Review and comments on the 2014 recommendations for parenteral nutrition usage by ASPEN

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Introduction:

The ASPEN guidelines on parenteral nutrition published in March 2014 at the Journal of Parenteral and Enteral Nutrition vol. 38 no. 3 (authors: Boullata et al) (1) came out with recommendations on parenteral nutrition (PN) ordering, compounding, labelling and dispensing. These were the issues covered: 1) effect of education on quality of PN ordering, 2) safe osmolarity of PN admixtures, 3) calcium and calcium phosphate ratios in PN, 4) clinical advantages of premade multichambered PN formulations compared with compounded PN formulations, 5) clinical advantages or disadvantages of 2-in-1 mixtures compared with 3-in-1 admixtures, 6) macronutrient dosing limits for a stable 3-in-1 admixture, 7) calcium and phosphate compatibility, 8) micronutrient contamination in PN stock solutions, 9) using PN admixture as a vehicle for non-nutrient medication delivery, 10) heparin inclusion in PN admixture, 11) safety of repackaging IVFE (intravenous fat emulsion) into smaller volumes and 12) beyond use date for IVFE.

Questions Raised

Questions on some of the above issues and recommendations were, however, raised in this institution (Clinical Nutrition Service, St. Luke’s Medical Center - Quezon City, Philippines). These are the following:

1) The recommendation that TNAs (Total Nutrient Admixtures) maintain final concentrations of amino acid ≥4%, monohydrated dextrose ≥10%, and injectable lipid emulsion ≥2% to be more likely to remain stable for up to 30 h at room temperature (25°C) or for 9 days refrigerated (5°C) followed by 24 hours at room temperature (GRADE: Strong).

2) The suggestion that commercially available premade multichambered PN formulations be considered as an available option for patients alongside compounded (customized or standardized) PN formulations to best meet an organization’s patient needs (GRADE: Weak).

3) The suggestion that PN with an osmolarity up to 900 mOsm/L can be safely infused
peripherally, but a lack of evidence to support the safety of higher osmolarity limits, especially when peripheral PN is prepared as a TNA (GRADE: Weak).

Question #1:

ASPEN 2014 recommendation:

Recommendation 6#: “We recommend that TNAs maintain final concentrations of amino acid ≥4%, monohydrated dextrose ≥10%, and injectable lipid emulsion ≥2% to be more likely to remain stable for up to 30 h at room temperature (25°C) or for 9 days refrigerated (5°C) followed by 24 hours at room temperature.” (In the Table 1 summary at page 336)

Comment:

We agree that “3-in-1” admixtures are stable for 30 hours at room temperatures. However, it was shown in old studies in the mid 1980s to 1990s (2-4) that the mixture (compounded solution) of all macronutrients and micronutrients, which were already refrigerated for days (ranging from 14 to 28 days) at around 4°C to 5°C, remained stable as to appearance, lipid droplet size and pH when transferred and placed in room temperature for two (2) days or 48 hours. It would then follow that the new “3-in-1” admixtures will be stable for 48 hours, which were in line with the observation of Driscoll et al. (5,6) What was barely mentioned in the ASPEN 2014 recommendation was the effect of the type of lipid used on the mixture’s stability where medium chain triglycerides (MCT) improved the stability of the total nutrition admixture especially when coming from a single source i.e. the “All-in-One” premixed admixture. This did not happen in the compounded admixtures. (5) Thus from a standpoint of which admixture has better stability – those with MCT:LCT at 50:50 ratios are better compared to those with pure LCT alone. The ESPEN recommendation on parenteral nutrition in 2009 support this. (7)

The latest data showing physicochemical stability with compounded PN mixtures of olive oil, MCT, LCT and fish oils also showed minimal changes in properties as long as the calcium content was within < 4 mol/L (while refrigerated at 4°C). (8) Finally the finding that presence of vitamins, trace elements and iron increase the presence of lipid peroxidation products, e.g. malondialdehyde or MDA, when combined with lipid emulsions within 24 hours was reported (this was a study in neonatal parenteral nutrition). (9) These lipid peroxidation products did not rise significantly when the admixture was protected from light and iron was not included in the mixture. This finding was not reported on admixtures done for adult patients so more studies may be needed, but at the moment the safety and stability of “3-in-1” TNA stand.

Therefore, the ASPEN 2014 recommendation of a 24-hour stability of a “3-in-1” PN admixture in room temperature is not entirely accurate.

The current multichambered bags available in the Philippines (see Appendix 1) are designed to be mixed only when about to be delivered to the patient, thus eliminating the need for
compounding, except when micronutrients and/or pharmaconutrients are to be added then refrigerating these while waiting to be infused to the patient. The lipid emulsions used in these “All-in-One” TNA range from LCT, MCT, fish oil, and olive oil. All premixed TNA preparations have the main components in different combinations and these are commonly used in Europe and the Asia-Pacific. Clinical data from admixtures with olive, fish oil, MCT and LCT showed safe results. (10,11) We have reported our experience with these parenteral nutrition TNAs and we have also observed no major clinical problems with use beyond thirty (30) hours. (12) We understand that these preparations are not readily available in the U.S. and they mainly use PN compounding in a sterile environment. They are not, however, in the position to make recommendations on a specific preparation (multi-chambered TNA) which is not readily available for them to use.

Our Recommendation:

We thus recommend that “All in One” multichambered parenteral nutrition solutions (or TNA) can be used at room temperature up to 48 hours. These are stable and can be delivered safely within this time frame. Laboratory and clinical experience support this.

In connection with this, we also recommend that the PN TNA bags be placed in refrigeration (refrigerator with 5°C temperature) when interruptions are done for whatever reason (e.g. blood transfusion with only a single line available) with the recommended urgency to reinfuse these back as soon as possible to avoid malnutrition in the patient and wastage. (12) (Note: stability in refrigeration at 4°C to 5°C for 14 to 28 days has been documented.)

Question #2

ASPEN 2014 Recommendation:

Recommendation #4: “We suggest that commercially available premade multichambered PN formulations be considered as an available option for patients alongside compounded (customized or standardized) PN formulations to best meet an organization’s patient needs.” (In the Table 1 summary at page 336)

Comment:

It would be better to say that premade multichambered PN formulations are the better options for parenteral nutrition use, but when not available, to do PN compounding (with its additional expenses) in order to best meet an organization’s patient needs. Premade multichambered PN preparations are not readily available in the U.S. thus they have no choice but to continue using PN compounding to meet the organization’s (ASPEN) patient’s needs. In the Philippines these multichambered PN formulations are readily available thus they fulfill the requirements of the society (PhilSPEN) and medical institutions to provide adequate nutrition to the patient when enteral nutrition fails or is inadequate.
Our Recommendation:

“All-in-One” PN preparations are the recommended formulations for use to deliver total parenteral nutrition to the patient. Compounding PN formulations, when available, are to be done for patients with specific nutrition needs e.g. pediatric patients or adult patients with specific macronutrient or pharmaconutrient requirements not met by the “All-in-One” PN preparations.

Question #3

ASPEN 2014 Recommendation:

Recommendation #2: “We suggest that PN with an osmolarity up to 900 mOsm/L can be safely infused peripherally. Higher osmolarity limits, especially when peripheral PN is prepared as a TNA, may also be tolerated, but the evidence to support a safe limit is lacking.” (in the Table 1 summary at page 330).

Comment:

Evidence showed that higher osmolar TNA admixtures above 800 mOsm/L were well tolerated peripherally. (13-15) Report by Praire et al also showed similar results. (12) There are phlebitis prevention protocols like rotating the IV (intravenous) site/cannula every three (3) days. (See Appendix 2)

Our Recommendation:

Premixed TNA formulations can be safely delivered peripherally and phlebitis will be minimized when protocols are followed (See Appendix 2).

Final Comment

We appreciate the efforts of ASPEN to come up with recommendations on the preparation and use of parenteral nutrition and these are commendable. However, recommendations are not encompassing and absolute - these have to be evaluated in the local setting. When the standards, recommendations and references on the use of parenteral nutrition in the country are based on inadequate or incomplete information, deviations from the quality of service and wastage will occur, which will be disadvantageous for the patient. (12) Thus it is required from the nutrition bodies or institutions of the country (e.g. PhilSPEN) to make efforts to ensure that optimum care will be given to the patient especially in the area of clinical nutrition.
References:

Appendix 1: Premixed “All-in-One” PN preparations used in the Philippines

1. BBraun: Nutriflex
2. Fresenius Kabi: Kabiven
3. JW: Combiflex
4. Baxter: Olimel

Macronutrient contents of TNA products available in the Philippines

<table>
<thead>
<tr>
<th>Contents</th>
<th>Nutriflex</th>
<th>SMOF Kabiven</th>
<th>Combiflex</th>
<th>Olimel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/100 ml)</td>
<td>✔ (3.2)</td>
<td>✔ (3.1)</td>
<td>✔ (2.4)</td>
<td>✔ (2.5)</td>
</tr>
<tr>
<td>Dextrose (g/100 ml)</td>
<td>✔ (6.4)</td>
<td>✔ (7.0)</td>
<td>✔ (6.7)</td>
<td>✔ (7.5)</td>
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<td>LCT (g/100 ml)</td>
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<td>✔ (0.8)</td>
<td>✔ (3.5)</td>
<td>✔ (0.6)</td>
</tr>
<tr>
<td>MCT (g/100 ml)</td>
<td>✔ (2)</td>
<td>✔ (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish Oil (g/100 ml)</td>
<td>✔ (0.4)</td>
<td>✔ (0.7)</td>
<td></td>
<td>✔ (2.4)</td>
</tr>
<tr>
<td>Olive Oil (g/100 ml)</td>
<td></td>
<td>✔ (0.7)</td>
<td></td>
<td>✔ (2.4)</td>
</tr>
</tbody>
</table>

Appendix 2: Phlebitis prevention measures: From: Intravenous Nursing – New Zealand web site
(Available at: http://www.ivnnz.co.nz/newsletter/Articles/Infection-Control/Phlebitis Accessed August 31, 2015)

- Adhering to aseptic technique during insertion, dressing changes, mixing or drawing up of solutions or medications, accessing ports or hubs on IV equipment.
- Cannula site rotation.
- Using the smallest gauge cannula in the largest vein.
- Adequate securement of the IV device.
- Close and regular monitoring of the IV site.
- Patient education of the signs and symptoms of phlebitis.
- IV device selection – When to Pick a PICC! (peripherally inserted central catheter)
- Following guidelines on dilution of solutions to prevent particulate matter and to ensure that the medication or solution doesn’t have too high or too low a pH or tonicity.