

Three-in-One Parenteral Nutrition in Neonates and Pediatric Patients: Risks and Benefits

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Nutrition in Clinical Practice
Volume 30 Number 3
June 2015 337–343
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for Parenteral and Enteral Nutrition
DOI: 10.1177/0884533615580596
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Abstract

Parenteral nutrition (PN) is a life-sustaining therapy designed to deliver essential nutrients to patients unable to meet nutrition needs via the enteral route. PN may be delivered via a 2-in-1 system (one solution containing amino acids, dextrose, electrolytes, vitamins, minerals, and fluids and one solution containing intravenous fat emulsions [IVFEs]) or via a 3-in-1 system (all nutrients mixed in one container). Although the use of 3-in-1 PN solutions is not necessarily therapeutically advantageous, certain benefits may exist such as the potential to reduce the risk of contamination due to decreased manipulations; ease of administration, particularly in the home care setting; possible cost savings; and reduced IVFE wastage. However, the incorporation of IVFE in 3-in-1 solutions also presents unique risks for the neonatal and pediatric population such as decreased stability, increased lipid globule size, decreased sterility and the potential for increased microbial growth/infectious complications, the need to use a larger filter size, precipitation and compatibility risks, and an increased chance of catheter occlusion. This review outlines the unique issues and challenges to be considered when formulating neonatal and pediatric 3-in-1 PN admixtures. While 3-in-1 PN solutions may be advantageous for certain pediatric populations, specifically those dependent on home PN, the risks do not outweigh the benefits in neonatal patients, and use should be avoided in this population. (*Nutr Clin Pract.* 2015;30:337-343)

Keywords

neonates; newborn infant; home parenteral nutrition; parenteral nutrition solutions; pediatrics; parenteral nutrition

Parenteral nutrition (PN) is a life-sustaining therapy designed to provide the necessary nutrients to patients unable to adequately meet nutrition needs through the enteral route. PN solutions are composed of macronutrients (dextrose, amino acids, intravenous fat emulsions [IVFEs]), micronutrients (electrolytes, vitamins, trace elements), and fluid, individually formulated and compounded to meet specific patient requirements. For hospitalized neonatal (ie, a full-term newborn 0–28 days postnatal age or a premature neonate who is >28 days postnatal age but ≤42–46 weeks postmenstrual age¹) and pediatric (ie, infants and children up to 18 years of age) patients, PN is typically delivered as a 2-in-1 system: one solution that contains dextrose, amino acids, fluid, and electrolytes, with IVFE delivered through a second independent system. However, the administration of all nutrients in one container (ie, 3-in-1, all-in-one, total nutrient admixture [TNA]) is also possible and was first described in 1974.^{2–4} Since the approval of the use of IVFE in TNA in 1983 and early reports demonstrating stability of these admixtures, this delivery technique has been used in a variety of populations and clinical settings, particularly in adults and in the home care environment.^{2–6} While use of 3-in-1 systems is not necessarily therapeutically advantageous compared with 2-in-1 systems, certain benefits may exist.

In August 2014, the Food and Drug Administration (FDA) approved a 3-chamber bag for the delivery of PN.^{7,8} The unique delivery device provides a premixed solution that is stable until activated for patient use. Once activated, the

solution is administered as a 3-in-1 admixture. This particular delivery device is not approved for use in neonatal and pediatric patients due to the premixed nutrient composition of the product, which is unsuitable for these populations, particularly those younger than 2 years. However, the possibility still exists to individually compound PN as a 3-in-1 vs a 2-in-1 formulation to meet specific neonatal and pediatric patient nutrition needs. It is important for pediatric practitioners to consider and understand the potential risks and perceived benefits of 3-in-1 PN formulations in the neonatal/pediatric population. This article presents factors to consider when compounding neonatal and/or pediatric 3-in-1 PN solutions,

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Financial disclosure: None declared.

This article originally appeared online on April 9, 2015.

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Table 1. Three-in-One PN Stability.^{5,9-12}

Factor Affecting Stability	Effect	Condition Leading to Destabilization
pH	Fat emulsions are most stable at pH 6.0–8.9; as pH decreases, emulsifying agent is neutralized, causing disintegration of emulsion	pH <5.3
Macronutrient concentrations (final concentration in PN solution)	Dextrose solutions have pH between 3.5 and 6.5, which may reduce surface potential and stability of emulsion Amino acid solutions provide buffering and stabilize pH alterations that occur in presence of dextrose solutions	Dextrose final concentration <10% Amino acid final concentration <2.5%; note A.S.P.E.N. recommends final concentration is ≥4% to maintain stability IVFE final concentration <2%
Micronutrient/electrolyte concentrations (final concentration in PN solution)	Surface potential of IVFE is negatively charged; therefore, addition of cations (ie, sodium, potassium, magnesium, calcium) has potential to destabilize the emulsion	>30 mEq divalent cations per liter (calcium and magnesium) >200 mEq monovalent cations per liter (sodium and potassium) Presence of trivalent cations (avoid addition of ferric ions)
Additive characteristics	Additives may disrupt the negative charge or phospholipid layer on lipid globules	pH <5 or electrical charge on molecule
Storage	Peroxidation of IVFE that leads to oxidative deterioration of polyunsaturated fatty acids	Freezing > room temperature
Aging	Peroxidation of IVFE that leads to oxidative deterioration of polyunsaturated fatty acids	>24 hours at room temperature >7 days refrigerated (4°C)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; IVFE, intravenous fat emulsion; PN, parenteral nutrition.

including the unique stability, sterility, and compatibility issues, as well as specific challenges associated with formulating neonatal and pediatric nutrition admixtures.

Stability

PN solutions are highly complex and subject to solubility and stability issues, due to the use of multiple ingredients that must concomitantly exist within a limited volume. This can be especially problematic in the neonatal and pediatric populations.^{5,9,10} Three-in-one PN solution stability is affected by several factors, including pH, final concentration of macronutrients and micronutrients, order of admixture, additive characteristics, and storage and aging of the formulation (Table 1).^{5,9-11} Due to the number of additives and variety of combinations of concentrations of ingredients within the admixture, predicting the absolute stability of the 3-in-1 PN solutions can be a challenge.¹⁰ However, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends that the admixture maintains final concentrations of amino acids ≥4%, dextrose ≥10%, and IVFE ≥2%.¹⁰ The inherently unstable nature of IVFEs subjects 3-in-1 PN solutions to additional solubility and stability issues.¹² IVFE is an oil-in-water emulsion in which triglyceride particles are dispersed in water. Optimal stability is reached when these particles are homogeneously dispersed throughout the aqueous phase. This is achieved through the addition of an egg yolk phospholipid emulsifier, which protects against the collision

of particles and coalescence, which occurs via 2 molecular mechanisms: adsorption of a molecular film around the lipid globule and net negative surface charges, which creates electrostatic repulsion.^{10,11,13} Disruption of this film or negative charge will create instability of the solution, resulting in emulsion creaming, aggregation, coalescence, and/or cracking. This poses considerable safety risks and the potential for clinical complications, rendering the PN unsafe for use. Addition of IVFE to amino acid- and dextrose-containing solutions may increase the potential to destabilize the IVFE component by disrupting the film or negative charge.¹²

The most common methods for assessing IVFE stability within 3-in-1 solutions are determination of particle size and size distribution, surface potential, and state of aggregation.⁵ When the IVFE is destabilized, the size of the triglyceride particle (ie, lipid globule) is altered. The lipid globule size is a critical component when assessing the stability and safety of administering 3-in-1 PN solutions. In stable IVFE, lipid globules range between 0.25 and 0.5 μm in diameter; this allows the particles to safely travel through human capillaries, due to size consistency with endogenous chylomicrons.^{9,10,13} Destabilization can cause the lipid globules to coalesce, thus causing the particle size to exceed 5 μm. This puts patients at risk for complications such as pulmonary capillary occlusion and fat emboli, making administration of solutions clinically problematic and unsafe.⁵ To prevent destabilization and for optimal stability of 3-in-1 solutions, a final concentration of IVFE of ≥2% is recommended.¹⁰

In 2004, the United States Pharmacopeia (USP) established specifications for lipid globule size limits and appropriate instrumentation to define size and emulsion stability in chapter 729.^{10,14} Two criteria were established by USP 729 for determination of lipid stability: (1) mean droplet size (MDS), which must not exceed 500 nm, and (2) the proportion of lipid globules >5 μm in diameter at the “tail” of the droplet globule-size distribution (GSD) curve, which cannot exceed 0.05%.¹⁰ The latter is also referred to as the percentage (volume: weight) of fat >5 μm (PFAT5). Of importance, for commercially available IVFE, the PFAT5 is consistently <0.05%. Therefore, if PFAT5 levels are >0.05%, this is representative of admixture instability. Driscoll et al^{13,15,16} report on the physicochemical stability of 3-in-1 PN and note that when >0.4% of lipid particles are >5 μm , the solution is unstable and emulsions will crack 85% of the time, and the solution is unfit for administration.¹² When <0.4% of particles are >5 μm , stability is expected 88% of the time.^{10,15,16} Although not extensively reported in the literature, neonatal and pediatric 3-in-1 PN solutions may be more prone to destabilization and lipid globule coalescence due to the presence of limited volume, alterations in pH, high electrolyte concentrations, and alterations in macronutrients. For example, while not approved for use in pediatric patients, a 2009 study indicated that 3-chamber bags produced larger globule sizes that did not meet USP 729 limits.¹⁷ Thus, further evaluation should occur prior to consideration of these delivery systems for neonatal and younger patients, as this group may be at higher risk for problems and clinical ramifications if unstable solutions are infused due to underlying clinical conditions such as chronic lung disease. Similarly, if individually compounding 3-in-1 PN solutions for neonatal and pediatric patients, it is critical to ensure that mechanisms are in place to evaluate lipid globule size and solution instability prior to administration such as automated prescribing systems with built-in safety limits and warnings (eg, soft stops, hard stops), visual inspection, and close clinical monitoring. This automation should be coupled with oversight and clinical evaluation performed by nutrition support pharmacists who can critically evaluate the safety of PN solutions.¹⁸

In addition to the general considerations discussed above, neonatal and pediatric practitioners must also consider several other factors that are specific to younger populations. First, the caloric requirements for the very young are significantly higher than those for older children and adults (ie, 100 vs 25–30 kcal/kg/d). As such, the final macronutrient concentrations may be altered and could affect the solubility and stability of 3-in-1 solutions.¹⁹ Also, neonatal and pediatric amino acid solutions contain higher amounts of branched-chain amino acids (ie, valine, leucine, and isoleucine) as well as taurine compared with adult formulations. Cysteine is also often added to neonatal PN solutions to improve calcium-phosphorus solubility.¹⁹ Calcium and phosphorus requirements for the very young are significantly higher than in older populations, to allow for appropriate bone mineralization and to prevent

the development of metabolic bone disease as well as the development of hypophosphatemia and hypocalcemia.^{19,20} Neonates and infants require a calcium to phosphorus ratio of at least 1.7:1 (mg/mg).^{10,20} To reach this optimal ratio, high concentrations of calcium are added to PN formulations, and an acidic pH of the PN solution is required for maximum solubility.²¹ As a consequence of these differences in amino acid formulations, a more acidic (4.8–5.4) PN solution results, which has an effect on the stability of 3-in-1 solutions (Table 1). The low pH affects IVFE solubility, which can increase lipid globule size, thus increasing risks to pediatric patients. Furthermore, the chance for calcium-phosphorus precipitates is an added concern, especially due to low PN volumes used in this population. These precipitates can lead to serious clinical consequences such as catheter occlusion, interstitial pneumonitis, and possible fatal reactions.^{20,21} Calcium-phosphate precipitation can occur secondary to high concentrations of electrolytes in low volumes or due to the added presence of IVFE, which increases the pH of the solution.²¹ If precipitation occurs in a solution that contains IVFE, the precipitation may be hidden by the milky, opaque solution.¹² An added consideration is the use of inorganic phosphates in PN in the United States, since organic phosphates have not been approved for use. However, organic phosphates may potentially improve the ability to provide more optimal amounts of calcium and phosphorus to young patients and may not carry the same compatibility concerns in 3-in-1 solutions. In a study that evaluated the physicochemical compatibility of 3-in-1 PN solutions for neonatal use, Ribeiro et al²⁰ found that high calcium and organic phosphorus concentrations did not affect stability. However, color changes and alterations in lipid film formation were observed, suggesting that additional studies are warranted to confirm the safety of 3-in-1 solutions for neonatal use.

Stability: IVFE and PN-Associated Liver Disease

A population that deserves special mention is the PN-dependent pediatric patient with intestinal failure, as additional considerations must be evaluated when compounding PN. This population is at risk for the development of PN-associated cholestasis (PNAC) and PN-associated liver disease (PNALD). While there are many therapeutic strategies to manage this risk (eg, cyclic PN, trace element dose adjustments, initiation of early enteral nutrition [EN], pharmacologic management, and prevention of sepsis), the use of reduced doses of soybean-based IVFE (ie, ≤ 1 g/kg/d) and/or the use of alternative IVFE products (eg, fish oil-based emulsions) are strategies that have been shown to be beneficial for the prevention and the treatment of PNALD.^{22–33}

While most studies supporting the use of reduced soybean-based IVFE are retrospective or small observational studies, many centers across the United States are using reduced doses

to successfully manage PNALD. When reduced doses of IVFE are used, maintaining a final concentration of $\geq 2\%$ for optimal stability in 3-in-1 solutions is a challenge. For example, a 5-kg patient receiving 100 mL/kg/d of volume and 1 g/kg/d of IVFE would have a final lipid concentration of 1%, which would likely result in instability and cracking of the 3-in-1 emulsion. Thus, this presents unique compounding challenges for patients receiving less than standard doses of IVFE. To circumvent the issue, many centers will divide the weekly total dose of IVFE and provide IVFE 3 days per week, rather than daily (ie, 2.5 g/kg 3 days per week vs 1 g/kg/d). This facilitates the ability to provide 3-in-1 PN solutions for home PN patients for convenience of administration. However, this technique may increase the risk of complications and/or medication administration errors due to the necessity for differing administration techniques (ie, 1.2- μm filter) on IVFE vs non-IVFE (0.2- μm filter) days. It is recommended that proper education and counseling on appropriate administrations techniques is provided to families and caregivers to minimize these risks.^{18,34}

Preliminary work has investigated the stability of medium-chain triglyceride/long-chain triglyceride (MCT/LCT) IVFEs in 3-in-1 neonatal PN solution.^{19,35} Some centers are using alternative emulsions such as fish oil-based fat emulsions, olive oil-based fat emulsions, or mixed-fat emulsions for the management of PNALD under compassionate use protocols, since these products are not FDA approved for pediatric use. Data are needed prior to widespread use of these alternative emulsions in 3-in-1 PN solutions, since they have not been vigorously studied to date.

Sterility/Infectious Risks

The use of 3-in-1 PN solutions offers a potential benefit of decreasing the number of manipulations required in preparation and administration of PN, which may subsequently decrease the risk for bacterial/fungal contamination during these processes.⁵ This is beneficial in both the inpatient and outpatient settings as it may secondarily lead to a decreased rate of PN-associated infections, although this is not well documented in the literature. From an administration standpoint, the use of 3-in-1 delivery systems simplifies PN infusion and decreases manipulations, especially in the home care setting, as infusion requires a single infusion device/pump rather than multiple infusion sets and the need for Y-site coinfusion. For older infants and pediatric patients dependent on home PN, 3-in-1 systems are preferred.

However, for neonatal patients, particularly those in the inpatient setting receiving multiple concomitant intravenous medications, the use of 2-in-1 systems with separate infusion of IVFE (typically Y-site coinfusion) allows for more control and is preferable. This population is more likely to have limited venous access and, in turn, increased rates of medication-PN incompatibilities, which may necessitate intermittent stopping or holding of IVFE, without discontinuing the amino

acid/dextrose solution, to accommodate medication administration.¹¹ When this is done, it is paramount that aseptic technique, guidelines for repackaging IVFE, and maximum infusion rates (ie, 0.125 g/kg/h) and hang times are strictly followed to minimize the risk for contamination, microbial growth within the IVFE, and adverse effects and to maintain sterility.^{10-12,36} It must also be noted that many institutions that care for neonatal patients repackage IVFE from the original container into patient-specific syringes, for ease of administration of small doses running at low rates (mL/h) on syringe pumps.¹⁰ Although not universally recommended due to the potential to promote the growth of microorganisms, this practice is common. As such, strict aseptic technique and a draw-down IVFE units methodology should be incorporated, and appropriate precautions should be taken to minimize the risk of contamination and infectious complications. Furthermore, if IVFE is repackaged into syringes, the beyond-use date should be 12 hours.¹⁰

The influence of 3-in-1 admixtures on sterility and infection is not straightforward, and additional factors must be considered. PN, in general, increases the risk for development of infection due to the presence of underlying clinical conditions and the nature of PN solutions, which may promote microbial growth. Studies have shown that patients receiving PN have a higher rate of bloodstream infection as compared with those not receiving PN.³⁷⁻⁴¹ Microbes such as *Escherichia coli* and *Pseudomonas aeruginosa* may grow poorly in 2-in-1 solutions, but *Candida albicans* has been shown to survive in these admixtures, which may ultimately lead to serious infections.⁵ The administration of IVFE is an additional risk factor for the development of infection.^{5,42,43} IVFE solutions are slightly alkaline, providing a favorable growth environment for bacteria.^{42,44,45} For this reason, the Centers for Disease Control and Prevention (CDC) recommends a maximum of a 24-hour infusion time and the necessity to replace tubing within 24 hours of initiating the infusion in the 2011 guideline; of note, in 2002, recommendations included completion of IVFE solutions within 12 hours when infused separately through peripheral venous catheters and 24 hours when infused via central venous catheters, including umbilical catheters.^{36,46} Although theoretically more favorable for microorganism growth, in a study designed to evaluate whether 3-in-1 PN solutions become contaminated at a higher rate than 2-in-1 solutions when infused over 24 hours, Vasilakis and Apelgren⁴⁷ found that the rate of positive cultures was identical (ie, 17%) between the 2 delivery systems, thus refuting this supposition. However, in a recent study that evaluated 1995 patients receiving PN, 12% experienced a complication, the most common of which was bloodstream infection.⁴⁸ Of those experiencing infection, the use of a single bottle (ie, 3-in-1) was associated with a significant increase in risk. The studies that support the growth of microorganisms in IVFE solutions alone must be interpreted with caution when applying the data to 3-in-1 solutions due to differences in final pH and osmolarity, but it is possible that the

infectious risk for pediatric patients receiving 3-in-1 PN solutions may be higher than those receiving 2-in-1, although additional confirmatory data are needed. Furthermore, currently available IVFEs in the United States contain polyunsaturated long-chain triglycerides, which have a negative effect on the reticuloendothelial system (RES).⁵ The RES is involved in the phagocytosis of microorganisms and debris; when polyunsaturated long-chain triglycerides deposit in the liver due to rapid, intermittent infusion, the ability of the Kupffer cells to sequester bacteria is reduced. When IVFEs are infused over 24 hours, however, RES function may be preserved.

One of the protective mechanisms against infection is the use of a 0.22- μm bacteria-retentive filter used in line when infusing 2-in-1 solutions.^{12,34,49} In-line filters are recommended to prevent the passage of microbes, insoluble particulates, and enlarged lipid globules into the vasculature.¹¹ As a direct consequence of the increased lipid globule size above 0.5 μm in 3-in-1, the use of 0.22- μm filters is precluded; rather, a 1.2- μm filter is used instead, which protects the integrity of the 3-in-1 solutions.^{5,49} While the 1.2- μm filter protects against infusion of larger particles, precipitates, air, and *Candida* species, it does not protect against infusion of smaller bacteria such as *Staphylococcus epidermidis* and *E coli* or bacterial endotoxin. This may put vulnerable neonatal and pediatric patients at risk. It is recommended that the in-line filter be changed every 24 hours for 3-in-1 PN admixtures. According to the recent 2014 clinical guidelines published by A.S.P.E.N., the main disadvantage of 3-in-1 solutions is the fact that a larger pore size filter is required.¹⁰

Compatibility, Cost, and Shortages

Another unique concern pertaining to neonatal patients is the risk for drug incompatibilities with 3-in-1 solutions, with heparin as an important example.⁵⁰ Heparin causes solution destabilization through binding of divalent cations. However, heparin is added at a dose of 0.5–1 unit/mL to neonatal PN solutions, at many centers, primarily to maintain catheter patency, with potential secondary benefits in decreasing infection and hypertriglyceridemia.^{51–55} While the literature suggests that low doses of heparin are unlikely to destabilize PN solutions, additional studies are warranted to validate this finding.^{50,56} Compatibility of other medications with 3-in-1 PN solutions in the neonatal population due to limited intravenous access in this population may also be problematic. It is not uncommon for neonates to have a single lumen available for administration of PN as well as all supportive medications. As mentioned above, administration of 2-in-1 PN may offer greater flexibility of medication administration in this population, due to incompatibility of several commonly used medications (eg, antibiotics) in this population with IVFE and 3-in-1 solutions.⁵⁷

Compounding PN solutions, particularly for neonates and pediatric patients, is time-consuming and costly.^{58–60} Three-in-one systems may reduce the time and costs associated with

preparation and administration due to several factors, including reduction in nursing time, the need for fewer infusion devices, and decreased waste of IVFE products.^{5,59} The modest cost savings may be offset, however, by increased time spent by the pharmacist in preparation and sterility, stability, and compatibility screening.⁵⁹ Catheter occlusion may also be more likely in pediatric patients receiving 3-in-1 solutions. In a study performed by Erdman et al,⁶¹ central line occlusion was more common among pediatric patients receiving 3-in-1 PN compared with the 2-in-1 solution. In addition to the clinical costs and ramifications associated with catheter occlusion, this may represent an additional healthcare cost due to the potential necessity to use additional medications (ie, fibrinolytics) as well as removal of the central venous access device and the need for surgical replacement, which may negate any 3-in-1 PN cost savings.

Over the past decade, nutrition support-related products have been subject to many ongoing shortages. As such, the use of alternative products has become necessary and common in the United States. Although a review of all shortages and recommendations is outside the scope of this article, when considering the compounding of 3-in-1 PN solutions, it is prudent to consider which products are used to compound PN and whether stability testing has been performed in 3-in-1 solutions with the alternative product concentrations and products. One product shortage that deserves special attention is the IVFE shortage, as it pertains directly to 3-in-1 admixtures. The IVFE products have been intermittently available over the past 5 years due to ongoing product shortages, and efforts have been made to conserve supplies where available and appropriate.⁶² IVFE products are typically available commercially in 100-mL, 250-mL, and 500-mL bags.⁶³ Neonatal and pediatric patients require lower doses, necessitating IVFE repackaging or wastage from administration of partial quantities from commercially available containers. When compounding a 3-in-1 PN solution, however, the exact dose of IVFE is added to the admixture, thereby reducing the amount of waste that may occur when using 2-in-1 systems. In addition to the cost benefit of reducing waste, this may have a secondary gain of conserving supplies when products are scarce.

Summary and Conclusions

If 3-in-1 PN solutions are to be compounded for neonatal or pediatric administration, the use of advanced, automating compounded systems that can interface with software that rigorously checks against manufacturer and institutional safety and stability limits is recommended.^{12,34,49,64} Potential benefits such as reduced labor costs, convenience of administration (particularly for home use), and potentially reduced risk of infection make 3-in-1 PN use an attractive PN delivery technique for select patients, primarily those receiving PN in the home setting. However, several risks associated with 3-in-1 PN delivery exist in neonatal and pediatric

Table 2. Benefits and Risks of 3-in-1 PN in Neonatal and Pediatric Patients.

Solution Type	Potential Benefits	Potential Risks
3-in-1 PN admixture	<ul style="list-style-type: none"> • Decreased manipulation/potential to decrease risk of contamination • Ease of administration • Potential cost savings • Reduced IVFE wastage • Mixed substrate/continuous IVFE infusion 	<ul style="list-style-type: none"> • Decreased stability (particularly in neonatal PN due to amino acid solutions, presence of cysteine, and increased macronutrient requirements) • Increased lipid globule size • Increased microbial growth • Need for larger filter size (1.2 micron) • Increased risk for calcium-phosphorus precipitation (especially in neonatal PN) • Increased risk for drug incompatibilities • Increased risk for catheter occlusion

IVFE, intravenous fat emulsion; PN, parenteral nutrition.

patients—namely, instability of complex solutions, increased lipid globule size, potential for increased microbial growth, the need to use a 1.2- μ m filter, and increased risks of precipitates, drug incompatibilities, and catheter occlusion. The potential benefits may not outweigh the significant risks posed to neonatal and pediatric patients (Table 2). Conclusive data supporting 3-in-1 over 2-in-1 administration are not yet available; thus, use in this population remains controversial. Due to the lack of strong data in the neonatal population and the multiple unique risks to the very young, 3-in-1 PN solutions should be avoided in this population. For select older infants and pediatric and adolescent patients, particularly those receiving home PN, 3-in-1 may be considered, but the risks and benefits should be weighed, and decisions should be made on a case-by-case basis.

Acknowledgments

The authors thank Justina Damiani, PharmD, BCPS, for her editorial assistance with this manuscript.

Statement of Authorship

Allison Blackmer and M. Luisa Partipilo equally contributed to the conception/design of the research; contributed to the acquisition, analysis, and interpretation of the data; drafted and critically revised the manuscript; and agree to be fully accountable for ensuring the integrity and accuracy of the work. Both authors read and approved the final manuscript.

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