Parenteral nutrition in the hospital setting/short-term parenteral nutrition

Sarah V. Cogle, PharmD, BCCCP, BCNSP, Department of Pharmacy, Clinical Programs, Vanderbilt University Medical Center, Nashville, TN, USA

Phil Ayers, BS, PharmD, BCNSP, FMSHP, FASHP, Clinical Pharmacy Services, Department of Pharmacy, Baptist Medical Center, Jackson, MS, USA

Mette M. Berger, MD, PhD, Service of Adult Intensive Care, Lausanne University Hospital (CHUV), Lausanne, Switzerland

David Berlana, PharmD, PhD, Pharmacy Service, Vall d'Hebron Barcelona Hospital Campus and Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain

Paul E. Wischmeyer, MD, EDIC, FCCM, FASPEN, Department of Anesthesiology and Surgery, Duke University School of Medicine, Durham, NC, USA

Joe Ybarra, PharmD, MS, BCNSP, Steward Health Care, Dallas, TX, USA

Sarah Zeraschi, BPharm, MRPharmS, Pharmacy Department and Nutrition and Intestinal Failure Services, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Joeri De Cloet, PharmD, Pharmacy Department, Ghent University Hospital, Ghent, Belgium

Address correspondence to Dr. De Cloet (Joeri.Decloet@uzgent.be).

https://doi.org/10.1093/ajhp/zxae080

Purpose: This article is based on presentations and discussions held at the International Safety and Quality of Parenteral Nutrition (PN) Summit concerning the acute care setting. Some European practices presented in this article do not conform with USP general chapter <797> requirements. Nevertheless, the purpose is to cover the challenges experienced in delivering high-quality PN within hospitals in the United States and Europe, in order to share best practices and experiences more widely.

Summary: Core issues regarding the PN process within an acute care setting are largely the same everywhere: There are ongoing pressures for greater efficiency, optimization, and also concurrent commitments to make PN safer for patients. Within Europe, in recent years, the use of market-authorized multi-chamber bags (MCBs) has increased greatly, mainly for safety, cost-effectiveness, and efficiency purposes. However, in the US, hospitals with low PN volumes may face particular challenges, as automated compounding equipment is often unaffordable in this setting and the variety of available MCBs is limited. This can result in the need to operate several PN systems in parallel, adding to the complexity of the PN use process. Ongoing PN quality and safety initiatives from US institutions with various PN volumes are presented. In the future, the availability of a greater selection of MCBs in the US may increase, leading to a reduction in dependence on compounded PN, as has been seen in many European countries.

Conclusion: The examples presented may encourage improvements in the safety and quality of PN within the acute care setting worldwide.

Keywords: acute care setting, compounding, cost-effectiveness, multichamber bags, parenteral nutrition, safety

Am J Health-Syst Pharm. 2024;81(suppl 3):S102-S111

Parenteral nutrition (PN) is an important therapeutic intervention used in a variety of settings for a number of indications, but it can be prone to errors because of its complexity, potentially resulting in patient harm.[1] To minimize the potential risks associated with PN, major nutritional societies and experts have advocated a variety of measures to standardize the PN process, such as standardized compounding processes or—as typically seen outside the United States—more widespread use of market-authorized multi-chamber bags (MCBs).[1-3] Within the US, the American Society for Parenteral and Enteral Nutrition states that "standardized, commercially available PN products may be viable options to manually compounded sterile PN products when compliance with USP Chapter <797> and accepted guidelines from patient safety organizations is not feasible."[2] MCBs are available in two formats: either as a 2-chamber bag (2CB) containing dextrose/glucose and amino acids or as a 3-chamber bag (3CB) containing dextrose/glucose, amino acids, and an intravenous lipid emulsion (ILE).[4]

Improving PN patient safety is an ongoing process and largely the result of continued shared efforts by PN experts from multiple disciplines. PN standardization initiatives have

largely been driven by academic centers or hospitals with ample PN expertise, though the paths taken may differ considerably (eg, between the US and Europe). In the US, high priority has been given to making prescription, transcription, and compounding safer, while market-authorized MCBs (primarily 2CBs) have predominantly been used in institutions with fewer daily PN prescriptions. In contrast, for many parts of Europe, compounded PN is used mainly for patients whose nutritional needs cannot be covered by standard MCB formulations.[3,5-7] MCBs became popular soon after they first became available, particularly after early adoption and development of customization techniques by numerous European academic PN experts.[3,5,8,9] By "customization" we refer to the amendment of micronutrients and, when required, an individualized electrolyte composition, and/or the inclusion of glutamine, all in alignment with compatibility and safety data.[3] As a result of this modus operandi, a broader variety of MCB formulations (typically 3CBs) became available in Europe, covering the nutritional needs of an increasing proportion of patients[3] (see Table 1).[10] This further facilitated the use of PN in centers with only a few PN prescriptions per day,[6] a trend that is increasingly now also noticed in the US. Thus, a survey of hospital pharmacy practices in the US found that the percentage of hospitals using 2CBs as the predominant form of PN preparations increased from 36% of hospitals in 2011 to 44.8% in 2017, an increase driven mainly by smaller institutions (<200 beds).[11] For these and numerous other institutions, particularly outside the US, MCBs offer opportunities for the standardization of the PN process and addressing some safety concerns. It is important to note that no PN preparation method relieves prescribers from carefully assessing each patient's nutritional needs, including the requirements for electrolytes or micronutrients, and pharmacists' responsibility to provide customized PN where this is needed. Individually compounded PN admixtures are needed when nutritional requirements of a patient cannot be met with a standardized formulation such as an MCB.[3] Thus, there will be always a coexistence of both systems. In general, caloric and protein requirements can be met with PN prepared with either method (compounded or MCB),[12-14] provided patients receive an admixture suitable for their nutritional needs.

This article focuses on the PN process in the acute care setting and provides insights into how the PN process has developed over time. Furthermore, it summarizes current challenges to deliver high-quality PN in US and European hospitals, with a focus on smaller institutions, and also provides suggestions to improve clinical practice. The insights provided may encourage international improvements in the safety and quality of PN within the acute care setting. It is important to note that different regulations, and hence practices, apply in different countries, and practices discussed within this article may be outside of the legal framework of another country. The content is based on presentations given by an international group of experts who attended the International Safety and Quality of PN summit, held November 8 to 10, 2021, at two locations (Charleston, SC, and Bad Homburg, Germany). The meeting outcomes suggested that the challenges experienced internationally are largely the same, such as increased pressure for efficiency, process optimization, concurrent obligations to make PN safer for patients, and that pragmatic approaches are required to handle PN-associated challenges within an established PN work setup.

It is important to understand that this article does not constitute any recommendations—these are to be found in the expert consensus statement publication[15]—but does present and summarize aspects from the international summit as a learning experience. When reading through the following real-world examples from the US and Europe, the subsequent consensus statements should be kept in mind: "In the PN preparation process, a high rate of standardization can be achieved by either a standardized PN compounding process and/or the use of market-authorized MCB PN formulations. Whether one PN application system is preferred over the other depends on the patient's nutritional needs, local expertise, local resources, local financial considerations, local regulatory requirements, and/or the variety of commercial formulations available."[15]

KEY POINTS

- Challenges within the parenteral nutrition (PN) process in the acute care setting are similar internationally: increased pressure for efficiencies and process optimization alongside an obligation to improve PN safety.
- Standardization of PN can improve PN safety and quality, such as through standardizing compounding processes or more widespread use of market-authorized multichamber bags.
- This article provides examples and insights into PN processes, summarizing current challenges to deliver PN in European and US hospitals (with a focus on smaller institutions), and provides suggestions to improve clinical practice.

Introducing PN process standardization within an organization of diverse types of US hospitals

The PN use process within a US hospital system was discussed with particular regard to experiences within Steward Health Care hospitals, which cover 9 states with hospitals ranging in size from 38 to 748 licensed beds,

Table 1. Parenteral Nutrition 3CBs Widely Available Across Europe[a]

Company	Brand name	Route of administration	Composition
Fresenius Kabi	Kabiven	Central, peripheral	Amino acids, ILE containing soyabean oil (Intralipid), dextrose/glucose with or without electrolytes
	SmofKabiven	Central, peripheral	Amino acids, ILE containing omega-3 (SO/MCT/OO/FO), dextrose/glucose with or without electrolytes
	SmofKabiven Extra Nitrogen	Central	Amino acids, ILE containing omega-3 (SO/MCT/OO/FO), dextrose/glucose with or without electrolytes
	SmofKabiven Low Osmo	Peripheral	Amino acids, ILE containing omega-3 (SO/MCT/OO/FO), dextrose/glucose with or without electrolytes
B. Braun	Nutriflex Lipid Plus/Special	Central	Amino acids, ILE containing omega-3 (SO/MCT/FO), dextrose/glucose with or without electrolytes
	Nutriflex Omega Plus/Special	Central	Amino acids, ILE containing omega-3 (SO/MCT/FO), dextrose/glucose with or without electrolytes
	Nutriflex lipid peri Novo	Peripheral	Amino acids, ILE containing omega-3 (SO/MCT/FO), dextrose/glucose with electrolytes
	Nutriflex Omega peri	Peripheral	Amino acids, ILE containing omega-3 (SO/MCT/FO), dextrose/glucose with electrolytes
Baxter	Olimel N5E, N7E, N9E, N12E	Central	Amino acids, ILE containing OO/SO, dextrose/glucose with or without electrolytes
	Oliclinomel Peripheral N4 550 E/ PeriOlimel N4E	Peripheral	Amino acids, ILE containing OO/SO, dextrose/glucose with electrolytes
	Finomel	Central, peripheral	Amino acids, ILE containing omega-3 (SO/MCT/OO/FO), dextrose/glucose with electrolytes

Abbreviations: 3CB, 3-chamber bag; FO, fish oil; ILE, intravenous lipid emulsion; MCT, medium-chain triglycerides; OO, olive oil; PN, parenteral nutrition; SO, soybean oil.
[a]Note that in Europe, PN products are authorized at a national level (and not centrally), and thus considerable variations can be observed across European countries, including variations in product names or formulations available.[10]

mostly in acute care. PN is governed by pharmacy and therapeutics committees at corporate and local levels and by regular meetings of institutional panels. These are ideally multidisciplinary, and include nutrition enterprise conference calls to develop standards for enteral nutrition, PN, and oral nutrition for adults, and monthly neonatal intensive care unit (NICU) enterprise meetings. An error prevention program is also in place. The program is overseen by the Enterprise Medication Safety Council, consisting of a multidisciplinary team led by the corporate chief medical officer, and involves use of medication error reporting software. Depending on the institution, PN tends to be ordered on paper, and this is done by either physicians, advanced practice providers, dietitians, pharmacists, or other medical staff. PN use processes vary according to hospital size. In small (<100-bed) and medium (100- to 250-bed) hospitals there is a mixture of outsourced pharmacy compounding, PN preparation by hand (with electronic calculations), and use of (market-authorized) 2CBs, with ILE given separately. However, in-house automated compounding devices are used in some medium-sized hospitals. In larger hospitals (>250 beds), PN is currently prepared by either outsourced pharmacy compounding, in-house automated compounding, or (market-authorized) 2CBs, with separate ILE administration.

Several measures have been undertaken across the Steward Health Care hospital organization to improve the safety and quality of PN from prescription to administration (Table 2) while also taking into account costs and pragmatic concerns. In alignment with expert recommendations,[3,7,16] these attempts relate to the overall standardization of the PN process, the consolidation of systems in use, the implementation of electronic order sets and systems, fostering interdisciplinary communication, pharmacovigilance surveillance for complications, and staff education. Implementing these measures into an already established PN work setup posed major issues and required a pragmatic approach. For example, one focus of the PN quality program is to reduce outsourced PN and PN compounded manually and move towards standardized formulations so most adults receive PN as market-authorized MCBs (with or without electrolytes added manually). However, this is not possible everywhere: Critical access and small hospitals continue to use outsourced PN, owing to a lack of

Table 2. Core Elements of Pragmatic PN Quality and Safety Undertakings at Steward Health Care Hospitals[a]

Aspect	Main efforts
PN formulation/prescription	• Create standards for all patient populations (through multidisciplinary team effort). • Implement electronic ordering sets.
PN ordering	• Where it is still practiced, move away from paper ordering and introduce an electronic ordering process.
PN preparation	• Reduce outsourced PN and minimize customized PN prepared by hand. • Expand the use of MCBs across all adult acute care populations.
Error prevention	• Demand mechanisms for reporting safety issues into medication safety programs at the corporate level.
Staff education	• Expand mandatory education to improve PN expertise by making use of internal educational programs (eg, Steward University) or educational programs offered by third parties (eg, ASHP modules).
Multidisciplinary collaboration	• Broaden multidisciplinary involvement with enterprise-wide nutrition meetings.
Shortages of PN components	• Explore strategies to mitigate PN component shortages.

Abbreviations: ASHP, American Society of Health-System Pharmacists; MCB, (market-authorized) multichamber bag; PN, parenteral nutrition.
[a]Some of the measures taken represent a compromise between an ideal PN process and what is practical to implement into an already established setup such as the heterogeneous system embodied by the Stewart Health Care Hospitals group.

appropriately renovated compounding sterile facilities, or prepare specialty PN formulations manually. Some providers refuse to use MCBs in the critical care setting, possibly owing to retrospective study data suggesting that intensive care unit (ICU) patients may not achieve maximum protein intakes or sodium requirements when receiving PN via 2CBs compared with compounded PN.[13] In addition, shortages of PN components require special attention, and newly acquired hospitals need to be familiarized with the standards in place. Moreover, medical cultures and their perspectives on standardization can differ across the US. A balance has to be found, whereas the overarching goal—improving the overall safety and quality of PN for all patients—should be kept in mind.

US medium-sized hospital: challenges using multiple PN systems for a small number of daily PN prescriptions

East Alabama Medical Center in Opelika, AL, is a community teaching hospital and acute regional referral center with 340 beds, an automated compounding device, and a comprehensive PN staff training program in place. Generally, there are fewer than 10 daily PN prescriptions for adults and fewer than 5 for neonates. Three different PN systems are used: (1) 2CBs for amino acids and dextrose/glucose (with ILE given separately), (2) in-house, hospital-compounded PN bags, and (3) outsourced, custom-compounded PN for neonates (recently replaced by in-house compounding). The challenges posed by maintaining these 3 systems in parallel include difficulties with inventory management of multiple components and concerns with storage/expiration dates. Potential confusion or mislabeling may occur when selecting among the high number of products. However, pharmacy staff and those administering PN require proper training to transition between these delivery systems. The importance of proper training, particularly when running several systems in parallel, was exemplified by a recent safety alert from the US-based Institute for Safe Medication Practices (ISMP).[17] The case reports included improperly activated MCBs and mixing up MCBs with and without electrolytes, suggesting staff unfamiliarity and lack of training with these products. These errors occurred during periods of drug shortages, which unfortunately have become commonplace in the US and highlight the need for adequate staff training and simplification of PN processes. None of these cases were from the East Alabama Medical Center. The center follows the recommendations endorsed by ISMP for safe use of MCB in clinical practice, which include (1) a preemptive and proactive risk evaluation to prevent mix-ups of MCBs at all steps of the PN process; (2) the activation and manipulation of MCBs is limited to hospital pharmacy staff working in a sterile environment; (3) the amendment of additives such as micronutrients and electrolytes occurs in alignment with manufacturers' stability data; (4) barcode-scanning technology for dispensing, compounding, and administration is employed throughout the process; and (5) a comprehensive staff training program, including calculation of macronutrients and electrolytes delivered by the prescribed infusion rate.[17]

In 2018, the center participated in a study evaluating the PN preparation time and resource utilization required for MCBs containing all 3 macronutrients (amino acids, dextrose/glucose, and an ILE) compared with hospital-compounded bags (HCBs).[18] This multicenter, prospective, observational

study was conducted in 3 centers in the US and evaluated time from transcription to completion of PN preparation, as well as associated costs. A total of 66 prescriptions for MCBs and 70 prescriptions for HCBs were assessed. Results suggested potential cost savings in favor of the MCBs compared with HCBs, with commercial MCBs reducing staff time by 62% and direct costs by 37% (Table 3).[18] However, the limited variety of MCBs available in the US remains a decisive factor hindering their broader use within clinical practice. Indeed, additional authorized products for the US market would be of value, as mentioned in a consensus statement at the summit (statement 4): "industrial manufacturers should introduce a broader variety of market-authorized MCBs to the US market to better meet the needs of diverse patient populations, and improve patients' safety and treatment effectiveness."[15]

European perspectives: the role of market-authorized MCBs in academic hospitals and smaller institutions

At the summit, attendees from 3 European academic centers (in Lausanne, Switzerland; Ghent, Belgium; and Barcelona, Spain) shared their personal experience of improvements to the safety and quality of PN. All 3 centers rely on a dual system, composed of compounded PN and market-authorized MCBs, the latter being the backbone of PN therapy. In these centers, MCBs are typically 3CBs containing amino acids, dextrose/glucose, and ILEs.

In Switzerland, 3CB use is common, mainly because 3CBs are preferred for increased safety and reduced cost.[19] With the preponderance of 3CBs across the country, compounding is generally only done in large university hospitals. Indeed, a 1996-1998 survey in Switzerland found that most PN for hospitalized adults was given as 3CBs, but PN compounding was still important for pediatric patients (because of individualized PN compositions and the lack of commercially available standard PN at the time).[6] Later studies have shown that about 50% of all compounded PN was used for pediatric populations in Swiss, French, and Belgian hospitals, with standard PN formulations used mainly for adult patients.[5]

Current data were shared regarding PN usage in the ICU of an academic teaching hospital in Lausanne (Lausanne University Hospital). This center's approach for energy provision in ICU patients is summarized in Box 1.[20-27] ICU patients requiring PN typically receive supplemental PN (PN in combination with enteral nutrition), showing this to be a cost-saving strategy.[25] In two-thirds of these patients, nutritional needs can be covered with market-authorized MCBs (with daily additions of vitamins and trace elements, customized electrolyte composition when needed, and additions of glutamine if a patient requires PN for more than 3 days). In the remaining one-third of the patients, individualized compounded PN is necessary. Physicians are in charge of PN prescribing and ordering laboratory tests to closely monitor the patients' nutritional status.

Ghent University Hospital is a tertiary teaching hospital with 1,062 beds. Principles regarding nutritional support are typically developed by a multidisciplinary nutrition support team consisting of physicians, pharmacists, nurses, and dietitians—a process that is well established and implemented over many years in Belgium and many other European countries. The hospital uses 36,000 PN bags per year for adult, pediatric, and NICU patients (hospital and homecare), with approximately 15,000 of these being either compounded bags or customized MCBs. The latter are (market-authorized) 3CBs containing 3 or more additives (ie, extra electrolytes, 5% dextrose/glucose in water, 0.9% sodium chloride injection, and/or glutamine) and are prepared at the hospital pharmacy as per the internal hospital process. However, 3CBs containing only multivitamins and trace elements as additives are directly handled at the ward by trained nurses—as nurses do for numerous other infusion therapies requiring these simple aseptic handling steps (eg, the reconstitution of antibiotics or the dilution of an antipyretic or antiemetic drug in an intravenous bag). Figure 1 gives an overview of how the PN process evolved over the past 20 years at Ghent University Hospital and provides insights into what triggered these changes.[28,29] Resource/efficiency optimization, new patient safety recommendations, and the commercial availability of additional 3CBs were generally the main drivers prompting adaptations in the PN

Table 3. Time Required for PN Procedures at East Alabama Medical Center Pharmacy and Costs per PN Bag[18]

	HCB	MCB	Comment
Time required for transcription, review, validation, and preparation of PN, mean (SD), minutes	14.3 (6.2)	5.5 (1.3)	$P < 0.001$
Cost per PN bag, mean[a]	$131.17	$81.60	Difference: –$49.57

Abbreviations: HCB, hospital-compounded bag; MCB, (market-authorized) multichamber bag (containing the 3 macronutrients: amino acids, dextrose/glucose, and intravenous lipid emulsion); PN, parenteral nutrition.
[a]Note: these costs included direct costs for PN products and medical consumables, equipment costs, and labor costs for each specified task within the PN workflow.

Box 1. Nutrition Support in the ICU: "One Size Fits All" Approach Is Not Appropriate[20-27]

Adequate nutrition support is vitally important in the management of patients in the ICU, as both underfeeding and overfeeding generate complications and should be prevented.[20] However, the optimal timing, energy supplied, and the role of supplemental parenteral nutrition (SPN) during the first 7 to 10 days of critical illness are still matters of debate.[21-23] The current trend is to individualize nutritional therapy based on the stage of critical illness and patients' caloric needs.[20,21]

Societies and experts advise feeding patients in the ICU enterally, and typically enteral nutrition is started within 48 hours of ICU admission and slowly progressed to avoid overfeeding. SPN can be used when nutritional targets are not reached.[20,21]

To decide when SPN is indicated, the center in Lausanne follows the criteria applied in the Swiss SPN trial.[24] This study, conducted in 2 hospitals (in Lausanne and Geneva), evaluated whether SPN could reduce infectious complications when adapted to each patient's energy requirements (assessed by indirect calorimetry) starting 4 days after ICU admission and was powered accordingly.[24] Patients not reaching their energy target from enteral nutrition were randomly assigned to SPN (n = 153) or enteral nutrition alone (n = 152). Those allocated to SPN were less likely to have infectious complications ($P < 0.05$), and associated costs were reduced by CHF 3,300 per case.[25] The main reasons for these financial savings were improved energy balance and reduced costs associated with anti-infection treatment. According to a biomarker substudy, SPN was associated with improved immunity, less systemic inflammation, and a trend towards less loss of muscle mass than occurred with enteral nutrition alone.[26]

Of note, the Swiss SPN trial enrolled patients (on day 3 after ICU admission) who had reached less than 60% of their energy target from enteral nutrition and would likely need a further 5 days of ICU treatment. The nutritional support was carefully individualized according to energy targets calculated using indirect calorimetry. Protein delivery was close to the target of 1.2 g/kg/day during the intervention. The complete achievement of energy targets in those assigned to receive SPN was verified twice daily. Furthermore, there was no attempt to compensate for patients' first 3 days of extrinsic energy deficit.[24,26] The determination of nutritional needs in ICU patients by indirect calorimetry is an approach recommended by ESPEN,[27] but there is a lack of clarity concerning recommendations for this technique in the US.[22,23]

There is no corresponding recommendation in the recent US ICU recommendations, which has been met with incomprehension.[23]

Abbreviations: CHF, Swiss francs; ESPEN, European Society for Clinical Nutrition and Metabolism; ICU, intensive care unit.

process.[28,29] Implementations had to be practical and pragmatic. For example, an expanding number of patients had to be provided for while the pharmacy workforce remained relatively constant. The involvement of trained nurses in activating 3CBs and adding multivitamins and trace elements to 3CBs freed up pharmacy resources. Crucial questions were: What can be done at the ward without putting the patients at risk, and when are pharmacy expertise and services mandatory? The hospital's internal rule now states that standard additions of multivitamins and trace elements to 3CBs for adult hospitalized non-ICU patients are done by trained nurses at the ward, but when more additives (including extra electrolytes) are required, then a PN bag must be prepared by the hospital pharmacy. For example, calcium additions to 3CBs are done at the pharmacy to prevent calcium phosphate precipitation (see Box 2 for clinical consequences of calcium phosphate precipitations).[15,30-32] This approach may not be allowed in other countries, such as the United States.[33] However, in Belgium these practices are permitted, and at Ghent University Hospital it is part of the nurses' responsibility to handle simple infusion therapies, as outlined above. Critics of this approach suggest that higher infection rates are associated with amendments to MCBs in the ward.[34-36] However, these data should be interpreted cautiously, as they are derived from retrospective claims database analyses lacking the specific details necessary for proper risk assessment, and so, as noted by the study authors, a cause-effect relationship cannot be established[34-36]; rather, such evaluations were viewed as hypothesis-generating for further research.[36] In Belgium, the process modification has not been accompanied by a specific safety evaluation, but infections (including catheter-related bloodstream infections) are under continuous monitoring at the hospital within the context of a national campaign to improve antibiotic use and, by law, a hospital-installed antibiotic steering committee, and no concerns were raised in relation to changes in PN practices. It may also be remarked that catheter care processes have undergone considerable changes and development to improve patient safety,[37] and that Ghent University Hospital continuously implemented recommendations. The aforementioned claims datasets largely lack data on catheter utilization.[34-36]

Other measures to improve patient safety in the context of PN at Ghent University Hospital included the introduction of an electronic ordering system, the provision of predefined medication order sets, and the standard use of MCBs for adult patients whenever possible, with all those measures being accepted and established strategies to reduce transcription, calculation or compounding errors, and stability and incompatibility issues, as well as lowering the risk of infections.[3,32,38,39]

Figure 1. Evolution of the parenteral nutrition (PN) process over the past 2 decades at Ghent University Hospital, Belgium. These developments allowed the management of increasing numbers of PN patients and improved patient safety, with relatively constant pharmacy resources. AIO indicates all-in-one formulation (proteins, lipids, and dextrose/glucose); Ca, calcium; EPD, electronic patient dossier; ESPEN, European Society for Clinical Nutrition and Metabolism; EVA, ethyl vinyl acetate; IV, intravenous; ICU, intensive care unit; ILE, intravenous lipid emulsion; MCB, (market-authorized) multi-chamber bag; PIF, pharmaco-technical information folder; RT, room temperature; TE, trace elements; VIT, vitamins.

PN for general ward

	Before 2002	2002–2005	2006–2009	2010–present
Systems in use/system-related advancements (rationale)	All compounded in EVA bags on a daily basis	Introduction of first commercial AIO MCBs (allowed to produce small batches, such as to cover weekends).	Smaller AIO MCBs became available (allowed to reduce the risk of fluid overload, such as in patients with concomitant IV medications).	MCBs with ILEs containing fish oil and electrolytes became available (scientific data on clinical benefit of PN containing fish oil).
		Individual/tailored compounded PN in case of abnormal fluid, electrolyte losses/disturbances, etc.		
MCB handling and supporting tool	–	All handled at the hospital pharmacy.	At the ward by trained nursing staff: mixing and adding VIT + TE, but ≤2 additions and max. stability of 24h at RT. Rigorous nurse-training program started.[a] At the hospital pharmacy: in case of ≥3 additions to MCB (i.e. customized MCB) to maintain sterility or monitor physicochemical stability.	At the ward by trained nursing staff: standard MCB bags.[a] By the pharmacist in charge: validation of customized/tailored PN prescription and physicochemical monitoring on a daily basis. Supporting tool: standardized checklist developed.
PN prescription process	PN individually prescribed (on paper).		PN electronically prescribed in EPD. Pre-defined medication order sets (e.g. PN+Vit+TE to reduce the risk of ordering errors).	

PN for ICU

	Before 2002	2002–2005	2006–2009	2010–present
Systems in use/system-related advancements (rationale)	Multi-bottle system at bedside.		Introduction of MCB without electrolytes (to reduce risk of infections). AIO bags customized on a daily basis according to laboratory values	Introduction of electrolyte-free MCBs including ILEs containing fish oil (scientific data on clinical benefit of fish oil containing PN).[28] ESPEN 2019 ICU guidelines[29] resulted in the use of MCBs with low-caloric/high-protein content.
Precautionary measures and MCB handling	–		- Intensive training program for pharmacists, physicians and nurses. - PIF tool introduced to allow physicochemical stability check (e.g. max. addition of electrolytes and conversion tool [meq↔mmol↔g]). - Mixing and adding of electrolytes, VIT + TE by trained nursing staff at the ward,[a] but no Ca additions to MCBs (Ca given via separate IV line, preventing Ca phosphate precipitation).	
PN prescription process	PN individually prescribed (paper).		PN prescribed electronically by internally developed prescribing program.	

Overarching principles

1. Optimize resource efficiency: (i) less time consuming; (ii) immediately available.
2. Improve patient safety: (i) better physicochemical stability/compatibility of PN admixtures (7 days at 2–8°C + 24h RT); (ii) when possible, abstain from compounding and rely on MCBs as they require fewer manipulation steps; (iii) reduce risk of infection (aim for as few manipulations as possible).
3. Provide clinically appropriate nutrition, while keeping preparation steps as few as possible to eliminate sources of errors.

[a]Simple infusion therapies are permitted common practice. Risk of infections, including catheter-related bloodstream infections [CRBSI], are under continuous monitoring at the hospital within the context of a national campaign to improve antibiotic use and by law in a hospital-installed antibiotic steering committee. No increase in infections was observed when these PN practices were introduced. See text for more information. Note that the practices outlined in this table may not be allowed in some other countries.

Finally, PN for pediatric patients is a subject of special interest to Ghent University Hospital, though this is somewhat beyond the scope of the summit. PN for pediatric patients is a shared project by the pharmacy department and the pediatric gastroenterology department.[40] This illustrates how shared efforts can improve the quality and safety of PN for this particularly vulnerable patient group, as summarized in Box 3.[41-43]

The University Hospital Vall'Hebron in Barcelona, Spain, uses a dual system of (1) MCBs (whenever possible), and (2) compounded PN for those whose nutritional needs cannot be met with commercial products or for patients with volume restrictions. Of the 15,000 PN bags requested per year (8,500 for adult and 6,500 for pediatric use), 8,000 are MCBs and 7,000 are compounded. All additions to MCBs are done in the pharmacy under aseptic conditions. According to the hospital's internal statistics, trace elements and vitamins are added to all 3CBs (unless recommended otherwise), close to 20% are amended with electrolytes, and approximately 8% are supplemented with glutamine (not Food and Drug Administration [FDA] approved for use in the US). Policies regarding nutritional support are typically developed by interdisciplinary expert teams consisting of physicians, pharmacists, and dietitians, a process that is well established and implemented.

The University Hospital Vall'Hebron performed or participated in a series of investigations evaluating the cost-effectiveness and safety of MCBs versus HCBs.[7,39,44,45] For example, as part of the hospital's PN standardization strategy, a retrospective survey was performed concerning the formal integration of MCBs for adult patients.[45] In this collaborative project by the nutrition support unit and the hospital pharmacy, 3-month periods shortly before and after the transition were evaluated. As well as quantitative measures, assessments included a number of quality criteria, including PN administration, nutrition assessment (targeted energy intake and nitrogen balance), safety, complications (eg, hyperglycemia, hypertriglyceridemia, hepatic complications, catheter-related infection), and global efficacy. Data from 296 patients and a total of 3,167 PN bags were analyzed. The use of MCBs increased from 47.5% before to 85.7% after the introduction of the new policies ($P < 0.05$). No differences were found in the quality criteria tested.

Box 2. Clinical Implications of Calcium Phosphate Precipitates in Association With PN[15,30-32]

Reedy et al[30] reported a case of microvascular pulmonary emboli secondary to precipitated calcium phosphate crystals in a patient receiving PN. Another 3 case reports described the potentially harmful clinical effects of drug incompatibilities in association with PN.[31] Clinical symptoms ranged from respiratory failure, including shortness of breath, chest tightness, and dry cough (with or without fever), to sudden death or cardio-respiratory arrest. Pulmonary morbidities seem mainly to be caused by the microemboli of crystal precipitates obstructing pulmonary vessels and generating granulomatous pulmonary arteritis and granulomatous interstitial pneumonitis. Severe arterial pulmonary hypertension associated with cardiac arrest can occur during a diffuse- and multiple-emboli procedure.[31]

ASPEN refers to validated solubility curves for determining the maximum amount of calcium and phosphate to be added to a PN solution.[32] On PN administration, precautionary measures to prevent precipitations are to use a dedicated IV infusion line for PN and to deliver medication on a separate IV line/lumen.[15]

Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; IV, intravenous; PN, parenteral nutrition.

Box 3. Efforts to Standardize PN for Pediatric Patients in Europe[41-43]

Until recently, individualized daily compounding was typical for pediatric PN.[41] However, concerns accrued regarding inadequate delivery of nutrients and prescribing and compounding errors, so proposals were made for standardized PN admixtures for pediatric use.[41,42] For the majority of pediatric patients, standardized PN admixtures could be used, and only a minority require electrolyte adaptations or individualized PN, particularly those receiving long-term PN.

Today, ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric PN express a preference for the use of standard PN over individualized PN solutions, when possible. Additionally, they advocate for adequate monitoring of the metabolic and nutritional status as "uncritical use of standard formulations in such patients, particularly over longer periods of time, may be less than optimal for growth and development."[43]

Although there are fewer MCBs available for pediatric PN than for adult patients, additional MCB formulations are starting to become available, although they are mostly for children over 2 years of age.

Abbreviations: CSPEN, Chinese Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; ESPR, European Society of Paediatric Research; MCB, (market-authorized) multichamber bag; PN, parenteral nutrition.

Mean costs of PN decreased by 19.5%, and the annual cost saving was calculated to be €86,700 for the hospital.[45] Costs of different PN systems (components, raw materials, and hospital staff) and PN-related errors were further explored in a prospective, observational study across 10 Spanish hospital pharmacy services.[7] The average cost savings and time savings per bag (among 295 MCBs and 97 HCBs assessed) were $5.71 and 38 minutes in favor of MCBs compared with equivalent HCBs ($62.11 vs $67.54 and 19.89 minutes vs 57.61 minutes, respectively; $P < 0.05$ for both comparisons). The error rate was 1% for MCBs and 5% for HCBs ($P < 0.01$).[7] The results of a systematic literature review also point towards potential clinical, ergonomic, and economic benefits for MCBs compared with HCBs (or multibottle systems), though methodological factors limited evidence quality.[39]

Conclusion

During the discussions at the International Safety and Quality of PN Summit, it became apparent that the core challenges regarding the PN process are largely the same everywhere, with pressure for efficiency, optimization, and concurrent obligations to make PN safer for the patients. The transatlantic exchange brought forth insights into how the PN process developed differently in the US and Europe. In both regions, a few centers with ample PN experience were often the main promoters for advances, but the paths taken differed considerably. In the US, compounding has been used as the main method to produce PN, and its process was continuously optimized and improved to increase quality and safety, but many European countries opted early on for a dual system of (market-authorized) MCBs (where possible) and compounding (where necessary). One drawback of this development in Europe is that currently only very few—typically the largest—European centers have the capability to compound PN. In return, MCBs are broadly accepted in European institutions, and this may have prompted the pharmaceutical industry to further develop MCBs to cover a wider range of nutritional needs. During the meeting, European experts reported that at their institutions they can generally select between about ten adult MCBs, giving them a good degree of flexibility. Colleagues from US centers, in particular, had much less choice. So far, FDA has approved only one adult

MCB (a 3CB) for central use and one for peripheral use. However, a variety of 2CBs for central or peripheral use are available in the US to be given with a separate ILE infusion. At the summit the experts agreed that ILEs should be an integral part of PN. However, some concerns were expressed over continued widespread use of pure soybean oil ILEs, particularly in the US, despite increasing evidence of improved clinical outcomes with more modern multicomponent ILEs containing fish oil.[46]

During the summit it was recognized that there is a need for additional MCBs to be made available in the US. Institutions requiring smaller PN volumes, in particular, would benefit from this approach. They may operate several PN systems in parallel, posing numerous logistical challenges, and the transition between delivery systems requires extra work to train pharmacy and nursing staff. In addition, it is often not worthwhile for smaller hospitals to procure the technical aids that enable state-of-the-art ordering or compounding, and outsourcing is not always an option. However, it will take time before a broad range of MCBs will become commercially available in the US. Until then, it is important to focus on what is possible currently to improve the PN process, and how to improve PN safety even within smaller budgets. The PN quality and safety initiative at Steward Health Care hospitals (for core elements, see Table 2), with its diverse and pragmatic approach, is a good example for others in similar situations. All such efforts contribute to the achievement of the overarching goal: to make PN as safe and as adequate as possible for all patients requiring nutritional support, irrespective of location.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

Fresenius Kabi Deutschland GmbH and Fresenius Kabi USA provided financial support to organize and invite experts to participate as speakers, based on knowledge and international reputation within the areas of clinical nutrition, to the International Safety and Quality of Parenteral Nutrition Summit, as well as financial support for the development of this summary of proceedings. Fresenius Kabi had no involvement in the study design, collection, analysis, and interpretation of data or writing of the manuscript. Dr. Martina Sintzel (mcs medical communication services, Erlenbach, Switzerland) drafted the manuscript, and Dr. Richard Clark (freelance medical writer, Dunchurch, UK) provided editorial and consultancy services; all were funded by Fresenius Kabi. These services complied with international guidelines for Good Publication Practice (GPP2022). Dr. Cogle has received consulting fees from Fresenius Kabi. Dr. Ayers is a consultant and speakers bureau member for Fresenius Kabi, and has received speaker's honoraria from Baxter. Dr. Berger has received speaker's honoraria from Baxter, Fresenius Kabi, and Nestlé. Dr. Berlana has received consulting fees and speaker's honoraria from Baxter and Fresenius Kabi. Dr. Wischmeyer has received investor-instigated grant funding related to his work from the National Institutes of Health, US Department of Defense, Abbott, Baxter, and Fresenius Kabi, Mend Inc., and Nutricia, consulting fees from Abbott, Baxter, Fresenius Kabi, Mend Inc., and Nutricia, and honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter, DSM, Fresenius Kabi, Nestlé, and Nutricia. He has received an unrestricted gift donation for nutrition research from Musclesound and DSM. Dr. Ybarra has received consulting fees from Baxter, Heron Therapeutics, and Fresenius Kabi. Dr. Zeraschi has received institutional support for pharmacy education and training from Baxter, B. Braun, and Fresenius Kabi. Dr. De Cloet has received research fund support for the Pharmacy Department of the University Hospital Ghent from Fresenius Kabi.

References

1. Ayers P, Boullata J, Sacks G. Parenteral nutrition safety: the story continues. *Nutr Clin Pract*. 2018;33(1):46-52.
2. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations. *JPEN J Parenter Enteral Nutr*. 2014;38(3):296-333.
3. Boullata JI, Berlana D, Pietka M, Klek S, Martindale R. Use of intravenous lipid emulsions with parenteral nutrition: practical handling aspects. *JPEN J Parenter Enteral Nutr*. 2020;44(suppl 1):S74-S81.
4. Barnett MI, Pertkiewicz M, Cosslett AG, Muhlebach S. Basics in clinical nutrition: parenteral nutrition admixtures, how to prepare parenteral nutrition (PN) admixtures. *E SPEN*. 2009;4:e114-e116.
5. Maisonneuve N, Raguso CA, Paoloni-Giacobino A, et al. Parenteral nutrition practices in hospital pharmacies in Switzerland, France, and Belgium. *Nutrition*. 2004;20(6):528-535.
6. Pichard C, Mühlebach S, Maisonneuve N, Sierro C. Prospective survey of parenteral nutrition in Switzerland: a three-year nation-wide survey. *Clin Nutr*. 2001;20(4):345-350.
7. Berlana D, Almendral MA, Abad MR, et al. Cost, time, and error assessment during preparation of parenteral nutrition: multichamber bags versus hospital-compounded bags. *JPEN J Parenter Enteral Nutr*. 2019;43(4):557-565.
8. Mirtallo JM, Guenter P. Introduction and goals of the A.S.P.E.N. parenteral nutrition safety summit. *JPEN J Parenter Enteral Nutr*. 2012;36(2 suppl):7S-9S.
9. DeLegge MH. Parenteral nutrition therapy over the next 5–10 years: where are we heading?. *JPEN J Parenter Enteral Nutr*. 2012;36(2 suppl):56S-61S.
10. European Medicines Agency (EMA). Article 57 database. Accessed November 28, 2023. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database
11. Schneider PJ, Pedersen CA, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: dispensing and administration—2017. *Am J Health-Syst Pharm*. 2018;75(16):1203-1226.
12. Berlana D, Barraquer A, Sabin P, et al. Impact of parenteral nutrition standardization on costs and quality in adult patients. *Nutr Hosp*. 2014;30(2):351-358.
13. Blanchette LM, Huiras P, Papadopoulos S. Standardized versus custom parenteral nutrition: impact on clinical and cost-related outcomes. *Am J Health-Syst Pharm*. 2014;71(2):114-121.
14. Sathyanarayana SA, Deutsch G, Singh N, Barrera R. A comparison between customized and premixed pretrial nutrition: cost really matters. *ICU Dir*. 2013;4:279-284.
15. Ayers P, Berger MM, Berlana D, et al. Expert consensus statements and summary of proceedings from the International Safety and Quality of Parenteral Nutrition Summit. *Am J Health-Syst Pharm*. 2024;81 (suppl 3):S75-S88.
16. Guenter P, Worthington P, Ayers P, et al. Standardized competencies for parenteral nutrition administration: the

ASPEN model. *Nutr Clin Pract*. 2018;33(2):295-304.
17. Institute for Safe Medication Practices. Multi-chamber bag parenteral nutrition is not without risk. Published July 28, 2022. Accessed November 22, 2023. https://www.ismp.org/resources/multi-chamber-bag-parenteral-nutrition-not-without-risk
18. Cogle SV, Martindale RG, Ramos M, et al. Multicenter prospective evaluation of parenteral nutrition preparation time and resource utilization: 3-chamber bags compared with hospital pharmacy-compounded bags. *JPEN J Parenter Enteral Nutr*. 2021;45(7):1552-1558.
19. Pichard C, Schwarz G, Frei A, et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. *Clin Nutr*. 2000;19(4):245-251.
20. Berger MM, Pichard C. Feeding should be individualized in the critically ill patients. *Curr Opin Crit Care*. 2019;25(4):307-313.
21. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. *Crit Care*. 2020;24(1):35.
22. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
23. Martindale RG, Klek S, Puthucheary Z, et al. Commentary on "Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition". *JPEN J Parenter Enteral Nutr*. 2022;46(6):1223-1225.
24. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*. 2013;381(9864):385-393.
25. Pradelli L, Graf S, Pichard C, Berger MM. Supplemental parenteral nutrition in intensive care patients: a cost saving strategy. *Clin Nutr*. 2018;37(2):573-579.
26. Berger MM, Pantet O, Jacquelin-Ravel N, et al. Supplemental parenteral nutrition improves immunity with unchanged carbohydrate and protein metabolism in critically ill patients: the SPN2 randomized tracer study. *Clin Nutr*. 2019;38(5):2408-2416.
27. Singer P, Blaser AR, Berger MM, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive care unit. *Clin Nutr*. 2023;42(9):1671-1689.
28. Calder PC, Adolph M, Deutz NE, et al. Lipids in the intensive care unit: recommendations from the ESPEN Expert Group. *Clin Nutr*. 2018;37(1):1-18.
29. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48-79.
30. Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated crystals in a patient receiving total parenteral nutrition: a case report and description of the high-resolution CT findings. *Chest*. 1999;115(3):892-895.
31. Benlabed M, Perez M, Gaudy R, et al. Clinical implications of intravenous drug incompatibilities in critically ill patients. *Anaesth Crit Care Pain Med*. 2019;38(2):173-180.
32. Boullata JI, Gilbert K, Sacks G, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr*. 2014;38(3):334-377.
33. US Pharmacopeia. General chapter <979>: pharmaceutical compounding – sterile preparations. Accessed November 22, 2023. https://www.usp.org/compounding/general-chapter-797
34. Mercaldi CJ, Reynolds MW, Turpin RS. Methods to identify and compare parenteral nutrition administered from hospital-compounded and premixed multichamber bags in a retrospective hospital claims database. *JPEN J Parenter Enteral Nutr*. 2012;36(3):330-336.
35. Pontes-Arruda A, Liu FX, Turpin RS, Mercaldi CJ, Hise M, Zaloga G. Bloodstream infections in patients receiving manufactured parenteral nutrition with vs without lipids: is the use of lipids really deleterious?. *JPEN J Parenter Enteral Nutr*. 2012;36(4):421-430.
36. Pontes-Arruda A, Zaloga G, Wischmeyer P, Turpin R, Liu FX, Mercaldi C. Is there a difference in bloodstream infections in critically ill patients associated with ready-to-use versus compounded parenteral nutrition?. *Clin Nutr*. 2012;31(5):728-734.
37. Kolacek S, Puntis JWL, Hojsak I; et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: venous access. *Clin Nutr*. 2018;37(6, pt B):2379-2391.
38. Kochevar M, Guenter P, Holcombe B, Malone A, Mirtallo J; ASPEN Board of Directors and Task Force on Parenteral Nutrition Standardization. ASPEN statement on parenteral nutrition standardization. *JPEN J Parenter Enteral Nutr*. 2007;31(5):441-448.
39. Alfonso JE, Berlana D, Ukleja A, Boullata J. Clinical, ergonomic, and economic outcomes with multichamber bags compared with (hospital) pharmacy compounded bags and multibottle systems: a systematic literature review. *JPEN J Parenter Enteral Nutr*. 2017;41(7):1162-1177.
40. De Cloet J, Van Biervliet S, Van Winckel M. Physicochemical stable standard all-in-one parenteral nutrition admixtures for infants and children in accordance with the ESPGHAN/ESPEN guidelines. *Nutrition*. 2018;49:41-47.
41. Meyer R, Timmermann M, Schulzke S, Kiss C, Sidler MA, Furlano RI. Developing and implementing all-in-one standard paediatric parenteral nutrition. *Nutrients*. 2013;5(6):2006-2018.
42. Krohn K, Babl J, Reiter K, Koletzko B. Parenteral nutrition with standard solutions in paediatric intensive care patients. *Clin Nutr*. 2005;24(2):274-280.
43. Riskin A, Picaud JC, Shamir R; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: standard versus individualized parenteral nutrition. *Clin Nutr*. 2018;37(6, pt B):2409-2417.
44. Berlana D, Sabin P, Gimeno-Ballester V, et al. Cost analysis of adult parenteral nutrition systems: three-compartment bag versus customized. *Nutr Hosp*. 2013;28(6):2135-2141.
45. Berlana D, Barraquer A, Sabin P, et al. Impact of parenteral nutrition standardization on costs and quality in adult patients. *Nutr Hosp*. 2014;30(2):351-358.
46. Pradelli L, Mayer K, Klek S, et al. ω-3 fatty-acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. *J Parenter Enteral Nutr*. 2020;44(1):44-57.