Commercially Premixed 3-Chamber Bags for Pediatric Parenteral Nutrition Are Available for Hospitalized Children¹⁻³

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Abstract

Hospitalized children are vulnerable to malnutrition during serious illness or recovery from injury and are at subsequent risk of increased morbidity and growth retardation. In cases in which enteral nutrition is not possible, parenteral nutrition (PN) can be used to ensure that patients at nutritional risk receive appropriate amounts of macro- and micronutrients. Nutritional needs cannot be met by 1 standard PN formulation in pediatric patients (term to 18 y) because of the wide range of needs according to age, weight, degree of maturity, and disease state. Preparation of individualized PN is associated with several limitations, including prescribing errors, stability issues, and risk of infection. These risks may be avoided by the availability of a range of pediatric PN formulations provided as commercial premixed 3-chamber bags (3-CBs). These 3-CBs were developed in conjunction with experienced neonatologists and pediatricians in accordance with international guidelines. A prospective study has previously shown the practical handling and ease of use of 2 formulations of these 3-CBs, 1 designed for term infants and toddlers up to 2 y of age and 1 for children and adolescents aged 2–18 y. The majority of pharmacists and nurses described the 3-CB as easy to use and favored it over individual bottles, bags compounded on the ward, ready-to-use compounded bags, and premixes prepared by the pharmacy and tailored to patient needs. These formulations offer a means of improving the quality of care in hospital pediatric units, particularly in the absence of a nutrition support team. J. Nutr. 143: 2071S–2076S, 2013.

Malnutrition in Hospitalized Infants and Children and the Need for Nutritional Support

Despite advances in many areas of pediatric medicine, studies from Europe and the United States still demonstrate a malnutrition prevalence of 6–32% among hospitalized pediatric patients, with little change in rates over the past 2 decades (1–3).

¹ Designed for term infants and toddlers up to 2 y of age and 1 for children and adolescents aged 2–18 y. The majority of pharmacists and nurses described the 3-CB as easy to use and favored it over individual bottles, bags compounded on the ward, ready-to-use compounded bags, and premixes prepared by the pharmacy and tailored to patient needs. These formulations offer a means of improving the quality of care in hospital pediatric units, particularly in the absence of a nutrition support team. J. Nutr. 143: 2071S–2076S, 2013.

Nutritional status may deteriorate and malnutrition may develop in hospitalized patients, with potentially serious consequences, including increased risk of adverse clinical events and longer hospital stays, which lead to additional health care costs (4–6). Malnutrition in children can have a significant impact on growth, as well as increasing susceptibility to infection (6). Therefore, assessment of nutritional risk in addition to nutritional status at time of admission is important. A study investigating the use of a scoring system to evaluate the risk of nutritional depletion in hospitalized pediatric patients showed that nutritional risk is related to both the underlying disease (which may increase the protein-calorie demand) and other factors (e.g., pain) that impair oral feeding and digestive tolerance (6). Short-term goals for nutrition support in sick children include obtaining linear or catch-up growth and body composition similar to age-matched children as well as maximizing long-term growth and neurodevelopment (7).

Critically ill children in pediatric intensive care units (PICUs) are at particularly high risk of developing malnutrition, which is

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considered a “second disease” and has been associated with increased morbidity and mortality (8–10). A study in infants undergoing cardiac surgery suggested that a low energy intake had an adverse effect on clinical outcomes, including increased duration of artificial ventilation, time to chest closure, and length of stay in the PICU and hospital (11). Nutritional support in critically ill children should aim to prevent catabolism as well as avoid overfeeding (3). Although optimizing nutritional condition in critically ill children may positively affect clinical outcomes (10), nutritional intake in this population is often inadequate and fails to meet target levels of protein and energy (3,10,12). However, the optimal form and timing of nutritional support for children in the PICU are still a matter of debate, with more research urgently needed (13), and there are no clear evidence-based guidelines on nutrition for this patient population.

**Indications for Parenteral Nutrition**

Parenteral nutrition (PN) is indicated for pediatric patients who cannot be fully fed by the oral or enteral route and are therefore at risk of malnutrition, in accordance with international guidelines for pediatric patients provided by the European Society for Clinical Nutrition and Metabolism and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (14).

Common indications for pediatric PN include all causes of intestinal failure (e.g., small bowel syndrome), severe malnutrition or failure to thrive associated with an inability to tolerate oral or nasogastric feeds, as well as other clinical scenarios in which the child is expected to receive nothing enterally for > 5 to 7 days (e.g., some critically ill patients) (7). Although PN can be life-saving, its use is associated with complications, including infection, other catheter-related complications, metabolic disorders, essential fatty acid deficiency, metabolic bone disease, and PN-associated cholestasis (7).

**Use of Individualized PN in Pediatric Patients**

As in adults, PN in the pediatric population may be provided as individualized or standardized formulations. The need for individualized PN is theoretically greater in pediatric patients (term to 18 y) than in preterm infants and adult patients because of the wide range of weights, degree of maturity and related changes, as well as variation in the specific conditions warranting PN; a single standard formulation would therefore be inadequate for all children (15).

Optimal individualized PN requires prescription by an experienced physician (16,17), compounding by trained pharmacy technicians following strict pharmaceutical rules (18), and delivery in the ward according to the expert guidelines. The ESPGHAN guidelines recommend the presence of a multidisciplinary nutritional support team (NST), including a senior pediatrician knowledgeable in nutrition, a dietician/nutritionist, a nurse, and, if possible, a pharmacist to improve the nutritional management of children in pediatric units (19). Individualized PN can be prepared either by automated or manual compounding in the hospital pharmacy (20). These resources are available in academic medical centers that specialize in children with rare digestive diseases such as short bowel syndrome, which is responsible for chronic intestinal failure (21). These patients receive long-term PN, often started at the hospital and then administered at home and are generally provided with a PN formulation prescribed according to individual needs by an expert physician and compounded in a specialized pharmacy unit (22,23). However, the majority of hospitals lack NSTs and pharmacies equipped for appropriate PN compounding. Therefore, nonexpert or junior physicians in Europe often prescribe PN admixtures that are manually prepared by the nurses in the ward without any pharmaceutical controls (e.g., glucose concentration, osmolarity, and calcium and phosphate ratio and concentrations). This can lead to quantitative errors due to poor estimation of the patient’s needs (lack or excess) and to qualitative errors, such as inadequate ratios between glucose and lipids, energy and nitrogen, and calcium and phosphate (16). Such errors may impair the patient’s nutritional and metabolic status. Other problems related to nonexpert prescription and compounding in the ward include the following: stability issues with the admixture (e.g., effect of storage temperature); risk of incompatibility with additions such as minerals, which may present clinical safety issues (e.g., presence of calcium phosphate precipitate) (24,25); microbial contamination and bloodstream infections (26,27); and mixing errors (28,29). Several recent retrospective studies showed that the rate of bloodstream infections was significantly lower in critically ill patients given standardized PN in the form of premixed multichamber bags than those given compounded PN (26,27,30). For these reasons, the American Society for Parenteral and Enteral Nutrition recommends using standardized processes for PN management, which may include the use of standardized PN formulations suitable for selected patient populations, prescribed by clinicians with expertise in nutrition support therapy (31).

Preparation of PN also represents a major care burden to staff, with high costs. A cost analysis of neonatal and pediatric nutrition in Europe demonstrated that PN costs differed between countries, with a large proportion of total costs related to staff time; wages accounted for 20–43% of the cost of compounding PN in infants and children across 4 countries (32). A U.S.-based study in adults showed that multichamber bag PN was associated with significantly lower costs than compounded PN with regard to both PN acquisition and potential avoidance of bloodstream infections, resulting in substantial savings (~$770 per patient eligible for standardized premixed PN) (33). The use of standardized PN formulations therefore has advantages in efficiency, economy, and clinical appropriateness compared with individualized PN formulations in selected patient populations (34).

**Commercially Premixed Standardized PN**

Adult standardized formulations are not nutritionally adequate for children. Until recently, only a few standardized PN formulations were available for children and, to our knowledge, none as 3-chamber bags (3-CBs). The need for a range of pediatric standard formulations has been addressed by commercially premixed 3-CBs, which are available in 2 different formulations (Baxter Healthcare Numeta SmPc 2011): 1 designed for term infants and toddlers up to 2 y of age (G16%E) and another designed for children and adolescents from 2 to 18 y of age (G19%E). One formulation designed for preterm infants weighing ≤1500 g (G13%E) is currently unavailable (Table 1). These PN formulations were developed in conjunction with expert neonatologists and pediatricians in accordance with international (European Society for Clinical Nutrition and Metabolism and ESPGHAN) guidelines for pediatric patients (14). Each 3-CB, regardless of formulation, includes compartments for lipids, amino acids with electrolytes, and glucose, with optional activation of the lipid chamber. If lipid administration is undesirable,
TABLE 1 Composition of 3-CB formulations for infants and children1

<table>
<thead>
<tr>
<th>Composition per 100 mL</th>
<th>3-CB G16%E (for infants aged ≤2 y)</th>
<th>3-CB G19%E (for patients aged 2–18 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macronutrients, g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrogen</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Amino acids</td>
<td>2.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Glucose</td>
<td>15.5</td>
<td>19.2</td>
</tr>
<tr>
<td>Lipids</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Energy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, kcal</td>
<td>103</td>
<td>114</td>
</tr>
<tr>
<td>Nonprotein, kcal</td>
<td>93</td>
<td>105</td>
</tr>
<tr>
<td>Nonprotein, kcal/g nitrogen</td>
<td>238</td>
<td>302</td>
</tr>
<tr>
<td>Electrolytes and minerals, mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>2.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Potassium</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Acetate</td>
<td>2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Malate</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Chloride</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Other characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approximate pH</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Osmolarity, mOsml/L</td>
<td>1225</td>
<td>1455</td>
</tr>
</tbody>
</table>

1 3-CB, 3-chamber bag (Baxter Healthcare Numeta SmPc 2011).

The design of the bag allows the possibility to activate only the peel seal between the amino acids/electrolytes and glucose chambers, leaving the peel seal between the amino acids and lipid chambers intact.

To date, there are limited published data demonstrating clinical experience with commercially prepared PN solutions for pediatric patients (35). Two published studies have demonstrated experience with a commercially premixed 3-CB–1 in preterm infants (25) and 1 in infants and children (36). A prospective, open-label, multicenter, noncomparative phase III clinicaltrial in preterm infants concluded that the formulation of the commercially premixed 3-CB developed for preterm infants was easy-to-use, well tolerated, and provided nutritional intake and weight gain within the recent PN recommendations for preterm infants (25).

Another prospective, open-label, multicenter, noncomparative phase III clinical trial assessed 2 formulations of the commercially premixed 3-CBs developed for infants and toddlers up to 2 y of age (Numeta G16%E) and children and adolescents from 2 to 18 y of age (Numeta G19%E) (36). The primary objective of the study was to assess practical handling and ease of use for pharmacists and nurses by using a questionnaire and a visual analog scale. Among infants and toddlers who received Numeta G16%E (mean ± SD age: 1.3 ± 2.3 mo; median: 0.2 mo), the main indications for PN were primary digestive disease (50%) and respiratory disease (18%), whereas in children receiving Numeta G19%E (mean ± SD age: 9.6 ± 4.3 y; median: 9.1 y), the most frequent PN indications were primary digestive diseases (33%), oncologic or hematologic diseases (28%), and digestive surgery (28%) (36). The majority (65–98%) of pharmacists and nurses described the commercially premixed 3-CB as easy to use on the basis of questionnaire responses to 5 positive descriptors relating to the ease-of-use of each formulation (overpouch easy to open; bag easy to remove from the overpouch; easy activation of the 2-in-1 configuration, without the lipid chamber; easy activation of the 3-in-1 configuration, including lipids; and quick homogeneity obtained). The use of 3-CBs was perceived as relieving the staff burden associated with preparing PN, especially in the wards in which PN was routinely administered as multiple individual bottles. Unit staff favored the premixed 3-CBs over their usual practices (individual bottles, ward-compounded bags, ready-to-use compounded bags made up at the hospital pharmacy or supplied by an external provider, and premixes prepared by the pharmacy and tailored to patient needs), as assessed by the visual analog scale, in which scores were consistently ≥6.0 (0 represented the worst performance and 10 the best performance of the 3-CB, compared with standard practice; Fig. 1) (36). The commercially premixed 3-CBs offered flexibility, because the formulations could be easily adjusted to meet the specific needs of the patient, appropriate for his or her age and according to ESPGHAN guideline recommendations (14). This included supplementation with vitamins and trace elements, which were added in the majority (>67%) of cases and the option to infuse with or without lipids (formulations were infused as 2-chamber bags, without lipids, for 20% of bags given to infants and 15% of bags given to children/adolescents) (36). Peak nutritional intakes for infants and toddlers and children/adolescents using the appropriate formulation are shown in Table 2. Among infants and children/adolescents, PN represented ~83% and 88% of the overall nutritional intake, respectively, with the premixed 3-CB contributing 91% and 68%, respectively, of the parenteral energy intake.

The use of the commercially premixed 3-CBs was well tolerated. Among 40 treatment-emergent adverse events reported during the phase III study (33), 4 (10%) were considered potentially related to the 3-CBs, including 2 cases of hypertriglyceridemia (1 mild and 1 moderate) and 2 mild cases of hyperglycemia, all in the infant group. For standardized PN formulations, metabolic complications (e.g., hyperglycemia, hypertriglyceridemia, or electrolyte imbalances) may be considered to be the consequence of nonexpert prescription rather than a complication of the formulation itself. Commercially compounded standardized formulations designed for infants and children are well balanced in terms of lipid-to-nonprotein energy ratio, glucose-to-nonprotein energy ratio, nonprotein energy-to-nitrogen ratio, and calcium-to-phosphate ratio. However, even the most balanced formulation may lead to a metabolic complication if it is inadequately prescribed. For example, a given amount of a formulation may meet the glucose needs of a child if delivered on a 24-h schedule; however, the same formulation delivered on a 12-h schedule may induce hyperglycemia because the rate of glucose delivery exceeds the oxidative capacities of the patient. Moreover, because glucose metabolism changes dramatically over childhood, a given rate of glucose delivery may be well tolerated by an infant <1 y of age but poorly tolerated by an older child. Glucose and lipid tolerance also change according to the course of the disease and treatment, e.g., infection, inflammation, and concomitant corticosteroid use.

**Expert Opinion on Clinical Experience with Commercially Premixed 3-CBs**

Clinical experience suggests that the use of PN as nutritional support in infants (term to 2 y) and children or adolescents...
(2–18 y) has increased in pediatric units over the past decade for various clinical indications, including surgery, hematology, oncology, and intensive care. The data from the recent studies cited previously demonstrate that these commercially premixed 3-CBs meet an unmet need for a range of nutritionally balanced PN formulations developed specifically for use in pediatric patients with a wide spectrum of nutritional needs according to age, weight, degree of maturity, and clinical condition. For example, in patients enrolled in the phase III study (36), the main PN requirements were short-to-medium term PN and/or nonexclusive

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**FIGURE 1** VAS results for industrially premixed 3-CBs for term infants and toddlers up to 2 years (A) and industrially premixed 3-CBs for children aged 2–18 y (B) compared with usual methods of administering parenteral nutrition (36). Values are means ± SDs. RTU, ready-to-use; VAS, visual analog scale; 3-CB, 3-chamber bag.

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**TABLE 2** Peak nutritional intake achieved by pediatric patients given parenteral nutrition using commercially premixed 3-CBs

<table>
<thead>
<tr>
<th></th>
<th>Infants/toddlers aged 0–2 y (n = 23)</th>
<th>Children/adolescents aged 2–18 y (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>ESPGHAN guidelines</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>3.3 ± 1.2</td>
<td>—</td>
</tr>
<tr>
<td>Peak nutritional intake</td>
<td>95 ± 25</td>
<td>80–160</td>
</tr>
<tr>
<td>Volume, mL/(kg·d)</td>
<td>2.56 ± 0.68</td>
<td>2–3</td>
</tr>
<tr>
<td>Amino acids, g/(kg·d)</td>
<td>15.3 ± 4.1</td>
<td>12–18</td>
</tr>
<tr>
<td>Glucose, g/(kg·d)</td>
<td>2.7 ± 1.2</td>
<td>1.5–3</td>
</tr>
<tr>
<td>Lipids, g/(kg·d)</td>
<td>87 ± 23</td>
<td>80–100</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs or ranges. ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology, and Nutrition; 3-CB, 3-chamber bag (Numeta G16%E for infants/toddlers and Numeta G19%E for children/adolescents).

2 In the infants/toddlers and children/adolescent groups 5 and 4 patients, respectively, withdrew prematurely from the study, most commonly due to improved health status.

3 ESPGHAN guidelines on pediatric parenteral nutrition (14).
PN in patients with standard needs (e.g., transitory respiratory distress syndrome in neonates, acute digestive diseases and digestive surgery, or as transitory nutritional support in oncology and hematology). Such standardized formulations would be particularly useful in all hospitals and units that do not benefit from an NST to prescribe and compound individually tailored admixtures. Many patients with long-term PN dependence and/or who require total PN because of severe, irreversible intestinal failure (e.g., some patients on home PN) receive individualized formulations.

Even in our university pediatric hospital, with a pediatric NST and a pharmacy to control and compound individualized PN formulations, expert pediatricians in the field of nutrition acknowledge that the use of commercially premixed 1- or 2-binary chamber bags, available for greater than 2 g, has improved the quality of care because it avoids the prescription of individualized formulation by inexperienced physicians. Moreover, the availability of commercially premixed bags may improve nutritional management of children in emergency situations, particularly during the evenings and weekends, when individualized PN formulations may not be prepared in optimal conditions. However, prescription of 1- or 2-chamber bags is often associated with the failure to administer lipids or inadequate prescription of lipids (wrong dose or choice of lipid emulsion). The availability of premixed 3-CBs may improve nutritional care because it will help to avoid such risks in patients who need total PN, including appropriate lipid intake.

In summary, PN remains a high-risk technique that requires expert evaluation of the patient’s nutritional needs, choice of the best formulation, and determination of the appropriate amount to infuse. Pediatric 3-CBs help to decrease the risks associated with nonexpert prescription of PN formulations and/or compounding on the ward.

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Literature Cited


