8401 Colesville Rd, Suite 510
Silver Spring, MD 20910
301.587.6315
www.nutritioncare.org

ASPEN Nutrition Guidelines for Beyond-Use Dating and Hang Time of Parenteral Nutrition: A Protocol

Introduction

Parenteral nutrition (PN) is a complex life-sustaining therapy for patients who cannot intake adequate oral or enteral nutrition. PN is considered a high-alert medication by the Institute for Safe Medication Practices due to the risk associated with a therapy that contains more than 40 ingredients and the variability between each PN formulation.[1] The aim of this document is to address misconceptions surrounding PN hang time and beyond-use dating (BUD) to ensure the safe delivery of PN therapy.[2] PN can be compounded by a hospital, home infusion pharmacy, or a 503A outsourced pharmacy for patient-specific use, or it can be compounded by a 503B outsourced pharmacy for non-patient-specific use (e.g. neonatal "starter" PN). Multi-chamber bag PN (MCB-PN) is a commercially available PN product that requires the same considerations as compounded PN. PN can be administered as a total nutrient admixture (TNA), where amino acids, dextrose, and lipid injectable emulsion (ILE) are combined with other PN components in a single container. This method is also referred to as 3-in-1 PN. The other method for PN administration is for the ILE to co-infuse or be administered separately with the dextrose-amino acid admixture. This method is also referred to as 2-in-1 PN. Regardless of the preparation or administration technique of PN, all these examples are considered PN. Clarification on the appropriate hang time and BUD that ensures a sterile, stable, and compatible product is needed.[3]

Objective

To provide clinical guidance on the appropriate BUD and hang time of PN.

Target Knowledge User

Any clinician involved in the PN use process (e.g., advanced-practice clinician, dietitian, nurse, pharmacist, physician, physician assistant).

Panel of Experts

The guideline is comprised of two panels, a Clinical Experts panel and a Bias panel.

The clinical panel of experts includes: Andrew Mays PharmD, MBA, BCNSP, CNSC, FASHP, FASPEN, Phil Ayers, **BS,** PharmD, BCNSP, FMSHP,FASHP,FASPEN, Sara Bliss, PharmD, BCPS, BCNSP, BCCCP, FASPEN, M. Petrea Cober, PharmD, BCNSP, BCPPS, FASPEN, Neil Ead, MSN, CPNP, FASPEN, David Evans, MD, FACS, FASPEN, PNS, Jessica Monczka, RD, CNSC, FASPEN; Diana W. Mulherin, PharmD, BCNSP, BCCCP, FCCM, FASPEN; Manpreet Mundi, MD, FASPEN, Katie Price, PhD, RDN, LDN, Gordon Sacks, PharmD, BCNSP, FASPEN, FCCP, Heather Stanner, MS, RDN, LD, CNSC, and Liam McKeever, PhD, RDN, FASPEN.

The Bias panel of experts will be formed to perform all bias analyses and provide commentary on the direct relationship between the recommendations made and the available evidence. The Bias panel will be comprised of doctoral level researchers with a background in nutrition to limit bias. The Bias panel will be trained and closely overseen by the methodologist and Editor-in-Chief, Liam McKeever, PhD, RDN, who will mentor the entire process and coordinate the actions of the Clinical Experts panel and the Bias panel.

Definitions:
For the purpose of this guideline, instability will be assessed as the presence of crystallization, adsorption, broken emulsion, hydrolysis, oxidation, PFAT5 greater than or equal to 0.4% for TNAs and 0.05% for commercially manufactured ILE products, mean droplet diameter, zeta potential, and free fatty acid concentration. Incompatibility will be defined as the presence of change in color, pH, osmolality, or viscosity; formation of a gas; or yielding of a visible or subvisible precipitate. Sterility will be defined as a lack of microbial contamination. Adverse events will be defined as the presence of nutrient deficiencies in the physical manifestation of deficiency symptoms and/or biochemical confirmation, infection, respiratory arrest, organ dysfunction, or death.

Request for Commentary

From the time this protocol is published electronically and up to 2 weeks following electronic publication, ***we welcome and request commentary on any and every aspect of this protocol***. We would like to hear from all key stakeholders including but not limited to all levels of dietitian, physician, nurse, speech language pathologist, pharmacist, epidemiologist, methodologist, public health expert, occupational therapist, etc.… We also welcome you to show this list of PICOT questions to select patients to provide us with feedback from the patient's perspective.

Timely comments from readers of this protocol are welcomed and requested. Any concerns, comments, or additions should be submitted via this form. We will receive comments for 2 weeks after the initial electronic posting of this protocol. This is an accelerated timeline and so your prompt responses are greatly appreciated.

Research Question(s):

Research Question 1: What is the longest BUD of PN that prevents adverse clinical outcomes and/or maintains product stability, compatibility, and/or sterility at varying temperatures (room temperature of 20-25 degrees C vs refrigerated to 2-8 degrees C)?

Research Question 2: How does adherence or lack of adherence to manufacturer and USP recommendations for PN storage impact product stability, compatibility, sterility, and/or clinical outcomes?

Research Question 3: What is the longest (hang time/infusion time/in use time) of PN that maintains product stability, compatibility, sterility, and/or impacts clinical outcomes?

PICOT Questions

PICOT Question 1a: In parenteral nutrition bags stored at 2-8 degrees C (refrigerated), does using a product beyond the beyond-use date vs. not impact product stability, compatibility, and sterility?

PICOT Question 1b: In parenteral nutrition bags stored at 20-25 degrees C (room temperature), does using a product beyond the beyond-use date vs. not impact product stability, compatibility, and sterility?

PICOT Question 2: In patients or animals receiving parenteral nutrition, does adherence to beyond-use dating vs. not impact the rate of adverse events?

PICOT Question 3: In parenteral nutrition bags, does a shorter (e.g. within 24 hours) vs longer hang time impact product stability, compatibility, and sterility?

PICOT Question 4: In patients or animals receiving parenteral nutrition, a shorter (e.g. within 24 hours) vs longer hang time impact the rate of adverse events?

PICOT Question 5: In parenteral nutrition solutions being actively infused, do medications added via the Y-site impact compatibility and/or stability of the parenteral nutrition?

Outcome Levels of Importance:
The label of ***Critical*** will be given to any outcomes pertaining to product stability, compatibility, or sterility. For patient-centered outcomes, critical outcomes will include infection, respiratory arrest, organ dysfunction, or death. Outcomes such as nutrient deficiencies will be labeled as ***Important but Not Critical*** outcomes. Outcomes labeled **Of Limited Importance** will not be considered.

Methods for Systematic Search:

Inclusion Criteria:

- All studies must be available in English
- PN includes extemporaneously prepared PN, ILE and ILE-free admixtures; multi-chamber bag PN with or without ILE; multi-chamber bag PN with or without electrolytes, multivitamins, and/or trace elements; neonatal starter PN
- In vivo studies:
    - All in vivo study designs will be collected in this patient safety issue to provide commentary on the state of the literature, though for in vivo studies, only randomized controlled trials, quasi-experimental trials, and prospective cohort studies will be considered appropriate to guide clinical decision-making. Therefore, only these designs will undergo a bias analysis and be considered in the quality of data available from the systematic review.
    - For in vivo studies, population includes any patient of any age in any care setting with any diagnosis receiving PN
    - For in vivo studies, study must examine shorter or longer BUD and/or shorter or longer hang times of the PN
    - Studies done in the United States or studies outside the United States that adhere to USP <797> guidelines
    - Studies published beginning in 2001 or later
    - Study must include at least one of the following outcomes as an adverse event of PN: nutrient deficiencies in physical manifestation of deficiency symptoms and/or biochemical confirmation; infection, respiratory arrest; organ dysfunction; and death
- Animal studies:
    - Animals must be provided PN as defined in the inclusion criteria
    - Study must examine BUD and/or hang time of PN
    - Studies published beginning in 1985 or later.
- In vitro studies:
    - In vitro studies must examine PN compatibility, stability, and/or sterility
    - Study must include at least one of the following outcomes: evidence of instability (crystallization, adsorption, broken emulsion, hydrolysis, oxidation, PFAT5), incompatibility (change in color, pH, osmolality or viscosity; formation of a gas; yielding of a visible or subvisible precipitate), and microbial contamination
    - Studies published beginning in 1985 or later
        - This would include using PN products no longer on the market, but we need to use clinical judgment when applying this data to our recommendations.

Exclusion Criteria:

- In vivo studies:
    - Studies outside the United States that do not state that they followed USP <797> guidelines
- Studies that use products that are not available in the US but are available in Europe
- Manufacturer data not published in a scientific journal
- Retracted articles
- Studies with incomplete information
- Studies not available in English
- In vivo studies published before 2001
- In vitro studies published before 1985

Search Strategy:

PubMed, CINAHL, Cochrane Central, Embase

Search terms:

Terms for PN

- Parenteral nutrition
- Total parenteral nutrition
- Intravenous nutrition
- Hyperalimentation
- Intravenous feeding
- Intravenous feeds
- Parenteral feeding
- Parenteral alimentation
- Parenteral nutrient solution
- Starter solution/admixture
- Base parenteral nutrition

Terms for BUD

- Beyond use date
- Expiration date
- Stability
- Shelf life
- Compounding
- Degradation

Terms for hang time, in-use time, infusion time

- Infusion duration
- Administration duration
- Stability
- In-use time
- Hang time

Terms for compatibility, stability, sterility, and adverse patient events:

- Adverse drug events
- Medication errors
- Adverse reactions
- Adverse effects
- Infusion-related reactions

- Compatibility testing
- Incompatibility
- Precipitation
- Solubility
- Container compatibility
- Microbial contamination
- Endotoxins in parenteral solution/admixture
- Bacterial contamination
- Compounding standards (e.g., USP <797>)
- Contamination control
- Aseptic technique
- Quality control
- Infection

Screening:
All citations will be uploaded into Covidence for screening. For any given article, all steps below will be performed in duplicate (by two reviewers), and discrepancies will be adjudicated by a third reviewer. First, citation titles and abstracts will be screened for relevance to our PICOT questions. Then, a full-text review will be performed for any citations that were deemed relevant in the previous phase of review. Articles that meet our inclusion criteria will be moved forward to the final phase of data extraction.

Data Extraction Phase:
Data will be extracted in duplicate in Covidence by researchers blinded to each other's data extraction. A third researcher will resolve conflicts as needed.

- For all study designs, data extraction will include author; year of publication; study design; total n, PN admixture details; BUD of PN; hang time of PN; temperature (for BUD studies only);
- For animal studies, data extraction will include: species, adverse events
- For in vivo studies, data extraction will include population details (age, sex, diagnosis, treatment setting); number of included participants; duration of PN; and adverse events related to the PN, including nutrient toxicities and/or deficiencies in physical manifestation of symptoms and/or biochemical confirmation, infection, respiratory arrest, organ dysfunction, and death
- For in vitro studies, data extraction will include evidence of instability (crystallization, adsorption, broken emulsion, hydrolysis, oxidation, PFAT5), incompatibility (change in color, pH, osmolality or viscosity; formation of a gas; yielding of a visible or subvisible precipitate), and microbial contamination.

Bias Assessment:

- Only randomized controlled trials, quasi-experimental trials, and prospective cohort studies will undergo a bias analysis for in vivo studies. In vivo studies of other designs will not be considered of high enough quality to inform clinical decision-making and, therefore, will not require a bias analysis. They will be included in the systematic review to provide commentary on the state of the literature.
    - The Risk of Bias 2 (ROB2)[4] tool will be used for bias assessment of randomized controlled trials.
    - The Risk of Bias in Non-randomized Study Interventions (ROBINS-I)[5] tool will be used for bias assessment of quasi-experimental trials.
    - The Newcastle-Ottawa scale[6] will be used for bias assessment of prospective cohort studies.
- In vitro study bias analysis will be assessed by a tool created by the expert author group because no gold standard exists to assess the bias of these studies.

Data Synthesis & Analysis:
Data will be tabulated and available for review.
Wherever three or more studies exist with interventions, comparators, outcomes, and populations similar enough to justify conflation, Forest Plots will be created with summary statistics using a random effects model to account for the minor population differences between hospitals. All forest plots will utilize a Knapp-Hartung adjustment. Heterogeneity will be assessed using the I^2 statistic. If the I^2 is greater than 0.5, we will perform sub-analyses as an attempt to explain the heterogeneity. Publication bias will be assessed through funnel plots and Egger tests wherever greater than or equal to 10 studies are available for conflation into a forest plot. If data are not sufficient for the methods mentioned above, the data synthesis will be narrative in nature.

Recommendations will be formulated using the GRADE Criteria. The GRADE process separates the body of evidence quality rating from the strength of the recommendation permitting a benefits and harms analysis. Evidence quality will be listed underneath each recommendation. Recommendations will be labeled as strong or weak based upon the balance of potential benefit and harm. Where the recommendation is strong, we will use the term “recommend” regarding our guideline recommendation. Where the recommendation strength is weak, we will use the term “suggest”.

Wherever possible, these recommendations will be based upon the data analyzed. Where inadequate data is present to guide a recommendation, the clinical panel will formulate a consensus of expert opinions using a modified Delphi technique. Briefly, the clinical panel will meet to discuss the various potential benefits and harms of the intervention in question. Based on this conversation, the chair will formulate recommendations for each PICOT question. This will be sent out to the clinical panel, who will either agree with the wording of the recommendation or return it with comments. These responses will be deidentified and returned to the chair. If each expert opinion recommendation has <70% agreement, the chair will alter the questions to be more agreeable to the panel and send them out again. This process will repeat until ≥70% agreement is achieved. The process will then start over with an external panel of at least 8 outside experts who will receive the current state of the recommendations from the chair and send back de-identified responses. When the external panel has ≥70% agreement on each expert opinion recommendation, the recommendation will be considered finalized. The external panel will have at least 1 patient representative to ensure input from this often-neglected stakeholder.

Expected Timeframe
This review is expected to take a maximum timeframe of 1 year.

Review
Upon completion, a draft of the guideline will be sent to external reviewers through the Journal of Parenteral and Enteral Nutrition. Before publication, the guideline must be approved by the ASPEN Board of Directors.

Updates
This guideline will be updated every 5 years.

References

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2. United States Pharmacopeial Convention. USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations
3. Boullata JI, Mirtallo JM, Sacks GS, et al. Parenteral nutrition compatibility and stability: A comprehensive review. *JPEN J Parenter Enteral Nutr*. 2022;46(2):273-299. doi:10.1002/jpen.2306
4. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. Published 2019 Aug 28. doi:10.1136/bmj.l4898
5. Hinneburg I. ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions. Nichtrandomisierte Studien bewerten ROBINS-I-Checkliste für die Überprüfung des Verzerrungspotenzials. *Med Monatsschr Pharm*. 2017;40(4):175-177.
6. Wells G, Shea, B, O'Connell, D, Peterson, J, Welch, V, Losos,M, Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses:http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.