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CLINICAL RESEARCH

Supplementations of industrial multichamber parenteral nutrition bags in critically ill children: Safety of the practice

Elise Jandot PharmD[1] | **Morane Savelli PharmD**[1] | **Guillaume Pinte PharmD**[1] | **Adam Sutherland MSc**[2] | **Thierry Quessada PharmD**[1] | **Frédéric V. Valla MD**[3,4]

[1]Pharmacy Department, Hôpital Universitaire Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

[2]Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health Sciences, University of Manchester, Manchester, United Kingdom

[3]Pediatric Intensive Care Unit, Hôpital Universitaire Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

[4]School of Health and Society, University of Salford, Manchester, United Kingdom

Correspondence
Elise Jandot, PharmD, Pharmacy Department, Hôpital Universitaire Femme Mère Enfant-Hospices Civils de Lyon, 59 Blvd Pinel, 69 677 Bron, Lyon, France.
Email: elise.jandot@gmail.com

Abstract

Background: Parenteral nutrition (PN) is sometimes required in critically ill children because of contraindication or intolerance to full enteral nutrition. European guidelines recommend favoring multichamber bag PN (MCB PN), when possible, for quality purposes and ease of use. The prescribers may adjust the MCB PN through supplementations to better fulfill patient needs. The objective of this study is to investigate the use and supplementations of MCB PN.

Methods: This observational, single-center, retrospective study was conducted in a pediatric intensive care unit (PICU). We collected prescriptions of MCB PNs and their supplementations added directly into PN bags. A descriptive analysis and a comparison of electrolyte supplementations with the manufacturer's recommendations were undertaken.

Results: One hundred thirty-five children (median age 39.2 months [7.0–118.8]) were included, 1449 MCB PNs were administered, and 1652 supplementations were carried out in 736 PN bags. Thirty-two percent of supplementations were vitamins, 32.2% were trace elements, and 35.8% were electrolytes. Around 10% of electrolyte supplementations in PN bags were outside the manufacturer's recommendations. These nonconformities primarily concerned phosphate.

Conclusion: This study showed the real-world clinical use of MCB PN in the PICU. Proper attention should be paid to septic risks and physicochemical risks to ensure efficient practice and safety of MCB PN use.

KEYWORDS
electrolytes, parenteral nutrition, parenteral nutrition solutions, pediatric intensive care units, pediatrics, safety, trace elements, vitamins

INTRODUCTION

Parenteral nutrition (PN) is required in critically ill children when enteral nutrition cannot fulfill their energy and substrate needs. These patients are at risk from nutrition compromise.[1,2] In practice, three types of PN formulations are available: pharmaceutical formulations in multichamber bags (MCB PNs) with marketing authorization, standardized formulations, and individualized formulations that are prepared by either hospital pharmacies or private manufacturers.[3] MCB PN is preferred in our pediatric intensive care unit (PICU), as recommended by 2018 European guidelines[4] (90% of patients). Individualized PN is prescribed for patients when MCB PN cannot meet their requirements (10% of patients).

MCB PNs are composed of water, macronutrients (dextrose, amino acids, and lipid injectable emulsion [ILE]), electrolytes, and minerals. MCB PNs without supplementation are the safest, as they are manufactured according to good manufacturing practice standards,[5] but they cannot fulfill the nutrition requirements of all critically ill children, who often present with plasma electrolyte disturbances.[6,7] MCB PNs do not contain select micronutrients, such as vitamins and trace elements.[8,9] Therefore, micronutrients must be administered daily and electrolyte supplementation is sometimes necessary.

Because of these formulation complexities, PN is vulnerable to compatibility issues. The stability of the mixture is affected by ingredient concentrations, pH, lipid content, and storage conditions.[10,11] Direct supplementation to PN solutions can disturb the physicochemical balance and increase the risk of microbiological contamination. In MCB PNs, some manufacturers have pretested common supplementations to provide maximum allowed limits for each additive. However, none have tested the ongoing microbiological stability of these solutions after supplementation.

Although supplementation MCB PN on the unit is not recommended practice in France[5,12] like in the United States,[13] this practice is common because of the lack of human and financial means. Supplementations also present a burden for the nurses who are tasked with administering them.

A few studies[14,15] have described the practice of supplementing MCB PN, yet these are considered high-risk manipulations (because of human errors, physicochemical instability, and microbiological risk). Consequently, this study aimed to describe the use of MCB PN in a PICU and to explore MCB PN supplementation in terms of good practice and safety issues.

MATERIALS AND METHODS

Study setting

A single-center, retrospective observational study was conducted in a 23-bed PICU at University Children Hospital. This PICU accommodates trauma, infectious disease, hematological disease, surgery, and solid organ transplantation. The age range of admitted patients is 3 days old to 17.9 years old. Cardiac patients and preterm infants are not admitted to this unit. This observational study monitored prescriptions of commercial MCB PNs and their supplementations (vitamins, trace elements, and electrolytes). All patients who received PN over a 2-year period (2016–2017) were included in the study. Study ethical approval was obtained in 2018 (local ethics board, approval number 18-20) and a waiver of written consent was obtained.

Patient characteristics

The study recorded demographic patient information, including age, sex, prognostic scores (Pediatric Index of Mortality 2), organ dysfunction scores (Pediatric Logistic Organ Dysfunction 2), intercurrent infections, duration of mechanical ventilation, length of stay, and death. Anthropometric measurements (including height and weight) were also collected to permit the calculation of body mass index and weight-for-age z scores according to World Health Organization charts. All data were collected from the electronic patient record (IntelliSpace Critical Care and Anesthesia; ICCA-Philips HealthCare) at the time of PN initiation.

Practices of PN and supplementations

All PN was prescribed electronically using the same electronic patient record system (ICCA-Philips HealthCare). In this study, the term "micronutrients" only includes vitamins and trace elements; electrolytes are excluded. Local guidelines for MCB PN supplementation changed between 2016 and 2017: in 2016, micronutrients were administered via a separate infusion once a day; in 2017, unit nurses directly supplemented MCB PN bags with micronutrients. Nurses had been trained by educated nurses on the use of MCB PN bags (how to break the sealing and homogenize the solution) and on how to manipulate the dedicated supplementation port in an aseptic manner to secure the supplementations. During the study period, electrolytes were always supplemented inside the MCB PN or enterally, when possible. Electrolytes

was dispensed by the hospital pharmacy. Most patients received more than one MCB PN. Data were collected for each administered bag, including the proprietary name of the PN admixture; the ILE inclusion status (whether the ILE compartment was activated or not); the daily administered volume; and the supplementations per PN bag (as micronutrients and electrolytes), including the dosage and the number of supplementations per day. Only supplementation performed by direct addition to the MCB PN was included. Supplementations via a Y-infusion or via the enteral route were outside the scope of the study. Enteral nutrition administration was also collected.

Comparison of electrolyte supplementations with the manufacturer's recommendations

To assess the physicochemical stability of supplementations, each dose of electrolyte supplementation in the MCB PN was compared for conformity with published data for supplementing MCB PN available in the Summaries of Product Characteristics (SPC) or package insert and a local manufacturer's stability database. There were no limitations on the number or volume of supplementations, and no control about stability formulation was realized before administration.

Statistical analysis

Categorical variables were expressed as whole numbers and percentages. Quantitative variables were expressed as median and interquartile range for population characteristics and as means and SD for MCB PN supplementations.

RESULTS

Patients

One hundred thirty-five patients were included in this study. Their characteristics are summarized in Tables 1 and 2. The median age was 39.2 (7.0–118.8) months and 42.2% of patients were girls. Within the cohort there were 11 deaths (8.1%) and 69 acquired infections (51.1%).

Prescriptions of PN and supplementations

In the study period, 1449 MCB PN bags were administered: 83% of these bags were administered as three-chamber bags (with ILE), 59.4% were Numeta G16%E, and 23.2% were Numeta G19%E (Baxter Healthcare Corporation) (Table 3).

A total of 1652 supplementations were made to 50.8% (736/1449) of MCB PNs. Among MCB PNs, 37% (535/1449) were supplemented with vitamins and/or trace elements. Other intakes in vitamins and trace elements were provided by the enteral route (in 2016 and 2017) or by Y-infusion (in 2016 only). Likewise, 28% (412/1449) of MCB PNs were supplemented with electrolytes. Among patients enrolled in 2016, 22.7% (201/885) of MCB PNs were supplemented, compared with 94.9% (535/564) of MCB PNs among patients enrolled in 2017, reflecting the change in micronutrient infusion practice in 2017. The mean number of supplementations per MCB PN were 0.3 (SD = 0.6) in 2016 and 2.5 (SD = 1.1) in 2017. Supplementations to MCB PNs are summarized in Table 4. Fifteen percent (217/1449) of MCB PNs had >2 supplementations and 6.8% (98/1449) had >3. Thirty-two percent (527/1652) of supplementations were vitamins, 32.2% (532/1652) were trace elements, and

TABLE 1 Population characteristics

Characteristics ($N = 135$)	n (%)	Median (Q1–Q3)
Age, months		39.2 (7.0–118.8)
Female sex	57 (42.2)	
Weight, kg		14.0 (7.3–26.8)
BMI,[a] kg/m^2		16.3 (15.0–18.3)
BMI-for-age z score,[a] SD		−0.03 (−1.03 to 0.80)
BMI-for-age z score ≤2 SD	16 (11.9)	
−2 SD < BMI-for-age z score <2 SD	104 (77.0)	
BMI-for-age z score >2 SD	11 (8.1)	

Abbreviation: BMI, body mass index.

[a]In four patients, BMI was not calculated because of the absence of a height measurement.

TABLE 2 Hospitalization and complications in the population

Characteristics ($N = 135$)	n (%)	Median (Q1–Q3)
PELOD2 score		12 (10–20)
PIM2 score		4.8 (2.1–13.3)
Mechanical ventilation	114 (84.4)	
Ventilation duration, days		4 (2–13.5)
Length of stay, days		11 (5–24)
Acquired infection	69 (51.1)	
Death	11 (8.1)	

Abbreviations: PELOD2, Pediatric Logistic Organ Dysfunction 2; PIM2, Pediatric Index of Mortality 2.

TABLE 3 Detail of commercial multichamber bag parenteral nutrition prescribed

Commercial PN prescribed ($N = 1449$)	*n*	%
NUMETA G16%E[a]	861	59.4
NUMETA G19%E[a]	336	23.2
OLIMEL-N9E[a]	88	6.1
SMOFKABIVEN[b]	59	4.1
AMINOMIX 800E[b]	47	3.2
SMOFKABIVEN E[b]	22	1.5
PEDIAVEN AP-HP NOUVEAU-NE 2[b]	16	1.1
AMINOMIX 500E[b]	9	0.6
PEDIAVEN AP-HP ENFANT G15%[b]	6	0.4
PERIOLIMEL N4E[a]	5	0.3

[a]From the Baxter Healthcare Corporation.
[b]From Fresenius Kabi.

TABLE 4 Characteristics of supplementations in multichamber bag parenteral nutrition

Number of supplementations per bag	Total ($N = 1449$) *n* (%)	2016 ($N = 885$), *n* (%)	2017 ($N = 564$), *n* (%)
0	713 (49.2)	684 (77.3)	29 (5.1)
1	163 (11.2)	159 (18.0)	4 (0.7)
2	356 (24.6)	32 (3.6)	324 (57.4)
3	119 (8.2)	9 (1.0)	110 (19.5)
4	72 (5.0)	1 (0.1)	71 (12.6)
5	24 (1.7)	0 (0)	24 (4.3)
6	2 (0.1)	0 (0)	2 (0.4)
>1	573 (39.5)	42 (4.7)	531 (94.1)
>2	217 (15.0)	10 (1.1)	207 (36.7)
>3	98 (6.8)	1 (0.1)	97 (17.2)
Nature of supplementations in bag	**Total ($N = 1449$), *n* (%)**	**2016 ($N = 885$), *n* (%)**	**2017 ($N = 564$), *n* (%)**
Vitamins	526 (38.8)	1 (0.1)	525 (93.1)
Trace elements	532 (36.7)	8 (0.9)	524 (92.9)
Electrolytes	412 (28.4)	200 (22.6)	212 (37.6)
Distribution of the nature of supplementations	**Total ($N = 1652$), *n* (%)**	**2016 ($N = 254$), *n* (%)**	**2017 ($N = 1398$), *n* (%)**
Vitamins	527 (31.9)	1 (0.4)	526 (37.7)
Trace elements	532 (32.2)	8 (3.1)	524 (37.5)
Electrolytes	593 (35.9)	245 (96.5)	348 (24.9)

35.8% (593/1652) were electrolytes. Water and macronutrients were never added. In line with the change in practice in 2017, almost every MCB PN was supplemented with vitamins and trace elements (93.1%). Vitamins were administered using Cernevit (Baxter Healthcare Corporation), and trace elements were administered using commercial trace elements preparations (Oligo-element pédiatrique OEP; Aguettant). The range of volume added in MCB PN was 1.3–30 ml for Cernevit and 0.6–120 ml for Oligo-element pédiatrique OEP.

Sixty-eight percent (990/1449) of MCB PNs were administered as the sole source of nutrition and 32% (459/1449) were administered as supplemental PN alongside incomplete enteral nutrition. The majority of supplementations (227/254 [89%] in 2016 and 851/1398 [61%] in 2017) were provided to children receiving solely PN, and 35% (27/254 [11%] in 2016 and 547/1398 [39%] in 2017) to children receiving supplemental PN. Among these supplementations, 9.4% (156/1652) were electrolytes and were carried out in patients receiving supplemental PN.

Compliance of electrolyte supplementations with the manufacturer's recommendations

Electrolyte supplementations to MCB PNs are summarized in Table 5. Among electrolyte supplementations, 9.6% (57/593) exceeded the manufacturer's recommendations. Eighty-four percent (48/57) of these noncompliant orders were related to phosphate and sodium citrate supplementation. Sixty-six percent (62/94) of phosphate additions were in line with manufacturer recommendations. This noncompliant electrolyte supplementation affected 3.7% (54/1449) of MCB PNs.

DISCUSSION/CONCLUSION

This study set out to explore the use of MCB PNs and their supplementation in a large PICU. All supplementations were made by nurses in the unit. Micronutrients represented 64.2% of these supplementations and were necessary to deliver the recommended daily requirements[8,9] and to optimize the in-use stability of MCB PN. Unit MCB PN supplementation with vitamins and trace elements is common practice,[14–16] but electrolyte supplementation has not been studied in such depth. Additionally, to our knowledge, this study is the first to compare electrolyte supplementations with the manufacturer's stability recommendations. It shows that 9.6% of electrolyte supplementations exceed

TABLE 5 Detail of electrolytes supplementations and noncompliance with manufacturer's recommendations

Electrolytes[a]	Number of supplementations, *n* (%)	Range of concentration added in MCB PN, min–max, mmol/l	Number of nonconforming supplementations, *n* (% per electrolytes)
Sodium	182 (30.7)	2.5–194.3	3 (1.6)
Potassium	193 (32.5)	2.5–165	0 (0)
Calcium	27 (4.6)	2.2–30	1 (3.7)
Magnesium	81 (13.7)	0.6–12	5 (6.2)
Phosphate	94 (15.8)[b]	3–99	32 (34)
Sodium citrate	16 (2.7)	8.4–11.2	16 (100)[c]
Total	593 (100)	—	57 (9.6)

Abbreviations: MCB, multichamber bag; PN, parenteral nutrition.

[a]Electrolyte intakes were adjusted by using 20% sodium chloride solution, 10% potassium chloride solution, 10% calcium gluconate solution, 10% magnesium sulfate solution, disodium glucose 1 phosphate (Phocytan; Aguettant), neutral potassium phosphate (K_2HPO_4) 174.2 mg/ml, and 10% sodium citrate solution.

[b]There were 92 supplementations with disodium glucose 1 phosphate (Phocytan; Aguettant) and two supplementations with neutral potassium phosphate (K_2HPO_4) 174.2 mg/ml.

[c]Sodium citrate adds were considered as noncompliant because of the absence of data.

the manufacturer's recommendations in practical use. Some studies[14,15] state that supplementation should be prescribed and made following the manufacturer's recommendations, but none of these studies explore if supplementations were actually in accordance with the manufacturer's recommendations.

The majority of MCB PNs in this study (72%) did not require electrolyte supplementation, suggesting that the electrolyte composition of MCB PN is mostly adequate for critically ill children. The literature suggests highly variable approaches to electrolyte supplementation in critically ill children receiving PN. Some studies showed more supplementations during the infusion of MCB PN because they included supplementations in bag or by a separate infusion (Y-line). Colomb et al[14] identified that 53% of MCB PN infusion days include supplementations of electrolytes (sodium and potassium). Similarly, Rigo et al[15] noted that electrolytes were added on 45.3% of MCB PN infusion days primarily using a Y-line. Unlike these studies, our local PICU guidelines recommend enteral electrolyte supplementation or in-bag PN supplementation (Y-site infusions are not routine practice).

In our PICU, MCB PN fulfilled the nutrition needs of most patients and did not require supplementations other than micronutrients. The MCB PNs used in our unit have been designed according to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines to meet children's requirements.[6,7] These systems are flexible with optional ILE components and nutrition compositions that allow tailoring to specific pediatric age groups.[4,14,15] Therefore, we support the position of current European guidelines[4,5] that MCB PN should be the first-line PN solutions for most children. Furthermore, the safety and tolerance profile is well documented in pediatric and preterm populations.[14–18] We also believe that, when supplementation is supported by adequate stability according to manufacturers' recommendations and protocol information, MCB PNs are superior to individualized PN in terms of ease of administration, appropriate use, and risk of error.

MCB PN offers the economic advantage of a relatively long shelf life that is not possible with individualized formulations. Licensed pharmaceutical formulations are subject to physicochemical and microbiological quality assessments that are not applied to individualized PN formulations.[15] However, in our study we have identified that some patients require additional electrolyte and micronutrient supplementation. In the manufacturers' recommendations, there is information available to support the prescribing and management of these supplementations, but there is still a lack of information for some electrolytes—notably phosphate.

Supplementation of MCB PN in the unit before infusion can expose the patient to various risks, such as dose calculation errors, handling errors, physicochemical incompatibility, and microbiological contamination.[5,10] Although this study was not designed to measure the risks of MCB PN in this pediatric population, it described its practical use, allowing us to discuss risks about MCB PN described in the literature. Indeed, in our study the move to MCB PN resulted in the need for more supplementation. To ensure adequate nutrition for

patients, micronutrients have to be added prior to administration. Additionally, supplementations of electrolytes are sometimes required in pediatric critical care. The need for supplementation in MCB PN and PN handling in the unit can represent a burden of care for the nurses. Adequate monitoring of electrolytes is required when prescribing PN, as recommended in the 2018 European guidelines.[19] Prescribers must assess the relevance of each supplementation and limit the number of supplementations in MCB PN to avoid the above described risks. There is also a risk of unintentional omission of micronutrients that must be prescribed separately. Thus, the use of MCB PN needs to be supported with clear and concise prescribing and administration protocols.

Furthermore, enteral feeding is always preferred to PN because it promotes gut integrity and may reduce the risk of infection.[1] In our study, we identify that a third of parenteral supplementations could have been given enterally rather than parenterally in a subgroup of children receiving enteral nutrition. Based on these results we produced a table of oral electrolyte supplementations and included this in local guidelines to support the enteral management of electrolyte abnormalities in patients (Table 6).

Several studies[10,16,18,20] have shown that MCB PN use may reduce the risk for infection in children compared with other types of PN. However, none of these studies addressed the risk of sepsis as an outcome measure. Few adult studies conducted have evaluated the impact of MCB PN on PN-associated bloodstream infections. Some studies[21,22] highlighted that MCB PN was associated with a lower incidence of bloodstream infections compared with individually compounded PN at the hospital pharmacy or by an industrial compounding unit. Unlike our study, these studies have not

TABLE 6 Local guidelines for enteral/oral electrolyte supplementations

Electrolyte	Pharmaceutical products: galenic form, dosage	Quantity of electrolyte, mmol	Dosing frequency/additional directions
Sodium (Na)	Sodium chloride capsules 500 mg[a]	8.5 mmol of Na	3–6 times daily
	Sodium chloride powder 1000 mg[a]	17 mmol of Na	3–6 times daily
Potassium (K)	Potassium gluconate H2P syrup 25 mg/ml[b]	0.64 mmol/ml of K	3–6 times daily
	Diffu-K capsule 600 mg[c]	8 mmol of K	3–6 times daily
			Capsule can be opened
			Do not crush granules inside capsule
	Potassium liberty pharma syrup 3%[b]	0.78 mmol/ml of K	3–6 times daily
Phosphate (P)	Phosphoneuros oral solution in drop[d]	5.9 mmol/ml of P	Do not give with calcium
		0.25 mmol/drop of P	3–6 times daily
	Phocytan intraveinous solution[e]	0.66 mmol/ml of P	Do not give with calcium
			Only when Phosphoneuros is not tolerated
			3–6 times daily
Magnesium (Mg)	Mag2 oral solution 122 mg/10 ml[a]	0.5 mmol/ml of Mg	2–4 times daily
			Contains ethanol (<10 mg/ml)
			Do not give with calcium
Calcium (Ca)	Calcidose powder 500 mg[f]	12.5 mmol of Ca	Do not give with phosphate and magnesium
	Calcidia granules 1.54 g[g]	38.5 mmol of Ca	Do not give with phosphate and magnesium
Bicarbonate	Sodium bicarbonate capsule 500 mg[a]	6 mmol of bicarbonate	3–6 times daily

[a]From Cooper.
[b]From H2 PHARMAFrance.
[c]From UCB PHARMA.
[d]From Bouchara recordati.
[e]From Aguettant.
[f]From Mayoly Spindler.
[g]From Bayer Healthcare.

explored supplementations of MCB PN in the unit. Only Turpin et al[23] showed that adding nutrients to MCB PN in the unit increased the risk of bloodstream infections almost twofold (hazard ratio = 1.85; 95% confidence interval = 1.17–2.94) when compared with MCB PN without supplementations. Pontes-Arruda et al[21] demonstrated a third more infections in those patients receiving traditionally compounded PN compared with MCB PN (13.2/1000 catheter days vs 10.3/1000 catheter days). Fifty-one percent of patients in our study developed an infection during MCB PN therapy. However, our study has not set out to elucidate the prevalence of this event, therefore it is impossible to attribute those infections directly to the supplementation of PN. But, in the context of these two studies, our study may suggest that there may be an increased risk of infection when supplements to MCB PN are made in uncontrolled unit environments. Further studies are required to better assess the risk of infection related to MCB PN handled in the unit, to implement bundles to control this risk, and to improve clinical outcome. In an attempt to mitigate this risk, recent French guidelines[5,12] recommend that supplementations should be made in controlled manufacturing environments in accordance with good manufacturing practice like the United States Pharmacopeia (USP general chapter 797).[13] However, in practice, there is a lack of capacity in French health services to comply with these recommendations.

After reconstitution, MCB PNs may be supplemented but these additions can be a challenge because of the complexity of admixture.[10,24] Supplementations must be prescribed and made following the recommendations provided by the manufacturer to ensure the physicochemical stability and safety of the MCB PN. No previous study has described supplementation compliance with the SPC or package insert and the manufacturer's recommendations. We have found that around 10% of electrolyte supplementations were outside the manufacturer's recommendations. Phosphate supplementation (3–99 mmol/L) was a common nonconforming moiety. The risk of physicochemical incompatibilities between phosphate, calcium, and magnesium are well documented.[10] The type of salts used in electrolyte supplementation is important to note. Chloride salts tend to a higher risk of interaction than sulfate salts.[25] Likewise, the use of organic calcium and phosphate salts for supplementation significantly reduces the precipitation risk.[26] In this study, electrolyte supplementations were carried out with salts reducing the incompatibility risk. We also note a mixture of salts for the same electrolyte between MCB PN composition and supplementation (eg, magnesium chloride and magnesium sulfate or calcium chloride and calcium gluconate). No study has explored the compatibility of these salt mixtures at this time. In this study, the stability was not established when the supplementation exceeded manufacturers' recommendations, resulting in a risk of physicochemical incompatibility because of its retrospective nature. MCB PNs were infused without particle filters because recommendations for the use of filters are not well defined.[19,27] To manage the physicochemical risk, automated prescribing systems should ideally integrate safety limits and warnings. Moreover, pharmacists should analyze and control PN prescriptions to critically evaluate the safety of PN solutions.[25,28]

This study has some limitations. As a retrospective, single-center study it is difficult to generalize into the wider pediatric critical care context. Furthermore, no cardiac patients were admitted to this PICU, who are the most likely to present with abnormal nutrition and electrolyte requirements; therefore, these results should be interpreted in this population with caution. In the early phases of this study, data on micronutrient and electrolyte supplementations made by a separate infusion were not collected; therefore, we have not been able to analyze the adequacy of the nutrition composition of these solutions. This is the first study comparing supplementations with the SPC and manufacturer's recommendations. More studies are needed to confirm the physicochemical safety of supplementations in MCB PN in clinical practices. Additionally, we have identified gaps in our knowledge about electrolytes that are supplemented in these bags, where physicochemical stability data are urgently needed. To ensure the efficient practice and safety of MCB PN management, local protocols should be implemented involving pharmacist control and counseling together with the proper training of hospital staff.

AUTHOR CONTRIBUTIONS

Elise Jandot, Frédéric V. Valla, Thierry Quessada, Morane Savelli, and Guillaume Pinte designed the study and participated in the acquisition, analysis, and interpretation of the data. Elise Jandot drafted the manuscript. Frédéric V. Valla, Thierry Quessada, and Adam Sutherland participated in coordination and helped to draft the manuscript. All authors have read and approved the final version of the manuscript to be published.

CONFLICT OF INTEREST

Frédéric V. Valla declares consulting fees received from Baxter (current) and Nutricia (past). Thierry Quessada declares consulting fees received from Baxter and Fresenius Kabi. The other authors have no conflict of interest to declare.

ORCID

Elise Jandot http://orcid.org/0000-0001-6752-2311

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