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Narrative Review

Safe and efficient practice of parenteral nutrition in neonates and children aged 0–18 years – The role of licensed multi-chamber bags

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SUMMARY

Parenteral nutrition (PN) is recognized as a complex high-risk therapy. Its practice is highly variable and frequently suboptimal in pediatric patients. Optimizing care requires evidence, consensus-based guidelines, audits of practice, and standardized strategies. Several pediatric scientific organizations, expert panels, and authorities have recently recommended that standardized PN should generally be used over individualized PN in the majority of pediatric patients including very low birth weight premature infants. In addition, PN admixtures produced and validated by a suitably qualified institution are recommended over locally produced PN. Licensed multi chamber bags are standardized PN bags that comply with Good Manufacturing Practice and high-quality standards for the finished product in the frame of their full manufacturing license. The purpose of this article is to review the practical aspects of PN and the evidence for using such multi-chamber bags in pediatric patients. It highlights the safety

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characteristics and the limitations of the different PN practices and provides some guidance for ensuring safe and efficient therapy in pediatric patients.

1. Introduction

Parenteral nutrition (PN) is indicated when oral or enteral nutrition is not possible, insufficient, or contraindicated to correct or prevent nutritional deficiencies. It can be live-saving for pediatric patients who have limited nutrient stores and high requirements for growth and development (Table 1) [1]. In the United States, PN is provided to around 250,000 patients in hospitals and 25,000 in homecare every year with pediatric patients <18 years of age representing 46% of the inpatients and 17% of the outpatients [2,3].

Besides its key role in the nutritional plan, PN is also recognized as a high-risk and complex therapy involving expertise through multiple steps. Pediatric PN practice is usually described as highly variable frequently resulting in suboptimal intakes and poor growth [1]. Such variability of practice is partially explained by the lack of high grade evidence [1,4]. It also often results from lack of resources or old-school routines [5–8]. The risk of adverse events (AEs) is also a concern during PN, especially in pediatric patients because of their immaturity and vulnerability [1,9]. Complications can occur because of the therapy itself or as the result of the multiple-step PN process. The variability of stakeholders and settings raise the potential for disparities in the knowledge and skills of the healthcare professionals who are responsible for the prescription, preparation (compounding, labeling, and dispensing), and administration of PN [10–12].

The regular review of the evidence and the development of consensus-based guidelines are important to increase the safety and effectiveness of PN practice and to reduce its variability [1,13–18]. In adult patients, standardized PN (SPN) solutions have been recommended whenever possible due to their positive impact on safety and efficacy [19–21]. Similarly, several pediatric PN guidelines and authorities have also recommended that SPN should be used over individualized PN (IPN) in the majority of pediatric and newborn patients including in very low birth weight (VLBW, <1500 g) infants [1,13,22]. It is also recommended to standardize the different PN processes and administer whenever possible PN admixtures that have been validated by suitably qualified institutions, in particular licensed manufacturers [1,10,13,22,23].

The purpose of this narrative review is to discuss several practical aspects of PN in pediatric patients, especially the use of licensed industrially prepared ready-to-use (RTU) multi-chamber bags (MCBs) that have become available in several countries during the last two decades.

2. Workflow of parenteral nutrition

PN is considered a complex therapy involving various stakeholders (i.e., dieticians, residents, physicians, pharmacists, compounding technicians, and nurses). It includes multiple steps from assessing the patient's need; prescribing the order; transcribing the order; compounding the admixture; labeling and dispensing the formulation; administering the PN; and monitoring the patient (Fig. 1). Each step requires verification processes and good communication between professionals. During the last decades, several organizations have provided guidelines and recommendations to implement better practices including standardized processes to guarantee safety and efficiency [1,15,16,22,24].

Errors or inadvertencies may occur at each step of the workflow due to challenges to apply safety recommendations [14,15]. Although these errors are not always reported, several studies have provided estimates of the burden they represent [11,12]. It was shown in 2009 that up to 1.6% of the PN prescriptions were associated with medication error related to prescribing (1%), order transcription (39%), preparation (24%), and administration (35%) [25]. In 2010, a voluntary staff incident-reporting system showed that PN and replacement preparations represent the largest (37%) category of adverse drug events in hospitalized pediatric patients [26]. In 2012, the Institute for Safe Medication Practices reported that more than 40% of the organizations had not put in place the expected precautions to prevent PN errors and harm despite guidance to do so [27]. In 2017, a study demonstrated a PN order error rate of 3.9% in a tertiary level neonatal and pediatric intensive care unit [28]. In 2021, the use of an error/intervention tool to capture data on prescription elements described that 0.6% of orders still require an intervention highlighting the need for institutions to develop systems to comply with published PN safety recommendations, including knowledgeable and skilled pharmacists to complete the order review and verification steps for this high-risk medication [12]. Consequently, minimizing errors and optimizing the safety and efficacy of PN should be a global priority, especially for highly vulnerable pediatric patients.

2.1. Venous access

Secured and reliable venous access is primordial when considering PN administration [1]. Either peripheral or central venous lines can be used. Central lines are positioned in a large central vein and may remain in place for long periods of time with appropriate

Table 1
Key differences in parenteral nutrition requirements according to age.

Age Category	Energy (kcal/kg/d)	Amino acid (g/kg/d)	Calcium (mmol/kg/d)
Premature infants	90–120	3.0–3.5	1.6–2.5
Term neonates	75–85	2.5–3.0	0.8–1.5
Infants 1–12 months	75–85	2.0–3.0	0.5–1.5
Children 1–6 years	65–75	1.5–2.5	0.25–1.0
Children 6–12 years	55–65	1.5–2.5	0.25–1.0
Adolescents 12–18 years	30–55	1.0–2.0	0.25–0.4
Adults	20–30	0.8–1.5	0.07–0.1

Adapted from ESPGHAN-ESPEN-ESPR-CSPEN(1), NICE (13), and ASPEN(17,104).

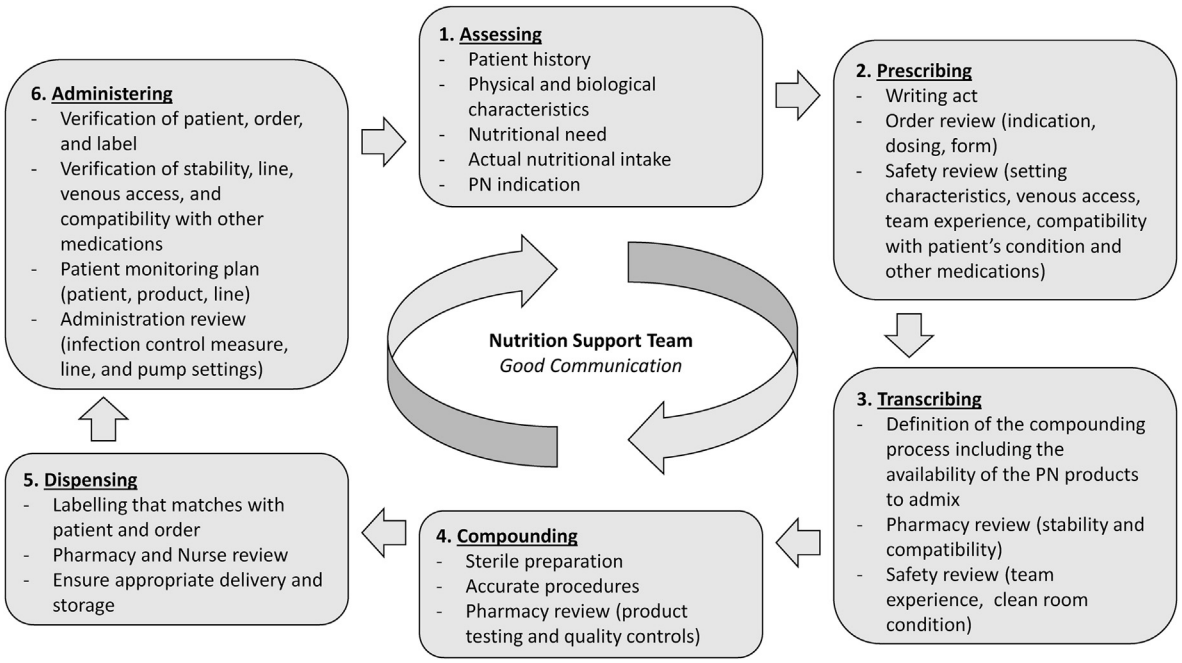

Fig. 1. Workflow of PN.

maintenance care. Central lines require placement skill expertise and include the risk of serious potential complications like bloodstream infection and venous thrombosis. Peripheral lines are sometimes used for short-term PN as their use seems easy and is perceived as requiring less expertise. However, peripheral PN also includes risks and may result in severe injuries due to extravasation and phlebitis [29,30]. These complications can be partially reduced by administrating diluted PN (osmolarity <900 mOsmol/L), using in-line filters, and frequent surveillance of the infusion site. The other limitation of peripheral PN is its effectiveness. Undernutrition may occur because of a lower nutrient density of diluted PN and because of the short life span of peripheral lines inducing frequent interruption of the PN administration [1].

The central administration of PN allows for the use of concentrated PN which ensure meeting the high nutritional requirement of the pediatric patients within a limited fluid volume [13,31,32]. Recent guidelines have reported that actual PN intake tends to be 20% less than prescribed when inadequate attention is paid to nutrition [1]. The use of concentrated PN formulations reduces such risk as it allows to administer the required amount of nutrients in a low volume and always within the patient fluid allowance. This is paramount in several clinical circumstances when total fluid allowance is restricted or a significant proportion of the fluid allowance is dedicated to drugs and other infusions (e.g., flushes/rinsages, arterial line, blood products). Concentrated PN allows the addition of separate intravenous solutions to customize the intakes and adapt to rapidly evolving fluid and electrolyte needs (e.g., high stoma losses, high insensible water loss, high urine output). Ideally, these additions should have been validated for ensuring safety when administrating PN [1,13,31,32].

Therefore, the recommended delivery site for pediatric PN is via a central line, although peripheral PN can also be given for short periods [1,13]. In neonates, it has been recently recommended to use peripheral PN only if (A) it would avoid a delay in starting PN (B) short-term use of peripheral venous access is anticipated (i.e., less than 5 days) (C) it would avoid interruptions in giving PN, and (D) central venous access is impractical [13].

2.2. Lipid administration

The administration of an intravenous lipid emulsion (ILE) during PN is essential for meeting the high energy and essential fatty acid requirements of pediatrics patients [1]. Recent guidelines have highlighted that ILEs should be an integral part of all pediatric PN, even in critically ill patients, and recommend to avoid any delay or interruption of the ILE during PN [1,13]. Only transient dose reduction may be applied when facing hypertriglyceridemia, in particular during critical illness [1,18,33,34]. Of note, delaying the introduction of the ILE during PN and low lipid dosage have been associated with unfavorable outcomes in premature infants [35–37].

During PN, lipids could be administered within an all-in-one (AIO) ternary PN admixture or separately to a binary admixture [16,38,39]. In hospitalized pediatric patients, the ILE is often administered separately as Y-line because of stability/compatibility concerns or to be able to adapt the infusion rate of the ILE or the binary aqueous PN admixture without modifying the other during their administration [33,39,40].

When administered separately, the ILE is frequently repackaged in syringes in pediatric patients to accommodate small volume and sometimes to reduce waste and cost [38]. Nonetheless, ILE repackaging implies some risk as microbial contamination may occur making this practice controversial [16,38]. Repackaging also favors the ILE oxidation that need to be prevented by photoprotection, air-sealing, and refrigeration [41].

Infusion rate errors and ILE overdose have been reported when infusing ILE separately [42,43]. A review of all medication errors in neonates showed that 4% of these involved the ILE with more than 90% occurring during administration, the most frequent being an excessive infusion rate [44]. After the report of several severe incidents within a short period of time in the United Kingdom, a review of mild incidents and near misses was performed and around 700 similar incidents involving separate ILE infusion were reported within a 3.5 year-period [45]. Of note, such error can be fatal in neonates [46]. Recent pediatric PN guidelines recommend

that the Y-line addition of an ILE to a binary aqueous PN admixture should be fully validated by the manufacturer or accredited laboratory, and if not, the ILE should be infused through an alternative separate line for safe compatibility reasons [1,39]. Consequently, the way of administering the ILE should be considered carefully for safety reasons.

The main recognized benefits of AIO PN are the convenience of administration, potential cost reduction, and reduced risk of infection suggesting they should be favored when possible [39]. A limitation for using AIO PN is they are at risk of destabilization, especially in pediatric patient who have high mineral needs [39]. Nonetheless, it has recently been shown that adequate stability testing, and quality controls could be performed and also validated in advance for pediatric AIO SPN [47]. A potential reduction in neonatal morbidities has also been suggested with AIO admixtures versus separate ILE administration in a study assessing the value of shielding PN from light in very premature infants [48]. Altogether, validated AIO admixtures represents an opportunity that may improve PN safety and efficacy in pediatric patients.

3. Pharmacy-compounded bags

3.1. Individualized parenteral nutrition

IPN – also called customized or bespoke PN – is an unlicensed admixture that is specifically prescribed and compounded by hospital pharmacies or external compounding centers for individual patients. Routine use of IPN is based on the principle that a specific PN order is necessary on a daily basis to adapt to a wide variety of clinical conditions and pathological processes [1,49].

The main and key advantage of IPN is its flexibility in term of patient specificity (Table 2). It implies having all the necessary resources to ensure its value [1,8,50,51]. The PN prescription implies indeed expertise and experience at each step of the PN process (Fig. 1). Compounding an IPN admixture is highly demanding in terms of pharmacy resources including clean room facilities. Literature data are used when the admixture cannot undergo exhaustive and specific quality controls for suitability, stability, sterility, and compatibility [10,52,53]. Although daily prescriptions are usually considered during IPN, this may not always be possible (e.g., weekend) and the IPN are sometimes prepared in advance and stored refrigerated. In pediatric patients, the limited or delayed availability of IPN has been identified as reasons for noncompliance with guidelines, especially in VLBW newborns for whom birth is considered a nutritional emergency (Table 2) [1,13,22,54]. The room for improvement in both clinical and organizational care of neonatal IPN practice has been demonstrated in the United Kingdom in 2010 when good practice was identified in only 23.5% of the neonates requiring PN [7]. Afterwards, the British Association of Perinatal Medicine (2016) stated that PN should be considered a pharmaceutical product recommending that the highest standards should be applied and that concentrated SPN were suitable and useful for the vast majority of babies [51]. However, high quality standards are not always applied, in particular when PN is compounded on the ward by nurses without the adequate pharmaceutical expertise and training [55]. In a recent (2020) quality and safety study in a Swiss neonatal intensive care unit, it was shown that 70% of PN admixtures were prepared by nurses on-ward, and 34% of these were not conformed to the pharmacopoeia concentration limits for compounded preparation (i.e., 90–110% conformity specification) [56]. These data highlight the importance of auditing the local PN practice to ensure compliance of each step of the practice with guidelines and to ensure that the theoretical benefits of IPN do not outweigh the risks and potential adverse consequences [51].

3.2. Standardized parenteral nutrition

Contrary to IPN, SPN implies the use of pre-defined admixtures. Their efficient and safe use is based on the tenet that many patients with similar condition have comparable nutritional needs allowing their management with one or several 'balanced' SPN formulations (Table 2) [32,47,57–61]. They may exist as either binary aqueous admixture without lipids or ternary AIO admixture with lipids. The physicochemical stability of a SPN can be tested and validated during its development [13,62]. Such validation can sometimes result in a shelf life of several weeks when the SPN is refrigerated [62,63]. When compounded in advance, SPN bags may be tested for sterility and have the advantages of being rapidly available when indicated. Their use allows some kind of customization within predefined limits after having considered and validated various additions, either mixed in the SPN bag or as Y-line co-infusion.

Several studies have shown that the use of 'balanced' age-appropriate SPN is safe, efficient, cost effective, and usually promotes good clinical practices, especially in premature infants [63–65]. Recent guidelines recommend that SPN should generally be used over IPN in the majority of pediatric patients including VLBW premature infants [1,13,22,66]. Among the rationales for using SPN are (A) these bags are suitable for most patients; (B) they can be stored and immediately available; (C) they simplify the processes of prescription, preparation, and delivery; (D) they can reduce the risks for errors, contamination, and incompatibility; (E) they can improve PN efficiency and compliance with guidelines; (F) they can improve quality controls for PN prescription, compounding, and administration; and (G) they have lower overall acquisition and usage costs [1,13].

The use of SPN has limitations (Table 2). They may not be optimally designed for meeting pediatric patient requirements, especially if developed by non-experts [49]. All the necessary vitamins and trace elements are often not included when prepared in advance because they can rapidly degrade within a few days in PN admixture [1]. However, vitamins and trace elements form an integral part of PN and should be added before administration if not already present in the SPN [1]. SPN sometimes requires some addition (e.g., amino acids, electrolytes) for customizing the intakes and adapting to individual circumstances [32,49,67,68]. The level of evidence for SPN remains low grade because mainly arising from cohort studies and high-quality trials are required to confirm their benefits [4]. Finally, IPN should be used when the nutritional requirements cannot be met by the available range of SPN admixtures with additions, in particular during critical illness, renal failure, or in patients with high stoma losses [1,13,22]. Nevertheless, several authors consider that most pediatric patients, including VLBW infants, can be adequately treated with one, or a few, SPN admixtures [1,13,47,57–59,61,63–66,68].

4. Licensed multi-chamber bags

4.1. Industry quality standards

Licensed MCBs are SPN manufactured by the industry under regulated quality and safety standards including terminal sterilization (Table 2). They are available either as two-chamber bags (2CBs) without lipids or 3CBs including lipids. Each MCB contains a sterile non-pyrogenic combination of compartments containing the different macronutrients (i.e., amino acids, glucose, or lipids) with or without electrolytes. They have a long shelf life and can be stored at room-temperature for up to 24 months. This allows for global distribution including in institutions without easy continuous access to sophisticated pharmacy compounding facility. Such MCBs

Table 2
Advantages and Limitations of IPN, SPN, and MCBs in pediatric patients requiring PN.

A. **Individualized Parenteral Nutrition (IPN)**
  a) Advantages
    - Flexibility and specificity to adapt to evolving clinical conditions
  b) Limitations
    - Evidence frequently shows high variability and frequent suboptimal practice
    - Require skilled and experienced healthcare professionals for the prescription, review, preparation (compounding, labeling, and dispensing), and administration of PN
    - Must be stored refrigerated
    - Limited or delayed availability because requiring sophisticated pharmacy resources
    - Do not always comply with high-quality standards (i.e., Pharmacopeia, expert recommendations)
    - Do not always have validated stability, sterility, and compatibility data

B. **Standardized Parenteral Nutrition (SPN)**
  a) Advantages
    - Suitable for most patients as many patients with similar condition have comparable nutritional needs
    - Physicochemical stability and microbiological sterility may be tested enabling stability/compatibility data to be validated and shelf life extended to several weeks in the refrigerator
    - Rapidly available when necessary if compounded in advance and stored refrigerated in the hospital
    - Predefined strategy simplifying the processes of prescription, preparation, and delivery
    - Potential customization when considering potential additions
    - Potential reduction of errors, contamination, and incompatibility
    - Potential optimized efficiency and compliance with guidelines
    - Potential overall acquisition and usage cost reduction
  b) Limitations
    - Require skilled and experienced healthcare professionals for defining the strategy
    - Locally developed SPN by non-experts may not be optimally designed and balanced
    - All the necessary vitamins and trace elements may not be included and need to be added or administered separately
    - May require addition (e.g., electrolytes, fluid, amino acid) to adapt to individual circumstances
    - Must be stored refrigerated
    - High-level of evidence is missing for demonstrating superiority over IPN, except when initiating PN immediately after birth in newborns

C. **Licensed Multi-Chamber Bags (MCBs)**
  a) Advantages
    - Include advantages of SPN
    - Manufactured under regulated high-quality standards for the finished product in the frame of regulatory submission requirements (i.e., full manufacturing license
    - Pharmacovigilance and continued safety insurance while on-market
    - Long shelf life at room temperature (up to 24 months)
    - Easily available for institutions without easy continuous access to sophisticated pharmacy compounding facility
    - Validated compatibility matrix tables for safe administration and customization of intakes
  b) Limitations
    - All the necessary vitamins and trace elements are not included and need to be added using validated stability/compatibility data or administered separately
    - May require addition (e.g., electrolytes, fluid, amino acid) to adapt to individual circumstances
    - Not all MCBs are specifically designed for pediatric patients
    - Cannot be rapidly adapted to new scientific evidence because new regulatory applications require time and are costly
    - High-level of evidence is missing for demonstrating superiority over IPN and SPN

have been developed and successfully adopted in adult patients for several decades [69,70].

Licensed MCBs must comply with Good Manufacturing Practice (GMP) and high-quality standards for the finished product in the frame of regulatory submission requirements, i.e., full manufacturing license [71]. Industry quality control applies for critical in-process parameters and quality testing occurs for each compartment and for the complete filled bag. A non-exhaustive list of parameters tested in final product batches includes (A) concentration of electrolytes, amino acids, glucose, fatty acids; (B) presence of impurities and degradation products; (C) titratable acidity; (D) useable volume of solutions in filled bag; (E) visible inspection of solution; (F) physical characteristics; (G) stability and particles in solution; (H) microbiological quality, sterility, and absence of endotoxins; and (I) visual inspection of the final packing including leaflet, integrity of overpouch, printing defects, barcode on labels, code, batch, and expiry date. Licensing also implies worldwide pharmacovigilance and continued safety insurance while on-market [71]. Of note, similar high-quality standards cannot always be similarly applied during pharmacy compounding. An example is illustrated in a recent study in a highly developed country where the authors acknowledged that their internal acceptable conformity specifications for their pharmacy-compounded bags were larger than the Pharmacopoeia concentration limits for compounded preparations [56]. In this example, it means that pharmacy-compounded bags can sometimes include a maximum variation of 20% for the concentration of certain components such as glucose, calcium, or magnesium, whereas Pharmacopeia specifications allow a 10% maximum variation of these concentrations compared to the prescription [56].

When developing MCBs, the industry supplier can develop validated compatibility matrix table anticipating for safe potential additions either in the bags or when infused as Y-line [72,73]. Such validated compatibility/stability data may allow for safe customization of the PN taking benefit of potential additions like electrolytes and macronutrients [74–76]. It is also particularly important to use validated compatibility data with common drugs for pediatric patients who are more vulnerable and whose venous access is generally challenging [74,75,77–80]. The same venous access is indeed often used simultaneously for medications and PN allowing for potential interactions [81–83]. Of note, this practice is often in contradiction with current guidelines that recommend using an individual dedicated intravenous line for only infusing PN [1,75,77–80].

Therefore, MCBs can improve safety by reducing the complexity of prescribing, preparing and administering PN, providing quality assurance and reducing the risk for compatibility issues, contamination, and operational errors [69,84]. MCBs can also reduce preparation time and cost, which can benefit to the overall economic burden of healthcare [69,84].

4.2. Pediatric licensed multi-chamber bags

Few pediatric-specific MCBs (PedMCBs) are available on the market (Table 3). Several pediatric 2CBs (Ped2CBs), not containing lipids, were introduced in France in 2007 and approved after a 4-year Temporary Authorization of use [85]. They have a license in several European countries but remain only available in France. Three pediatric 3CBs (Ped3CBs) were approved in Europe in 2011 after the completion of an international registration trial [74,86,87]. The design of these 3CB includes the possibility to administer the PN with or without lipids, either as a 3-in-1 ternary or a 2-in-1 binary admixture respectively [74,87]. They are now used in many countries worldwide.

The data for the existing Ped2CBs remains scarce, even though they have been available for 15 years. The evidence mainly relies on the absence of key safety signals during their Temporary Authorization of use [85]. The evidence for the existing Ped3CBs arises from cohort studies [31,59,74,76,87–93]. These studies have shown that the Ped3CBs were easy-to-use and reduce the preparation and prescription-to-infusion times [74,87,88]. Most studies have shown that the actual intakes can more easily meet nutritional recommendations when transitioning from IPN or SPN to a Ped3CB, most frequently activated as ternary admixture [31,59,74,76,87–93]. Their use have reduced the risk of poor growth, especially in VLBW infants [31,59,74,76,88,91]. Among the evidence, a large cohort study in VLBW infants ($n = 953$) showed that the introduction of a Ped3CB allowed to meet amino acid target intake 3–7 day earlier when compared to a hospital-compounded IPN and a locally developed SPN [90]. Another study showed that the introduction of a Ped3CB being administered as 2-in-1 binary admixture with Y-line ILE, significantly improved the protein and energy PN intake in VLBW infants during the first postnatal week when compared to a pharmacy-compounded SPN [31]. In this study, the transient intervention during the PN phase improved growth during the first 28 days of life, with a persistent significant difference at 36 weeks postmenstrual age for both weight and length [31]. These authors have also confirmed previous data with balanced SPN that the practice of minimizing sodium, potassium, and phosphate intake during the first days of life may not be optimal in VLBW infants [68,92,94]. They showed that providing electrolytes in PN from birth onwards with a Ped3CB (on average 2.0, 1.2, and 1.1 mmol/kg/d of sodium, potassium, and phosphorus, respectively, during the first three days of life) did not increase the risk of hypernatremia but reduced the risk of hypokalemia and hypophosphatemia during the first week of life [92]. No safety concerns were reported during all these studies using Ped3CB [59,74,87–92]. Interestingly, a morbidity reduction (e.g., hypertriglyceridemia, sepsis, patent ductus arteriosus) was sometimes observed in premature infants when compared to IPN and SPN [59,92]. These observations may have been noticed by chance and further properly powered randomized studies are required to evaluate the real clinical benefits of such Ped3CBs.

Besides the evidence in premature infants, several cohort studies have shown that a Ped3CB may also be efficiently and safely used in older pediatric patients either in the hospital or at home [87,89,91,95–97]. A recent study showed that MCBs were used in 90% of patients in a pediatric intensive care unit including Ped3CBs (82.6%), Ped2CBs (1.5%), and adult MCBs (15.9%) [97]. During home PN, several authors suggested that their stability at room temperature and their long shelf life may offer more flexibility and quality of life than pharmacy-compounded PN bags that need to be stored in temperature-controlled refrigerators for up to one week [91,95,96].

A few studies have assessed the Y-site compatibility of common pediatric medications providing independent data on top of the ones provided by the manufacturer [75,77–79]. From a health economics perspective, a cost-consequence analysis showed that a 10% increase in the utilization of Ped3CB in neonates could provide notable resource and cost savings to hospitals and improve clinical outcomes when compared to PN practices in Belgium, France, Germany, Italy, Portugal, Spain, and the United Kingdom [98].

4.3. Limitations of MCBs in pediatric patients

All the necessary vitamins and trace elements are not readily present in MCBs because several are not stable and progressively degraded when mixed in a PN admixture (Table 2) [1]. Even if several of these micronutrients may sometimes be provided by the oral/enteral route, they usually have to be added aseptically to the activated MCB before its administration using validated stability/compatibility data to be in agreement with existing guidelines [74,75,97]. Not meeting the pediatric high requirements for vitamins and trace elements may lead to potentially life-threatening deficiencies [99].

A second key limitation of MCBs is that they are not all specifically designed for pediatric patients, in particular adult MCBs even if they include an indication for children over two years of age and are sometimes used in pediatric patients [91,97]. Of note, these adult MCBs usually do not allow to meet all the pediatric nutrient requirements, mainly because of low energy content, inadequate protein to energy ratio, insufficient essential/semi-essential amino acid content, low electrolyte content, and low calcium to phosphorus ratio (Table 1) [1,100,101].

The pre-defined formulation made to a set composition that does not vary is usually considered as a limitation for MCBs, as for SPN. Even if the 'one size fits all' approach appears counterintuitive, we have to acknowledge that many clinicians have approved and demonstrated efficacy and safety with both MCBs and well-balanced SPN, including in VLBW neonates and critically ill children, justifying the recent recommendations to favor such an approach [1,13,22]. The use of MCBs has to be considered with the potential additions taking benefit of validated stability data and also considering the oral/enteral route [74,75,77–79,97]. Of note, the need for additions should be considered taking into account all the intakes from enteral/oral nutrition, medications, and other intravenous solutions noting these may not be negligeable, especially in VLBW infants [102,103].

Another limitation of MCBs is that they cannot be rapidly adapted to new scientific evidence because new regulatory applications require time and are costly. Thus, the design of some existing PedMCBs may not be optimal. It highlights the importance of favoring PedMCB with evidence and auditing local practice.

Finally, most of the currently existing evidence results from observational cohort studies. The level of evidence of these studies is considered low. It implies high quality trials are needed to confirm – or not – the observed benefits and safety properties of PedMCBs versus IPN and SPN [4].

4.3.1. Practical considerations

Pediatric PN guidelines provide several recommendations and nutritional ranges for optimizing PN practice. Different requirements are described according to different age categories (Table 1) [1,13,104]. These recommendations are not always easy to translate in a PN prescription and may explain the variable and suboptimal PN practice that is frequently observed in pediatric patients, especially in premature infants.

Great attention should also be paid to several ratios during PN to ensure optimal use of each nutrient, especially in young pediatric patients who have higher requirements (Table 1) [1,13]. Generally, the non-nitrogen energy split should be 60–70% from

Table 3
Currently available licensed pediatric multi-chamber bags (PedMCBs).

Brand name	Pediaven NN1 (Kidiamix Neo 1)	Pediaven NN2 (Kidiamix Neo 2)	Pediaven NN2 without Trace Element	Numeta G13E		Numeta G16E		Pediaven G15 (Kidiamix G15%)	Pediaven G20 (Kidiamix G20%)	Pediaven G25 (Kidiamix G25%)	Numeta G19E	
Producer	Fresenius Kabi NV	Fresenius Kabi NV	Fresenius Kabi NV	Baxter Healthcare Corporation		Baxter Healthcare Corporation		Fresenius Kabi NV	Fresenius Kabi NV	Fresenius Kabi NV	Baxter Healthcare Corporation	
Container	2CB	2CB	2CB	3CB		3CB		2CB	2CB	2CB	3CB	
Storage condition	<25 °C (do not freeze)	<25 °C (do not freeze)	<25 °C (do not freeze)	Do not freeze		Do not freeze		<25 °C (do not freeze)	<25 °C (do not freeze)	<25 °C (do not freeze)	Do not freeze	
Shelf life	18 months	12–18 months	2 years	18 months		18 months		12–18 months	12–18 months	12–18 months	24 months	
Age indication	Neonates first 24–48 h	Neonates from D2 to 1 m (1 m CA for PTi)	Neonates from D2 to 1 m (1 m CA for PTi)	Preterm infants <37wks PMA		Term neonates 0-2 y		infant 1 m-2y, children2-11 y, and adolescents11-18 y	infant 1 m-2y, children2-11 y, and adolescents11-18 y	infant 1 m-2y, children2-11 y, and adolescents11-18 y	Children 2-18 y	
Composition	2CB	2CB	2CB	3CB	2CB	3CB	2CB	2CB	2CB	2CB	3CB	2CB
Osmolarity (mOsmol/L)	715	790	1250	1150	1400	1230	1585	1090	1400	1790	1460	1835
Total volume (mL)	250	250	251	300	240	500	376	1000	1000	1000	1000	775
Amino acids (g/dL)	1.5	1.7	2.03	3.1	3.9	2.6	3.5	1.5	2	2.5	2.3	3.0
Nitrogen (mg/dL)	214	244	29	470	590	390	520	214	285	356	350	450
Glucose (g/dL)	10	10	15	13.3	16.7	15.5	20.6	15	20	25	19.2	24.7
Lipid (g/dL)	0	0	0	2.5	0	3.1	0	0	0	0	2.81	0
Total Energy (kcal/dL)	46	47	68	91	82	103	96	66	88	110	114	111
Non-protein energy (kcal/dL)	40	40	60	78	67	93	82	60	80	100	105	99
Glucose:Amino acid (g/g)	6.7	5.9	7.4	4.3	4.3	6.0	6.0	10.0	10.0	10.0	8.3	8.3
Lipid:Non protein energy (%)	0%	0%	0%	29%	0%	30%	0%	0%	0%	0%	24%	0%
Sodium (mmol/dL)	0.45	2	2	2.2	2.7	2.4	3.1	3	3	4	4.6	5.8
Potassium (mmol/dL)	0	1.7	2	2.1	2.6	2.3	3.0	2.5	2.5	4	3.2	4.1
Chloride (mmol/dL)	0.5	2.6	2	3.1	3.9	2.8	3.7	3.9	3.9	6	4.3	5.5
Acetate (mmol/dL)	–	–	–	2.4	3.0	2.9	3.9	–	–	–	3.71	4.8
Malate (mmol/L)	–	–	–	1.1	1.3	0.86	1.1	–	–	–	0.88	1.1
Lactate (mmol/dL)	–	–	0.4	–	–	–	–	–	–	–	–	
Gluconate (mmol/dL)	–	–	1.8	–	–	–	–	–	–	–	–	
Calcium (mmol/dL)	0.94	0.76	0.9	1.3	1.6	0.62	0.82	0.6	0.6	0.8	0.38	0.50
Phosphorus (mmol/dL)	0	0.91	1.1	1.3	1.3	0.87	0.85	0.8	0.8	1	0.93	0.93
Magnesium (mmol/dL)	0.21	0.16	0.2	0.16	0.20	0.31	0.41	0.4	0.4	0.6	0.26	0.33
Chrome (mcg/dL)	0.2	0.3	–	–	–	–	–	2	2	4	–	–
Cobalt (mcg/dL)	–	–	–	–	–	–	–	15	15	30	–	–
Copper (mcg/dL)	23	26	–	–	–	–	–	25.5–30	25.5–30	51–60	–	–
Iron (mcg/dL)	–	–	–	–	–	–	–	50	50	100	–	–
Fluorine (mcg/dL)	8	9	–	–	–	–	–	50	50	100	–	–
Iodine (mcg/dL)	1	1	–	–	–	–	–	5	5	10	–	–
Manganese (mcg/dL)	0.6	0.6	–	–	–	–	–	10	10	20	–	–
Molybdenum (mcg/dL)	–	–	–	–	–	–	–	5	5	10	–	–
Selenium (mcg/dL)	1.9	2.1	–	–	–	–	–	3.5–5	3.5–5	8–10	–	–
Zinc (mcg/dL)	203	230	–	–	–	–	–	200	200	400	–	–

Table 4
Different macronutrient recommendations for premature infants on the first day of life, during the growth phase, or during the acute phase of critical illness.

Clinical Condition	Energy (kcal/kg/d)	Amino acid (g/kg/d)
First day of life	40–55	1.5–2.0
Growth phase from 4 days of life	90–120	3.0–3.5
During critical illness		
Early acute phase	40–55	1.0–2.0
Late acute phase	60–80	2.0–3.0
Recovery phase	90–120	2.5–3.5

Adapted from ESPGHAN/ESPEN/ESPR/CSPEN 2018 (1), NICE 2020 (13), ASPEN (17,104), and ESPGHAN 2021 (18).

carbohydrates and 30–40% from lipids to ensure balanced energy intake. The ratio between energy and amino acid intakes should also be considered to optimize amino acid utilization. It is usually recommended to provide 30–40 kcal total energy (26–36 kcal non-protein energy) per gram of amino acid [1,13]. This suggests the optimal glucose to amino acid ratio may be close to 5.2 g/g, with a range varying from 3.9 to 6.8 g/g. Optimal electrolyte and mineral intakes are also key for reducing the risk of refeeding-like syndrome and bone metabolic disease. According to recent guidelines, the calcium to phosphorus ratio should be close to 0.8–1 mol/mol from birth up to 12 months of age, and slightly lower afterwards in older children (i.e., close to 0.5 mol/mol) [1,13]. These ratios are important when choosing a PedMCB and are quite different for adults for whom the total energy to amino acid ratio is close to 25 kcal/g, the glucose to amino acid ratio close to 3 g/g, and the calcium to phosphorus ratio close to 0.2 mol/mol.

The PN intake needs to be adapted according to varying clinical conditions. Even if minimum amino acid intake is required for optimizing nitrogen retention and growth during pediatric PN, recent evidence has highlighted the need for also avoiding excessive intake [1,13,18]. Table 4 provides an example of the different macronutrient recommendations for premature neonates on the first day of life, during the growth phase, or during the different phases of critical illness [1,13,18].

Recent pediatric PN guidelines have recently favored lower glucose intake to reduce the risk for hyperglycemia [1]. Several trials have assessed glucose tolerance from existing Ped3CBs in premature neonates and infants below two years of age and none has reported an increased risk of hyperglycemia or more frequent insulin treatment when using a glucose to amino acid ratio of 4.3 g/g in premature infants and 6.0 g/g in infants 0–2 years of age [31,59,74,89].

As mentioned here above, recent evidence and guidelines have recommended higher phosphorus, sodium, and potassium supply from PN from birth onwards in premature infants for reducing the risk for both hypophosphatemia and hypokalemia [1,13,92]. It can explain why several trials have reported the frequent addition of sodium and phosphorus when using a Ped3CB in VLBW infants and taking benefit of validated stability data [74,92].

5. Conclusions

PN practice remains a high-risk and challenging therapy in pediatric patients and actual practice should be regularly audited for compliance with recommendations and good practices. Recent guidelines recommend the use of SPN with validated stability data in pediatric patients to improve both safety and efficacy. It may not only reduce the risk of suboptimal PN and poor growth, but also reduces the complexity of prescribing, preparing, and administering PN. The full manufacturing license of MCBs offers safety advantages over unlicensed compounded PN because of high-quality manufacturing standards and validated compatibility/stability matrix for performing additions either in the bag or as Y-line infusions. There are few PedMCBs on the market and the available evidence from cohort studies showed that the use of Ped3CBs in pediatric patients seems easy to use, has been associated with improved nutritional outcomes, and can reduce the workload and costs. Therefore, the development and use of Ped3CBs represents an opportunity for improving PN practices in pediatric patients, especially when the access to a sophisticated pharmacy compounding facility is uneasy or discontinuous.

6. Future perspectives

- Auditing practice is necessary for identifying PN practice challenges, actual unmet needs, and for defining strategies to optimize practice.
- High-grade evidence from randomized control trials should further define the efficacy and safety characteristics of SPN and PedMCBs, including their ideal design and usage.
- New studies should highlight the areas for improvement of currently available SPN and PedMCBs and further define the patients and conditions where they should be used and where IPN may be advantageous.
- The health economics benefits of SPN and PedMCBs need to be better defined assessing the multiple steps of the PN process.
- A way to simplify the safe addition of vitamins and trace elements in SPN and MCBs should be investigated.
- The need for new pediatric-specific PN products including PedMCBs should be investigated for adapting further to the requirements of pediatric patients, especially premature infants.

Role of contributors

All authors participated in this narrative review conceptualization, the drafts, and the critical revision of the manuscript before approving the final version.

Conflict of Interest

VC, MD, NH, JR, MSDP, ST, FV, DW, and CvdA have received honoraria from Baxter Healthcare Corporation for symposium participation or scientific education activity.

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