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Safe Practices for Parenteral Nutrition

Task Force for the Revision of Safe Practices for Parenteral Nutrition: Jay Mirtallo, MS, RPh, BCNSP, Chair, Todd Canada, PharmD, BCNSP, Deborah Johnson, MS, RN, Vanessa Kumpf, PharmD, BCNSP, Craig Petersen, RD, CNSD, Gordon Sacks, PharmD, BCNSP, David Seres, MD, CNSP, and Peggi Guenter, PhD, RN, CNSN

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Special Report

Safe Practices for Parenteral Nutrition

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APPROVED BY A.S.P.E.N. BOARD OF DIRECTORS JULY 21, 2004

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 healthcare 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 have been voluntarily submitted by practitioners to a national Medication Errors Reporting Program (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 environment to another, it is the opinion of the A.S.P.E.N. Board of Directors that the practice guidelines in the

"Safe Practices for Parenteral Nutrition" are the standard of practice for the provision of PN in all healthcare settings.

The original 'Safe Practice' document was specific to PN and the practice of pharmacy.[1] 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%). There is no consistent method of ordering PN electrolytes. Phosphorus is usually ordered as millimoles (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 ordering PN in the category of 1–25%, 12% in the 26–50% category, 8% in the 51–75% category and 17%

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,[2] 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*.[3] "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.

The members of the Task Force for the Revision of Safe Practices for Parenteral Nutrition are as follows:

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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.

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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 therapy in the management of patients with dysfunctional GI tracts. However, PN formulations are

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).[1] 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.[2] 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.[3] 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.[4]
- An incident involving the misinterpretation of a label resulted in iron overload and liver toxicity in a child receiving PN with iron dextran.[5] 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 result of receiving contaminated PN admixtures.[6] *Enterobacter cloacae* was cultured from disposable 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.[7]
- Two premature infants developed extreme magnesium toxicity while receiving PN that was the result of an automated PN compounder malfunction.[8]

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.[9] 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.

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SECTION II: ORDERING PARENTERAL NUTRITION

BACKGROUND

As reported in the introduction to this document, life-threatening errors continue to occur in the preparation and delivery of PN admixtures to patients. Many of the errors that occur are related to the order-

ing process. Responses to the 2003 Survey of PN Practices confirm a lack of uniformity in the ordering process from institution to institution, and clinical errors were frequently related to the manner that orders were created and communicated, as well as incorrect units of measure, and errors of omission.

Research has demonstrated the benefit of standardized order writing processes in reducing prescription errors.[1–3] Standardized PN order forms:

- Incorporate more precise guidelines for PN prescribing, including standing orders for PN initiation and discontinuation[2,4–6].
- Provide physician education,[2–4,6–7] especially important for clinicians unfamiliar with PN therapy.
  - Reduce prescribing errors by a range of 9% to 82%,[1,2,4,6,7] primarily by reducing the incidence of incompatible concentrations of electrolytes, inappropriate concentrations of dextrose, amino acids and IVFE, and omissions of nutrients.
  - Improve efficiency and productivity of nutrition support, primarily in hospitalized patients.[1,3,6] The rate of total calorie and protein overfeeding was decreased by 18%, imparting a 55% reduction in the cost of processing and preparation of an initial PN order for a standardized solution.
- Allow comprehensive nursing and dietary care of the patient[2,6,8] by reducing nursing order interpretation problems and improving documentation of each bag administered.
  - Reduce pharmacy inventory and costs[1,3,6,7,9–11] by reducing PN wastage, standardizing PN solutions, and implementing pharmacy formulary control of various amino acids and IVFE products, resulting in annual savings from $10,000 to $76,803.

It should be noted that one study reported an increase in prescriber errors after a standardized PN form was introduced. Problems occurred with PN infusion rates, electrolyte composition, and amino acids concentration, when using a standardized PN order form.[2] Therefore, creating and maintaining a standardized PN order form that meets the needs of patients and minimizes errors still requires a continual quality assurance effort and patient safety commitment by each institution.

Common factors associated with the majority of PN prescribing errors include:[12]

- Inadequate knowledge regarding PN therapy
- Certain patient characteristics related to PN therapy (e.g., age, impaired renal function)
- Calculation of PN dosages
- Specialized PN dosage formulation characteristics and prescribing nomenclature

Parenteral nutrition has been reported to be second only to anti-infective agents as a class of medications associated with errors (22% of reports).[12] Education was cited as necessary for successful implementation in most published reports. Therefore, the PN order form shall be designed to serve as an educational tool for prescribers.[2–4,6,7]

Finally, to minimize errors in all prescription practices, accrediting bodies,[13] USP,[14] the National Coordinating Council for Medication Error Reporting and Prevention[15] and the Institute for Safe Medication Practices (ISMP)[16] have made recommendations for medical documentation. These recommendations specify avoiding potentially dangerous abbreviations, acronyms and symbols.

A set of minimum standards for creating a PN order are herein recommended, based on these principles and published clinical experiences and best practices, in order to reduce errors and improve patient safety. These standards are a result of a review of the literature. A review of PN order forms submitted by survey responders aided in identifying components of PN order forms that were universally acceptable to most institutions. The standards are divided into three sections, Mandatory for Inclusion, Strongly Recommended for Inclusion, and Worthy of Consideration for Inclusion (Table I).

TABLE I
Components of PN order forms

MANDATORY FOR THE PN ORDER FORM
Clarity of the form
• Clearly written and understandable to anyone who might utilize it
• Organized and easy to scan for completeness
• Complete enough to address anticipated institution specific concerns
• Ingredients listed in same order as PN label
• Decimals and percent concentrations avoided
• All components ordered in grams/milligrams/ milliequivalents/millimoles per day or per kg per day
Contact number for person writing the order
Contact number for assistance with PN ordering
Time by which orders need to be received for processing
Location of venous access device (central or peripheral)
Height, weight/dosing weight, diagnosis, PN indication
Hangtime guidelines
Institutional policy for infusion rates
Information regarding potential incompatibilities
STRONGLY RECOMMENDED FOR INCLUSION ON PN ORDER FORM
Educational tools (e.g., dosing guidelines)
Guidelines to assist in nutrient/volume calculations
Recommended PN lab tests (baseline, monitoring, and special circumstances)
Guidelines for stopping/interrupting PN
Contents of multivitamin and trace element preparations
Brand names of products (e.g., amino acids, IVFE)
Guidelines for use of insulin
Guidelines for recognizing additional calorie sources
WORTHY OF CONSIDERATION FOR INCLUSION ON PN ORDER FORM
Identification of who will review the order, in addition to pharmacy
Guidelines for nutrient restriction in various disease states
Guidelines for long-term PN (e.g., Selenium, Iron administration)
Guidelines for special amino acids (e.g., Trophamine + cysteine)

MANDATORY FOR INCLUSION

Overall Design: Clarity of the Ordering Form

Order forms shall be created in such a way as to be understandable to all healthcare professionals who interact with the form, including the ordering clinicians and staff interpreting the PN order (dietitian, nurse and pharmacist). The following are specific prin-

ciples recommended to promote order form clarity:

Organization. The form shall be organized in a simple manner. All nutrients in PN, as well as final volume, and infusion duration, shall be clearly identified on the form. Final volume shall be the sum of all components of the PN solution, including IVFE in a TNA. The process of entering specific components on the order should follow an obvious visual pathway, making it easy to scan for completeness.

Institutional policies. The form shall contain enough information to address anticipated institutional policies and procedures. Institution-specific concerns shall be incorporated into the order form as written instructions. For example, institutional policies may specify that certain clinical requirements be met, such as specific diagnoses or the completion of baseline laboratory tests, before PN is prepared by the pharmacy.

Continuity. The PN order form shall list all components in the same format (e.g. amount per day and in the neonatal or pediatric patient, both amount/day and amount/kg/day) and sequence as the PN label (described in Section III). In keeping with labeling guidelines, electrolytes shall be ordered as the quantity of associated salt to be added to the PN formulation. This will facilitate the verification of the PN contents against the PN order.

Writing the order. The use of a standardized PN order form will reduce the need for prescriber handwritten items, thus, potentially reducing misinterpretation.[6] However, adequate space for clear handwriting shall be provided where needed. The use of decimals and trailing zeroes shall be avoided whenever possible. Orders containing unclear handwriting, or other incorrect or confusing marks, shall not be compounded until the pharmacy has clarified these with the clinician generating the order.

Units of measure. The form shall be designed using standard units of measure (e.g. protein in grams, potassium in mEq, and phosphate in mmol) for dosing PN components. Review of sample PN order forms submitted to the Task Force found doses of macronutrients expressed in different units on the same order form (e.g., dextrose in calories, protein in grams and fat as volume of a specific concentration). The use of percent concentration in PN orders is not recommended, to avoid confusion.[17] Misinterpretation of orders using percent concentration has led to patient harm and death.[18]

TABLE II
*Determining the estimated osmolarity of PN formulations**

PN Component	mOsm	Example, 1 L volume	
		PN Content	mOsm/L
Dextrose	5 per gram	170 g	850
Amino Acids	10 per gram	60 g	600
Fat Emulsion, 20%	0.71 per gram (product dependent)	20 g	14
Electrolytes	1 per mEq	243 mEq	243
			Total = 1707

*Based on approximations of the osmolarity of the PN components and used as an estimate only.

Specific Components

The following are items considered to be mandatory for inclusion on the PN form. They include both data to be collected on the form, as well as information that must be communicated to the clinician ordering the PN. It is assumed that areas for ordering the necessary components of the PN (dextrose, protein, IVFE, electrolytes, vitamins, minerals, etc) will be incorporated into the form.

- For the purpose of clarifying unclear or inappropriate orders, the PN order form shall provide contact information for the person writing the PN order. There shall also be a space on the form for the contact information of institutional resources, such as individual consultants or a nutrition support service.
- The order form shall specify the time by which PN orders need to be submitted for pharmacy processing. The specified deadline should be chosen by the institution to assure adequate time for a comprehensive order review, safe compounding, and scheduled delivery of the PN formulation. There shall also be a standardized hang time specific to each institution. The preparation and hang time of each PN solution that is not refrigerated should not exceed 30 hours due to stability concerns.[19] Additionally, all components of the PN order form shall be completed in their entirety when reordering for an existing patient. Each institution shall dictate the frequency of PN reordering (e.g., daily).
- The PN order form shall contain the location of the venous access device, in order to assure that venous access is appropriate for the osmolarity (Table II) of the ordered PN formulation. A checkbox on the order form may be used to denote whether the catheter tip lies in a peripheral or central venous position, and whether position has been confirmed by x-ray for central venous catheters.
- The order form shall contain fields for patient height, dosing weight, and PN indication. Knowledge of patient dosing weight is vital in assessing nutrient needs and identifying nutrient dosing errors, especially in the pediatric population, where total nutrient dosing varies dramatically based upon weight.
- Institutional policy for maximum or minimum nutrient hang times (and corresponding infusion rates), maximum dextrose infusion rate or IVFE infusion rate, or maximum allowable hang time for separately infused IVFE, if 2-in-1 solutions are utilized, shall be indicated on the order form. Written infusion instructions for either 24-hour or cycled PN must comply with institutional policies.
- The PN order form shall contain a general statement warning of the potential for PN formulation incompatibilities. Calcium and phosphorus compatibility shall be specifically addressed, as it is common for prescribed concentrations of these nutrients to exceed PN solubility limits, which may result in patient harm or death from calcium phosphate precipitates instigating diffuse microvascular pulmonary emboli.[20]

STRONGLY RECOMMENDED FOR INCLUSION

These items, although not mandatory, are strongly recommended for inclusion on the PN order form (or back of the form):

- Basic PN education tools to guide prescribers in creating an appropriate initial order with maximum dosage recommendations for peripheral or central infusion and for various ages or weights for pediatrics.
- Example calculations to guide prescribers in determining patient-specific total calories, protein, fluid, and electrolyte requirements. This should also include the recommended ranges for these nutrients (e.g., dextrose and IVFE infusion rates).
- Guidelines for ordering appropriate baseline laboratory tests, including levels requiring daily (e.g., potassium, glucose) or less frequent monitoring (e.g., liver enzyme tests).
- Guidelines for stopping or tapering of PN, to avoid rebound hypoglycemia and to provide patient safety in the event of this complication.
- Specific contents of commercial multivitamin and trace element preparations available within the prescribing institution, with daily age-specific recommendations.
- Brand names of products, such as amino acids or IVFE, available at the prescribing institution, with specific characteristics of these products (e.g., pH, phosphate content).
- Specific guidelines for the use of insulin, including the type appropriate for inclusion in the PN solution (e.g., regular insulin). Insulin guidelines should be institution-specific to age and patient populations served.
- Guidelines for recognizing additional sources of calories (e.g., fat emulsion vehicle for propofol [Diprivan®] infusions, dextrose in IV solutions).

WORTHY OF CONSIDERATION FOR INCLUSION

Several additional items are felt to be helpful, but of less importance in the order writing process. Due to the number of items felt to be mandatory or strongly recommended, these items are presented as suggestions for inclusion where room and organization of the order form will allow.

- Persons involved in reviewing the order, other than the prescriber and the pharmacist, may be identified for ease of contact and continuity. This may be helpful when an institution utilizes a clinician or committee to oversee the quality or appropriateness of PN orders.
- Guidelines for nutrient restriction or supplementation in various disease states, such as restriction of copper in hepatic failure, may be included. These recommendations should follow published clinical guidelines.
- PN therapy in acute care institutions is on average 10–14 days in duration.[21] Guidelines for long-term PN administration may be beneficial when therapy is for extended periods of time in the acute care or alternative care setting. These may include, for example, recommendations for monitoring or supplementation that is specific to long-term PN patients. These guidelines should also address the use of cyclic versus continuous PN infusion. Persons without advanced knowledge in nutrition support may not be familiar with the utility, or more accurately the general lack of utility, of specialty amino acids. Therefore, guidelines for the use of these formulations may be helpful.

ADULT PN ORDER FORM TEMPLATE (FIG. 1)

A sample PN order form template has been created to facilitate a standardized ordering process among institutions and facilities preparing PN formulations. The Task Force does not endorse a specific PN dosage regimen or formulation. A few points about the sample PN order form template should be clarified:

- A field for allergies is included on the form so that potential adverse reactions to heparin, IVFE products, latex components of parenteral products, or bisulfites can be averted.
- The units of measure for the peripheral IV administration route are designated in mOsm/L, since the decision for central or peripheral PN administration should be dictated by the total osmolarity of the PN formulation, rather than solely on final dextrose or amino acids concentration.
- A field for laboratory tests and monitoring information is provided, so that fluid and electrolyte imbalances and signs/symptoms of CVC infections can be assessed. Specific monitoring parameters used to determine the efficacy or detect complications of PN therapy are not listed on the form. Laboratory values such as visceral proteins, CBC with differential, or PT/PTT, are not included on the form, since the necessity or frequency for obtaining these tests varies between institutions and facilities.
- The amount per day of macronutrients (i.e., dextrose, protein, fat) is not specified on the form. Many facilities have developed "standardized" formulations for use within their healthcare organizations to improve the efficiency and productivity during the preparation process. Standardized PN dosage formulations may be included on institution-specific order forms. Inclusion of a blank field is recommended so that a formulation can be customized for nutrient restriction or supplementation in various disease states.
- For illustration purposes only, both a 2-in-1 and a TNA formulation are listed on the form. Realizing most institutions utilize only one type of delivery system (e.g., 2-in-1 vs. TNA), it is not necessary to list both of these PN formulations on the order form.
- If a facility only uses TNA formulations, it is not necessary to include maximum hang times or infusion rates for separately infused IVFE.
- The "Additives Section" is specifically designed to separate the field for regular insulin from the other additives. Responses to the 2003 Survey of PN Practices indicated that doses for other additives (especially H_2 antagonists) were misinterpreted for insulin dosages when the field for regular insulin was placed in close proximity to other additive fields on

Figure 1

Physician Orders
PARENTERAL NUTRITION (PN) - ADULT

Primary Diagnosis: _____ **Ht:** _____cm **Dosing Wt:**_____kg

PN Indication:_____ **Allergies:** _____

Instructions: This form must be completed for a new order or continuation of PN and faxed to the Pharmacy by **[Insert Time]** to receive same day preparation. PN administration begins at **[Insert Time]**. Contact the Nutrition Support Service at (XXX) XXX-XXXX for additional information.

Administration Route: ☐ CVC or PICC *Note: Proper tip placement of the CVC or PICC must be confirmed prior to PN infusion*
☐ Peripheral IV (PIV) (*Final PN Osmolarity ≤ _____ mOsm/L*)

Monitoring: Daily weights, Strict input & output, Bedside glucose monitoring every _____ hours
☐ Na, K, Cl, CO_2, Glucose, BUN, Scr, Mg, PO_4 every _____
☐ T. Bili, Alk Phos, AST, ALT, Albumin, Triglycerides, Calcium every _____

Base Solution: *Select one* — *Parenteral nutrition **MUST** be administered through a dedicated infusion port and filtered with a 1.2-micron in-line filter at all times. Discard any unused volume after 24 hours.*

☐ PERIPHERAL 2-in-1
Dextrose _____ g
Amino Acids (*Brand* _____) _____ g
For patients with PIV and established glucose tolerance; Provides _____ kcal; Maximum Rate not to exceed _____ mL/hour

☐ CENTRAL 2-in-1
Dextrose _____ g
Amino Acids (*Brand* _____) _____ g
For patients with CVC or PICC and established glucose tolerance; Provides _____ kcal; Maximum Rate not to exceed _____ mL/hour

☐ CENTRAL 3-in-1
Dextrose _____ g
Amino Acids (*Brand* _____) _____ g
Fat Emulsion (*Brand* _____) _____ g
For patients with CVC or PICC and established glucose / fat emulsion tolerance; Provides _____ kcal; Maximum Rate not to exceed _____ mL/hour
Use of additional fat emulsion not required with 3-in-1 base solution

RATE & VOLUME: _____ mL/hour for _____ hours = _____ mL/day
Must specify

or **CYCLIC INFUSION:** _____ mL/hour for _____ hours, then _____ mL/hour for _____ hours = _____ mL/day

Fat Emulsion (*Brand* _____) – ***via PIV or CVC with 2-in-1 base solutions*** *(Select caloric density & volume)*

☐ 10% ☐ 250 mL Infuse at _____ mL/hour over _____ hours Frequency _____
☐ 20% ☐ 500 mL *(Note: Infusions < 4 or > 12 hours not recommended)* *Discard any unused volume after 12 hours.*

Additives: *(per day)*		***Normal Dosages***
Sodium Chloride	_____ mEq	*1-2 mEq Sodium/kg/day*
as Acetate	_____ mEq	*pH or CO_2 dependent*
as Phosphate	_____ mmol of PO_4	*Consider if hyperkalemic*
Potassium Chloride	_____ mEq	*1-2 mEq Potassium/kg/day*
as Acetate	_____ mEq	*pH or CO_2 dependent*
as Phosphate	_____ mmol of PO_4	*20-40 mmol/day (1 mmol Phos = 1.5 mEq K)*
Calcium **Gluconate**	_____ mEq	*5-15 mEq/day*
Magnesium **Sulfate**	_____ mEq	*8-24 mEq/day*
Adult **Multivitamins**	_____ mL/day	*Contains Vitamin K 150 mcg*
Adult **Trace Elements**	_____ mL/day	*Zn __ mg, Cu __ mg, Mn __ mg, Cr __ mcg, Se __ mcg (with normal hepatic function)*
H_2 Antagonist _____	_____ mg	*____ mg/day with normal renal function*
Other:		

Additives: *(per day)*
Regular Insulin _____ units
Recommend if hyperglycemic, start with 1 unit for every 10 g of dextrose

Pharmacy Use Only: **Ca/PO_4 Limit Checked** ____
(Note: Some brands of amino acids contain phosphate)

Physician's Signature: _____ **PagerNumber:**_____ **Date/time:**_____
Orders transcribed by: _____ **Date/time:** _____ **Orders verified by:** _____ **Date/time:**_____

SEND COMPLETED ORDERS TO PHARMACY

FIG. 1. Sample Adult PN Order Form. This Adult PN Order Form Template is intended to serve as a guide to meeting the criteria for mandatory and strongly recommended components of a PN Order Form. These components are not intended to be guidelines for formulas or monitoring. Those recommendations may be found in the Nutrient Requirements and PN Administration sections. The PN Order Form content shall be adapted to meet the needs of the individual institution based on patient population, prescribing patterns, and judgment by the healthcare professionals.

the form. To prevent errors and promote clarity in ordering regular insulin, an attempt should be made to separate this field from other additives.
- Although not depicted in the sample PN order form template, basic PN education tools should be included on the back of the form to assist prescribers in correctly filling out the form. Information such as nutrient dosage recommendations, example calculations, specific contents of multivitamin and trace element preparations, and dosing recommendations for insulin can be helpful to the prescriber during the order writing process.

The format for a Pediatric PN order form would be very similar to the Adult PN order form template except the fields for macro- and micronutrients are specific for age or weights of the pediatric patients.

PRACTICE GUIDELINES

1. Standardized order forms (or order entry screens) shall be developed and designed for adult and pediatric PN formulations to aid prescribers in meeting the estimated daily patient nutritional requirements and improve order clarity.
2. The clinician and compounding pharmacist shall assess the PN formulation to determine whether its contents are within an acceptable standard range based on the specific patient population (e.g., adult or pediatric). They shall also assess whether a clinical disease state or condition warrants a dose outside the standard range.
3. The use of percent concentration in PN orders should not be used. The use of total daily dose is encouraged.
4. Potentially dangerous abbreviations and dose expressions should be avoided. Specifically:
   - Do not use trailing zeros (e.g. 5 mg, and not 5.0 mg)
   - Use leading zeros for doses less than one measurement unit (e.g. 0.3 mg and not .3 mg)
   - Spell out the word UNITS (e.g. never U which could be easily mistaken as a zero)
   - Spell out routes of administration and all intended instructions.
5. All components of the PN order must be re-written when PN is reordered.

Special Considerations

According to the 2003 Survey of PN Practices, the computerized prescriber order entry (CPOE) system for PN orders is used in only 29% of organizations surveyed. The best CPOE method or process for PN orders is not yet described in the literature. Converting standard paper orders to the computer creates unique challenges.[22] For example, one institution utilizing CPOE has noted problems when an adjusted or dosing weight that is different from the patient's actual or admission weight is used when calculating caloric and protein requirements.

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SECTION III: LABELING PARENTERAL NUTRITION FORMULATIONS

BACKGROUND

The manner in which PN ingredients are labeled varies considerably[1]. PN base components (dextrose, amino acids, and IVFE) are labeled as:
- the volume of the percent of original concentration added (250 mL of 50% dextrose),
- the percent of final concentration after admixture (25% dextrose), and
- the grams per liter or grams in the total volume of PN admixed (250 g per liter or 375 g per total volume).

Additives, especially electrolytes, are labeled as mmol or mEq per liter or per volume. For example,

sodium chloride (NaCl) in a dose of 80 mEq/L admixed in a PN with a volume of 2 liters may be labeled as follows:

- NaCl 80 mEq/L
- NaCl 160 mEq per total volume
- Na 80 mEq/L, Cl 80 mEq/L
- Na 160 mEq and Cl 160 mEq per total volume.

This lack of standardization causes a great deal of confusion when patients are transferred between healthcare environments. As such, an essential component of a patient transfer between healthcare environments is a pharmacist-to-pharmacist interaction to resolve potential problems with transfer of the prescription. Misinterpretation of a PN label that led to a patient death[2] exemplifies what may occur if this interaction does not occur. To avoid misinterpretation, the labels for PN formulations should be standardized. All PN labels in any health care environment shall express clearly and accurately what the patient is receiving at any time.

Each method of labeling has distinct advantages and disadvantages. The use of the percent of original dextrose or amino acid concentration is specific for the product used by the pharmacy in compounding the PN formulation. However, interpretation of this label requires knowledge of pharmaceutical calculations in order to determine the nutrient value of the PN formulation. This involves training professionals in several health care disciplines to determine the nutrient value of the PN admixture being administered. Using the percent of final concentration of dextrose, amino acids, or IVFE still requires calculations to determine the caloric value or dose being administered, but it is traditionally the most accepted type of label because it is consistent with the label of the original commercial products as shipped from the manufacturer. To minimize calculation errors and provide a label more consistent with dispensing a PN formulation as a nutrient, some programs have used grams of base components per liter. This simplifies the conversion of the nutrients to calorie and gram doses being provided, but still must be converted to daily doses. This label also supports those programs that only compound PN formulations in liter quantities so that prescriptions may be written as quantity per liter and thus consistent with the additive as it appears on the label.

Finally, grams per total volume, with use of a 24-hour nutrient infusion system is most consistent with that of a nutrient label, requiring the least number of calculations to determine the calorie or gram dose per day. It also supports the most cost-effective system of PN compounding and delivery, which is the 24-hour nutrient infusion system.[3] This system has been determined to decrease PN wastage and to reduce personnel time in compounding and administering PN. Conceptually, this system is successful when acute electrolyte disorders are managed separately from the PN, until the time that electrolyte changes in the PN go into effect. This system also requires the use of automated compounding devices, which have been shown to be more accurate and faster than gravity-fill PN admixture systems.

PN LABEL TEMPLATE

The sample PN label templates provide a format to standardize labels for adult, pediatric and neonatal patients. A supplemental label template for IVFE is also provided for those instances when IVFEs are administered separate from the PN admixture. Due to the complex nature of the label, there are several points that should be clarified:

- The amount per day is the only column required on the adult label, but some programs accustomed to amounts per liter may supplement the label by adding a second column reflecting quantity per liter in parenthesis. The components are labeled as amount per day to facilitate review of the order for appropriate nutrient doses. However, certain additives expressed as quantity per liter in parenthesis on the PN label template, may be useful to the clinician in determining whether the PN may be infused via peripheral or central vein. It is also useful to the pharmacist in determining electrolyte compatibility since these are reported by concentration rather than amount. Those familiar with ordering PN electrolytes (similar to other intravenous fluids) as mEq/L, will be able to interpret the mEq/L electrolyte content easier if provided in this format on the PN label. Finally, many programs order additives as quantity/liter. Labeling as such allows for the final check of the PN by the nurse versus the physician's order, prior to its administration. This final check to confirm that the PN content is the same as the physician's order is an essential component of the PN system. In the neonatal and pediatric patient, it is common to order PN components in amount/kg. Therefore, the PN label for these patients shall also express components as amount/kg/day, in addition to amount/day. The label can be further supplemented by an additional column expressing components as amount/liter or amount/100 ml in parenthesis, for those who are accustomed to ordering in this format. Care should be taken in developing a label that is clear and concise and of a size that fits neatly on the PN admixture. Accordingly, some may choose to dispense the PN with a supplemental form providing these optional details that may also be used for documenting PN administration in the patient's chart.
- The PN label specifies the route of administration.
- The administration date and time and beyond-use date and time are expressed clearly on the label. The administration date and time, as the term denotes, is the date and time the PN is scheduled to be administered to the patient. This may be the same day that it was compounded and is different from the date and time of admixture, which should be included on the compounding worksheet but is not necessary on the label.
- The dosing weight is provided so that anyone evaluating the contents of the label may determine if the doses of nutrients are appropriate. Dosing weight refers to the weight used in calculating nutrient doses.
- The inorganic phosphorus content is provided as both

Standard PN Label Template
Adult Patient

Institution/Pharmacy Name, Address and Pharmacy Phone number		
Name	Dosing Weight	Location
Administration Date/Time	Do Not Use Afer: Date/time	
Base Formula	Amount/day	(Amount/L)
Dextrose	**g**	(g/L)
Amino acids[a]	**g**	(g/L)
IVFE[a]	**g**	(g/L)
Electrolytes		
Sodium chloride	**mEq**	(mEq/L)
Sodium acetate	**mEq**	(mEq/L)
Sodium phosphate	**mmol of P**	(mmol/L)
	(mEq of Na)	(mEq/L)
Potassium chloride	**mEq**	(mEq/L)
Potassium acetate	**mEq**	(mEq/L)
Potassium phosphate	**mmol of P**	(mmol/L)
	(mEq of K)	(mEq/L)
Calcium gluconate	**mEq**	(mEq/L)
Magnesium sulfate	**mEq**	(mEq/L)
Vitamins, trace elements and medications		
Multiple vitamins[a]	**mL**	
Multiple trace elements[a]	**mL**	
Insulin	**Units**	(Units/L)
H_2 - antagonists[a]	**mg**	
Rate _____ mL/hour	Volume _____ mL	Infuse over___hours

Formulation contains_____ mL plus _____mL overfill
Discard any unused volume after 24 hours

*****Central Line Use Only*****

[a] Specify product name.
g = gram.

the mmol quantity of phosphorus as well as the mEq quantity of the additive salt's cation; potassium or sodium.
- If the PN formulation includes overfill, it is clearly stated on the label.
- Rate is expressed in mL/hour over 24 hours. If the PN formulation is cycled, the infusion duration and rates are to be expressed on the label.
- For home care, additives to be admixed at home are labeled as Patient Additives.

Standard PN Label Template

Neonate or Pediatric Patient

Institution/Pharmacy Name, Address and Pharmacy Phone number		
Name	Dosing Weight	Location
Administration Date/Time	Do Not Use After: Date/time	
Base Formula	Amount/kg /day	Amount/day
Dextrose	**g/kg**	**g**
Amino acids[a]	**g/kg**	**g**
Electrolytes		
Sodium chloride[b]	**mEq/kg**	**mEq**
Sodium acetate[b]	**mEq/kg**	**mEq**
Potassium chloride[b]	**mEq/kg**	**mEq**
Potassium acetate[b]	**mEq/kg**	**mEq**
Potassium phosphate[b]	**mmol of P/kg (mEq of K)/kg**	**mmol of P (mEq of K)**
Sodium phosphate[b]	**mmol of P/kg (mEq of Na)/kg**	**mmol of P (mEq of Na)**
Calcium gluconate	**mEq/kg**	**mEq**
Magnesium sulfate	**mEq/kg**	**mEq**
Vitamins, trace elements and medications		
Multiple vitamins[a]	**mL/kg**	**mL**
Multiple trace elements[a]	**mL/kg**	**mL**
L-cysteine	**mg/kg**	**mg**
H_2 antagonists[a]	**mg/kg**	**mg**
L-Carnitine	**mg/kg**	**mg**

Rate _____ mL/hour Volume _____ mL Infuse over 24 hours

Admixture contains _____ mL plus _____mL overfill

*****Central Line Use Only*****

[a] Specify product name.

[b] Since the admixture usually contains multiple sources of sodium, potassium, chloride, acetate, and phosphorus, the amount of each electrolyte/kg provided by the PN admixture is determined by adding the amount of electrolyte provided by each salt.

- An auxillary label may also be desired that would list the individual electrolytes as mEq, and the phosphorus content as mmol provided per day. The auxillary label could also express the total calories provided per day, as well as the percent of total calories provided by carbohydrate and fat.
- Notation of who prepared and checked the PN formulation is not required on the label if this is done on a compounding worksheet maintained in the pharmacy.
- If IVFE are not included in the PN formulation, this line may be omitted from the label.

PRACTICE GUIDELINES

1. The labels for PN formulations shall be standardized and include:
   - The amount per day is the only column required

Standard IVFE Label Template
Adult, Neonate or Pediatric Patient

Institution/Pharmacy Name, Address and Pharmacy Phone Number

Name Dosing Weight Location

Administration Date/Time Do Not Use After: Date/Time

	Volume	Amount/kg /day	Amount/day
Intravenous fat emulsion[a] (%)	_____ mL	_____gram/kg	____gram

Infusion rate _____mL/hour Infuse over _____ hours

May contain overfill - Discard any unused volume after 12 hours

*****For peripheral or central line administration*****

[a] Specify brand name

on the label for the base formula, electrolyte additives, micronutrients and medications. This supports the use of the 24-hour nutrient infusion system.
- Using the quantity per liter option in parenthesis supports those programs that continue to admix PN in 1 liter volumes.
- The dosing weight is required on the label.

2. Auxillary labels or information may be used.
3. Patient transfer between healthcare environments requires pharmacist-to-pharmacist communication and documentation to insure the accurate transfer of the PN prescription.
4. The PN label is compared with the PN order and for beyond-use date before administration.

Special Considerations

The concepts used in developing the practice guidelines were developed for hospitalized patients and for institutions and organizations having a relatively large number of patients receiving PN therapy. It is assumed that these concepts apply to alternative health care settings, as well as those hospitals with only a few patients receiving PN. It may be that the cost of implementing a once-per-day nutrient infusion system that includes automated compounding would be excessive for pharmacies with small numbers of patients receiving PN. Various alternatives to achieving the concepts for labeling in these circumstances may be successful, but have yet to be determined objectively.

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SECTION IV: NUTRIENT REQUIREMENTS

BACKGROUND

PN formulations should be designed to meet individualized nutrient requirements. The clinician needs to be familiar with an acceptable standard range for each nutrient and when to adjust nutrients within and outside this range. The ordered quantity of protein, carbohydrate, fat, fluid, electrolytes, vitamins, and trace elements should all be assessed for appropriateness before compounding. Acceptable ranges for each of these nutrients should be based on age and normal physiologic requirements. The purpose of providing standard nutrient ranges is to serve as a reference point and guide the health care professional in safe practice. However, determination of individual nutrient requirements may vary, based on factors such as organ function, disease state, metabolic condition, and medication usage.

TABLE I
Daily protein & calorie requirements for the adult

Protein	
Maintenance	0.8–1 g/kg
Catabolic patients	1.2–2 g/kg
Chronic renal failure (renal replacement therapy)	1.2–1.5 g/kg
Acute renal failure + catabolic	1.5–1.8 g/kg
Energy	
Total calories	20–30 kcal/kg
Fluid	30–40 mL/kg

NUTRIENT REQUIREMENTS: ADULTS

General guidelines for protein, calorie, and fluid requirements in adult patients are provided in Table I. A dosing weight shall be determined for each patient. Various methods for adjusting the body weight of obese patients have been suggested, but none have been clearly validated.[1,2] Assessment of energy expenditure in obese patients can be problematic. Indirect calorimetry may be required to improve the accuracy of energy requirement estimations, due to limitations of predictive equations in obese patients.[3,4]

Protein requirements have been estimated based on metabolic demand. Restriction of protein is seldom required in patients with renal or hepatic disease.[5] In patients receiving renal replacement therapy, protein may need to be supplemented. In patients with liver disease, protein restriction should be implemented for the acute management of overt hepatic encephalopathy only when other treatment modalities have failed. Protein restriction is not indicated in the management of chronic hepatic disease.

The standard distribution of nonprotein calories is 70–85% as carbohydrate and 15–30% as fat. This distribution may be adjusted based on tolerance; however, there is limited clinical benefit when fat content exceeds 30% of nonprotein calories.[6] Further methods to estimate dosing are based on body weight. In adult patients, it is recommended that the fat content of the PN formulation not exceed 2.5 g/kg/day and carbohydrate content not exceed 7 g/kg/day.

Although rare in recent years, essential fatty acid deficiency (EFAD) may still occur in the contemporary period of specialized nutrition support. Failure to provide at least 2% to 4% of the total caloric intake as linoleic acid and 0.25% to 0.5% of total caloric intake as alpha linolenic acid may lead to a deficiency of these two essential fatty acids. Manifestations of this syndrome can include alterations in platelet function, hair loss, poor wound healing, and dry, scaly skin unresponsive to water miscible creams. The time in which EFAD may develop during administration of fat-free PN is variable, based upon the underlying nutritional status, disease state, and age of the patient. In general, the majority of hospitalized adults who receive no dietary fat, develop biochemical evidence of EFAD after 4 weeks of fat-free PN. Hypocaloric feeding may provide some protection against development of EFAD while receiving fat-free PN. This is presumed to be secondary to the liberalization of essential fatty acids (EFAs) from endogenous fat stores into the circulation. Although 2 weeks of a high-protein, hypocaloric fat-free PN regimen has been shown to maintain plasma linoleic acid levels in postsurgical patients,[7] clinical signs of EFAD have been detected in obese patients who received no exogenous EFAs for 20 days.[8] Studies of patients receiving home PN have shown that biochemical evidence of EFAD syndrome may develop after several months of not receiving IVFE.[9] The amount of fat taken by mouth and the efficiency of absorption were identified as factors influencing the need for the continued provision of IVFE. In determining the adequacy of EFA provision, it is important to recognize the varying EFA content of various IVFE sources. For example, commercially available IVFE in the United States contain approximately 55–60% of total calories as linoleic acid and 3–4% of total calories as alpha linolenic acid. Structured lipid products available in Europe contain significantly lower proportions of EFAs, owing to the substitution of long-chain EFAs by medium-chain fatty acids. Topical EFA application has been shown to be effective in preventing EFAD in some patients but it has demonstrated poor efficacy when used to treat an already existing EFAD.[10,11]

Standard ranges for parenteral electrolytes assume normal organ function and normal losses (Table II). Sodium and potassium requirements for a given patient are highly variable and generally not limited by compatibility restraints; however, large quantities of these cations may destabilize IVFE. In general, sodium and potassium requirements in the PN formulation are 1–2 mEq/kg/day, but should be customized to meet individual patient needs. Restrictions of potassium, phosphate, or magnesium may be required in patients with renal disease due to impaired excretion. Conversely, requirements of these electrolytes may be increased due to excessive losses, intracellular shifts, or increased metabolic demands. As discussed in section VI, the parenteral supplementation of phosphate, magnesium, and calcium in the PN formulation is limited by physical compatibility. Some commercially available amino acid injection products contain phosphorus, the content of which shall also be considered in determining compatibility. Chloride and acetate content should be adjusted to maintain acid-base balance. In general, acid-base balance can be maintained by using approximately equal amounts of chloride and acetate, but may require adjustment based on the clinical situation. Amino acid solutions themselves contain various amounts of chloride and acetate, depending on the individual product, for buffering purposes.[12] For

TABLE II
*Daily electrolyte additions to adult PN formulations**

Electrolyte	Standard Requirement
Calcium	10–15 mEq
Magnesium	8–20 mEq
Phosphorus	20–40 mmol
Sodium	1–2 mEq/kg
Potassium	1–2 mEq/kg
Acetate	As needed to maintain acid-base balance
Chloride	As needed to maintain acid-base balance

*Standard intake ranges based on generally healthy people with normal losses.

TABLE III
*Daily requirements for adult parenteral vitamins**

Vitamin	Requirement
Thiamin (B_1)	6 mg
Riboflavin (B_2)	3.6 mg
Niacin (B_3)	40 mg
Folic acid	600 mcg
Pantothenic acid	15 mg
Pyridoxine (B_6)	6 mg
Cyanocobalamin (B_{12})	5 mcg
Biotin	60 mcg
Ascorbic Acid (C)	200 mg
Vitamin A	3300 IU
Vitamin D	200 IU
Vitamin E	10 IU
Vitamin K	150 mcg

*FDA requirements for marketing an effective adult parenteral vitamin product.[13]

this reason, it is necessary to state the specific amino acid product name used in compounding on the PN label in order to account for its electrolyte content. However, it is not recommended that the electrolyte components of the amino acid solution be listed on the PN label with the electrolyte additives as this may lead to confusion.

All patients receiving PN should receive a parenteral vitamin preparation daily. Available commercial products for adults contain 13 or 12 known vitamins (i.e. with or without vitamin K). In April 2000, the FDA amended requirements for marketing of an "effective" adult parenteral vitamin formulation and recommended changes to the 12-vitamin formulation that has been available for over 20 years.[13] The requirements for increased dosages of vitamins B_1, B_6, C, and folic acid as well as addition of vitamin K are based upon the recommendations from a 1985 workshop sponsored jointly by the American Medical Association's (AMA) Division of Personal and Public Health Policy and FDA's Division of Metabolic and Endocrine Drug Products. Specific modifications of the previous formulation include increasing the provision of ascorbic acid (vitamin C) from 100 mg/day to 200 mg/day, pyridoxine (vitamin B_6) from 4 mg/day to 6 mg/day, thiamin (vitamin B_1) from 3 mg/day to 6 mg/day, folic acid from 400 mcg/day to 600 mcg/day, and addition of phylloquinone (vitamin K) 150 mcg/day (Table III). When using the 12-vitamin formulation, vitamin K can be given individually as a daily dose (0.5–1 mg/d) or a weekly dose (5–10 mg one time per week). Patients who are to receive the anticoagulant warfarin should be monitored more closely when receiving vitamin K to assure the appropriate level of anticoagulation is maintained. It is reasonable to supplement the PN with thiamin (25–50 mg/d) in PN patients who have a history of alcohol abuse, especially when they did not receive thiamin at hospital admission, or in times of parenteral vitamin shortages (common in the U.S. in the 1990s). The United States has been plagued with two periods of short supply of parenteral vitamin products in the 1990s. This has resulted in vitamin deficiencies in patients receiving PN without parenteral vitamins. Several recommendations emanated from A.S.P.E.N. following the latest parenteral vitamin shortage: (1) use oral vitamins when possible, especially liquid vitamins of defined content via feeding tubes, (2) restrict the use of vitamin products in PN during periods of short supply, such as one infusion three times per week, (3) administer thiamin, ascorbic acid, niacin, pyridoxine, and folic acid daily as individual entities in the PN during periods of short supply, (4) administer vitamin B_{12} at least once per month during periods of short supply.

Guidelines for parenteral trace element requirements in adults are provided in Table IV.[14,15] The guidelines should be considered approximations, and it should be recognized that variations among individual patients may exist. Reductions in manganese and copper dosing should be considered in patients with hepatobiliary disease due to impaired excretion. In addition, many of the components of the PN formulation have been shown to be contaminated with trace elements such as zinc, copper, manganese, chromium, selenium, and aluminum.[16] Therefore, patients receiving long-term use of PN therapy are at risk of trace element toxicity and serum monitoring is necessary.

Iron is not routinely recommended in patients receiving PN therapy and is not a component of current injectable multiple trace element preparations.[17] Parenteral supplementation of iron should be limited to conditions of iron deficiency when the oral route is ineffective or not tolerated. In patients with iron deficiency anemia, therapeutic (replacement) doses of iron may be estimated based on weight and hemoglobin concentration. Provision of maintenance iron therapy is generally not required but has been used in patients receiving long-term PN. In the absence of blood loss, a parenteral iron dose of 25 to 50 mg once monthly is estimated to meet maintenance requirements. However, it is important to monitor iron status on a routine basis (e.g., serum ferritin every 1–3 months) whenever providing ongoing doses of iron in order to minimize the risk of iron overload. Iron dextran has been added to nonIVFE-containing PN formulations, but requires caution due to compatibility limitations. It shall not be added to TNA because it can destabilize the IVFE and result in the formation of large oil droplets that may be harmful if infused (see compatibility section). Iron sucrose and sodium ferric gluconate provide therapeutic options for the parenteral supplementation of iron, but compatibility data with PN formulations is not available.

TABLE IV
*Daily trace element supplementation to adult PN formulations**

Trace Element	Standard Intake[14,15]
Chromium	10–15 mcg
Copper	0.3–0.5 mg
Iron	Not routinely added
Manganese	60–100 mcg†
Selenium	20–60 mcg
Zinc	2.5–5 mg

*Standard intake ranges based on generally healthy people with normal losses.
†The contamination level in various components of the PN formulation can significantly contribute to total intake. Serum concentrations should be monitored with long-term use.

TABLE V
Daily fluid requirements for pediatric patients[18]

Body weight	Amount
<1500 g	130–150 mL/kg
1500–2000 g	110–130 mL/kg
2–10 kg	100 mL/kg
>10–20 kg	1000 mL for 10 kg + 50 mL/kg for each kg >10
>20 kg	1500 mL for 20 kg + 20 mL/kg for each kg >20

TABLE VII
Daily energy requirements (total kcal/kg) for pediatric patients

Preterm neonate	90–120
<6 months	85–105
6–12 months	80–100
1–7 yr	75–90
7–12 yr	50–75
>12–18 yr	30–50

NUTRIENT REQUIREMENTS: PEDIATRICS

Standard nutrient ranges for infants and children receiving PN have been established. Rapidly changing organ function, metabolic immaturity, and normal but rapid weight gain, particularly in neonates and infants, result in age-related descriptors of nutrient need. Therefore, each table characterizes ranges for neonates, infants, children, and adolescents (Tables V through X). As can be readily appreciated, requirements for fluids,[18] protein, and energy are substantially higher on a unit-of-weight basis for children than for adults. Careful monitoring of growth is necessary, as a component of assessing adequacy of nutrient provision. Above 18 years of age, estimated nutritional requirements should be established using nutrient ranges suggested for the adult population.

Protein restriction in certain disease states such as hepatic and renal failure should be done with caution and in consideration of the need for adequate protein to support growth in the pediatric population. Additionally, protein losses during dialysis need to be considered and appropriately replaced.

Manufacturers of neonatal/infant amino acid formulations recommend the addition of L-cysteine hydrochloride to the 2-in-1 PN formulation just prior to administration. A commonly recommended dose is 40 mg L-cysteine hydrochloride per gram of amino acids.[19] Current practice suggests supplementation with L-cysteine hydrochloride for the first year of life, although practice varies widely. Addition of L-cysteine hydrochloride to the PN formulation reduces the pH, thereby improving calcium and phosphorus solubility.[20] It has also been shown to normalize plasma taurine levels.[21]

The distribution of PN nonprotein calories for pediatric patients does not vary significantly from that for the adult receiving PN; however, it is worth noting that the typical enteral diet of the neonate or infant derives approximately 50% of nonprotein calories from fat. Therefore, a PN formulation appears less physiologically similar to standard enteral feedings in the neonate or infant than in the older child and adult.

There is evidence that the 20% IVFE is preferable to the 10% product, especially for use in neonates and infants. In addition to its greater caloric content per unit volume, the lower content of surface active agents (egg phosphatides) per gram of fat results in more normal concentrations of components of circulating lipoproteins, especially low density lipoproteins.[22] In the very low birth weight infant, the use of the 20% IVFE does require accurate and low flow pump delivery systems. In general, 3 g/kg/day is the accepted limit for IVFE administration in the small for gestational age neonates and preterm neonates less than 32 weeks gestational age.[23,24] Concerns regarding EFAD are addressed in the adult section of nutrient requirements.

TABLE VI
*Daily protein requirements (g/kg) for pediatric patients**

Preterm neonates	3–4
Infants (1–12 months)	2–3
Children (>10 kg or 1–10 yrs)	1–2
Adolescents (11–17 yrs)	0.8–1.5

*Assumes normal age-related organ function.

A limited endogenous store of fatty acids in neonates and infants versus adults contribute to the discrepancy in time in which EFAD syndrome may occur. Neonates have been reported to develop biochemical signs of EFAD as early as the second day of life and up to 2 weeks after fat-free PN.

Standard ranges for electrolytes, vitamins, and trace elements for infants and children with normal organ function are provided in Tables VIII through X. Calcium and phosphorous requirements of the neonate and infant are substantially different from those of the older child and are dramatically different from the adult requirements (Table VIII). These differences in needs are reflected in the composition of neonatal and infant formulas and human milk. When one attempts to meet these increased requirements in pediatric PN formulations, problems can arise because of incompatibility of calcium and phosphate salts. In a child weighing more than 50 kg, adult electrolyte dosage guidelines should generally be used.

Guidelines for vitamin and trace element additions to PN solutions for pediatric patients up to age 11 have been published (Tables IX and X).[25] Adult multivitamins should be used for a child who weighs more than 40 kg or is greater than 11 years of age. Like adults, the guidelines should be considered approximations of need, with individual patient variation to be expected. Alteration of trace element dosage may be required in cases of hepatic or renal dysfunction. The long-term use of multiple trace element products at recommended doses has been associated with excessive serum concentrations of chromium.[26] The ratio of trace elements in commercially available pediatric multiple trace element products results in excessive intake of manganese if recommended doses of zinc are given. It is clear that micronutrient requirements for children receiving PN is a fertile area for research and an area in which further commercial product development is required. In general, the recommendations for the use of iron in pediatric PN are consistent with those pre-

TABLE VIII
*Daily electrolyte and mineral requirements for pediatric patients**

Electrolyte	Preterm neonates	Infants/children	Adolescents and children > 50 kg
Sodium	2–5 mEq/kg	2–5 mEq/kg	1–2 mEq/kg
Potassium	2–4 mEq/kg	2–4 mEq/kg	1–2 mEq/kg
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq
Acetate	As needed to maintain acid-base balance	As needed to maintain acid-base balance	As needed to maintain acid-base balance
Chloride	As needed to maintain acid-base balance	As needed to maintain acid-base balance	As needed to maintain acid-base balance

*Assumes normal age-related organ function and normal losses.

sented previously for adults. However, total iron needs can be dramatically lower in the pediatric patient, compared to adults. This necessitates vigilance, regarding the iron dose administered. The concentration of some parenteral iron preparations can result in life-threatening doses, even with the use of <1 mL of these commercial iron preparations.

Aluminum contamination. Since the late 1970s, evidence has been accumulating to show that small volume parenteral products, large volume parenteral products and pharmacy bulk packages used in compounding PN formulations are largely contaminated with aluminum.[27] Contamination occurs primarily from the introduction of raw materials during the manufacturing process, with the aluminum-contaminated product sources of primary concern being calcium and phosphate salts, heparin, and albumin. Variable levels of contamination have also been noted with some trace element and vitamin products. Infants and children are extremely vulnerable to aluminum toxicity due to immature renal function and the likelihood for long-term PN. Alterations in bone formation, mineralization, parathyroid hormone secretion, and urinary calcium excretion have been attributed to aluminum toxicity in long-term PN patients or patients with renal impairment.[28] Although they may not be receiving PN, thermal injury patients are at an increased risk for aluminum toxicity from the large quantities of human albumin and calcium gluconate they receive in the treatment of their burn injuries.[29–31] The FDA recently mandated that manufacturers of products used in compounding PN shall measure the aluminum content of their products and disclose it on the label by July 2004.[32,33] Large volume parenterals (i.e., amino acid solutions, concentrated dextrose solutions, IVFE and sterile water for injection) have a maximum limit of 25 mcg/L of aluminum. Small volume parenterals (i.e., electrolyte salts) and pharmacy bulk packages (i.e., parenteral multivitamins, trace element solutions) must be labeled with the maximum level of aluminum in the product at expiry. The FDA identified 5 mcg/kg/day as the maximum amount of aluminum that can be safely tolerated and amounts exceeding this limit may be associated with central nervous system or bone toxicity. The intent of the FDA ruling is to educate health care practitioners about aluminum exposure and facilitate the administration of low-aluminum parenteral solutions to patients in high-risk groups.

PRACTICE GUIDELINES

1. Determination of protein, calorie, fluid, electrolyte, vitamin, and trace element components of a PN formulation should be based on standard nutrient requirements. The dose of each nutrient should fall within the accepted age-based standard range except when warranted by specific clinical situations.
2. IVFE in a dose sufficient to prevent EFAD should be provided to adult and pediatric patients who are NPO. Adults who fail to receive EFAs for 20 days are at risk for development of EFAD. In the absence of EFAs, children can develop EFAD over a shorter period of time, with neonates at risk of EFAD within 2 days of initiating lipid-free PN.
3. All patients receiving PN should receive a parenteral vitamin preparation on a daily basis.
4. Health care providers should choose PN components with the lowest aluminum content when possible to minimize parenteral aluminum exposure.
5. When the use of a commercially available multiple trace element combination product results in or

TABLE IX
Daily dose recommendations for pediatric multiple vitamins†*

Manufacturer		AMA-NAG	
Weight (kg)	Dose (mL)	Weight (kg)	Dose
<1	1.5	<2.5	2 mL/kg
1–3	3.25	>2.5	5 mL
>3	5		

*Assumes normal age-related organ function.
†Pediatric multiple vitamin formulation (5 mL): A 2300 IU, D 400 IU, E 7 IU, K 200 mcg, C 80 mg, $B_1$1.2 mg, $B_2$1.4 mg, $B_3$17 mg, $B_5$5 mg, B_6 1 mg, B_{12}1 mcg, Biotin 20 mcg, Folic acid 140 mcg.

TABLE X
Trace element daily requirements for pediatrics†*

Trace element	Preterm neonates <3 kg (mcg/kg/d)	Term neonates 3–10 kg (mcg/kg/d)	Children 10–40 kg (mcg/kg/d)	Adolescents >40 kg (per day)
Zinc	400	50–250	50–125	2–5 mg
Copper	20	20	5–20	200–500 mcg
Manganese	1	1	1	40–100 mcg
Chromium	0.05–0.2	0.2	0.14–0.2	5–15 mcg
Selenium	1.5–2	2	1–2	40–60 mcg

*Assumes normal age-related organ function and normal losses.
†Recommended intakes of trace elements cannot be achieved through the use of a single pediatric multiple trace element product. Only through the use of individualized trace element products can recommended intakes of trace elements be achieved.[25]

increases the risk of trace element toxicity or deficiency states, the use of individual trace element products is warranted.

6. Parenteral iron shall not be routinely supplemented in patients receiving PN therapy. It should be limited to conditions of iron deficiency when oral iron supplementation fails and followed closely in an ongoing monitoring plan.

Special Considerations

Further work is required to determine optimal parenteral trace element requirements in adult and pediatric patients and develop commercially available multiple trace element solutions that better meet these requirements. The use of currently available multiple trace element solutions may result in toxicity or deficiency of certain trace elements in some disease states. This problem may be compounded by trace element contamination, particularly aluminum, found in large volume parenterals and additives.

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SECTION V: STERILE COMPOUNDING OF PARENTERAL NUTRITION FORMULATIONS

SCREENING THE PN ORDER

Background

Serious disorders and death have been attributed to PN formulations having inappropriate nutrient compositions. Deficiencies of trace elements and EFAs have been reported in both pediatric and adult patient populations.[1,2] The most dramatic, yet insidious, example of the dangers associated with the omission of micronutrients occurred during the 2 periods when there was a national parenteral vitamin shortage.[3,4] At that time, omission of parenteral vitamins resulted in three deaths of patients predisposed to vitamin deficiencies. Specifically, a refractory lactic acidosis led to the death of three patients associated with thiamin deficiency

that was accentuated by the administration of dextrose in the PN formulation. Similarly, a death related to the omission of dextrose from a neonatal PN caused irreversible brain damage. Finally, life-threatening deficiencies have resulted when patients received phosphate-free PN.[5] Overdoses of nutrients included in PN may also be harmful. As explained in Section I, the incorrect admixture of PN resulting in excessive dextrose infusions led to a patient's death, and a 50-fold error in an iron dextran solution caused serious liver damage in a child. In all these cases, there was inadequate review of the PN prescription for appropriateness of dose and adequacy of nutrient composition. It is the responsibility of the pharmacist-by education, training, and experience to review each prescription for appropriate indication, dose, and route of administration, and the potential for drug-drug, drug-nutrient and drug-laboratory interactions.[6] Patient information such as height, dosing weight, serum electrolyte and glucose values, hepatic and renal and gastrointestinal function should be available to assess the adequacy of the PN prescription.[7]

For those systems requiring that the PN prescription be rewritten each day, the potential exists for transcription errors that omit or significantly increase nutrient doses. In this regard, it is important when refilling the day's order for PN therapy that the pharmacist review the contents of the PN for consistency with the previous day's prescription. Major deviations should be questioned, to avoid nutrition-related complications. For example, the pharmacist should clarify with the prescribing clinician a prescription for a patient if regular insulin was present in the previous day's order at a dose of 20 units and the present order is for 100 units without a change in the quantity of dextrose received between the two days. In this case, it is both professionally appropriate and clinically reasonable to question the order. Other orders that might be appropriately questioned are drug and nutrient quantities; other large-scale changes including omissions, dramatic increases, or decreases; and other types of extreme day-to-day fluctuations.

PRACTICE GUIDELINES

1. The calorie, protein, fluid, electrolyte, vitamin, trace element and medication content is reviewed for each and every PN prescription to assure that a complete and balanced nutrient formulation is provided. *Balanced* is defined as the presence of the proper proportion of calories, protein, fluid, electrolytes, vitamins and trace elements, to assure adequate use by and assimilation into the body.
2. Each of the PN components should be assessed for appropriateness of dose and for the potential of a compatibility or stability problem.
3. Any dose of a nutrient outside a normal range, that is *not* explained by a specific patient condition or history, shall be questioned and clarified before the PN is compounded.

Special Considerations

Traditionally, the pharmacist is assigned the responsibility of verifying the indication, dose, and use of a drug or nutrient, as is the case with PN. It is recognized that because of the variety in the organization of nutrition support teams, this responsibility may be reassigned to other team members in addition to the pharmacist. Also, some computer programs for PN admixture may be programmed to cue the pharmacist that the PN formulation is inappropriate when nutrient doses are outside an acceptable range.

PN COMPOUNDING

Background

The 1994 FDA Safety Alert (referred to in Section I) highlights the serious consequences that are possible when quality-compounding practices are not in place. The responsibility of the dispensing pharmacist is to assure that the PN is prepared, labeled, controlled, stored, dispensed, and distributed properly.[7] PN formulations are considered medium-risk sterile preparations because of the large number of chemical entities found in the admixture process and the complex nature of PN admixing, whether with gravimetric or automated compounding.[8–10] Serious harm may come to patients receiving a PN formulation that has precipitates resulting from a chemical interaction between components that are present in an excessive dose, exposed to extremes of temperature, or admixed in an improper sequence. Automated or manual methods of PN compounding are available. The compounding of the PN formulation can be accomplished manually through the separate addition of nutrients via syringe and needle delivery or with the aid of sterile solution transfer sets. The manual method allows the pharmacist to decide the order of mixing and should be carefully undertaken to avoid potentially lethal incompatibilities. Alternatively, automated compounding devices are widely available that admix PN under computer-assisted commands connected to special hardware housed with sterile, disposable compounding sets. According to The American Society of Health System Pharmacists (ASHP) guidelines, the risk level of the compounding procedure for automated PN preparations is such that it is recommended that the pharmacist verify data entered into the compounding device prior to PN preparation; perform end-product checks to verify compounding accuracy and, periodically observe the operation of the device to assure it is working properly.[9] Assistance in optimizing the compounding sequence for automated compounding devices should be obtained through consultation with the manufacturer of macronutrients currently used at the institution as well as the manufacturer of the compounding device because brand-specific issues might influence compatibility of the final formulation. PN products premixed by the manufacturer are available in a variety of forms that include, for example, crystalline amino acids with electrolytes, amino acids/dextrose kits as either separate entities or in the same container separated by a divider that can be released or activated to

produce the final admixture. However, even these preassembled units of use packaging may require some level of pharmaceutical compounding in an aseptic environment prior to use.

Professional organizations have published guidelines for compounding and dispensing sterile products. ASHP had published guidelines[10] in 2000 on quality assurance for pharmacy-prepared sterile products, while the United States Pharmacopeia (USP) recently published the official compendium *The United States Pharmacopeia and The National Formulary,* which includes a chapter on pharmaceutical compounding of sterile preparations in 2003.[8] Sterile products are divided into three levels of risk based upon the probability of exposing multiple patients to microbial contaminants (microorganisms, spores, endotoxins) and physical contaminants (foreign chemicals and physical matter). ASHP and the USP use slightly different terminologies for the risk levels of microbial contamination for sterile products compounded within pharmacies. The ASHP guidelines utilize the risk-level classification to the patient from least (level 1) to greatest (level 3) potential based upon the danger of exposing patients to inaccurate ingredients or pathogens. It is also based upon microbial growth factors influenced by product storage time, temperature and product ability to support microbial growth, surface and time exposure of critical sites, and microbial bioload in the environment. Drawing a sterile product into a sterile syringe or transferring a sterile product from a vial into a commercially produced intravenous bag is an example of an ASHP risk level 1 (or a USP low-risk process). Risk level 2 within the ASHP guidelines applies to the automated compounding of PN formulations due to the complex and numerous manipulations of sterile ingredients obtained from licensed manufacturers into a sterile container by using closed-system aseptic transfer. The newer USP compounded sterile preparations (CSP) risk levels are designated as low, medium, and high based upon the corresponding probability of contaminating a sterile preparation with microbial and chemical/physical contamination. These risk levels apply to the quality of CSP immediately after the final aseptic mixing and were adopted as required standards for pharmacies/pharmacists in the United States. Compounding PN formulations is classified by USP as medium-risk level given the multiple injections, detachments, and attachments of nutrient source products to be delivered into a final sterile container. If a non-sterile ingredient such as glutamine is added to the PN formulation, the risk level increases to high. According to the ASHP guidelines and USP standards, all compounded sterile preparations shall be prepared in a class 100 environment, such as a certified horizontal- or vertical-laminar-airflow workbench. Personnel are required to wear clean gowns or cover-alls, as scrub attire by itself is not acceptable. Gloves, masks, hair covers, shoe covers and removal of hand, finger and wrist jewelry are recommended during the compounding process. Mishandling of these preparations has resulted in reports of septic morbidity and even death due to extrinsic contamination.

TABLE I
Beyond-use dating

USP risk level	Controlled room temperature	2°–8°C	≤−20°C
Low	≤48 hours	≤14 days	≤45 days
Medium*	≤30 hours	≤7 days	≤45 days
High	≤24 hours	≤3 days	≤45 days

*Level assigned to PN formulation compounding from USP Chapter 797.

There are two critical factors in establishing beyond-use dating (currently designated as "do not use after" dating) for a PN formulation, namely microbial sterility and chemical stability. Unfortunately, microbial sterility testing of batch-prepared PN formulations rarely occurs in most pharmacies. If sterility testing within the pharmacy is not performed for a PN formulation and literature sources are unavailable supporting beyond-use dating, then the beyond-use dating of the preparation cannot exceed the published limits by the USP (Table 1). Chemical stability is defined as a PN formulation maintaining its labeled strength within 10% until its beyond-use date and is rarely based on preparation-specific chemical assay results. Exposure temperatures during storage and use, characteristics of the sterile container used (e.g., multilayer bags), and hydrolysis or oxidation of ingredients are only a few of the time-dependent factors used to establish chemical stability.

Observing the physical appearance of the final PN formulation is one of the most fundamental quality assurance measures that pharmacists routinely apply. Although it represents a crude measure of compatibility, it does identify gross particulate matter that likely represents the greatest clinical risk of embolic events if infused into the patient. The process generally includes a detailed assessment of the final formulation against a dark background under high-intensity illumination. For translucent intravenous solutions, the highly trained eye is searching for the presence of insoluble particulate matter, such as 'cores' from elastomeric vial enclosures, cotton fibers from alcohol wipes, as well as characteristic indicators of an incompatible formulation such as gas formation, turbidity or haziness, and crystal formation. It is important to remember that in the absence of any obvious physical signs of incompatibility, visual clarity does not equate with safety. Subvisible particulate matter may exist and are capable of inducing an embolic event that originates at the level of the capillaries. However, visual assessments are valuable and necessary in the routine quality assurance process, but they should be supplemented with other safety-enhancing measures that include sufficient documentation of the concentrations of nutrients prepared, use of filters in the manufacturing process or during the infusion, and possibly particle-size analysis when available. Documentation of the daily compounding activities for PN, irrespective of the products or procedures used, should include batch records for all formulations prepared that are consistent with institutional policies and procedures.

For opaque parenteral dispersions such as TNAs, visual assessments can still be performed. The princi-

pal aim of these assessments is focused on signs of phase separation, in which the unstable emulsion is manifested by the presence of free oil either as individually discernible fat droplets or a continuous layer at the surface of the formulation. In general, light creaming is a common occurrence and not a significant determinant of infusion safety except in extreme cases.

PRACTICE GUIDELINES

1. The additive sequence in compounding shall be optimized and validated as a safe and efficacious method.
2. If the manual method currently in use at an institution has not been recently reviewed, or if the contract with a particular manufacturer of macronutrients is about to change, then a review of the compounding method is strongly recommended. This review shall include an evaluation of the most current literature as well as consultation with the manufacturer when necessary.
3. Manufacturers of automated methods of PN compounding shall provide an additive sequence that ensures the safety of the compounding device. This compounding sequence should be reviewed with the manufacturer of the parenteral nutrient products used by the institution. As most institutions in the U.S. are represented by buying groups with many participants, such buying groups should not only ensure the safety and support of the automated compounding device, but should avoid splitting PN contracts (mixing brands of amino acids, dextrose and IVFE) unless such combinations have adequate physicochemical data that ensures the stability, compatibility and safety of the final formulations commensurate with the data for single source PN products.
4. Each PN formulation compounded should be visually inspected for signs of gross particulate contamination, particulate formation and/or phase separation of TNAs.

QUALITY ASSURANCE OF THE COMPOUNDING PROCESS

Background

Numerous cases have been reported of adverse events associated with erroneous final concentrations of dextrose in parenteral fluids. Also, infectious events have occurred from microbial contamination of pharmacy-prepared PN formulations.[11]

In-process or end-product testing of PN should be performed in accordance with USP standards and ASHP guidelines for sterile product admixture.[8–10] Because of the complex nature of PN formulations, these processes may be modified to accommodate the special physicochemical characteristics of PN with use of the methodologies for gravimetric, chemical, or refractometric analysis and in-process testing.

Gravimetric Analysis

Weight-based delivery of PN additives is the principal method by which automated compounders prepare PN formulations. These devices provide a high degree of accuracy and accomplish it in a fraction of the time it takes with use of manual, gravity-fed compounding techniques. In general, as a final check, the PN formulation is weighed and is expected to be within an acceptable margin of error. However, while some automated compounding devices evaluate only the weight of the total contents, other compounding devices weigh the final admixture as well as individual additives. To ensure that certain additives having a narrow margin of safety are assessed individually, pharmacists can apply gravimetric techniques similar to those used by the compounding device. This is particularly important for additives such as potassium chloride and highly interactive salts such as phosphates. In the case of potassium chloride, a 2000-mL final PN volume with a 5% compounding error acceptance means that a 100-mL overfill would be tolerated. If the entire overfill came from the potassium chloride container(s), it could be lethal. Thus individual monitoring of certain PN additives is recommended, and this monitoring can be simply accomplished within the sterile compounding facility each day. The gravimetric method is preferred, with use of the analytical balance associated with the automated compounder.

Chemical Analysis

A random, but continuously applied assessment of the final dextrose concentration is reasonable. One approach is through the use of glucose measuring devices that allow for *direct* assessment of the dextrose concentration. Although these instruments have a limited effective range of detection, appropriate dilutions may be made from a PN aliquot to measure the final concentrations of dextrose and to assure that they are in accordance with the prescribed quantities intended for the patient. When this quality assurance method is devised, it is important to outline a stepwise procedure, validate the findings against appropriate control dextrose solutions, and apply the appropriate error analysis that gauges an acceptable margin of error.

Refractometric Analysis

Refractometers have been used in pharmacy practice for determining dextrose content. However, they may require training and experience in order to obtain consistent and reliable results. In addition, because refractometry measures a physical characteristic of dextrose (e.g., refractive index), it is an *indirect* determinant of dextrose concentration and is subject to interference by other components, as well as to variation in technique from one operator to another and in subsequent interpretation of the final results. As with direct measurement techniques of dextrose concentration, the procedures should be validated in a similar manner to assure the integrity of the results. Refractometers are rendered inoperable with TNAs, and therefore are of no use for these formulations.

In-Process Testing

There are three ways to test the integrity of the sterile compounding process of PN formulations, and

all three can be accomplished at any time before, during, or after the hours of operation for PN preparation. For purposes of this summary, 'in-process' can include any one of the aforementioned periods. The amount of potassium chloride used after each stock bottle exchange, along with the appropriate density conversion for the additive tested, can be determined gravimetrically at multiple points during the day, within the compounding facility. As long as the number of patients who received a portion of the stock from a container is properly recorded, the pharmacist can determine whether the delivery is accurate by analyzing a subset of the PN formulations and can take appropriate action for only those formulations affected, thereby reducing the costs associated with waste if they need to be remade. Similarly, individual PN containers can be analyzed for dextrose content during chemical or refractometric analysis, which can be applied in a cost-effective manner.

In addition to these assessments of hardware function, the software can be similarly challenged to see whether the response is appropriate to the command. For example, if an extraordinary amount of calcium and phosphorus are entered into the compounding program, does the software recognize a potential incompatibility? However, such challenges to the software program are best performed either before or after PN admixture, rather than during the time of operation. Such tests run the risk of an inadvertent compounding command that may be overlooked and could result in dispensing an incompatible and potentially dangerous formulation.

Process validation of aseptic procedures is recommended for PN formulations.[8,10] Individuals involved in PN compounding should successfully complete a process validation of aseptic technique prior to being allowed to admix PN. Process simulation of the PN formulation may also be used but is more difficult since the PN formulation itself may limit or inhibit microbial growth if inadvertently contaminated during the compounding process.

PRACTICE GUIDELINES

1. Gravimetric analyses that indirectly assess the accuracy of the individual additives delivered or the final contents of the PN can be readily applied in the pharmacy practice setting. Particular attention should be focused on the most dangerous additives that tolerate the least margin of error, such as the potassium salts.
2. Chemical analyses that directly measure the final content of the individual additives can be incorporated into the PN compounding operations of the pharmacy. The accuracy of the PN dextrose content is an example of an additive that may be associated with significant morbidity and mortality.
3. Refractometric analysis is an alternative, as well as an indirect measure of the final additive concentration. For example, dextrose concentration is frequently assessed by this technique. However, this method is limited to PN formulations that do not contain IVFE.
4. In-process or end-product testing of PN formulations is recommended daily so as to assure a safe, final formulation is dispensed to the patient.
5. End-product testing of PN formulations prepared with automated compounding devices is recommended to verify compounding accuracy.
6. The aseptic sterile preparation of intravenous admixtures intended for patient administration should adhere to the USP (797) Pharmaceutical Compounding-Sterile Preparations Chapter[8] and the ASHP Guideline on Quality Assurance for Pharmacy-Prepared Sterile Products.[10]

Special Considerations

Use of dual-chamber bags for PN formulations resolve the long-term stability issues of TNA especially for home PN patients. However, aseptic technique issues related to IVFE transfer from the original container to the dual chamber compartment may be similar to those for transfer to syringe as discussed in the PN administration section. This is not known and a process should be in place to assure sterile admixture, storage and administration of the IVFE component of the dual-chamber bag.

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SECTION VI. STABILITY AND COMPATIBILITY OF PARENTERAL NUTRITION FORMULATIONS

PN STABILITY

Background

The stability of PN formulations principally focuses on the degradation of nutritional components over

time. The Maillard reaction ('the browning reaction') is well-known and involves the complexation of carbohydrates by certain amino acids such as lysine, which is facilitated by temperatures used for sterilization of commercial products. Thus the combination of amino acids and dextrose is usually prepared in the pharmacy with stability of the final formulation determined by its storage conditions prior to administration. It is generally recognized that the sterile compounding of any PN accelerates the rate of physicochemical destabilization. Presently, certain amino acids, vitamins and IVFE are most susceptible to instability. Except for an isolated case report, the discoloration of commercial amino acid products forming a bluish hue is not associated with adverse effects. However, the oxidation reaction involving tryptophan that produces the discoloration should be prevented by storage away from light and, preferably, keeping the manufacturer's protective packaging intact until the time of use.

From a clinical perspective, the physicochemical stability of PN formulations is largely focused on vitamins, several of which are known to deteriorate substantially over time and in the presence of oxygen. For the most part, despite their degradation, very few produce clinically significant disturbances in the acute care setting. They tend to be more important in patients with marginal body stores and who are dependent on long-term PN support. The clearest example of this was demonstrated in a case report of a home PN patient who received weekly batches of PN prepared by a hospital pharmacy in which the vitamins were added for a period of up to 7 days. Within 6 months, the patient had night blindness, was treated with a large intramuscular dose of vitamin A, and the symptoms resolved. Six months later, the patient had a relapse in symptoms, prompting an investigation into why the parenteral vitamin supplement was insufficient in meeting the patient's needs. Because the vitamins were added up to a week before the solution was administered, substantial amounts of vitamin A were lost to degradation and adsorption into the plastic matrix of the infusion container. Adding the vitamins to the PN formulation daily just prior to infusion resolved the problem.[1]

Similarly, when ascorbic acid was added in a batch fashion, it degraded and resulted in the formation of a large, discernible precipitate in the PN formulation. Careful analysis revealed that the precipitate was calcium oxalate. Oxalic acid is a degradation product of vitamin C that readily reacts with free calcium. Significant degradation can be avoided by adding vitamins just prior to infusion.[2]

The sterile preparation of L-glutamine for addition to PN poses several concerns. L-glutamine has limited stability in PN formulations, and it requires specialized parenteral manufacturing techniques not routinely available in most institutional or home care pharmacies. The formulation needs to be evaluated to assure that its final contents meet the desired concentration and that it is sterile and free of pyrogens. Assuming the sterile compounding facility is qualified to make such a product, it is the pharmacist's responsibility to quarantine the product and ensure that it passes the aforementioned tests prior to its infusion. In most cases, the quarantine period is at least 7 days in order to complete the microbiological analyses for the appearance of slow-growing pathogens. For products with limited stability, however, USP standards do allow for release of the product prior to the end of the quarantine period. Therefore, although less than ideal, quality control issues arising after quarantine can be dealt with retrospectively.

In addition to the above concerns for PN formulations, the stability of submicron lipid droplets shall also be maintained in TNA dispersions during the period of infusion. Because an anionic emulsifier stabilizes the TNA dispersion and numerous destabilizing cations (e.g., calcium, magnesium, sodium and potassium) are routinely included, the risk of infusing an unstable and potentially dangerous formulation is present. Generally, when producing a TNA, the manufacturer of the IVFE product clearly delineates its physicochemical limitations. The pharmacist is urged to use this brand-specific information and not extrapolate to other products.

The use of dual-chamber bags, whereby for example, the IVFE is physically separated from the remaining admixture components, can enhance the shelf life of TNAs. It's greatest utility appears to be in the home-care setting where batch preparation of PN formulations is most common. Once all the nutrients from both chambers are combined for infusion, the new beyond-use date for completion of infusion should not exceed 24 hours and compatibility should be based on parameters for TNAs.

Although TNAs have been formulated for use in the neonate/infant, stability of lipid particles within the formulation shall be established for each combination of additives before use. The higher content of divalent cations (e.g. calcium and magnesium) can reduce particle zeta potential (negative surface charge), resulting in coalescence. Additionally, the higher content of calcium and phosphate in neonatal/infant PN formulations increases the risk of precipitation, which can go undetected because of TNA opacity.

PN COMPATIBILITY

The complex formulations typical of PN pose several possible physicochemical incompatibilities. The most serious risk of incompatibility in PN formulations and thus the most imminent threat to the patient arises when macroprecipitates exceeding 5 microns develop in the formulation and pass into the central circulation. Two forms of precipitates (solid and liquid) may appear in the prepared formulation. Commonly, the existence of crystalline matter is most frequently cited in PN formulations, yet with the use of TNA, phase separation with the liberation of free oil constitutes the liquid precipitate.

Solid precipitates can develop when an incompatible combination of various salts is added to a PN formulation; this results in the formation of insoluble product. Calcium salts are one of the most reactive compounds and readily form insoluble products with a number of additives. Dibasic calcium phosphate ($CaHPO_4$) is an

example of one of the most dangerous incompatible combinations and has resulted in embolic deaths when infused in the clinical setting. This can be avoided through a variety of measures. First, calcium gluconate is the preferred form of calcium used in multi-component PN formulations. Calcium chloride is far more reactive than an equivalent amount of calcium gluconate salt. Therefore, solubility curves for calcium gluconate cannot be applied to calcium chloride. Second, the order of compounding is extremely important in order to avoid the formation of an insoluble precipitate that would otherwise be soluble if added in the correct sequence. Generally, phosphate should be added first, and calcium should be added near the end of the compounding sequence to take advantage of the maximum volume of the PN formulation. Other risks of forming solid precipitates include the use of bicarbonate salts when indicated to correct a base deficit through the PN. Again, bicarbonate reacts with calcium to form the insoluble product calcium carbonate. If an alkalinizing salt is indicated, then sodium or potassium acetate should be used. The dose of the alkalinizing salt is the same for either bicarbonate or acetate (1 mEq of bicarbonate has the same alkalinizing power as 1 mEq of acetate). Finally, ascorbic acid is a highly unstable vitamin that is sometimes added in supraphysiologic quantities (up to 2000 mg per day) in the PN for its antioxidant effects. However, because of its unstable characteristics, it readily degrades in the presence of oxygen to form oxalic acid, which is also highly reactive with calcium, forming the insoluble product calcium oxalate. Thus the use of this vitamin in supraphysiologic quantities should be given via separate infusion and not in the PN formulation.

Phase separation and the liberation of free oil from the destabilization of TNAs can result over time when an excess of cations is added to a given formulation. The higher the cation valence, the greater the destabilizing power; thus trivalent cations such as Fe^{+3} (from iron dextran) are more disruptive than divalent cations such as calcium and magnesium. Monovalent cations such as sodium and potassium are least disruptive to the emulsifier, yet when given in sufficiently high concentrations, they may also produce instability. There is no safe concentration of iron dextran in any TNA.[3] Of the divalent and monovalent cations, most adult patients' clinical needs can be met without significant concern of producing an unstable and potentially dangerous formulation. Even the order of compounding can cause instability of TNAs, and the compounding sequence shall not place destabilizing additives such as the cations or hypertonic dextrose in close sequence with a minimally diluted IVFE. In general, the pharmacist should be guided by the instructions of the manufacturer for the macronutrients and the automated compounder in use to assure that all PN formulations are compounded optimally, and that they are safe and compatible.

The presence of enlarged lipid globules can be successfully identified if the proper techniques are used. There are only two stages of emulsion destabilization that are visually detectable by the naked eye, namely creaming and coalescence. As visual observation is the most routinely applied quality assurance method employed by practicing pharmacists, an appreciation of the physical signs of TNA integrity is essential. The initial stage in emulsion breakdown is creaming which occurs almost immediately upon standing once IVFE has been mixed with the other chemical constituents. The presence of a cream layer is visible at the surface of the emulsion as a translucent band separate from the remaining TNA dispersion, although the lipid particles in the cream layer are destabilized; their individual droplet identities are generally preserved. As such, this phase (creaming) of emulsion breakdown is still safe for patient administration.

The terminal stage of emulsion destabilization is the coalescence of small lipid particles forming large droplets that may vary in size from 5–50+ microns and pose potential clinical danger yet escapes visual detection. The existence of coalesced lipid particles in a TNA formulation is characterized by the variable presence of yellow-brown oil droplets at or near the TNA surface. In its usual presentation, the free oil may exist as individual spherical droplets or as segmented (discontinuous) oil layers. Careful observation of each TNA formulation is required to detect the subtle appearance of coalescence. In its most extreme form, the oil presents as a continuous layer of yellow-brown liquid at the surface of the formulation that is readily discernible from the remaining dispersion, and can be accompanied by marbling or streaking of the oil throughout the formulation. In either case, the presence of free oil in any form in a TNA should be considered unsafe for parenteral administration[4]. The danger associated with the infusion of unstable lipid droplets enlarged through electromechanical destabilization is unclear. However, the existence of lipid globules 5 microns in diameter comprising 0.4% of the total fat present has been shown to be pharmaceutically unstable, and such formulations are considered unfit for intravenous administration.[3]

Finally, standard PN formulations have been useful to organizations whereby the physicochemical stability and compatibility are assured via adequate documentation by the institution or the manufacturer of PN products. Such standardization limits the risk of compounding and dispensing potentially unstable or incompatible PN formulations. However, any change in the composition of standard formulations needs to be applied cautiously and with adequate assurance that the new or revised formulation is stable and compatible.

Medication Administration with PN

Since PN is infused intravenously, it is often considered as a vehicle for medication administration. Due to the complex nature of PN and potential for physicochemical interactions with drug-nutrient combinations, admixture of medications with PN is not advised. However, there are occasions when there is no other reasonable alternative. When this occurs, the predominant admixture issues that need to be resolved include the following[5]:

- medication stability and compatibility with the PN or TNA is assured;
- evidence supports the clinical value of the medication administered in this manner.

Insulin use with PN. Insulin is commonly administered with PN. As noted in the Introduction, it is also associated with frequent harmful events. This is related to the variable methods used to control blood glucose levels in patients receiving PN. No one method of glucose control has been shown to be superior. Insulin requirements are generally higher and most variable during the first 24 hours of intensive care for critically ill patients. Strict serum glucose control at a value less than 110 mg/dL with a separate continuous insulin infusion has been shown to improve clinical outcomes (i.e. shorter ICU stay, ventilator use and mortality) in select surgical critically ill patients.[6] Due to the potential for serious adverse events, insulin use in PN should be done in a consistent manner adhering to a defined protocol, in which healthcare personnel have adequate knowledge. One such approach can be summarized as follows:

Hyperglycemia and insulin resistance occur frequently in patients receiving PN. Diabetic patients receiving PN have been shown to have a 5-fold increase in catheter-related infections compared to nondiabetics.[7] Clinical studies suggest that carbohydrate administration via PN greater than 4–5 mg/kg/min or greater than 20–25 kcal/kg/day exceeds the mean oxidation rate of glucose, giving rise to significant hyperglycemia, lipogenesis, and fatty liver infiltration.[8] Although no clear consensus exists for the ideal level of glucose control in the hospitalized patient receiving PN, a reasonable target is a blood glucose level of 100 to 150 mg/dL.

Many approaches can be used to achieve appropriate glucose control in patients with diabetes or stress-induced hyperglycemia receiving PN. Patients should not receive more than 150 to 200 grams of dextrose on day 1 of PN. For patients previously treated with insulin, oral hypoglycemic agents, or patients with a fasting glucose concentration 200 mg/dL but in whom hyperglycemia is likely to occur, no more than 100 grams of dextrose per day should be administered. A basal amount of human regular insulin should also be added to the PN formulation to keep blood glucose concentrations less than 150 mg/dL in patients previously treated with insulin or oral hypoglycemic agents. (NOTE: only regular human insulin is compatible with PN formulations; other insulin products such as NPH, ultralente, lente, lispro, aspart, and glargine are NOT compatible with PN). A common initial regimen is 0.1 units of insulin per gram of dextrose in the PN infusion. If the patient is already hyperglycemic (>150 mg/dL), 0.15 units of insulin per gram of dextrose should be used.[9] If the blood glucose is 300 mg/dL, PN should not be initiated until glycemic control is improved (< 200 mg/dL). Obese patients with type 2 diabetes may require as much as 0.1 units of insulin for every 0.5 grams of dextrose whereas thin, type 1 diabetics may require only 0.1 units of insulin per 2 grams of dextrose.[10] In general, the dextrose content of the PN should not be increased until glucose concentrations during the previous 24-hour period are consistently <200 mg/dL. If glucose is controlled with a specific insulin dose, the dose of insulin must be reassessed whenever the dextrose dose is modified.

Capillary glucose levels should be monitored every 6 hours and supplemented with an appropriately dosed sliding-scale insulin coverage given subcutaneously as needed to maintain glucose in goal range. Once glucose concentrations are stable, the frequency of measuring capillary glucose concentrations often can be decreased. The insulin dosage in the PN formulation ratio is modified daily based on the amount of insulin given with sliding-scale insulin coverage over the previous 24 hours. If hyperglycemia persists when 0.3 units of insulin per gram of PN dextrose is exceeded, initiation of a separate intravenous insulin infusion should be used to achieve more appropriate glycemic control. In a patient whose insulin needs are dynamic or difficult to predict (e.g. infection, inflammatory response), a separate intravenous infusion is preferred.

Another method of medication administration with PN is co-infusion through the same intravenous tubing. This should be avoided unless physical and chemical compatibility of the medication with the PN formulation is assured prior to its administration in this manner. Studies[11,12] of medication compatibility with PN found that the compatibility differed for TNA versus 2-in-1 formulations, emphasizing that compatibility in one formulation does not predict compatibility in the other. As such, compatibility information should be derived for PN that closely match the formulation prescribed for the patient in question. If the medication is not compatible with PN, the PN infusion should not be interrupted for medication administration. The medication should be administered via another intravenous route. Finally, the compatibility of some medications with a TNA may be dependent on drug concentration. For example, morphine sulfate is compatible with TNA at a concentration of 1 mg/ml but not 15 mg/ml.

PRACTICE GUIDELINES

1. The dose, admixture preparation, packaging, delivery process, and storage and administration method should be confirmed to ensure that the PN is stable and all components are compatible.
2. The responsible pharmacist should verify that the administration of drugs with PN either admixed in the PN or co-infused through the same intravenous tubing is safe, clinically appropriate, stable, and free from incompatibilities.
3. If there is no information concerning compatibility of the medication with PN, it should be administered separately from the PN.
4. Compatibility information should be evaluated according to concentration of the medication used

and whether the base formulation is a 2-in-1 or a TNA.
5. Insulin use in PN should be done in a consistent manner according to a method that healthcare personnel have adequate knowledge.
6. Decisions related to stability and compatibility are made according to the most reliable information available from the literature or manufacturer of intravenous nutrients. If no information exists, stability and compatibility of the PN shall be determined in consultation with the manufacturer before it is dispensed to the patient.
7. Given the limited amount of published stability information available, the use of a 2-in-1 formulation with separate administration of IVFE is recommended for neonatal/infant patients.

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SECTION VII: PARENTERAL NUTRITION ADMINISTRATION

Optimal, safe PN administration requires an adequate understanding of multiple integrated key concepts. Comments from respondents to the 2003 Survey of PN Practices noted several problems with administration including; incorrect PN rate and volume and PN administered to the wrong patient or via the wrong venous access site. This section will address the concepts pertinent to safe administration of PN including: proper venous access device selection, care and assessment; appropriate use of the medical equipment needed to deliver the PN solution; the chemical properties of the PN formulation itself and monitoring the patient's response to the PN therapy. The institutional use of PN from home or another facility is an issue addressed in this section.

VENOUS ACCESS SELECTION, CARE AND ASSESSMENT

To safely and properly administer PN, the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters and appropriate infection control measures to prevent catheter-related infections shall be understood.

The proper selection of a venous access site (central vs peripheral vein) depends on nutrient requirements and duration of PN.[1–6] Due to the hypertonic nature of most PN formulations, it is recommended that the PN be administered through a central venous access catheter (CVC) with tip placement in the superior vena cava[2] adjacent to the right atrium.[4,7] Proper catheter tip placement also reduces the risk for cardiac injury[7] and decreases the chance for problems infusing or withdrawing fluids from the catheter.[4] Infusion of PN via a peripheral vein requires careful consideration of the formulation's osmolarity along with judicious monitoring of the venous access site for signs of phlebitis and/or infiltration. Since 10% and 20% IVFE products are isotonic, they may be infused separately via a peripheral vein or as part of a TNA when osmolarity does not exceed 900 mOsm/L.[8]

In general, selection of the most appropriate parenteral access device is based on the patient's vascular condition, vascular anatomy, vascular access history, type and duration of therapy, coagulation status, care setting (acute care, long-term care, and home care) and underlying disease. Additional considerations when selecting a venous access device for PN include the patient's physical ability to care for the catheter, cognitive function, activity level, body image concerns and caregiver involvement. Temporary percutaneous nontunneled CVCs (subclavian, jugular) are most often used in the acute care setting for short duration therapy. Femoral CVC's are associated with a higher risk of venous thrombosis and catheter related sepsis; they are not recommended for PN administration unless no other venous access can be attained.[9] In circumstances where the tip of the femoral catheter is not located in the inferior vena cava, adjustment of the PN content to effectively reduce the osmolarity similar to peripheral PN is recommended. Care and maintenance of the femoral catheter should be with the same vigilance as any other CVC. Tunneled percutaneous catheters (e.g. Hickman®, Groshong®) or implanted subcutaneous infusion ports are most appropriate for long-term therapy outside of the acute care setting. The peripherally inserted central catheter (PICC) for central venous access is used for PN administration in a variety of health care settings. The PICC is a reasonable CVC option to consider if the anticipated length of PN is weeks and not long-term provided the appropriate placement of the catheter tip can be achieved and verified. Generally, tunneled catheters or implanted ports should be considered for longer access durations and more permanent therapy.

Guidelines have been developed for the daily care and maintenance of the catheter once the proper CVC is inserted.[3,6] Prior to the initial administration of PN through a CVC, and any other time there are signs/symptoms indicative of a compromised catheter position, the catheter tip location shall be verified radiographically. Proper catheter tip placement shall also be confirmed and or validated in the pediatric patient as growth and maturity occur. The infectious complications of PN administration are also reduced when catheter access devices are dedicated solely to PN usage (or the designation of one port solely for PN administration if a multi-lumen catheter is used) and catheter manipulations are minimized.[3] Reductions in catheter associated sepsis have been reported when nurses are educated in the proper care of the CVC based on established standards and guidelines.[1,3] If continued care and monitoring is required beyond the acute care setting, it is the health care provider's responsibility to ensure education of the patient and/or caregiver in proper care techniques.

MEDICAL EQUIPMENT FOR PN ADMINISTRATION

Filters

The use of in-line filters has been recommended during the administration of intravenous products such as PN formulations.[6,10–12] The rationale for this recommendation is related to the filter's ability to eliminate or reduce infusion of particulates, microprecipitates, microorganisms, pyrogens and air. Due to the multiple additives used to prepare PN formulations, a large number of *particulates* may contaminate the fluid being administered. Particles of 5 microns or larger are capable of obstructing blood flow, which could lead to complications such as pulmonary embolism. These foreign particles may also produce phlebitis at the injection site, a therapy-limiting problem when PN is administered peripherally. An in-line filter can reduce the incidence of phlebitis.

M*icroprecipitates* form under certain pH and temperature conditions such that the rate and extent are dependent on these factors in addition to the concentration of PN additives. Microprecipitates of calcium phosphate are known to cause serious problems. Initial visual inspection of PN is a primary method to avoid problems with microprecipitates but this cannot be relied upon since it is unlikely the precipitate will form instantaneously. In most situations, precipitates may take hours to develop. As such, visual inspection of the PN formulation should be done periodically throughout the compounding, dispensing and administration processes. Visual detection is limited however since particles <50 microns cannot be easily detected with the unaided eye and problems are possible with particles of this size. Since particles may clog filters, filters have been criticized because they may require frequent nursing interventions. It should be recognized that a clogged filter and associated infusion pump alarm is a potential sign of a precipitate. It is never appropriate to remove a clogged filter and allow the formulation to infuse without a filter.

Use of a 0.22 micron filter for PN administration can remove *microorganisms* but this practice is limited to use with 2-in-1 formulations. The integrity of the IVFE is compromised when infused through filters <1.2 microns in size. A 1.2 micron filter however does not remove most microorganisms from a contaminated PN formulation even though it is effective in removing particulates and microprecipitates. PN formulations are considered high-risk admixtures and can become contaminated during compounding or administration setup. There have been frequent reports of patient infections caused by contaminated PN fluids. The use of aseptic technique in preparation and administration of PN formulations is critical to avoid infections due to contaminated PN formulations.

Filters have been shown to be effective in removing pyrogens from 2-in-1 formulations and those with air venting can prevent air emboli. The use of filters may reduce the potential for contaminated PN formulations to infect a patient but do not eliminate the possibility. As such, the CDC does not recommend in-line filters solely for infection control purposes.[3]

Use of in-line filters has limitations. They can cause decreased flow rates, clogs, or air locks. This may lead to increased manipulation of the intravenous administration set, creating a potential for microbial contamination. For PN administration, a 0.22 micron filter is recommended for a 2-in-1 formulation. A 1.2 micron filter should be used for TNAs. When considering particulate and microprecipitate contamination only, a 1.2 micron filter can be used for all PN formulations.

Infusion Pumps and Administration Sets

Specific recommendations also exist to guide the use of PN administration tubing sets. PN administration sets shall be changed using aseptic technique and universal precautions.[3] Changes of "add on devices" to the PN administration set (e.g., extension tubing, filters or needle-less devices) should coincide with changing of the PN administration set to maintain the entire PN administration system as a closed system.[6] TNA administration sets are changed every 24 hours and immediately upon suspected contamination or if the product integrity has been compromised.[2,3,6] Administration sets used for separate IVFE infusions (not TNA) are discarded after each unit is infused, unless additional units are administered consecutively. When separate IVFE infusions are administered consecutively, the administration set shall be replaced every 24 hours.[3,6] As with TNA, lipid emulsion sets are changed immediately if contamination is suspected or if the product integrity has been compromised. Administration sets infusing PN formulations containing only dextrose and amino acids shall be changed every 72 hours.[3] PN final containers and administration sets free of the plasticizer; di (2-ethylhexyl) phthalate (DEHP) shall be used to prevent DEHP contamination of TNAs or separate IVFE infusions.[13] Since DEHP is highly lipophilic, IVFE are capable of extracting DEHP from the polyvinylchloride (PVC) final containers and administration sets. Concern over adverse effects from DEHP is related to its potential for neurotoxicity, car-

cinogenicity, and hepatotoxicity in animals. Use of DEHP-free bags and tubing is especially important in chronic long-term patients, pregnant patients, and pediatric patients receiving PN.

Intravenous (IV) infusion pumps are an integral component of PN administration.[2,5,6] Use of an electronic infusion pump to safely administer PN is recommended.[2,6] Infusion pumps assure accurate volume (rate) control and contain safety alarms (visual and auditory) for sensing air and pressure changes in the IV tubing; some pumps also have a programmable rate cycling feature to minimize infusion errors. These features are important to PN because of the hypertonic nature, fluid volume, dextrose and potassium content of PN formulations. JCAHO National Patient Safety Goals include recommendations for infusion pumps.[14] Free-flow protection is important to the safety of PN administration to avoid serious harm caused by rapid administration of potassium and dextrose. Regular preventative maintenance and testing should assure proper functioning of clinical alarm systems because health care practitioners administering the PN, and individuals receiving the PN, rely on those alerts to optimize safe infusion of the PN formulation.

Safe administration guidelines are not only intended to protect those patients receiving PN, they are also important to protect the health care provider administering PN from blood-borne pathogens. Health care providers face daily exposure to blood when administering PN via a venous access device. Among the risks are human immunodeficiency virus (HIV), hepatitis B and hepatitis C. Federal government agencies have published standards to prevent needle-stick injuries in health care settings, as well as, enforcement procedures for the occupational exposure to blood-borne pathogens.[15,16] In 2000, the Needle-stick Safety and Prevention Act was signed into law and in 2001, incorporated into the revised OSHA Blood-borne Pathogen Directive.[17] The Act highlights the importance of using new technologies and requires employers who are currently covered by the Blood-borne Pathogen Standard to evaluate and implement medical devices that reduce the risk of needle-stick injuries, as well as, eliminate or reduce exposure to blood-borne pathogens. Health care providers administering PN should take an active role in identifying, evaluating and selecting effective medical devices to reduce their exposure to blood-borne pathogens. Examples of compliance for PN administration is the use of a commercially available needle-less system to draw blood or applying a needle-free catheter patency device to a CVC to eliminate the back flow of blood into the catheter lumen. It is important to note that the Needle-stick Safety and Prevention Act changes OSHA's 1991 Blood-borne Pathogens Standard from an "agency directive" to a law, enforceable in the same manner as any other OSHA public law.

ADMINISTRATION ISSUES RELATED TO PN ADMIXTURE PROPERTIES

Prior to PN administration, the identity of the patient is verified using at least two identifiers.[14] The PN label is reviewed for accuracy, expiration date and patient identity. Also, the PN formulation and container is visually inspected for leaks, color changes, emulsion cracking, clarity and expiration dates. Do not use any parenteral fluid that has expired, has visual turbidity, leaks, emulsion cracking or particulate matter.[3] The TNA presents a more complex scenario for inspection because of the inability to visualize precipitate or particulate matter in the opaque admixture.[18] It is essential to visually assess the TNA for destabilization or separation of the lipid components. Any TNA that exhibits evidence of destabilization (heavy creaming, cracking or discoloration) shall not be administered or shall be discontinued immediately if the solution is already infusing.[19,20] The pharmacist evaluates the TNA formulation before dispensing, and the nurse, patient and/or caregiver is responsible for ongoing evaluation of the TNA while it is infusing.

As discussed previously, IV medications are frequently prescribed for patients receiving PN. Published information regarding PN compatibility with parenteral medications is available, but limited.[1,20–23] The appropriate administration of parenteral medications to individuals receiving PN is based on stability and compatibility data. It is recommended that stability and compatibility data be validated if the medication is expected to have direct contact with the PN. If an incompatibility or unstable condition exists, or if there is no information available, the medication should be administered separate from the PN.

The characteristics of IVFE favor an environment in which pathogenic organisms can thrive. These 10% and 20% preparations are nearly iso-osmotic (250–290 mOsm/L), have a near-neutral alkaline pH (pH = 7.5), and contain glycerol, all of which are conducive to the growth of microorganisms. However, when IVFE are combined with crystalline amino acids and hydrated dextrose to form TNA, the pH drops (pH~6.0) and the osmolarity increases to provide a poor growth medium.[24] Several reports of microbial growth potential in commercially available IVFE bottles prompted the Centers for Disease Control and Prevention in 1982 to limit the "hang time" to 12 hours after the manufacturer's container is spiked with the appropriate administration set. IVFE have been associated with reports of fungemia in the neonatal population, including both *Candida* species and *Malassezia furfur*.[25–27] It appears that IVFE were administered as separate infusions in these reports. When IVFE is transferred from its original container to another sterile device (e.g., syringe) or recipient container for infusion separate from PN, one could argue that a more conservative 6-hour hang time should be followed. This recommendation would be consistent with the FDA-approved labeling for propofol (Diprivan®) emulsion when manipulated for administration via a syringe delivery system, even with the existence of antimicrobial agents not present in IVFE manufactured for nutritional use. A standard for product dating of prepared sterile dosage forms when the product is altered from its original packaging has recently been revised by the United States Pharmacopeia (USP).[28] The USP refers to this newly assigned date as the "beyond-use date" and it limits the time period in which the product can be used in patients.

Because of the concern for microbial contamination, the USP recommends that IVFE products be used within 12 hours of opening the original container if they are to be infused as a separate infusion. The infusion rate should not exceed 0.125 g/kg/hr, thus a 200-mL bottle of 20% IVFE should not be infused more rapidly than over 6 hours (0.095 g/kg/hour) in the 70-kg reference man. If a slower infusion is desirable and the selected rate of administration exceeds 12 hours, then the lipids shall be given in two separate bottles so as not to exceed a 12 hour hang time for any single container. If the IVFE is admixed directly to the PN to form a TNA, the final PN formulation can be infused over a 24-hour period since it provides a safe vehicle with respect to infectious risks.

Patient Response to PN Administration

No discussion of safe PN administration would be complete without briefly mentioning a few key monitoring concepts unique to the patients receiving PN. Considerable cost and serious complications are often associated with PN administration. Once it is determined that the individual will receive PN, goals for nutrition support should be set with specific markers and outcomes to be measured.[1,29] These goals may include improved or replenished protein stores, normalization of clinical laboratory values, and reduction in morbidity/mortality and improvement in quality of life or optimization of clinical outcomes. Monitoring individuals receiving PN is necessary to determine the efficacy of the specialized nutrition therapy; detect and prevent complications; evaluate changes in clinical condition and document clinical outcomes. All patients receiving PN should be monitored for fluid and electrolyte imbalances, proper blood glucose control and signs/symptoms of CVC infections. Typically, laboratory monitoring of serum chemistries and visceral proteins are more frequent when PN is initiated and then decrease in frequency as clinically indicated. The health care provider is also alert to potential changes in fluid status and should closely monitor intake and output, edema, vital signs and weights with attention to changes, patterns or trends that could indicate problems or progress toward achieving nutritional goals. Regular assessment and meticulous care of the parenteral access device assures a reliable delivery system for the PN and minimizes the chance for infection. It is important that the healthcare provider periodically compare the actual PN nutrients delivered to the patient with the recommended measured or estimated nutrition needs to assure optimal treatment. Patients may tolerate the PN infusion better if the refrigerated PN is removed from the refrigerator 30–60 minutes prior to the scheduled infusion times; PN patients occasionally complain of discomfort while the chilled solution is infused into the central circulation.[6] Individuals receiving their first PN formulation should be monitored closely for any adverse reactions. Compatibility and stability of a new parenteral medication shall be assured along with a review of the medication profile for potential effects on safe administration of other medications. It is also important to reassess gastrointestinal function and readiness for oral/enteral feeding if the patient's clinical condition should change.

IVFE infusion in hypertriglyceridemic patients. Confusion surrounds the safe administration of IVFE in patients with hypertriglyceridemia. As previously mentioned, several investigators have determined that the rate for infusion of IVFE not exceed 0.125 g/kg/hour in order to avoid serious metabolic effects.[30] Thus, IVFE should be infused at rates to avoid serum triglyceride levels >400 mg/dL in adults and >200 mg/dL in neonates. The clinical consequences associated with hypertriglyceridemia in both adults and neonates include an increased risk of pancreatitis, immunosuppression, and altered pulmonary hemodynamics, while hypertriglyeridemia in the preterm infant with physiologic jaundice and hyperbilirubinemia (>18 mg/dL) is associated with kernicterus. Doses of IVFE should be limited to the provision of EFAs (e.g., 250 mL of 20% IVFE, once or twice weekly) when triglyceride concentrations rise above 400 mg/dL in adult patients. Temporary interruption of IVFE infusions for 12 to 24 hours are recommended when serum triglyceride concentrations exceed 275 mg/dL in neonates and infants; a decrease in infusion rate by 0.02–0.04 g/kg/hour is suggested when IVFE infusions are restarted.[31] Withholding IVFE in adults shall be considered when serum triglyceride concentrations are greater than 500 mg/dL. The presence of excess phospholipid content of 10% versus 20% IVFE is also associated with greater plasma lipid alterations. The excess phospholipids produce lipoprotein X-like substances that can compete with chylomicron remnants for hepatocyte binding sites. This can interfere with lipid clearance by delaying peripheral hydrolysis of triglycerides by lipoprotein lipase. Use of 20% IVFE allows for more efficient triglyceride clearance and metabolism.

In conclusion, there is extensive attention directed towards monitoring the patient's physiologic response to PN therapy; it is equally important that the individual's developmental, emotional and psychological responses to the PN also be assessed and monitored.

Use of PN Prepared by Another Facility

Organizations commonly admit patients from another facility or home who are receiving PN. The admission may or may not be directly related to the PN or underlying disease. These organizations are frequently in the position of dealing with PN formulations brought in from home or infusing into patients transferred from other inpatient facilities. Due to the complex nature of PN formulations from a dosing, compatibility, sterility and stability perspective, the use of the PN by the organization is a difficult issue. Evidence to support, guide or describe current practices is lacking so the issue was addressed in the 2003 Survey of PN Practices. As discussed in the introduction, there was no consensus as to whether PN formulations compounded elsewhere should be administered in the admitting organization's facility. Several points for consideration (pro or con) were identified in the comments to the survey question along with Task Force input (Table I).

TABLE I
Pros and cons: use of PN compounded by another facility

Reasons for use	Reasons not to use
Prevents wastage of unused home PN	Inability to adequately validate PN integrity from a stability and sterility perspective
Provides specific information concerning PN contents and therapy	Creates billing and reimbursement issues
PN formula may contain products not available to admitting organization	Medico-legal responsibility for PN administration problems unclear
Avoids an interruption in therapy	Unfamiliar PN tubing set or infusion pump

If the PN was infusing at the time of patient admission, responders to the question stated that it was allowed to finish then the hospital pharmacy prepared all subsequent PN formulations. In another scenario, if the PN was compounded by the health care systems' own home infusion pharmacy, the PN was allowed to be used.

There is no consensus to the problems addressed therefore; it is difficult to provide specific guidelines. Guidelines for use of oral medications from home referred to as 'bring-in' medications (i.e., patient's own supply) have been developed and may provide some insight when considering PN formulations brought in from an outside facility. Principles addressed in these guidelines[32] are outlined as follows:

- The use of a patient's own supply in the hospital should be avoided unless they are not obtainable by the pharmacy;
- If used, a physician order shall be written.
  - The identity of the medication should be verified
    - If not identifiable, it shall not be used.
  - It should be dispensed as a part of the pharmacy distribution system, not separate from it.

PN formulations are much more complex than oral medications. It may also be prudent to consider the following for PN:

- A policy and procedure is developed to address the issue.
- When the use of PN is allowed, a physician's order is required.
  - All components of the PN formulation are entered into the patient's medical record as an active order.
- Issues related to maintaining PN integrity during storage, delivery and administration are resolved.
- If there is any reason that the compounding or storage conditions of the PN formulation have been compromised, its use shall not be allowed.
- The appropriateness of the PN formulation for the patient's current condition is assured prior to its administration.

PRACTICE GUIDELINES

1. Central PN is administered via a CVC with the distal tip placed in the superior vena cava adjacent to the right atrium.
2. The use of femoral catheters for PN administration should be avoided.
3. Proper CVC tip placement shall be confirmed prior to initial PN administration and/or any other time signs/symptoms indicate an improper catheter position. Proper CVC tip placement shall also be confirmed/validated in the pediatric patient when there has been significant growth.
4. Care and maintain venous catheters used for PN according to published standards.
5. Equipment used to administer PN formulations shall be selected based on the safest mode of delivery for both the patient and the healthcare provider.
6. A 1.2 micron filter may be used for all PN formulations. Alternatively a 0.22 micron filter may be used for 2-in-1 formulations.
7. A filter that clogs during PN infusion may be indicative of a problem and may be replaced but shall never be removed.
8. PN final containers and administration sets shall be free of the plasticizer, DEHP if IVFE is a component of the nutrient regimen.
9. Administration sets for IVFE infusions separate from PN formulations shall be discarded after use or if the IVFE is infused continuously, at least every 24 hours.
10. Administration sets for TNA are changed every 24 hours.
11. Administration sets for 2-in-1 formulations are changed every 72 hours.
12. PN is to be administered via an infusion pump having adequate protection from 'free flow' and reliable, audible alarms.
13. Medical devices for PN administration should be used that minimize risk of needle-stick injuries and exposure to blood-borne pathogens.
14. Prior to PN administration, the patient's identity is verified and the PN label is reviewed for accuracy and expiration dates.
15. Visually inspect each PN prior to administration, do not infuse the PN formulation if visual changes or precipitates are apparent.
16. The PN infusion shall be completed within 24 hours of initiating the infusion.
17. IVFE infused separately from PN formulations shall be completed within 12 hours of entry into the original container.
18. The patient receiving PN should be monitored to determine the efficacy of the PN therapy; detect and prevent complications; evaluate changes in clinical conditions; and document clinical outcomes.
19. A policy and procedure should be in place to deal with the use of PN formulations prepared by an outside facility.

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