

## Special Report

### Safe Practices for Parenteral Nutrition

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**NOTICE:** These A.S.P.E.N. Practice Guidelines for Safe Practices for Parenteral Nutrition are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of providing parenteral nutrition feeding formulations. The underlying judgment regarding the propriety for any specific practice guideline or procedure shall be made by the attending health professional in light of all the circumstances presented by the individual patient and the needs and resources particular to the locality. These guidelines are not a substitute for the exercise of such judgment by the health professional, but rather are a tool to be used by the health professional in the exercise of such judgment. These guidelines are voluntary and should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed toward obtaining the same result.

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#### GLOSSARY OF TERMS

**Automated Compounding Device:** A device used in the preparation of parenteral nutrition. It automates the transfer of dextrose, amino acids, fat emulsion, and sterile water, as well as small volume injectables, such as electrolytes and minerals to the final PN container. The device is driven by computer software.

**Beyond-use Date:** The date established by health-care professionals from the published literature or manufacturer-specific recommendations beyond which the pharmacy-prepared product should not be used.

**Compatibility:** The ability to combine 2 or more chemical products such that the physical integrity of the products is not altered. Incompatibility refers to concentration-dependent precipitation or acid-base reactions that result in physical alteration of the products when combined together.

**Computerized Prescriber Order Entry (CPOE):** A prescription ordering system where the prescriber enters orders directly into a computer.

**DEHP:** Di (2-ethylhexyl) phthalate, a plasticizer used in various intravenous administration sets or plastic infusion bags.

**Dosing Weight:** The weight used by the clinician in determining nutrient doses. Dependent on institutional or professional preference, the dosing weight may be the actual, ideal or adjusted body weight of the individual.

**Drug-nutrient Interaction:** An event that occurs when nutrient availability is altered by a medication, or when a drug effect is altered or an adverse reaction caused by the intake of nutrients.

**Dual-chamber Bags:** A bag designed to promote extended stability of a PN formulation by separating the IVFE from the rest of the formulation. It consists of 2 chambers separated by a seal or tubing that is clamped. At the time of administration, the seal or clamp is opened to allow the contents of both chambers to mix and create a TNA.

**Expiration Date:** The date established from scientific studies to meet FDA regulatory requirements for commercially manufactured products beyond which the product should not be used.

**Hang Time:** The period of time beginning with the flow of a fluid through an administration set and catheter or feeding tube and ending with the completion of the infusion.

**Institute of Safe Medication Practices (ISMP):** A nonprofit organization that works closely with healthcare practitioners and institutions, regulatory agencies, professional organizations and the pharmaceutical industry to provide education about adverse drug events and their prevention. The Institute provides an independent review of medication errors that

(MERP) operated by the United States Pharmacopeia (USP).

**Intravenous Fat Emulsion (IVFE):** An intravenous oil-in-water emulsion of oil(s), egg phosphatides and glycerin. The term should be used in preference to lipids.

**MEDMARX:** The internet-based medication error reporting program operated by the U.S. Pharmacopeia that complements quality improvement activities at the local and national level. MEDMARX is available through subscription service only.

**Osmolarity:** The number of osmotically active particles in a solution, expressed as milliosmoles per liter of solution. The osmolarity of a PN formulation needs to be considered, when determining whether that solution can be administered through a peripheral vein.

**Parenteral Nutrition:** Nutrients provided intravenously.

**Central:** Parenteral nutrition delivered into a high flow vein, usually the superior vena cava adjacent to the right atrium.

**Peripheral:** Parenteral nutrition delivered into a peripheral vein, usually of the hand or forearm.

**Percent Concentration (weight/volume):** A standardized unit of concentration determined by the amount of drug or nutrient within a given volume, whereby 1% (w/v) is equivalent to 1 g of drug or nutrient per 100 mL of volume.

**Stability:** The extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture.

**Total Nutrient Admixture (TNA):** A parenteral nutrition formulation containing IVFE as well as the other components of PN (carbohydrate, amino acids, vitamins, minerals, trace elements, water and other additives) in a single container.

**Medication Error Reporting Program (MERP):** U.S. Pharmacopeia's spontaneous reporting program for medication errors that is operated in cooperation with the Institute for Safe Medication Practices for use by any healthcare professional or interested party.

**Venous Access Devices (VAD):** Catheters placed directly into the venous system for infusion therapy and/or phlebotomy.

#### PREFACE

The members of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) are health care professionals representing the fields of medicine, nursing, pharmacy, and dietetics. A.S.P.E.N.'s mission is to serve as the preeminent, interdisciplinary nutrition society dedicated to patient-centered, clinical practice worldwide through advocacy, education, and research in specialized nutrition support.

Patients may be treated with parenteral nutrition (PN) in any of several care settings including hospitals, long-term care or rehabilitation facilities, or at home. Because patients transfer from one health care envi-

“Safe Practices for Parenteral Nutrition” are the standard of practice for the provision of PN in all health-care settings.

The original ‘Safe Practice’ document was specific to PN and the practice of pharmacy.<sup>1</sup> The objective of this revision is to deal with PN in a comprehensive manner realizing the interdisciplinary nature of this therapy. A new section is added that addresses the ‘ordering of parenteral nutrition’. The nutrient range section is expanded to provide dosage recommendations that go beyond normal requirements and include components not addressed in the initial guidelines (e.g., iron and the potential for developing an essential fatty acid deficiency). Further, the PN filtration section is renamed and expanded into: “Administration of parenteral nutrition”. This section includes hang time for intravenous fat emulsion (IVFE) and PN, formula review prior to administration as well as institutional use of PN brought from home or sent with the patient on transfer from another facility.

Unfortunately, practice for some of these latter areas have little, if any, published evidence to support good practice. As such, the Task Force conducted the 2003 Survey of PN Practices. This provided an overview of the variance and consistency of current practices. The survey was organized in the following sections: demographics, writing PN orders, computer order entry of PN orders and problems with PN orders. There were 667 responses, mostly from hospitals (85%), with dietitians (55%) and pharmacists (32%) being the predominant professionals responding to the questionnaire. In the home health care environment, responses were from pharmacists (76%) and dietitians (17%). The average daily census for organizations responding was 100 patients. Most organizations used a once daily nutrient infusion system (76%). The number of adult PN patients per day was from 0–20 for 85% of responders. However, 4.9% of responders reported more than 40 adult PN patients per day. For organizations that had neonate and pediatric patients, the number of PN patients per day was 0–5 for both.

Over half (54%) of responders had a performance improvement program that monitored the appropriate use of PN, accuracy of PN orders, metabolic complications and catheter and infectious complications. Physicians and nurses selected these categories more frequently than pharmacists and dietitians. Quality control of PN compounding and PN costs were not monitored as frequently (<50%).

It was noted that physicians were the professional group responsible for writing PN orders. However, there was also significant involvement by dietitians as well as pharmacists. It is noteworthy that nurse practitioners and physician assistants were also involved with writing PN orders. Oversight of writing the PN order was performed predominantly by the pharmacist with significant involvement by a nutrition support service, medical staff committee and nutrition and dietetics department. For PN components, the base formula was ordered in terms of percent final concentration (47%) or as the percent of stock solution (31%).

(mmol) of phosphorus or as both mmol of phosphorus and milliequivalents (mEq) of associated cation. Electrolytes as components of the amino acid formulation were not usually considered when writing PN orders (71%). Multiple electrolyte formulations were used in 62% of organizations, according to the summary of responses, but only 46% of the time according to the pharmacist response (in this case, the pharmacist response should be more accurate). In 62% of responders, the pharmacist adjusts the chloride and acetate content of the PN formulation. Trace elements are ordered as a standard volume (87%) with only some organizations adjusting the content based on the patient’s clinical condition (22%). Standard order forms are used by 87% of responders of which 96% are for adults and 40–42% are for pediatric and neonatal patients. Home infusion services are the outlier in this group where standard order forms are used in only 32% of organizations. Standard orders for laboratory tests and patient care orders are used in only 54% of cases. Data for the hang time or maximal infusion rate of IVFE were more difficult to interpret since a write-in answer was required. The maximum hang time for a total nutrient admixture (TNA) was 24 hours and intermittent, separate IVFE infusion of 12 hours. Responses to minimum hang time (related to maximal infusion rates) were not consistent.

Only 29% of organizations used a computerized prescriber order entry (CPOE) system for PN orders. Of these, 88% used it for adults and 54% and 58% used it for pediatric and neonatal patients. The majority of pharmacies (88%) used an automated compounding device. Order input to the automated compounding device was done by the pharmacist 84% of the time due to a lack of an interface with the CPOE system. Only 15% of organizations outsourced PN formulations. Of those that did, a pharmacist at the organization reviewed the order where the order originated (95%) prior to it being sent to the compounding pharmacy.

Problems with PN orders were queried in the following manner; number of PN orders written per day, percent of orders requiring clarification, reasons orders needed to be clarified, frequency of errors in PN therapy, categories of PN adverse events and severity of adverse events. Most (55%) organizations deal with 0–10 PN orders per day while 15% had more than 30 orders per day. These orders need to be clarified <25% of the time for 88% of responders and <10% of the time for 61% of responders. The most frequent reasons orders need to be clarified are macronutrient content, illegible orders, incompatibility, nutrient dose outside the normal range, infusion rate not prescribed and incorrect PN volume. Seldom, if ever, were orders clarified for a pharmacy compounding error. The highest ranked reason, very often (5% of responders) was illegible orders. The frequency of reported errors per month for PN was low (none in 26%, 1–5 in 60% and 6–10 in 10% of responders). These events were related to electrolytes (69%), dextrose (31%), insulin (31%), amino acids, vitamins and IVFE (15% and 26%). Of these errors, 55% of responders related them to errors in

in the 76–100% category. For adverse events that had occurred in the last 2 years, 44% of responders were not aware of any events, 64% of the events required no treatment or just an increase in monitoring. Only 10% responded that none of these events occurred. Of interest are the reports by a few responders of harm, temporary (13%, N = 61 responders) or permanent (2%, N = 7 responders), near-death (3%, N=16 responders) or death (2%, N =7 responders). Whether hospitals allowed PN formulations compounded by organizations other than their own was queried and results were mixed (43% - Yes, 58% - No).

Realizing that the original Safe Practice guidelines are not consistently implemented,<sup>2</sup> the Task Force used this information to identify practices pertinent to the revision of the Safe Practice guidelines. The survey results presented in this document are those findings pertinent to the development of the guideline. A more in-depth and complete analysis of the 2003 Survey of PN Practices will be conducted and reported by the Task Force within the next year. This snapshot of current practices and expert opinion or consensus provided by both external and internal reviews was compiled into the current Safe Practices.

Guidelines will be presented in a format similar to the A.S.P.E.N. *Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patient*.<sup>3</sup> “Safe Practices for Parenteral Nutrition” is organized into seven sections.

- Introduction
- Ordering parenteral nutrition
- Labeling parenteral nutrition formulations
- Nutrient requirements
- Sterile compounding of parenteral nutrition formulations
- Stability and compatibility of parenteral nutrition formulations
- Parenteral nutrition administration

Each section includes an introduction to the practice area addressed, with examples where clinical data (including patient harm) support the need for practice guidelines to ensure patient safety; specific practice guidelines based on consensus of the Task Force members; summary of areas requiring special consideration; and a list of supporting references.

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This document was internally reviewed by the A.S.P.E.N. Standards Committee as well as the Dietetic, Nursing, Medical, and Pharmacy Practice Sections and approved by the A.S.P.E.N. Board of Directors after external review by individuals and other associations of health care professionals. A.S.P.E.N. recognizes that the practice guidelines will have broad ramifications in changing clinical practice in many health care settings for pharmacists, physicians, nurses, dietitians, and technical support personnel. It is hoped that these guidelines will be accepted and used to prevent future patient harm, and will serve as a catalyst for future research.

#### REFERENCES

1. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition: Safe practices for parenteral nutrition formulations. *JPEN J Parenter Enteral Nutr.* 1998;22:49–66.
2. O’Neal BC, Schneider PJ, Pedersen CA, Mirtallo JM. Compliance with safe practices for preparing parenteral nutrition formulations. *Am J Health-Syst Pharm.* 2002;59:264–269.
3. A.S.P.E.N. Board of Directors and The Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26 (Suppl):1SA–138SA. (Errata:2002;26:144).

#### SECTION I: INTRODUCTION

Over the past four decades, parenteral nutrition (PN) has become an important primary (e.g., intestinal failure) and adjunctive therapy in a variety of disease states. Parenteral nutrition refers to all PN formulations; total nutrient admixtures (TNA) are PN formulations that include intravenous fat emulsions (IVFE); and 2 in 1 formulations are PN formulations that do not include IVFE. PN benefits patients having significant disruption in gastrointestinal (GI) function becoming a lifeline for those who have a permanent loss of the GI tract such as patients with GI fistulas or short bowel syndrome. New knowledge and technology have improved patient selection for PN therapy. Refinement of PN will continue to make it a useful

extremely complex admixtures containing 40 or more components including amino acids, dextrose, fat emulsions, water, electrolytes, trace elements, and vitamins. Each of these components is a regulated prescription drug product. Serious harm and death have occurred from improperly prepared and administered PN formulations. With a potential for significant benefit to many patients, its complexity warrants an effective process of ordering, preparation, administration and monitoring to assure a quality outcome from therapy. Early PN programs focused on minimizing the frequency, severity, and type of complications that could result from this therapy. The interdisciplinary approach was found to improve efficacy, reduce complications, and facilitate efficient, cost-effective PN therapy. Despite the highly successful use of PN for many years, the following adverse events demonstrate the types of PN errors that can result in serious harm and even death:

- Two deaths related to errors in PN compounding led to a Safety Alert being issued by the U.S. Food and Drug Administration (FDA).<sup>1</sup> Autopsy of the patients involved found diffuse microvascular pulmonary emboli. There were also at least two other cases of respiratory distress occurring in patients at the same institution. These patients had received total nutrient admixtures (TNA) thought to contain a precipitate of calcium phosphate that resulted from improper admixture practices in the pharmacy.
- Hospital personnel misinterpreted the dextrose content on the label of a PN formulation used in home care, which resulted in a pediatric patient's death.<sup>2</sup> The home care label read: "300 mL of 50% dextrose." The hospital pharmacy interpreted this as a final concentration of dextrose 50% (up to twice the concentration typically used in PN therapy). The patient died after 2 days of receiving infusion of the incorrect formula.
- Two other fatal incidents have been reported involving pharmacy-compounding operations for pediatric dextrose solutions.<sup>3</sup> One infant was overdosed with dextrose when the PN was prepared with amino acids and two bags of 50% dextrose in place of one bag of 50% dextrose and one bag of sterile water. The other infant was underdosed with dextrose while receiving a 1.75% final concentration of dextrose solution rather than a 17.5% concentration.
- Another PN formulation was compounded with no dextrose, resulting in irreversible brain damage when administered to a neonate.<sup>4</sup>
- An incident involving the misinterpretation of a label resulted in iron overload and liver toxicity in a child receiving PN with iron dextran.<sup>5</sup> In this case, the PN label read, "iron dextran 1 mL," the intention being to use a 1-mg/mL concentration prediluted by the pharmacy. However, the solution containing the undiluted, 50-mg/mL concentration was used in compounding and resulted in a 50-fold error in the dose administered.
- Four children were infected, two of whom died as a

tubing that was used in the automated compounding of these PN admixtures.

- A 2-year old child receiving home PN died after an excessively high level of potassium was identified in the PN formulation. The most likely explanation provided for the death was human error in the manual preparation of the PN formulation.<sup>7</sup>
- Two premature infants developed extreme magnesium toxicity while receiving PN that was the result of an automated PN compounder malfunction.<sup>8</sup>

PN has the potential for serious adverse events involving many PN components as well as system breakdowns. Analysis of data reported to the United States Pharmacopeia Medication Error Reporting Program (MERP), presented in cooperation with the ISMP, and the MEDMARX medication error database suggests that PN events are low in frequency but have the capacity to cause patient harm. Errors were related to wrong drug preparation, improper dose, labeling and problems with automated compounding devices. The PN components most commonly associated with errors were electrolytes, concurrent drug therapy, insulin and dextrose.<sup>9</sup> It is unclear what proportion of actual PN-associated errors are actually reported to the USP.

The information provided in the 'Safe Practices for Parenteral Nutrition' document provides guidelines along with supporting evidence to foster quality PN therapy. The intent is for the principles provided in the document to become incorporated into healthcare organization practice for the purpose of minimizing the risk of PN. The complexity of this therapy cannot be understated. There is good evidence in support of practices that favor positive patient outcomes.

#### REFERENCES

1. Food and Drug Administration. Safety Alert: Hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm.* 1994;51:1427–1428.
2. Carey LC, Haffey M. Incident: Home TPN formula order misinterpreted after hospital admission. *Home Care Highlights.* 1995; (spring):7.
3. Cobel MR. Compounding pediatric dextrose solutions. Medication error alert. *ASHP Newsletter.* 1995;(Aug):3.
4. Gebbart F. Test hyperal solutions? Florida mom says yes. *Hosp Pharm Report.* 1992;(Feb):35.
5. Iron overdose due to miscommunication of TPN order. Error alert. *Pharmacy Today.* 1995;(Sep).
6. Two children die after receiving infected TPN solutions. *Pharm J.* 1994;(Aug):3. 2.
7. [www.hopkinsmedicine.org/Press\\_releases/2003/12\\_19\\_03.html](http://www.hopkinsmedicine.org/Press_releases/2003/12_19_03.html).
8. Ali A, Walentik C, Mantych GJ, Sadiq HF, Keenan WJ, Noguchi A. Iatrogenic acute hypermagnesemia after total parenteral nutrition infusion mimicking septic shock syndrome: two case reports. *Pediatrics.* 2003;112(1 Pt 1):e70–e72.
9. The U.S. Pharmacopeia Center for the Advancement of Patient Safety medication error reporting programs—MEDMARX<sup>SM</sup> and the Medication Errors Reporting Program.

## SECTION II: ORDERING PARENTERAL NUTRITION

### BACKGROUND

As reported in the introduction to this document, life-threatening errors continue to occur in the prepa-

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