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Clinical Considerations for Neonatal Starter Parenteral Nutrition

Document Contents:

Note: These clinical considerations do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, the primary component of quality medical care is the result of the professional judgment of the healthcare professionals providing care. The information presented here is not a substitute or replacement for the exercise of professional judgment by healthcare professionals; rather, it is intended to supplement professional training and judgment. Circumstances and patient specifics in clinical settings may require actions that differ from those recommended in this document; in such cases, the judgment of the treating professionals should prevail. Use of this information does not in any way guarantee any specific benefit in outcome or survival.

Questions regarding these recommendations should be directed to clinicalpractice@nutritioncare.org.

Introduction

The American Society for Parenteral and Enteral Nutrition (ASPEN) is aware of the announced discontinuation of certain 503B sterile compounding services that have historically supplied standardized compounded neonatal starter parenteral nutrition (PN) products to healthcare organizations throughout the United States.

Neonatal starter PN is an important component of care for premature and critically ill newborns, providing timely initiation of amino acids and dextrose during the first hours of life while patient-specific PN formulations are prescribed and prepared.[1] The anticipated reduction in availability of these products has the potential to create operational and clinical challenges for hospitals that care for this vulnerable population, particularly those facilities with limited compounding capabilities. For many of these facilities, there may be no readily available alternative that provides the same combination of immediate availability, standardized formulation, and extended beyond-use dating as the previously outsourced products.

ASPEN recognizes the importance of identifying safe, evidence-based strategies to maintain timely access to neonatal nutrition support while minimizing risks associated with workflow changes, in-house compounding, and alternative approaches. These clinical considerations are intended to support clinicians and organizations in providing safe, appropriate, and timely nutrition support to neonates.

Methods

ASPEN convened an interprofessional group of clinicians with expertise in neonatal starter PN to support this effort. A narrative review of the literature was conducted, and draft considerations were created based on available evidence, clinical expertise, and interprofessional discussion. A critical review of these considerations was conducted by a broader group of interprofessional subject-matter experts and partner organizations, including the American Society of Health-System Pharmacists, the Children's Hospital Association, the Institute for Safe Medication Practices, and the Pediatric Pharmacy Association. These considerations were approved by the ASPEN Board of Directors.

Definition and Purpose of Neonatal Starter PN

Neonatal starter PN is a standardized PN formulation intended for use in indicated neonates as a temporary bridge until a patient-specific PN formulation is prepared. It should be initiated promptly after birth, once appropriate venous access has been established.[2] Neonatal starter PN is a high-alert medication,[3] subject to PN-specific guidance and recommendations.[4,5]

Patients should be transitioned to a patient-specific PN formulation within 24 hours, but no later than 48 hours of birth. Neonatal starter PN should not be used as a substitute for a patient-specific PN formulation because it does not provide the complete macronutrient and electrolyte requirements for each patient.[2]

Indications for Neonatal Starter PN

Neonatal starter PN should be initiated promptly after birth, once appropriate venous access has been established, in patients with **very low birth weight (<1500 g).**[6] Clinical judgment should be used to determine whether a higher birth weight threshold is appropriate based on the infant's clinical condition. A patient-specific PN formulation should be initiated as soon as feasible, within 24 hours, but no later than 48 hours of birth.

Institutions should establish and protocolize criteria for the use of neonatal starter PN, considering patient population, clinical indications, compounding capabilities, and other institution-specific workflow and operational considerations.[7]

Composition of Neonatal Starter PN

Neonatal starter PN formulations are standardized, and the use of a minimally complex formulation may reduce the risk of prescribing, compounding, dispensing, and administration errors. Historically, neonatal starter PN formulations have contained pediatric-specific amino acids, dextrose, calcium, and heparin.[8] Both the literature examining the safety and efficacy of neonatal starter PN that omits calcium and/or heparin and clinical experience with neonatal starter PN that omits calcium and/or heparin are limited. Additionally, there is insufficient evidence to support one specific neonatal starter PN formulation as superior to another with respect to patient outcomes. Therefore, formulation selection should be guided by clinical judgment, available stability and compatibility data, and institutional protocols. When inclusion of calcium and/or heparin adds complexity to compounding that impacts safety or limits the availability of neonatal starter PN, a simplified formulation containing the following at a minimum may be considered:

1. **Pediatric-specific amino acids** (e.g., Trophamine, Premasol, and Aminosyn-PF) **at a final concentration between 3-4%.**
2. **Dextrose at a final concentration between 5-10%.** Consider whether the prescribed volume provides an appropriate glucose infusion rate for the intended patient population.

The inclusion of calcium and heparin may be considered based on clinical judgment, patient population, anticipated duration of therapy, and the results of specific institutional risk assessments related to institutional protocols. The rationale for the potential inclusion of calcium and heparin is described below.

Calcium:

It is well established that calcium is an essential nutrient for neonates to support calcium homeostasis and bone mineralization,[1,9] and it is a required component of patient-specific PN formulations intended to meet nutrient requirements.[10] However, to date, there is limited evidence comparing outcomes of neonates who received calcium versus those who did not in neonatal starter PN during the first 24-48 hours of life. Additionally, there is some clinical experience with neonatal starter PN formulations without calcium, with anecdotal reports of safety and effectiveness. Importantly, these reports are based on initiating a patient-specific PN formulation that includes calcium, ideally within 24 hours and at most within 48 hours of birth.

Therefore, calcium is not considered an inherent requirement of neonatal starter PN, though there is sound physiologic reasoning for its early inclusion in neonatal nutrition support. A specific organizational risk assessment should be conducted before determining whether to include calcium in neonatal starter PN.

Heparin:

Due to concerns regarding catheter patency in neonates, heparin has historically been added to neonatal starter PN for two primary reasons: 1) to prolong catheter patency and 2) to potentially reduce catheter-related complications (eg, thrombosis, occlusion).[11] Importantly, heparin is a high-alert medication with the potential for medication-related harm.[3]

Current available evidence on the addition of heparin to neonatal infusions is difficult to directly apply to whether heparin is required in neonatal starter PN.[12-16] Neonatal starter PN administration is short in duration, limiting the applicability of a catheter-patency benefit or of clinical outcomes such as time to catheter or vessel occlusion. Additionally, catheter-related complications vary by catheter type,[17] limiting the applicability of literature examining a specific catheter type because neonatal starter PN may be administered through different types of vascular access devices. The amount of heparin in the PN and the methods of administration also differ across studies. Importantly, evidence of a catheter-related benefit does not establish its requirement in neonatal starter PN.

Therefore, heparin is not considered an inherent requirement of neonatal starter PN. However, organizational vascular-access and catheter-management practices should be considered when determining whether to include heparin in neonatal starter PN.

Additional Composition-Related Considerations:

- **Volume:** The volume of neonatal starter PN should be appropriate for the anticipated needs of the patient population. Avoiding unnecessarily large volumes may help minimize waste, facilitate appropriate storage, and prevent administration errors.
- **Compatibility and Stability:** Manufacturer-specific stability and compatibility data should guide compounding practices.
- **Osmolarity:** When PN is administered peripherally, the final formulation should be limited to a maximum osmolarity of 900 mOsm/L.[5]

Ordering and Compounding Considerations for Neonatal Starter PN

Institutions that compound neonatal starter PN should ensure compliance with USP <797> requirements.[18] Appropriate equipment, PN components, personnel training, and quality assurance processes should be established before initiating in-house compounding.

A formal risk assessment should be performed to determine whether neonatal starter PN can be compounded safely within the institution's existing pharmacy infrastructure and workflow. Beyond-use dates (BUDs) should be assigned in accordance with applicable USP <797> requirements and should consider the compounding category and process, sterility assurance, storage conditions, and available stability data. Despite the longer maximum BUD permitted for Category 2 Compounded Sterile Preparations (CSPs) using only sterile starting components under current USP <797>, these limits are based on sterility considerations and do not account for PN stability considerations.[17] **In the absence of stability data supporting a longer BUD, the BUD of neonatal starter PN compounded under USP <797> Category 2 conditions should not exceed 9 days refrigerated or 30 hours at controlled room temperature, consistent with PN-specific limits previously established in USP <797>.[19,20] Category 1 CSPs, which may be compounded in a segregated compounding area rather than a cleanroom suite, are subject to shorter BUDs under USP <797>.** Preparation of neonatal starter PN under the USP <797> immediate-use provision (eg, preparation on the nursing unit) is not recommended.

Whenever possible, institutions should limit the variety of standardized neonatal starter PN formulations. Minimizing formulation complexity and limiting the number of available formulations may reduce the risk of prescribing, compounding, dispensing, and administration errors. The least complex formulation that meets the intended clinical need should be used. A pharmacist should review the final compounded neonatal starter PN prior to dispensing.

Automated Compounding Device

The Institute for Safe Medication Practice's Guidelines for Sterile Compounding and the Safe Use of Sterile Compounding Technology[21] calls for organizations to implement automated compounding devices (ACDs) that are interfaced with the electronic health record (EHR) to eliminate transcription errors. If an interface is not available, a process must be in place for transcribed orders/prescriptions to be verified by a second individual using an independent double-check, and the technology should prompt for the second check. Institutions using an ACD to prepare neonatal starter PN should establish processes to minimize the risk of calculation, programming, ingredient-selection, and compounding errors. Standardized formulations and validated order-entry and compounding procedures should be used whenever possible.

Additional Considerations for ACD Use May Include:

- Standardizing ACD formulations and ingredient libraries
- Evaluating the clinical decision support that is available (in the EHR and/or ACD) and utilizing soft warnings and hard stops to warn practitioners when approaching or exceeding limits

- When setting up the ACD, scanning the barcodes of all products for verification and ensuring proper line tracing. Conducting quality control checks and verification of replacement solutions on the compounder, if used. All source containers used should be presented to the pharmacist for verification, not just a representative vial when multiple vials are used.
- Providing appropriate training and competency assessment of pharmacy personnel
- Regularly reviewing alert overrides to determine appropriateness and to improve the safety of PN practices
- Maintaining appropriate preventive maintenance and calibration of equipment
- Establishing procedures for managing equipment downtime or other interruptions in compounding capability

Manual Compounding

When an ACD is not available, and manual compounding is necessary, an IV workflow management system should be used when available. Institutions should create a master formulation record for neonatal starter PN. Standardized procedures designed to minimize calculations and support accurate measurement, selection, and labeling should be used to prevent errors. Appropriate independent verification should be incorporated into the process based on institutional risk assessment and applicable standards. Preparation of neonatal starter PN compounding should be completed in accordance with USP <797>.

When an IV workflow management system is not available, additional considerations for manual compounding may include:

- Standardized worksheets or electronic calculations
- Independent verification of calculations and ingredient selection
- Clear labeling and standardized nomenclature
- Defined procedures for ingredient preparation, final product verification, and storage
- Staff training and competency assessment

Commercial Multi-Chamber Bag PN (MCB-PN) is Not an Appropriate Substitute for Neonatal Starter PN

Commercial MCB-PN is a standardized PN formulation available from a manufacturer that requires fewer compounding steps before administration, which utilizes a multi-chamber bag to separate some components (eg, Clinimix, Kabiven). Based on currently available commercial MCB-PN products in the United States, commercial MCB-PN is not recommended for use as neonatal starter PN[22] for the following reasons:

1. Lack of pediatric-specific amino acids. Currently available commercial MCB-PN products do not provide the pediatric-specific amino acid composition needed for neonates.
2. Potential for inappropriate infusion of electrolyte-containing and/or lipid-containing MCB-PN product.
3. Large bag volume. Currently available commercial MCB-PN products are supplied in a minimum volume of 1 L. This may increase the risk of exceeding the maximum hang time before the bag is fully utilized, leading to product waste and limiting the practicality of MCB-PN for these patients.

Key Clinical Considerations

- **Initiate neonatal starter PN promptly after birth** in eligible neonates once appropriate venous access is established.
- **Transition to patient-specific PN as soon as feasible**, ideally within 24 hours and no later than 48 hours after birth.
- **Use standardized, minimally complex formulations**. A simplified formulation containing pediatric-specific amino acids and dextrose may be considered when additional components add complexity to compounding that impact safety or limit availability.
- **Consider calcium and heparin based on clinical judgment and institution-specific risk assessment**.
- **Assign beyond-use dates based on applicable USP <797> requirements and available PN stability data, using the shorter applicable limit.**
- **Perform an institutional risk assessment** before initiating or expanding in-house compounding, with appropriate safeguards for automated or manual compounding.
- **Practice interprofessional collaboration** when developing and implementing institutional neonatal starter PN protocols.
- **Consider institution-specific workflow and operational capabilities**, including staffing, compounding resources, venous access, and contingency plans.
- **Provide competency assessments related to workflows and associated technologies** (eg, ACD), including a broad range of scenarios that staff may encounter in practice (eg, incorrect drug alert upon scanning). Establish a formal training process and validate competency for pharmacy technicians who compound starter PN and for pharmacists who check the final solution.
- **Establish processes for medication-error and adverse-event reporting** and report medication-related errors, including those related to PN, through appropriate safety-reporting systems and the Institute for Safe Medication Practices.
- **Report relevant drug shortages** through appropriate national drug-shortage reporting mechanisms.

Resources

- Guidelines for parenteral nutrition in preterm infants: The American Society for Parenteral and Enteral Nutrition
- When is Parenteral Nutrition Appropriate?
- ASPEN PN Shortage Recommendations
- Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations
- Report significant drug product shortage information to the FDA CDER Drug Shortage Program and the ASHP Drug Shortage Team.
- Report patient adverse events or medication hazards related to shortages to the ISMP Medication Errors Reporting Program (MERP), and FDA MedWatch.

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About ASPEN

The American Society for Parenteral and Enteral Nutrition (ASPEN) is dedicated to improving patient care by advancing the science and practice of nutrition support therapy and metabolism. Founded in 1976, ASPEN is an interdisciplinary organization whose members are involved in the provision of clinical nutrition therapies, including parenteral and enteral nutrition. With members from around the world, ASPEN is a community of dietitians, nurses, nurse practitioners, pharmacists, physicians, PAs, researchers, scientists, and students from every facet of nutrition support clinical practice, research, and education. For more information about ASPEN, please visit www.nutritioncare.org.