, and is therefore diagnosed at late stages leading to malnourishment in about 29% of patients (2). The main GI manifestations are gastro-oesophageal reflux, gastroparesis, intestinal pseudo-obstruction, bacterial overgrowth, and malabsorption resulting in protein–energy malnutrition (PEM). Deterioration of nutritional and functional status has a severe impact on the prognosis and quality of life (QoL) of these SSc patients with GIT involvement (3–5).

As early recognition of PEM is crucial, screening of nutritional status should be implemented in every physician consultation (6). Nutritional counselling and oral nutritional supplements, between-meal snacks and fortified food should be recommended as a first-line approach (6). From our experience, this first-line strategy is effective at early stages of GI dysfunction. At energy intake below 75% of the requirements, complementary artificial nutrition should be considered; as soon as the resorptive capacity of the intestine is too low, the only possible option is life-sustaining, long-term home parenteral nutrition (HPN) (7).

At present, there is a scarcity of literature on malnourished SSc patients and the effectiveness and safety of HPN. Over the past 20 years, several authors have seen beneficial, and sometimes striking, effects of complementary HPN in this population. The aim of our pilot study was to show improvement in nutritional state and QoL during 1 year of HPN and to motivate physicians to discuss this palliative option with SSc patients suffering from severe GIT involvement.

Method

Patients

We conducted a retrospective, single-centre database analysis of SSc patients regarding a 12-month

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period of HPN at an interdisciplinary University Unit/team for nutrition and rheumatic diseases. Data were extracted from paper and electronic medical records. We documented medical history relevant to the topic, demographics, HPN regime, and anthropometric and clinical data during the observational period.

Nutritional status

Energy intake measured in kilocalories (kcal) was estimated by a dietician according to recall protocols. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Nutritional risk was assessed based on the internationally validated Nutritional Risk Screening (NRS 2002) system to predict outcomes based on identified risk parameters (8). Scores range from 0 to 7, classifying patients as malnourished (score ≥ 3) or not (score < 3).

QoL

QoL scores were assessed by the Short-Form Health Survey (SF-36) questionnaire comprising 36 questions regarding physical and mental status, as described previously (9). Evaluation leads to a physical component summary (PCS) score and a mental component summary (MCS) score (10).

Ethics

The study was conducted in accordance with the ethical standards of the local ethics committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983 (Ref. no. KEK-BE 035/12).

Statistics

Descriptive statistics are expressed by mean values and their respective standard deviations (sd) where applicable.

Results

Between 2008 and 2013, HPN was initiated in five consecutive SSc patients (four females and one male, mean age 62.2 years) suffering severe malnutrition due to GIT involvement (for a patient overview, see Table 1). Specific anti-Scl70 antibodies were present in one patient, anticentromere antibodies were found in another, both anti-Scl70 and anticentromere antibodies were positive in one, and no specific antibodies were found in another two patients. The maximum modified Rodnan skin score ranged from 13 to 34 (mean 23).

Organ involvements were cardiac in three patients with one lethal outcome, interstitial lung disease (ILD) in three patients, with associated pulmonary arterial hypertension (PAH) being oxygen dependent in one female patient. Muscle weakness was moderate to severe in all patients. Kidney involvement was found

Table 1. Demographic and anthropometric outcome data.

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender (female or male)	Female	Male	Female	Female	Female
Age (years)	64	41	76	58	72
Age at SSc diagnosis (years)	58	39	74	50	69
SSc subtype	Diffuse	Limited	Limited	Diffuse	Diffuse
Time between diagnosis of SSc and HPN (years)	6	2	2	8	3
Energy requirements before HPN (kcal)	2300	2600	1700	1600	1700
Energy intake before HPN (kcal)	1000	200	500	750	800
Height (cm)	178	194	162	157	152
Weight loss since SSc diagnosis until start of HPN (kg/year)	41/5	23/1	12/2	17/3	23/2
BMI at SSc diagnosis (kg/m^2)	32.5	25.3	22.9	24.3	30.3
BMI at start of HPN (kg/m^2)	19.6	19.9	18.3	17.4	20.3
BMI 6 months after start HPN (kg/m^2)	22.4	19.9	19.0	19.9	22.5
BMI 1 year after start of HPN (kg/m^2)	23.4	20.7	18.3	19.5	22.9
NRS 2002 score at start of HPN	4	4	5	4	5
NRS 2002 score 1 year after HPN	1	1	2	1	2
Percentage of energy intake before HPN (=oral intake) compared to the requirements	43	8	30	47	47
PCS score	17.4/40.8	11.2/87.8	12.2/66.2	44.2/58.2	84.6/85.6
MCS score	50.2/82.4	5.2/78.7	8/83.8	68.9/73.4	116/128

SSc, Systemic sclerosis; HPN, home parenteral nutrition; BMI, body mass index; NRS, nutritional risk screening; PCS, physical component summary; MCS, mental component summary.

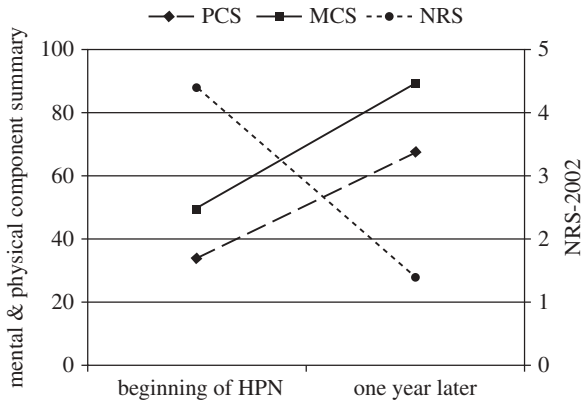

Figure 1. Follow-up mental (MCS) and physical component summary (PCS) and nutritional risk screening (NRS 2002) scores (data shown as mean) at the start of home parenteral nutrition (HPN) and 1 year later.

in two patients, one with acute renal failure. The most prevalent GIT symptoms were: feeling of fullness, pseudo-obstruction, abdominal distension, constipation, dysphagia, heartburn, regurgitation, and diarrhoea as signs of malabsorption. In case of suspected bacterial overgrowth of the small intestine (SIBO), we performed a hydrogen breath test to confirm or exclude the diagnosis. Upon suspicion of gastro-oesophageal reflux, we performed an upper GI endoscopy and manometry, and then by indication a 24-h pH test. Motility disorders of the oesophagus were diagnosed by cinematography. None of the patients suffered from SIBO; however, all patients suffered reflux oesophagitis and oesophageal motility disorders of the oesophagus. The motility of the GI tract was assessed by whole-gut transit with a radio-opaque marker, showing generalized dysmotility in all patients.

According to the NRS 2002, all patients were severely malnourished (Figure 1). The mean energy intake before HPN was 35% of the calculated requirements, revealing catabolic metabolism. Indications for complementary HPN were low caloric intake (< 75%) and subsequent deterioration of nutritional status. All patients received a cyclical nocturnal parenteral nutrition infusion daily. Commercial, standard three-chamber bag systems (all-in-one) with the following components were used: lipids, proteins, and carbohydrates (standard product: StructoKabiven®, 1477 mL, Fresenius Kabi, Switzerland; content of 1000 mL (1115 kcal): 38.5 g structured triglycerides, 51 g amino acids, and 127 g glucose). All patients were given their full energy requirements within the first week.

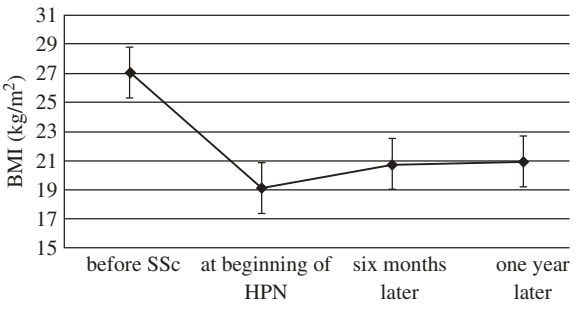

Figure 2. Body mass index (BMI) follow-up (data shown as mean ± sd).

The mean BMI increased from 19.1 kg/m^2 (range 17.4–20.3) at the start of HPN to 20.8 kg/m^2 (range 19.0–22.5) 6 months later and stabilized at 21.0 kg/m^2 (range 18.3–23.4) after 12 months of HPN (Figure 2, Table 1).

Analysis of SF-36 after 1 year yielded benefits in all parameters (Table 1). PCS and MCS scores both improved (PCS: 33.92 before vs. 67.72 after; MCS: 49.66 before vs. 89.27 after) (Figure 1, Table 1).

Prior to HPN, patients were malnourished and in a catabolic state, manifesting fatigue, asthenia, and exhaustion, as well as lack of energy for daily activities such as vacuuming, shopping, walking, or getting dressed. Additionally, pain was reported as subordinate in comparison to nutritional and digestive problems. After starting HPN, all components of the SF-36 questionnaire showed amelioration.

As an example, the male patient aged 39 years at diagnosis of SSc with a daily energy intake of 200 kcal reported difficulties in playing football with his sons prior to HPN. After HPN, he reported rapid mental and physical improvement leading to more physical activity and finally enabling cycling tours.

Three patients reported technical difficulties, such as functional impairment of their hands, which made it difficult to administer the HPN. For example, they experienced problems connecting the filigree catheter kits.

No further HPN-related complications were detected. Two patients suffered one catheter-related infection each, with subsequent surgical removal and reinsertion.

Discussion

There is scarce literature about SSc patients with GIT dysfunction and the effect of complementary HPN on QoL. Recent data show benefits from long-term HPN representing a safe and effective feeding method in these patients (7, 11). In line with these reports, our data show that administration of HPN over 1 year is able to improve anthropometrical parameters, nutritional state, and QoL.

Thus, HPN should be considered in malnourished, catabolic patients unable to maintain their nutritional status with subsequently declining body functions. In our patients, nutritional goals were already reached within 1 week of HPN, with maintained nutritional status and body function after another year of treatment.

At present, there are no data on QoL assessment using the SF-36 in SSc patients with GIT dysfunction for

comparison. The benefit of the parenteral nutrition on QoL has been demonstrated in small case studies only (maximum of 15 cases) with assessment tools being different from the SF-36 (7, 12). Only Jawa et al showed an insignificant effect of HPN on the functional state of SSc patients (13).

In our pilot study, physical as well as mental health categories of the QoL questionnaire increased considerably after 1 year of HPN treatment. Of note, the mental characteristics presented a slightly higher benefit in comparison to the physical ones (Figure 1). From our prior studies we know that mental performance and mood do improve in malnourished patients if adequate nutritional support is ensured (14). Present-day application of HPN with all-in-one bags is well accepted by patients and their relatives; patients soon feel better with HPN, and are motivated to participate in social events and family activities; nocturnal infusions render patients independent and physically active during the daytime. Our cohort reported having more energy for daily activities, a better health situation, renewal of participation in social events, and enjoyment of travel (data not shown).

As also reported by Brown et al, our cohort experienced technical difficulties, rendering HPN handling difficult (7). In this context, family members, relatives, community nurses, and home care providers should be trained in managing HPN by themselves. Sleep disturbance, as a consequence of pump-related noises, unfortunately could not be overcome.

Overall, the severity and rate of medical complications can be kept low by correct and careful management, hopefully eliminating catheter-related infections.

Study limitations are the retrospective nature and the small number of patients hampering relevant statistical tests, yet our cohort is the only one simultaneously assessed for HPN and changes in nutritional status and QoL.

Conclusions

HPN in severely malnourished SSc patients is a feasible option leading to improved anthropometric parameters and QoL. We suggest that HPN should be considered in malnourished, catabolic patients unable to otherwise maintain their nutritional status. The effects of HPN on organ function and survival should be verified within a prospective study.

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4.4 Assessment of PN stability and compatibility of medication in AiO PN formulations

Simple drug compatibility testing and physicochemical stability assessment with all in one parenteral nutrition admixtures: the Levetiracetam example

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Physicochemical stability and compatibility testing of levetiracetam in all-in-one parenteral nutrition admixtures in daily practice

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ABSTRACT

Background: Parenteral antiepileptic drugs are frequently used in critically ill patients for seizure control therapy or prevention. Many of these patients require additional parenteral nutrition (PN). Therefore, a parallel infusion of the frequently used antiepileptic drug levetiracetam (LEV) is interesting in terms of the restricted i.v. lines (e.g., neonates). The potential interactions of the complex PN admixture with the drug product and the appropriate admixing of a drug at effective dosages require physicochemical lab assessments to obtain specific and reliable pharmaceutical documentation for the intended admixing.
Aim: To assess the of compatibility and stability of LEV, a neutral and hydrophilic drug, in commercial all-in-one (AiO) PN admixtures using simple validated tests to provide necessary data in a timely manner and to allow convenient, documented and safe treatment with PN as the drug vehicle.
Methods: Different concentrations of LEV were injected into two different AiO PN admixtures with no further additives. Stability and compatibility tests for the drug and the PN admixtures were performed over seven days at +4 °C, +23 ± 1 °C and +37 °C without light protection. Stability and sample characteristics were observed by visual inspection and the validated light microscope method. Moreover, the pH level of the admixture was checked, as were the concentrations of LEV over time in the PN admixtures, using an established LC-MS/MS method.
Results: The stability controls of LEV at different temperatures were within absolute ± 20% of the theoretical value in a concentration range of 98.91–117.84% of the initial value. No changes in pH occurred (5.55 ± 0.04) and no microscopic out of specification data or visual changes were observed. The mean value of the largest lipid droplet in each visual field over seven days was 2.4 ± 0.08 μm, comparable to that of the drug-free AiO admixture. Samples stored at +37 °C showed yellowish discolorations after 96 h of storage.
Conclusion: LEV showed compatibility and stability over seven days in the selected PN admixtures, and the described methods represented a valuable and timely approach to determine the stability and compatibility of the highly hydrophilic, not dissociated LEV in AiO admixtures under conditions of use. Further studies with clinically relevant and representative examples of physicochemically different drug classes are needed.

1. Introduction

Most hospitalized patients, especially critically ill patients requiring parenteral nutrition (PN) require additional intravenous (i.v.) medications. To prevent or to treat malnutrition, PN is necessary when the gastrointestinal feeding is inefficient, nonfunctional or not possible (Dudrick, 2009). All-in-one (AiO) admixtures represent the standard for PN regimen and include an oil/water (o/w) emulsion containing approximately 50 individual and potentially reactive soluble components. Therefore, the potential physicochemical interactions among the components, the container and admixes, such as electrolytes, vitamins, trace elements to individualize the regimen, or even i.v. medications, are numerous. The formulation is too complex to be evaluated bibliographically. Accordingly, a lab analysis of the specific composition is needed. In principal, AiO PN admixtures do not represent suited vehicles to carry drugs, but in certain situations they may be convenient or otherwise beneficial (e.g., with limited separate i.v. access, as in neonates, or for compliance, in the home PN setting). Co-administering i.v. medications via Y-site together with PN or as added to AiO PN admixture, without documented compatibility/stability as a prerequisite for both drug and PN efficacy and safety is deemed unacceptable and represents an avoidable medication error. At a minimum, short-term physicochemical compatibility and stability data are required to guarantee

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quality and tolerance of such an individual pharmaceutical formulation. In current nutrition practice commercial multichamber AiO PN admixtures are used at least in the short term. Documented stability of such regimens are mandatory (Mühlebach, 2009). The most common instabilities from the o/w emulsion are creaming and coalescence; physicochemical reactions may be visible by colour or pH changes and by the formation of precipitates as a result of the degradation of components or reactions between nutrients and/or drugs. These reactions depend on various factors, including concentration, light exposure, temperature, catalyst actions, trace elements, or other components, such as electronically charged ions (e.g., dissociated drugs, electrolytes) (Mühlebach, 2005). This can also lead to major, even fatal complications, such as a venous catheter occlusion or blood vessel obstruction due to precipitates or enlarged lipid droplets (>5 μm) or deposits (Hill et al., 1996; Sobotka, 2011; Driscoll, 2006). The United States Pharmacopeia requires that the mean droplet size (MDS) of a parenteral lipid emulsion has to be <5 μm and the volume-weighted percent of fat globules ≥ 5 μm ($PFAT_5$) has to be <0.05% (globule size distribution) (United States Pharmacopeial Convention, 2008). To assess lipid emulsion deteriorations, simple analytical methods are mandatory to be used in a timely, reliable and cost-effective manner in daily (pharmaceutical) hospital practice to ensure the stability or compatibility of ready-to-use individual AiO PN admixtures.

There are many studies on the compatibility and stability of different medications that are admixed in PN (Bullock et al., 1989; Cano et al., 1988; Trissel et al., 1999; Husson et al., 2003a). However, most of these investigations are older (>10 years) and are done with analytical methods and techniques, not more state of the art. Furthermore, the composition of ready-to-use PN admixtures and the specific i.v. drug formulations have not been tested or have changed over time, and they may differ between manufacturers (e.g., generic drugs or individually manufactured, non- commercial hospital products). Therefore, it is very important to evaluate and document individual admixtures to achieve the best impact on medication practice and to avoid medication errors, especially when evaluating drugs that are frequently used in patients with PN.

Antiepileptic drugs such as levetiracetam (LEV) i.v. are frequently used in critically ill patients for seizure control therapy or prevention and treatment of a status epilepticus (e.g., in patients after traumatic or surgical brain injury, cancer patients or neonates) (DeWolfe & Szaflarski, 2013). Such patients mostly receive multiple lifesaving and potent parenteral medications and often require simultaneous administration with PN. LEV is a new-generation antiepileptic drug that is used with a larger therapeutic range with linear kinetics, in contrast to older antiepileptic drugs. There is a lack of published clinical data on the comparative efficacy of LEV given separately or admixed to a daily PN portion. In general, there is also limited literature about PN as a drug carrier for LEV or other antiepileptics.

The aim of the present study was to evaluate the physicochemical compatibility and stability of LEV, which is an almost neutral and hydrophilic drug (see Fig. 1), admixed to commercialized PN AiO admixtures under practice conditions. In addition, suitable tests for timely assessment were proposed. Data are necessary to document this treatment framework because the possibility using of PN as a drug carrier presents a new formulation with associated individual pharmaceutical quality responsibility.

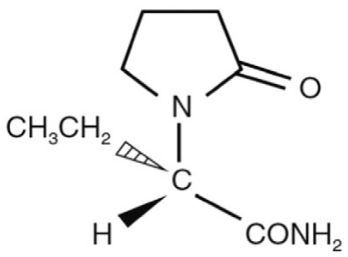

Fig. 1. Formula for Levetiracetam ($C_8H_{14}N_2O_2$; MG = 170.2 g/mol; logP −0.6; pH 7.0) (AHFS, 2013).

2. Material and methods

The investigations were done from January to August 2015 in the laboratory medicine unit of the Cantonal Hospital (Aarau). The LEV injection solution of 500 mg/5 mL (Levetiracetam Sandoz® concentrate for infusion; active pharmaceutical ingredient: Levetiracetam 100 mg/mL (Fig. 1) (AHFS, 2013), excipients: sodium acetate trihydrate, sodium chloride, water for injections for 1 mL) was obtained from Sandoz Pharmaceuticals AG, (Rotkreuz, Switzerland). Water, acetonitrile (ACN) and methanol (MeOH) were of LC-MS/MS grade and obtained from Sigma (Buchs, Switzerland). All other chemicals used were from Sigma (Buchs, Switzerland) and of analytical grade or otherwise indicated. Nutriflex® Lipid Special [NLS], 625 mL (lot:0333 F1) and Nutriflex® Omega Special [NOS], 625 mL (lot:0679 F1) (B Braun, Medical AG, Sempach, Switzerland), were used as PN admixtures (three-chamber-bags with separate lipid, glucose and amino acids compartments, Table 1). Three different LEV concentrations were used, representing a commonly adapted dosage range (20 mg/kg body weight) added to current PN regimens/volumes yielding LEV concentrations in the PN admixture of 0.4 mg/mL (≈2.35 mmol/L), 1.6 mg/mL (≈9.40 mmol/L) and 4.8 mg/mL (≈28.20 mmol/L). Stability and compatibility tests were performed over seven days at 0, 24, 48, 72 and 168 h after admixing LEV injection solution into a PN sample. To prepare the test samples, the bag compartment seals were broken by mechanical pressing on the PN container. The bag was turned upside down five times for homogenization. Three samples (5 mL of PN) of each homogenized PN were transferred into 10 mL glass tubes using a 5 mL manual pipette. LEV injection solution was dosed by admixing 20 μL, 80 μL or 240 μL to the PN sample aliquots in the glass tubes, using manual pipettes. All pipettes in the range of 20–10,000 μL used had to pass the lab-internal testing within a specified accuracy of ±1.0% and a coefficient of variation (CV) of ±0.50%. The glass tube samples were covered with an air-tight seal to provide an air- and fluid-tight seal. The test samples (PN with LEV) were stored in a refrigerator at +4 °C; at room temperature (23 ± 1 °C) in the laboratory; or at +37 °C (water bath). The samples were stored in transparent normal glass tubes without additional light protection. Samples stored and handled in the laboratory at room temperature or in the water bath at elevated temperatures were exposed to

Table 1
Product information of the composition of tested TPN (NOS and NLS), in 625 mL bags.

Ingredient	Unit	NuTRIflex® Omega Special	NuTRIflex® Lipid Special
Volume glucose solution	*mL*	*250*	*250*
Glucose monohydrate	g	99.0	99.0
Sodium dihydrogen phosphate dihydrate	g	1.56	1.56
Zinc acetate dihydrate	mg	4.39	4.39
Volume fat emulsion	*mL*	*125*	*125*
Soya-bean oil	g	10.0	12.5
Medium-chain triglycerides	g	12.5	12.5
Omega-3 fatty acids	g	2.5	–
Monounsaturated fatty acids	%	11.4	13
Polyunsaturated fatty acids	%	34.0	30.7
Ratio Ω-3:Ω-6		1:2.7	1:7
Essential fatty acids	%	31.7	30.7
Volume amino acid solution[a]	*mL*	*250*	*250*
Amino acid content	g	35.9	35
Nitrogen content	g	5	5
Carbohydrate content	g	90	90
Lipid content	g	25	25
Non-protein energy	kJ (kcal)	2505 (600)	2505 (600)
Total energy	kJ (kcal)	3090 (740)	3088 (738)
Osmolality	(mOsm/kg)	2170	2090
pH-value		5.0–6.0	5.0–6.0

[a] Not detailed.

daylight or artificial light (practical condition); samples stored in the refrigerator were protected from light by the closed door ("in the dark"). At each test time point, the samples in the tubes were visually inspected for discolorations, creaming, phase separation, or precipitates. Before taking an analytical sample, the tubes were turned upside down and back three times to guarantee a homogenous admixture. Three aliquots of each sample were measured by LC-MS/MS and then statistically calculated for drug concentration (mean ± SD for each sample). For the identification and quantification of LEV, a Thermo Fischer Ultimate 3000 UHPLC system (Thermo Fisher, San Jose, CA, USA) coupled to an ABSciex 4500 quadrupole mass spectrometer (ABSciex, Darmstadt, Germany) was used with a commercial kit (AED MassTox panel, Chromsystems, München, Germany). Mobile phases I and II were from Chromsystems, München, Germany (AV 92921, 2012). The MS was run in the multiple reactions monitoring (MRM) mode using two transitions for each analyte. The Turbo V ion source run in positive ESI mode. Preparation and clean-up of the samples was performed according to the manufacturer's protocol for serum samples (AV 92111, 2014). Matrix effects and extraction recoveries were determined for serum and PN, as proposed by Matuszewski et al. (2003). Three aliquots of all three concentrations were used. Thereby, the stock solution was diluted 1 + 1 (1:2) and also 1 + 99 (1:100). Sample aliquots of 50 μL were put into Eppendorf tubes, mixed with 25 μL of extraction buffer, vortexed for 10 s and then incubated for 2 min at room temperature. The internal standard mix (250 μL, containing precipitation reagent) was added, vortexed for 30 s and then centrifuged for 5 min at 13,000 rpm. 10 μL of the supernatant was mixed with 1090 μL of dilution buffer. The injection volume was 10 μL, and the LC flow rate was 0.6 mL/min. The injection was done by a thermo-controlled autosampler at room temperature (Thermo Scientific, Dionex UltiMate 3000), and the quantification was done according to a calibration curve, normalized to the corresponding internal standard.

Light microscope investigations for lipid droplet assessment and pH measurements (Metrohm 744 pH Meter) were performed for NOS and NLS as blanks and with concentrations of 1.6 mg/mL LEV (9.40 mmol/L) at +4 °C, +23 ± 1 °C and +37 °C. Before each pH measurement, a two-point calibration of the pH meter was done, each with a buffer solution of pH 9.00 and pH 4.00, respectively (Metrohm calibration buffer). The pH 7.00 solution was used afterwards as a control. Between the calibration steps, the electrode was rinsed with distilled water and wiped dry.

The physical stability of lipid emulsion was assessed by lipid droplet measuring in a light microscope (BX51 Olympus) with an upper droplet size of ≥1 μm. Each microscopic sample (10 μL by a manual pipette) was analysed with 100-fold magnification and oil immersion (Schmutz, 1993). Five individual visual fields were inspected per microscopic sample (15 total visual fields/aliquot): four in the corner and one in the middle of the preparation. The size of the lipid droplets in the visual field was determined using an ocular micrometre (0.01 mm). The diameter of the largest lipid droplet (LLD) and the number of lipid droplets > 5 μm were measured and counted in each of the 15 visual fields tested per aliquot. The stability-indicating data were measured and calculated according to Schmutz (thesis). The specifications (Schmutz, 1993) of microscopic screening are shown in Table 2.

The statistical assessment was performed with IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp. Released 2010, Armonk, NY, USA) and Prism 6 for Mac OS X, Version 6.0 (GraphPad Software). The results are reported as the means with standard deviations (mean ± SD) or as numbers and percentages (*n*, %). In addition, 95% confidence intervals, R^2, two-tailed P test, and one/two-way ANOVA were calculated. A *p*-value < 0.05 was considered statistically significant.

Table 2
Specifications of microscopic i.v. fat emulsion stability screening in 15 visual fields (Schmutz, 1993).

Microscopic parameter	Abbreviation	Unit	Specification
Largest lipid droplet in 15 fields	LLD 1–15	[μm]	≤8
Mean LLD	$MLLD_{max}$	[μm]	<4.5
Standard deviation	SDLLD	[μm]	≤2.0
Number of lipid droplets >5 μm	LD > 5 μm	[*n*]	≤9

3. Results

3.1. Microscopic analysis

The microscopic results of NOS and NLS with LEV (1.6 mg/mL) are shown in Table 3. The mean of the largest lipid droplet in μm out of 15 visual fields (*n*) ($MLLD_{max}$) of 4.5 μm as the upper limit value for the emulsion stability was never reached by any sample over the seven-day analysis period. The mean value of the $MLLD_{max}$ for NOS (at all temperatures and throughout the storage duration) was 2.3 ± 0.60 μm ($n = 180$) and for NLS was 2.6 ± 0.63 μm ($n = 180$). There was a trend for the droplet size to increase over time, as shown in Fig. 2. The upper limit specification (specifications shown in Table 2) of a LLD in 15 visual fields of ≤8 μm was always reached. The LLD measured had a diameter of 8 μm ($n = 1$). The highest SD was 1.99 μm and was thus always smaller than the 2.0 μm specification. Similarly, the number of lipid droplets > 5 μm was three was thus always smaller than the specification of nine.

The $MLLD_{max}$ of NOS and for NLS as blank samples at all temperatures and over the entire storage duration was 2.6 ± 0.77 and 2.7 ± 0.69, respectively, showing comparable emulsion characteristics, and the data were within the specifications. There was no statistically significant difference between the blank samples and the samples with added LEV ($p = 0.1602$, two-way ANOVA). These specifications were not dependent on temperature (4–37 °C), and no difference of the different lipid compositions of NOS and NLS could be detected. The microscopic assessment of lipid droplets per sample (15 visual fields) took approximately 20 min.

3.2. pH determination

The pH of the different PN admixtures samples (with and without 1.6 mg/mL LEV) at three different temperatures decreased negligibly over time in NOS and NLS but ranged in all samples from 5.47 to 5.63 (mean ± SD: 5.55 ± 0.04, $n = 48$), with no detectable changes during the test period. There was no difference regarding the different lipid compositions, and no temperature dependency was shown.

3.3. Visual inspection

Over seven days, no visual changes were observed in the test samples stored at +4 °C or at room temperature. There was no creaming or discoloration, except for the samples stored at +37 °C which showed yellowish discolorations after 96 h. However, neither precipitates nor flocculation were visible. A visual inspection was done for the assessment of large particle formation in the critical size 1–5 μm.

3.4. LC-MS/MS analysis

Extraction recoveries and matrix effects for PN and serum were tested for two LEV concentrations. Serum analysis is described because this lab method was validated for therapeutic drug monitoring (TDM) in serum samples and has therefore to be checked when alternative samples were measured. Since the PN admixtures samples used produced no matrix effects, the analysis could be directly used for the stability measurements in NOS and NLS. The extraction recovery for PN samples for the lower concentration (0.4 mg/mL) was 98.7% ($n = 5$, SD = 5.53) resp. 86.0% ($n = 5$, SD = 5.77) for the higher concentration (4.8 mg/mL). The recovery rate for serum samples was 99% ($n = 5$, SD = 5.01) resp. 92.7% ($n = 5$, SD = 6.35). No matrix effects were observed:

Table 3
Emulsion stability assessed by microscopic analysis of LEV (1.6 mg/mL) admixed to NOS and NLS and stored at three different temperatures.

PN		NOS			NLS		
Temperature		23 ± 1 °C	+37 °C	+4 °C	23 ± 1 °C	+37 °C	+4 °C
Parameter	$MLLD_{max}$ [μm]						
Storage duration	0	1.5	1.2	1.8	1.7	2.3	1.5
	24	2.3	2.1	1.9	2.5	3.3	2.2
	96	3.3	2.4	2.9	2.4	3.3	3.1
	168	2.7	2.7	2.6	3.3	2.5	3.1
Parameter	LLD 1–15 [μm]						
Storage duration	0	3	3	4	5	4	3
	24	6	4	5	5	6	4
	96	6	4	6	5	5	6
	168	6	5	8	7	5	6
Parameter	SDLLD [μm]						
Storage duration	0	0.74	0.77	0.86	1.23	1.22	1.06
	24	1.68	1.06	1.03	0.99	1.53	1.08
	96	1.45	1.12	1.41	1.18	1.22	1.30
	168	1.45	0.90	1.99	1.53	1.46	1.33
Parameter	LD > 5 μm [n]						
Storage duration	0	0	0	0	0	0	2
	24	1	0	0	0	3	0
	96	2	0	1	0	0	1
	168	3	0	0	2	0	1

LEV: levetiracetam; NOS: Nutriflex® Omega Special; NLS: Nutriflex® Lipid Special; RT: room temperature.

the matrix effect for PN samples ranged from 90.9–101.3% and from 97.2–105.1% for serum samples.

No differences between NOS and NLS (as blanks) were observed for selected incubation/storage temperatures (one-way ANOVA: $F = 1.357$, $p = 0.2655$, $R^2 = 0.0677$). The three different LEV concentrations in NLS at +37 °C measured over 7 days were 0.43 ± 0.02 mg/mL, 1.76 ± 0.07 mg/mL, and 5.07 ± 0.15 mg/mL respectively. At room temperature, the following LEV concentration over time resulted: 0.43 ± 0.01 mg/mL, 1.83 ± 0.11 mg/mL resp. 5.11 ± 0.23 mg/mL. No storage temperature dependency was detectable, when comparing room temperature vs. +37 °C (two-tailed *t*-test, $p = 0.3078$). Also no significant difference was shown regarding concentration dependency (one-way ANOVA: $F = 3.084$, $p = 0.0643$, $R^2 = 0.2044$). The measured LEV concentrations in NOS at +37 °C were 0.43 ± 0.02 mg/mL, 1.72 ± 0.07 mg/mL resp. 4.96 ± 0.21 mg/mL. The measurements in NOS at room temperature resulted in 0.41 ± 0.01 mg/mL, 1.8 ± 0.05 mg/mL resp. 5.25 ± 0.28 mg/mL. There was no significant change of the LEV concentration detectable over seven days when comparing the data at RT and +37 °C (two-tailed *t*-test, $p = 0.2029$). Additionally, there was no significant concentration dependency detectable (one-way ANOVA: $F = 3.037$, $p = 0.0646$, $R^2 = 0.1836$). All results were in the range of ±20%. The imprecision was within ±20%. As the LEV measurements were done in highly complex o/w PN samples comparable to bioanalytical samples, the 20% range for deviation was applied. Although the best fit line showed negative trend over the storage time ($y = -0.0259x + 108.7$, $R^2 = 0.0847$), no significant decline of the concentration resulted from one-way ANOVA: $F = 2.124$, $p = 0.1076$, $R^2 = 0.2537$. The individual dot in the stability over time plot indicates the mean of the three measurements expressed in % of initial concentration of LEV in NOS at room temperature and at +37 °C. (Fig. 3).

4. Discussion

Although this stability assessment procedure is aimed for a more general approach how to evaluate on a short term base drug-PN stability and compatibility request in a hospital setting with easy to realise lab investigations available in teaching hospitals and pharmacies, it is important to validate the approach by appropriate investigations on representative and relevant drug products. In this study we selected LEV (Fig. 1), a highly water soluble (>100 g/100 mL of water) low molecular pyrrolidine anticonvulsant representative. This amid drug has a pKa of −2 and is almost not protein-bound. Therefore, it represents a very hydrophilic (logP of −0.6), neutral not dissociated drug compound used

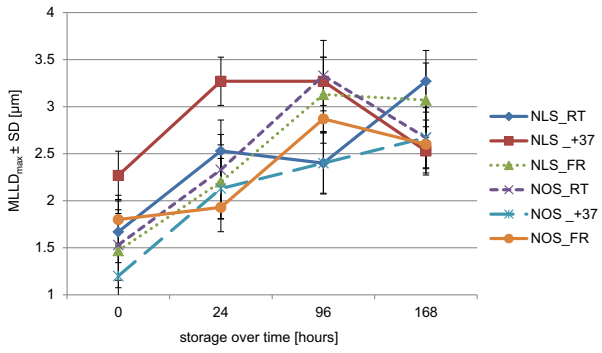

Fig. 2. Mean values of the largest lipid droplet of NOS and NLS with LEV over time at three different temperatures.

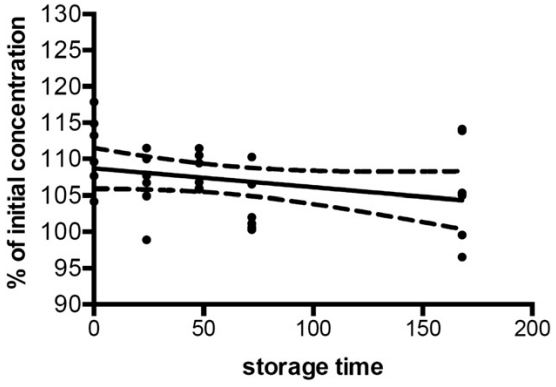

Fig. 3. Stability of LEV in NOS over time determined by LC-MS/MS in mg/mL (room temperature and at +37 °C).

therapeutically in molar doses (1000 mg–6 mol) (AHFS, 2013; http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM414456.pdf). A review showed that anticonvulsants are often used together with PN in traumatic brain injuries and in cancer patients (Salih et al., 2010). Stability and compatibility data with PN are scare, although it is a relevant and frequently used drug for critically ill patients or neonates. Medications often describe Y-site administration and do not address the chemical stability, which is important for efficacy and safety.

LEV in a dose range of 0.4–4.8 mg/mL (2.35–28.20 mmol/L) is a highly dosed i.v. drug and may thus have compatibility concerns. There was no significant decrease over seven days in NOS and NLS at three different temperatures. The assessment of the chemical stability of LEV was done using a validated stability-indicating LC-MS/MS quantification method that is also used for TDM. LC-MS/MS investigations involve highly sensitive, state-of-the-art identification and quantification methods with drug-specific detection available in most tertiary hospital medical labs (see chromatogram of LEV in Fig. 4). The advantages of the LC-MS/MS method vs. HPLC-UV or -FLD (with fluorescence detector) - are the most simple and fast sample preparation, substantially less interference e.g. by co-medications, a shorter run-time and consequently a higher sample throughput and selectivity - clearly predominate a potential lower precision. But using a (deuterated) internal standards, a complete and good precision through all clean-up steps of the analysis can be achieved. Therefore, and as the drug stability/compatibility evaluation in PN can rely on an existing validated and verified LC-MS/MS method used within the TDM-panel in the institutional routine operation of a hospital, their use is within the scope of the investigation for relatively easy access methods to get stability indicating data.

The analysis of the matrix effect and the extraction recovery showed the applicability for PN samples and using the serum sample cleanup. The three different LEV concentrations chosen correspond to the usual LEV dosing from 2 × 250 mg to 2 × 1500 mg applied in usual PN volumes (administered daily). The lower level (250 mg) and upper level (3000 mg) concentrations admixed to 625 mL PN yielded a concentration of LEV of 0.4 mg/mL, 1.6 mg/mL and 4.8 mg/mL. Admixed into 1250 mL PN (for adults), this would result in a concentration of 0.2 mg/mL, 0.8 mg/mL and 2.4 mg/mL. In addition, it was shown that LEV could be dosed in half of the volume due to its high solubility.

All of the measured concentrations of LEV in NOS and NLS were in the range of ±20% of the theoretical value. The different temperature (storage) conditions used for two different high drug concentrations showed no influence on the stability of LEV. The variability (higher concentration after storage) can be explained by pipetting errors during the sample preparation or by the dilution, which yields an incorrect 100% target value. The volume ratio for the PN sample and the drug admixture was ≥1:20 and was therefore sensitive to small pipetting errors. The accuracy of the pipettes is shown above.

The AiO PN admixtures that were chosen are representative treatments for patients; they require PN administration through a centrally placed i.v. catheter (osmolality ≫ 800 mosmol). The two products differ in the fatty acid (FA) composition of the fat emulsion (Table 1). These PN products are prefilled, stable, three-chamber formulations, that can readily be made and used in most patients. Commercially available lipid emulsions have a mean particle size of approximately 0.25–0.5 μm in diameter, which corresponds to chylomicrons. The growth of the lipid droplets into large fat globules could also block small blood vessel (>5 μm), e.g., in the lung, and are dangerous formulations that should not be used in patients (Sobotka, 2011; Pertkiewicz et al., 2009). The light microscope method according to Schmutz et al. is highly sensitive and practicable, with a simple equipment and a conventional method validated by Photon Correlation Spectroscopy (PCS) and the Coulter^R method. Using a microscope with a 100-fold magnification allows the detection of particles approximately 1 μm in size or enlarged emulsion particles up to 20 μm in size. Furthermore, other non-lipid globules (such as particulate matters or precipitations) can also be detected using this method. The method provides an easy, sensitive, cost-efficient, time-sparing, and convenient way to test the physical stability of a lipid emulsion in the critical droplet size to indicate destabilisation (large fat droplet assessment ≥ 1–2 μm), and it is suitable for drug incompatibility testing in AiO PN admixtures (Schmutz, 1993).

LEV did not affect the lipid droplet sizing in microscopy assay over at least 24 h and only showed only a slightly increasing $MLLD_{max}$ over a week at elevated temperatures (Figs. 2,3). Because the chemical analysis with LC-MS/MS showed that LEV possessed good stability in all three concentrations, only the concentration of 1.6 mg/mL was analysed by microscope. No influence of the FA composition on lipid stability could be detected. A single in vitro study showed LEV stability over 91 days in Ora-Sweet (a syrup vehicle used to simplify the process of flavouring and sweetening) and Ora-Plus (suspension adjuvant) at two different temperatures (Ensom et al., 2011). Our results showed that $MLLD_{max}$ in each visual field over seven days at three different temperatures

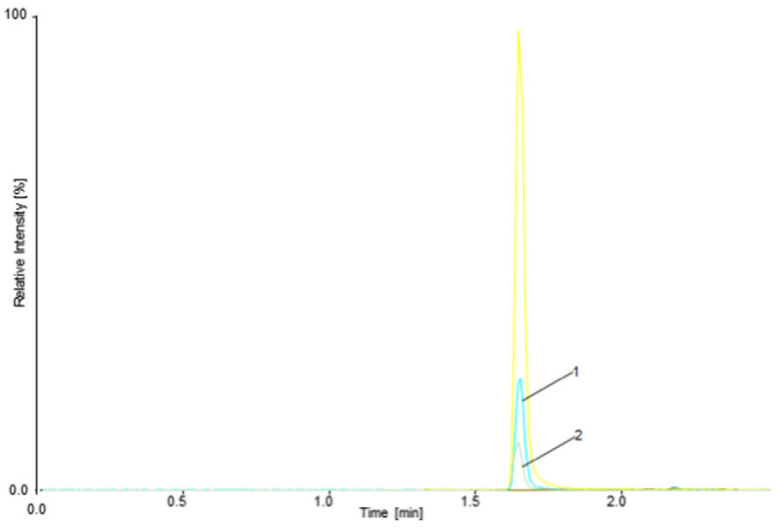

Fig. 4. Extracted ion chromatogram (XIC) of levetiracetam (1; yellow and cyan) and internal standard (2; grey).

was 2.3 ± 0.60 μm for NOS resp. 2.6 ± 0.63 μm for NLS and did not differ from the PN without the drug. No trend for an increase in the mean droplet size was seen when 9.40 mmol/L LEV was added. All other parameters were according to the specs. This supports the position of using physicochemical drug characteristics as a first evaluation of the incompatibility risk or the critical emulsion deterioration potential. Nevertheless, a lab analysis for such complex pharmaceutical formulation is necessary to document the pharmaceutical appropriateness of such medication and needs pharmaceutical expertise in the NST.

The aim of the present study was to use simple and time-saving evaluation tests to assess physicochemical stability and compatibility of LEV admixed to two common commercial AiO PN admixtures. The investigation was able to demonstrate easy-to-administer tests and document the compatibility and stability of the drug in these PN products. Pharmacists could use such tests in daily practice upon the request of such data as a prerequisite for safe and efficacious treatment advice and to prevent incorrect handling and medication errors (Taxis & Barber, 2003). Another factor indicating the stability of PN AiO admixtures is the pH. The pH decreases over time in PN admixtures because of the hydrolysis of fat triglycerides. Additional chemical reactions yielding base or acidic products also affect the pH. For the lipid stability and lecithin emulsifier, a pH range of 5–8 is necessary. The negatively charged surface (phosphate moiety) prevents the coalescence of the lipid globules (Mühlebach, 2009). A pH below 5.0 favours lipid instabilities (Driscoll et al., 2009). In our study, there was only a slightly decreasing pH over time (most affected the samples at + 37 °C) because of destabilisation, degradation, and polymerisation but not a LEV-specific reaction.

All of the presented data are based on tests that were done in 10 mL glass tubes, whereas in reality, the two solutions would be mixed in either a Y-line, or in the PN bag if the drug was added there. Previous studies have evaluated the compatibility between PN admixtures and medications in a static manner (Husson et al., 2003b; McKay et al., 2009) or by simulating Y-site administration (Husson et al., 2003a). This study with the aim to get a response on drug stability and compatibility quickly in a given design simulates “worst-case” conditions with a defined contact time between the PN admixtures and a given drug concentration (LEV) but also to check the stability for drug and PN at daylight and storage at room temperature and at + 37 °C but only in glass containers. To transfer the data to other containers or medical device materials, further studies have to be done, especially if reports e.g. drug adsorption or absorption exist like for lipophilic drugs and some plastics like PVC. This is not the case for LEV.

A limitation of the study is the fact that these results are related to PN regimen without vitamins or trace elements and the need for (home) PN, but there is a low risk from the LEV characteristics that additional interactions with these micronutrients would occur (red-ox reactions). An additional limitation is that only one specialty of LEV and only two different PN were checked. However, again, there is limited evidence of major differences among originator and generic i.v. formulations, although generic drugs may potentially not have identical ingredients or pH differences. Other PN regimes might differ in composition, but with a hydrosoluble, almost neutral drug such as LEV, there is a low risk for major incompatibility. In either case another series with different PN regimens could be done in a relatively short time. Additionally, the neonatal situation was not specifically assessed. Neonates often have very limited line access, individual PN regimes and lower medication dosage, and LEV is a candidate for such an admixture. Because we performed in vitro pharmaceutical analysis and no in vivo clinical assessment, it would be beneficial to assess this stable pharmaceutical formulation in vivo. The absence of data on in vivo effects is a limit of these stability assessments and would be valuable for common drugs. The aim of this study was to demonstrate how incompatibilities and, therefore, unsafe and ineffective admixtures can simply be tested via a pharmaceutical approach.

5. Conclusion

We investigated the compatibility and stability of LEV in two common, commercially available PN AiO admixtures in adults at conditions of usual handling in a hospital. LEV demonstrated compatibility and stability in NOS and NLS in a concentration of 1.6 mg/mL (9.40 mmol/L) at three different temperatures. In addition, these results illustrated a valuable approach for determining the pharmaceutical stability and compatibility of drugs with PN in practice. This timely and cost-effective pharmaceutical approach of documenting the quality of complex therapeutic regimens increases the convenience and avoids medical errors in the clinical setting. It is crucial to combine methods to obtain a robust analysis of the chemical and physical stability of such admixtures. The demonstrated example of LEV admixed to AiO PN is important in patient care, is representative of drugs that are hydrophilic-neutral or that have weak acidity, and documents pharmacists' support for critical medication treatments in hospital practice. This procedure can be easily applied in daily clinical practice to fulfill the demands of determining stability and compatibility of different drugs in PN mixtures, when co-administration with PN and medications cannot be avoided. In future studies, we will analyse drugs with varying physicochemical profiles and clinical importance to further validate the procedure.

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5 Conclusion and outlook

As concluded in the presented studies, pharmacists support the quality management of PN and reduce administration, handling and medication errors.

(I) The steady education and training of health care professionals in clinical nutrition management is a prerequisite to detect and treat patients at nutritional risk, which is an essential task of the pharmacist in an NST. The first study showed that a single online educational intervention alone was not effective to increase the nutritional knowledge and to improve malnutrition management in residents. Consequently, pharmacists in an NST should continually mention, model and provide opportunities to observe best practices in malnutrition management. Suitable procedures could be professional support by a pharmacist during clinical visits and a continuous education program (during graduate and post-graduate education) on the basics of clinical nutrition and clinical skills training for all healthcare staff, including pharmacists. Nutrition is often neglected during medical education and there is a lack of residency training and medical practice. Further research is needed to explore multimodal and more compulsory educational interventions including well-structured and validated, prolonged training programmes containing didactical activities such as bedside teaching, life teaching sessions, clinical skills training and problem-based learning. With the help of periodical and interactive sessions, nutrition awareness and responsibility will increase. The pharmacist can play an important role in education and training of health care professionals to maintain the responsibility of professional competencies in nutritional support. For this reason, a new study is planned and the previous study will be modified in order to improve the knowledge of the resident and senior physicians and also the number of prescribed nutritional therapies significantly.

(II a +b) Monitoring, quality assurance and the guarantee of a safe and effective treatment are further aspects of pharmaceutical competencies in an NST, especially at the interface hospital – at home, when the patient goes home with a HPN treatment, the pharmacist of an NST plays a relevant role undertaking coordinative and educative functions. Monitoring of HPN patients over a longer period of time enables the evaluation and comparison of HPN recommendations and best clinical practice to improve treatment quality and patient safety. This unique national study about HPN patients showed different quality aspects, indicating improved anthropometric parameters and QoL over this rather short observational period. A limitation of the Swiss HPN study was the short follow-up period of three months. In order to receive data with more significance, a prospective, observational follow-up study is planned, which should take place over a longer period of time (follow-up of six months over two years). Additional aspects emphasising infectious and mechanical catheter-related complications will be included.

In the third study of patients affected by systemic sclerosis and GIT dysfunction, it could be demonstrated that HPN is a feasible and safe method leading to a health benefit in terms of improved anthropometric parameters and QoL in HPN patients with a specific disorder. Both studies showed that good monitoring and implementation of HPN therapy can lead to an improvement in the QoL of patients with HPN. Thus, the pharmacist is obligated in his professional capacity to ensure well-structured monitoring as well as training and education of the patients and their caregivers in aseptic handling whether in a hospital pharmacy or in a community pharmacy (homecare). This in return can lower the complication rate and improve the well-being of these patients. The pharmacist can further contribute to an NST and patient well-being by ensuring the supply of materials and nutritional products, providing advice about medication and possible additions to the PN and individual compounding (best pharmaceutical practices).

(III) The involvement of the pharmacist in the process of nutritional intervention and quality assurance also includes the compounding and stability assessments of PN admixtures. The physicochemical stability and compatibility aspects of PN admixtures are important pharmaceutical issues with possible clinical implications. The last study showed in an example with the antiepileptic levetiracetam the necessary stability and compatibility investigations and their documentation before admixing into an AiO admixture. The results of the presented study showed that levetiracetam was stable over seven days in two different PN admixtures and also a valuable approach how to determine stability and compatibility of drugs with PN in daily practice to support complex therapeutic schemes in a clinical setting. This timely and cost-effective pharmaceutical support to document the quality of complex therapeutic regimes increases convenience and avoids medical errors in the clinical routine. The tested methods are time-efficient, easy to use, sensitive, convenient and low cost to apply in a daily routine to determine stability and compatibility of levetiracetam in PN mixtures and to apply best pharmaceutical PN practices. Further aspects of pharmaceutical best practices are compounding (GMP) and checking of the PN admixtures, medication and nutritional care plan. All these are prerequisites for a safe and effective treatment. Further studies are needed, to analyse drugs with different physicochemical profiles and clinical importance to further validate the procedure.

According to the presented studies, the question remains, how to ensure the pharmacist becomes a necessary NST member? Pharmaceutical responsibility in education, monitoring, GMP and compounding is required and has gained in importance in clinical nutrition, especially in PN. Are the pharmacists ready for a new and different challenge in the current, basic education at university? However, the pharmacist is no longer only responsible for the preparation/compounding process. Their expertise is required in community pharmacies and homecare, as well as in hospital pharmacies, to provide safe and effective

treatment, to prevent medication errors and complications (especially in HPN) and to optimise the comfort, autonomy and QoL of these patients. Knowledge and appropriate skills are required in order to achieve these challenges and must be integrated into the basic education and training of the pharmacists in the future. Accordingly, the curriculum and course content at the universities need to be reconsidered and adjusted appropriately going forward.

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7 Appendix

7.1 Curriculum Vitae

Only in the original document