Significant Published Articles for Pharmacy Nutrition Support Practice in 2016

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Abstract

Purpose: To assist the pharmacist engaged in nutrition support therapy in staying current with pertinent literature. **Methods:** Several clinical pharmacists engaged in nutrition support therapy compiled a list of articles published in 2016 considered important to their clinical practice. The citation list was compiled into a single spreadsheet where the author participants were asked to assess whether the paper was considered important to nutrition support pharmacy practice. A culled list of publications was then identified whereby the majority of author participants (at least 5 out of 8) considered the paper to be important. Guideline and consensus papers from professional organizations, important to practice but not scored, were also included. **Results:** A total of 103 articles were identified; 10 from the primary literature were voted by the group to be of high importance. An additional 11 organizational guidelines, position, recommendation, or consensus papers were also identified. The top-ranked articles from the primary literature were reviewed. **Conclusion:** It is recommended that pharmacists, engaged in nutrition support therapy, be familiar with the majority of these articles as it pertains to their practice.

Keywords

consensus, enteral nutrition, guidelines, outcomes, parenteral nutrition

Staying current with the literature is an essential requirement for the informed pharmacist who maintains an evidence-based clinical practice. This requirement has become more challenging to fulfill as the practice model of the traditional full-time pharmacy nutrition support specialist has changed at many institutions. Many former specialists now practice within an integrated model whereby the clinical pharmacist provides pharmacotherapy services along with nutrition support responsibilities. As a result of this change, clinicians are responsible for staying current within numerous therapeutic areas that interface with clinical practice including nutrition support. Because nutrition support therapy is integrated with many divergent specialized fields, it is an extremely daunting task for one individual to screen the abundant amount of available journals each month to seek out those clinical studies, position papers, or clinical guidelines that may enhance or change clinical practice. The intent of this article is to provide an updated source of new pertinent literature published in 2016.

Methods

To assist pharmacy clinicians engaged in nutrition support in staying current with the most pertinent literature, the principal

author participant of this article (R.N.D.) invited 7 additional clinical pharmacists to participate in this project. The potential author participants were invited based on the principal author's perception of their active involvement in the field as supported by their educational, research, or professional committee involvement in pharmacy nutrition support, particularly in the American Society for Parenteral and Enteral Nutrition (ASPEN). All authors are board certified. Four author participants are board certified solely in pharmacy nutrition support, whereas others are certified in areas whereby nutrition support is part of their practice or have

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multiple board certifications. The duration of individual practice experience of the group members ranges from 2 years to more than 30 years. Members of this authorship group have advanced practice roles with direct patient care responsibilities for prescribing enteral nutrition (EN) and/or parenteral nutrition (PN), laboratory analysis, and pharmacotherapy integrated with nutrition therapy (eg, fluid and electrolytes, vitamins, trace elements, prokinetic drugs, insulin, antidiarrheal and laxative therapy), and some have administrative or supervisory roles with respect to nutrition support therapy. This authorship group has a broad range of practice experiences. Most authors are acute care-based, but some have long-term care (home PN [HPN] and EN) responsibilities. Current practices of the group range from pediatrics to geriatrics. Some members have a diverse patient population, whereas others practice within a focused patient population (eg, pediatrics, oncology, trauma/thermal injury).

The author participants were asked to provide citations of articles published from January 2016 to December 2016 that they have personally accumulated which resulted in a change or affirmation of their current clinical practice or that they considered to be important for future clinical practice. However, it should be noted that this methodology with lack of a structured literature search strategy is a limitation as it may have led to omission of pertinent articles applicable to practice that were published in less common journals not routinely read by the author participants. Only those articles available in print format were allowed for potential inclusion. Articles available only in preprint electronic format (with intention of publication by the journal in 2017 or later) were not evaluated. The citation list was compiled into a single spreadsheet where the author participants were asked to denote whether the paper was considered important to pharmacy nutrition support practice. An abstract and complete citation of each paper was provided along with the electronic scoring spreadsheet to assist the author participants with the evaluation process in the event that the details of the paper could not be recalled. To ensure an independent voting process without influence from the other participant members, only the principal author participant was aware of each individual's rankings. To prevent influence from the other author participants on the principal participant author, scoring of all the papers by the principal participating author was completed prior to receipt of the results from the other contributors. The votes were tallied. The article was considered important if the majority of the author participants (at least 5 out of 8) considered it to be of high priority in its relevance to pharmacy nutrition support practice. From this scoring system, a culled list of the most important articles was created.

Results

A total of 103 articles were collectively collated for initial evaluation by the authorship group. Ninety-one papers were from the primary literature and scored by the authorship group. An average of 20 papers (range, 10-32) were denoted

as significant by members of the author group. According to a majority consensus vote, 10 papers from the primary literature collective were identified as most important for pharmacy nutrition support practice.¹⁻¹⁰ An additional 11 articles comprising of organizational guidelines, consensus, recommendation, and position papers were not evaluated or scored but were automatically included separately as important papers to our practice.¹¹⁻²¹ Of these 21 finalist publications, 8 were published in *Journal of Parenteral and Enteral Nutrition*, 5 were from *Nutrition in Clinical Practice*, and 3 were published in *Clinical Nutrition*. The remaining 5 papers were from 3 different medical journals. Individual rankings, based on relevancy to pharmacy nutrition support clinical practice according to the author participant group, are given in Table 1. The finalist articles from the primary literature are summarized in the discussion along with a narrative regarding their implications for pharmacy nutrition support practice. A narrative regarding guidelines, position, recommendation, and consensus papers was not provided but are listed in Table 2. The 82 citations, not part of the finalist group, are available online as a supplement to this article.

Discussion

1. Fivez et al. Early versus late parenteral nutrition in critically ill children.⁵

A recent randomized controlled trial in critically ill adults has questioned the benefit of early PN.²² However, macronutrient deficiency may develop quickly in children. Therefore, the authors of this study aimed to determine whether withholding PN for 7 days is superior to early initiation of PN in critically ill children.

This prospective, international, multicenter, randomized, controlled trial (PEPaNIC) compared late initiation (intensive care unit [ICU] day 8) of PN with early (within 24 hours of ICU admission) initiation of PN in 1440 critically ill pediatric patients. Term newborns to children 17 years of age admitted to a pediatric ICU with an expected stay of ≥ 24 hours and with a score of ≥ 2 on the STRONGkids (Screening Tool for Risk on Nutritional Status and Growth) tool were eligible for study. The late PN group received intravenous crystalloid fluids, containing dextrose and saline, and micronutrients until PN began. Until 80% of target calories from EN was achieved, the early PN group received supplemental PN and intravenous micronutrients. Both groups received insulin infusions to maintain euglycemia. Baseline demographics between PN groups were similar. Forty-five percent of children were < 1 year of age for both groups with a median age of 1.5 and 1.4 years. New infections occurred in 11% and 18% of children in the late PN and early PN groups (odds ratio [OR], 0.48, $P < .001$). Similarly, the mean duration of stay in the ICU was 6 and 9 days, respectively ($P = .002$). A post hoc analysis in 209 neonates indicated the benefits of late PN were similar between those < 4 weeks and > 4 weeks

Table 1. Rankings of Significant Articles for Pharmacy Nutrition Support Practice.^a

First author	Title	No. of authors who indicate high importance ^b
Fivez ¹	Early versus late parenteral nutrition in critically ill children	7
Nicolo ²	Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study	6
Petros ³	Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized pilot trial	6
Al-Dorzi ⁴	Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis	5
Anderson ⁵	Physical compatibility of calcium chloride and sodium glycerophosphate in pediatric parenteral nutrition solutions	5
Dibb ⁶	Central venous catheter salvage in home parenteral nutrition catheter-related bloodstream infections: long-term safety and efficacy data	5
Elke ⁷	Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials	5
Olthof ⁸	No clinical or biochemical evidence for essential fatty acid deficiency in home patients who depend on long-term mixed olive oil- and soybean oil-based parenteral nutrition	5
Yeh ⁹	Adequate nutrition may get you home: effect of caloric/protein deficits on the discharge destination of critically ill surgical patients	5
Ziegler ¹⁰	Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients: an American multicenter randomized controlled trial	5

^aPapers were listed in descending order by the number of author contributors who indicated that they were of high importance followed by alphabetical order of the last name of the first investigator or author.

^bOut of a total of the 8 participating authors evaluating these papers.

Table 2. Significant Guidelines, Position, Recommendations, and Consensus Papers (in Alphabetical Order by First Author).

Author	Title
Arends ¹¹	ESPEN guidelines on nutrition in cancer patients
Boullata ¹²	ASPEN safe practices for enteral nutrition therapy
Boullata ¹³	Standardized competencies for parenteral nutrition order review and parenteral nutrition preparation, including compounding: the ASPEN model
Klek ¹⁴	Management of acute intestinal failure: a position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group
McClave ¹⁵	ACG clinical guideline: nutrition therapy in the adult hospitalized patient
McClave ¹⁶	Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)
Pironi ¹⁷	ESPEN guidelines on chronic intestinal failure in adults
Plogsted ¹⁸	Parenteral nutrition electrolyte and mineral product shortage considerations
Plogsted ¹⁹	Parenteral nutrition trace element product shortage considerations
Plogsted ²⁰	Parenteral nutrition amino acids product shortage considerations
Plogsted ²¹	Parenteral nutrition multivitamin product shortage considerations

of age. Patients in the late group were weaned from mechanical ventilator support earlier (4 vs 6 days, $P = .01$), had a lower need for renal replacement therapy (OR, 0.49, $P = .04$), and shorter hospital stay (17 vs 21 days, $P = .005$).

The authors conclude that withholding PN for 1 week in the pediatric ICU was superior to providing early PN, resulting in fewer infections, shorter ICU stay, and shorter hospital stay. However, this study has limitations. Greater than 75% of the patients in the late group were discharged from the ICU by day 8 and 50% of the patients in the early group were discharged by day 4, having never received PN. Energy requirements were estimated with equations which are potentially unreliable and may lead to the detrimental effects of overfeeding affecting the study results.^{23,24} The STRONGkids tool has not been validated in critically ill children.²⁴ A large proportion of patients were young, which may limit transferability to an older pediatric population. Late PN resulted in more episodes of hypoglycemia compared with early PN. It is unclear whether this may influence long-term impaired neurocognitive outcomes.^{25,26} Several responses to this study outlined additional concerns, and it is recommended to review these prior to implementation of late initiation of PN in all pediatric critical care settings.^{23,25-27} This study provides compelling data pertaining to the benefits that may be observed in late versus early initiation of PN in critically ill children; however, nutrition therapy should be individualized and carefully managed. Further study is warranted before these results can be broadly applied.

2. Nicolo et al. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study.⁶

The intent of this retrospective observational study was to evaluate the impact of prescribed protein delivery on mortality and time to discharge alive using previously collected data from the International Nutrition Survey 2013. The data sample included patients who were in the ICU for at least 4 days ($n = 2828$) and a subsample of patients who were in the ICU for at least 12 days ($n = 1584$). About two-thirds of patients were medical ICU patients. Mean protein intake was 51 and 57 g/d for each group, respectively (61% and 67% of prescribed target intake of 1.2 g/kg/d). Caloric intake was 1100 and 1200 kcal/d (64% and 71% of prescribed target intake of 24 kcal/kg/d) for each group. The investigators stratified patients based on a protein or energy intake of $\geq 80\%$ of prescribed protein intake. Achieving a protein intake of $\geq 80\%$ of prescribed was associated with reduced mortality for each duration of ICU stay group (25% vs 33% and 20% vs 27%; OR of 0.68 and 0.60 for the ≥ 4 and ≥ 12 day groups, respectively) and a shorter time to discharge alive with higher protein intake in the 12-day subgroup. However, achievement of $\geq 80\%$ of goal energy intake was not associated with improved outcomes. The investigators concluded that achieving a higher protein intake may be important for survival and shorter time to discharge alive in ICU patients and that efforts to achieve prescribed protein intake should be maximized.

These data support other recent studies that have associated improved clinical outcomes with increased protein intake.^{28,29} Together, these studies infer the importance of providing adequate protein intake and may offer an explanation as to why other recent nutritional intervention trials, which focused on caloric intake while giving “inadequate amounts” of protein, failed in terms of improving clinical outcomes. However, the observational nature of this investigation⁶ and that of others limit the interpretation. In particular, the etiology for why patients only received 60% of what was prescribed was elusive. Trials to identify the amount of protein required to improve clinical outcomes for critically ill patients are warranted. These future randomized controlled trials will need to be conducted in homogeneous ICU patient populations as not all ICU patients are the same with some exhibiting more catabolism than others. Currently, clinician experts recommend a protein intake of at least 1.2 g/kg/d with doses up to 2 to 2.5 g/kg/d depending on the patient’s severity of catabolism.³⁰ These emerging data indicate the importance of achieving adequate protein intake in critically ill patients.

3. Petros et al. Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized pilot trial.⁸

The objective of this single-center pilot trial was to compare the impact of a hypocaloric feeding regimen with a

normocaloric regimen over the first 7 days in the ICU. Patients anticipated to require artificial nutrition support for at least 72 hours were assigned to receive either a normocaloric nutrition regimen (equivalent to daily energy expenditure; $n = 54$) or a hypocaloric nutrition regimen (50% of daily energy expenditure; $n = 46$). Energy requirements were determined via indirect calorimetry (IC) or by using the Ireton-Jones equation³¹ if IC was unavailable. Enteral nutrition was preferentially used, although patients could receive PN or supplemental PN with EN.

The study groups were similar with respect to age, body mass index (BMI), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, although more patients in the hypocaloric arm had diabetes mellitus and chronic respiratory disease. Patients who were malnourished (BMI < 18.5 kg/m²), > 80 years old, or those receiving immunosuppressive therapy were excluded. A higher incidence of nosocomial infections was observed in the hypocaloric group (26.1% vs 11.1%, $P = .046$) without any differences in ICU, hospital, or 28-day mortality. Patients in the hypocaloric group had lower insulin requirements ($P < .05$), but experienced more episodes of hypoglycemia ($P = .03$). Diarrhea was more frequent in the normocaloric group on days 4 and 5 ($P = .036$). The authors concluded hypocaloric feeding over the first 7 days of ICU stay was associated with more nosocomial infections but improved glycemic control and less gastrointestinal intolerance.

The findings of this study should be interpreted cautiously. Patients with higher nutrition risk (eg, preexisting malnourishment, preexisting medical conditions, elderly patients), who may benefit more from nutrition therapy, were poorly represented or excluded from study enrollment. The intent of this study was to compare full feeding with hypocaloric feeding, but the normocaloric group received only 75.5% of the prescribed regimen. Many clinicians would consider both groups to have been permissively underfed. It is likely that neither group received recommended amounts of protein (1.2–2 g/kg/d) according to the Society of Critical Care Medicine (SCCM)-ASPEN guidelines.¹⁶ Recent data suggest that protein provision may be more significant in improving outcomes than caloric adequacy in critically ill patients^{6,16,29,32} which may have confounded the results of this study. Therefore, it is difficult to extrapolate the results of this study to more diverse ICU populations. Other studies evaluating permissive and trophic feeding strategies have demonstrated lack of outcome benefit or harm with full feeding,^{33,34} but included a narrower patient population, with few patients more likely to experience a higher nutrition risk. While it appears hypocaloric, low protein feeding may be better tolerated in this patient subset, it may be associated with increased risk of nosocomial infections and should be cautiously utilized in broader ICU populations until more evidence is available.

4. Al-Dorzi et al. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis.¹

The intent of the systematic review and meta-analysis was to compare the dose of enteral caloric intake and survival in critically ill patients. Only randomized trials from critically ill patients published until November 2015 that compared 2 doses of EN and had a difference in caloric intake (statistically significant or $\geq 10\%$) between the 2 groups were included. Twenty-one trials were included, with 4717 patients in the lower caloric intake group and 2352 patients in the high caloric intake group. Seven studies compared caloric restriction directly, and 14 studies evaluated interventions that led to significant differences in caloric intake.

No difference was seen in hospital mortality (relative risk [RR], 0.95), and the association between higher caloric intake and hospital mortality was not different when comparing caloric restriction and noncaloric restriction trials. There were no mortality differences based on demarcations in age (≥ 65 years), APACHE II score (≥ 20), caloric intake ($\geq 60\%$ of target intake), or differences in caloric intake ($\geq 20\%$). Lower caloric intake was associated with fewer bloodstream infections (RR, 0.718) and less renal replacement therapy (RR, 0.711). Hospital stay was longer with lower caloric intake ($P = .005$) in caloric restriction trials, but no differences in ICU mortality, nosocomial infections, days of mechanical ventilation, ICU length of stay (LOS), or hospital LOS were observed.

The authors concluded that a lower caloric intake was not associated with differences in mortality, incidence of pneumonia, or duration of mechanical ventilation, but lower caloric intake had less risk for bloodstream infections and renal replacement therapy. These results must be interpreted carefully. Although the authors attempted to control for confounders such as age and severity of illness, the analysis consisted largely of medical ICU patients. Also, studies where PN was the primary intervention were excluded. Patients in the higher caloric arms generally did not receive target caloric requirements; therefore, both groups of patients may have been underfed to some degree, making it difficult to truly compare differing feeding strategies. Last, the authors were unable to assess protein provision, which may be a key factor in improving outcomes with nutrition support.^{6,28,29} The authors imply benefit with lower caloric intake for decreased bloodstream infections and renal replacement therapy requirements; however, further investigation is required.

5. Anderson et al. Physical compatibility of calcium chloride and sodium glycerophosphate in pediatric parenteral nutrition solutions.²

National shortages of intravenous electrolyte solutions continue to present challenges in the formulation of PN. Calcium gluconate injection shortage has prompted clinicians to explore the feasibility of using calcium chloride, which is historically not a preferred product for PNs compounding due to its high risk for calcium-phosphate precipitation compared

with the gluconate salt. With the ongoing sodium phosphate shortage, sodium glycerophosphate (NaGP) injection, an organic phosphate salt currently approved for use in the European Union, has been temporarily available in the United States through a special Food and Drug Administration (FDA)-regulatory discretion. Studies have shown that NaGP has a more favorable serum pharmacokinetic profile and a lower propensity to precipitate with the divalent calcium ion compared with inorganic phosphate.³⁵⁻³⁷ The purpose of this study was to assess the physical compatibility of calcium chloride with NaGP in PN solutions intended for pediatric patients.

The macronutrient components of the PN formulations were compounded to contain a final dextrose concentration of 15% with variable concentrations of amino acids (TrophAmine), cysteine, and Intralipid. Each macronutrient combination was mixed with one of the following 5 options: 10 mEq/L Ca + 10 mmol/L of NaGP, 20 mEq/L Ca + 20 mmol/L of NaGP, 30 mEq/L Ca + 30 mmol/L of NaGP, 40 mEq/L Ca + 40 mmol/L of NaGP, or 50 mEq/L Ca + 50 mmol/L of NaGP. An aliquot of each PN solution was tested at room temperature and 37°C for 24 hours. Solutions were considered physically compatible if the microscopic crystal count was <12 and <2 particles/mL measuring ≥ 10 μm and 25 μm in diameter, respectively. Overall, all 90 tested samples were considered physically compatible. Haze, color change, and precipitation by visual inspection were not observed. All solutions were absent of crystals ≥ 25 μm in diameter based on microscopic inspection.

This study confirmed the previous findings that NaGP offers advantage over sodium phosphate from the solubility and compatibility standpoint in compounding PN. Specifically, it allows relatively higher total calcium and phosphate content at the physical condition, pH, and solute concentration tested, including the use of calcium chloride. However, there are intrinsic limitations to this study. For example, human eyes cannot reliably detect microcrystals even at 100 $\times$. The gold standard for quantitative analysis would employ the use of light obscuration or light extinction. These approaches would provide a more definitive and conclusive assessment of calcium-phosphate compatibility. Likewise, trace elements were not included in the study samples. Although the impact of multiple trace element on calcium-phosphate compatibility is likely negligible due to the small volume, it is unknown how the addition of extra trace elements may disrupt solubility. For example, zinc chloride injection has a pH of 2.0, which may have a more significant effect in altering the pH of the final solution and can disrupt the stability of lipid content in TNA. Finally, the compatibility data cannot be extrapolated to the newer alternative lipid emulsions (LEs).

Overall, this study suggests a promising role for NaGP as the phosphate salt form for compounding PN. It is also worth noting that NaGP contains lower aluminum content than sodium phosphate at equimolar concentrations. Although the

single-component NaGP injection has not received full FDA-approval, this salt is used in some FDA-approved multi-chamber PN products. Despite these promising findings, until NaGP becomes widely available in the United States and more confirmative data are published, calcium gluconate should be the calcium salt of choice in compounding PNs.

6. Dibb et al. Central venous catheter salvage in home parenteral nutrition catheter-related bloodstream infections: long-term safety and efficacy data.³

For patients requiring long-term HPN, the ability to maintain central venous access is vital. Any catheter-related bloodstream infection (CRBSI) event that results in central venous catheter (CVC) removal and replacement increases the risk of thrombotic occlusion that may ultimately lead to loss of central venous access. It is therefore prudent to limit CVC replacement to those CRBSI events that fail or are anticipated to fail medical management. The purpose of this study was to evaluate the efficacy and safety of a standardized protocol that incorporated CVC salvage for patients requiring long-term HPN who presented with suspected CRBSI.

The study included 588 patients receiving long-term PN from a maintained database over an 18 year period (1993-2011). Diagnosis of CRBSI was based on quantitative and qualitative assessment of central and peripheral blood cultures and pour plates.³⁸ Two hundred ninety-seven CRBSI episodes in 137 patients and an overall infection rate of 0.38 per 1000 catheter days were identified. The CVC was removed in 49 CRBSI episodes due to septic shock, fungal infection, mechanical complications, or tunnel infection. CVC salvage was attempted in the remaining 248 CRBSI episodes. The standardized treatment protocol for CVC salvage included initial treatment with vancomycin (systemic and CVC lock), urokinase CVC lock, and prohibited infusion of PN via the CVC. Antibiotic therapy was adjusted based on microbiologic data, when available, and continued for 14 days. CVC salvage was successful (defined as no recurrent CRBSI within 30 days) in 73% of the CRBSI episodes.

This report is significant because the success of CVC salvage is not well documented and it can have a major impact on maintaining long-term central venous access in this patient population. Even though European guidelines encourage CVC salvage whenever possible for patients with a long-term CVC,³⁸ this recommendation is not consistently recognized as standard of care in the United States. This study outlines a standardized approach to the diagnosis and management of CRBSI that appears safe and effective. There are other aspects of this protocol that may differ from standard of care in the United States, such as the use of antibiotic and urokinase CVC lock and the practice to withhold infusion of PN via the CVC during the entire 14-day course of treatment. It is unclear how these differences may impact

success of CVC salvage. However, the study does support attempts at CVC salvage in patients requiring long-term HPN.

7. Elke et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials.⁴

The 2016 SCCM-ASPEN guidelines suggest the use of EN over PN in critically ill patients who require nutrition support therapy.¹⁶ EN has historically been associated with less infectious complications than PN.³⁹⁻⁴⁴ In contrast to previous literature, a recent large randomized controlled trial demonstrated no differences in outcomes between EN and PN.⁴⁵ The purpose of this systematic review and meta-analysis was to evaluate the effect of the route of nutrition (EN vs PN) on clinical outcomes in critically ill adult patients.

In this meta-analysis, 18 studies met inclusion criteria for evaluating critically ill adult patients who were randomized to receive EN (n = 1681) or PN (n = 1666). There was no difference in overall mortality with EN compared with PN. When compared with PN, EN was associated with a significant decrease in infectious complications (RR, 0.64). This significant difference was maintained in the subgroup analysis in which the PN group received higher caloric intake than the EN group (RR, 0.55). However, in trials where EN and PN groups received similar caloric intake, there was no difference in infectious complications. EN compared with PN was associated with decreased ICU LOS, but there was no significant difference in hospital LOS or length of mechanical ventilation. The authors concluded that the use of EN rather than PN does not impact mortality but decreases infectious complications and ICU LOS.

The authors acknowledge limitations of the study. There were missing outcome data points for some of the included studies, and only 4 trials reported data for ICU LOS and duration of mechanical ventilation. There were variations in the reporting of caloric intake, timing of nutrition intervention, and definitions used for identifying infections. Covariates, such as protein provision by enteral versus parenteral routes, that were not adjusted for in the meta-analysis may have impacted the observed findings. The homogeneous population makes it difficult to evaluate the effect of route of nutrition in subpopulations of critically ill patients (eg, high nutrition risk on admission).

While this study appears to counter the recent literature suggesting there is no difference in clinical outcomes such as infectious complications with EN versus PN, the authors suggest that the differences between groups may be due to avoiding complications associated with overfeeding with PN rather than the route of nutrition delivery. Alternatively, the reduction in infectious complications observed with EN may be the result of the positive effects of EN on gut integrity and immunity. Additional studies are needed to ascertain the potential immunologic role of EN versus overfeeding and

complications of PN. Cost-effectiveness and ease of access were not assessed in this meta-analysis, but these factors in combination with the reduction in ICU LOS with EN support the use of the enteral route. Therefore, the interpretation of this meta-analysis should be affirmation of guideline recommendations to preferentially use EN in critically ill adult patients with functional gastrointestinal tracts.¹⁶

8. Olthof et al. No clinical or biochemical evidence for essential fatty acid deficiency in home patients who depend on long-term mixed olive oil- and soybean oil-based parenteral nutrition.⁷

The objective of this study was to determine whether essential fatty acid (EFA) intake was adequate in long-term patients who are dependent on HPN utilizing an 80% olive oil/20% soybean oil LE. Thirty adult patients with short bowel syndrome or a gastrointestinal motility disorder who received the mixed olive oil-soybean oil emulsion at a dose of 0.97 g/kg/d as part of the required HPN for 5 to 7 days per week for 3 months were evaluated. The lipid profiles of the HPN patients were compared with 30 sex- and age-matched healthy controls.

The investigators demonstrated that the triene (eicosatrienoic or mead acid)/tetraene (arachidonic acid) ratio (a biochemical marker for evidence of EFA deficiency) was significantly higher in HPN patients compared with controls (0.019 vs 0.015, respectively) but remained well below the upper limit of the normal range (0.2). None of the HPN patients exhibited other evidence (eg, skin lesions or innate immune cell dysfunction) of EFA deficiency. Other studies that employed the use of olive oil/soybean oil LE in PN patients have also demonstrated the efficacy of this alternative LE in prevention of EFA deficiency.^{46,47}

It is important to consider the dosage of EFA when evaluating adequacy of the parenteral lipid intake as soybean oil and olive oil have differing EFA content. The amounts of linoleic acid (LA) and alpha-linolenic acid (ALA) in soybean oil are approximately 53% and 8%, respectively, compared with 80% olive oil/20% soybean oil LE with 19% and 2.5% LA and ALA content, respectively. Thus, the mixed olive-soybean oil-based product has a notable 65% reduction in EFA amounts. Estimated intakes of the EFAs, LA, and ALA were 0.17 and 0.02 g/kg/day for patients in this study, respectively. These daily doses of the EFAs would be considered adequate for HPN patients weighing 50 kg or more.⁴⁸

In summary, alternative LEs appear to provide adequate EFAs when given 4 to 7 days per week (~1-1.3 g/kg/d) in long-term patients.^{7,49} This is in contrast to use of 100% soybean LE whereby minimal doses of 500 mL of 20% emulsion weekly⁴⁸ and 5 to 10 g daily⁵⁰ have been shown to prevent EFA deficiency. Unfortunately, this alternative LE product, despite approval by the FDA in 2013, is currently not commercially available in the United States. Only a 100% soybean oil and a 30% soybean oil, 30% medium chain triglycerides, 25% olive

oil, and 15% fish oil LE are available for use in the United States. Clinicians must recall this dosage difference in commercially available LEs for prevention of EFA deficiency especially if the patients are unable to adequately absorb enteral sources of fat.

9. Yeh et al. Adequate nutrition may get you home: effect of caloric/protein deficits on the discharge destination of critically ill surgical patients.⁹

The objective of this study was to determine whether adequate nutrition intake during ICU stay was associated with discharge destination to home or nonhome in critically ill surgical patients. This was a prospective, observational cohort study in adult patients admitted to the surgical ICU who received EN for at least 72 hours. Patients continued in the study until either ICU discharge, receipt of 14 consecutive days of EN, achievement of sustained oral intake, or death. Caloric and protein goals were 25 to 30 kcal/kg/day and 1.5 to 2 g/kg/day, respectively. Caloric and protein deficits were determined by calculation of actual daily intakes from goal intakes. Each patient was stratified as either high (≥ 6000 kcal) or low (< 6000 kcal) total caloric deficit and high (≥ 300 g) or low (< 300 g) protein deficit for comparison.

A total of 213 patients (mean age of 63 years, BMI of 25.6 kg/m², and APACHE II score of 14) were studied. Most patients ($n = 141$) were designated as low deficit for both calories and protein. Patients in high total caloric and high protein deficit groups received EN for a significantly greater number of days (14 vs 7 and 14 vs 6 for caloric and protein deficit groups, respectively, $P < .0001$ for both). Thirty-three patients (15%) were discharged to home. On univariate analysis, the researchers found that a high macronutrient deficit was associated with less favorable discharge disposition (OR of 0.25 for caloric deficit and OR of 0.30 for protein deficit). High macronutrient deficit was also found to significantly decrease 28-day ventilator-free days (14 vs 22, $P < .001$), lead to more complications (3 vs 1, $P < .001$), longer ICU LOS (20 vs 10 and 23 vs 10 days for caloric and protein deficit groups, respectively, $P < .001$ for both), and longer hospital LOS (33 vs 21 and 35 vs 20 days for caloric and protein deficit groups, respectively, $P < .001$ for both). The researchers concluded that inadequate nutrient delivery was associated with lower rates of discharge to home and that adequate nutrition delivery may lead to favorable clinical outcomes after critical illness in surgical ICU patients.

This is the first trial to look at both caloric and protein deficits as it relates specifically to discharge disposition in surgical ICU patients. Other trials have focused on the effects of caloric deficits on traditional in-hospital, short-term outcomes such as mortality, complications, and LOS. Results of such trials have been mixed with some showing positive outcomes related to adequate nutrition intake⁵¹⁻⁵³ and others suggesting adequate or aggressive nutrition delivery resulting in a lack of benefit or potential harm.^{34,54-56} Reasons for these differing

outcomes include patient selection, method of nutrition delivery, lack of study participants to meet predefined nutritional goals, unknown baseline nutritional status, small number of patients discharged to home, observational design, and single study site leading to possible skewed results and reduced external validity. In summary, while it appears that limiting the total caloric and protein deficits provide a better chance of discharge to home, reduction in LOS, complications, and time requiring mechanical ventilation, large intervention-based trials are needed to fully address this question.

10. Ziegler et al. Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients: an American multicenter randomized controlled trial.¹⁰

The purpose of this study was to evaluate whether PN supplemented with glutamine (GLN) dipeptide improves clinical outcomes in surgical ICU patients using a prospective, randomized, controlled, double-blind, parallel-group, intent-to-treat, multicenter study design. A total of 150 adult patients who were <14 days postoperative following cardiac, vascular (nonneurologic), esophageal, gastric, or intestinal surgery and expected to require PN for ≥ 7 days were enrolled. Energy and protein goals were 1.3 times basal energy expenditure and 1.5 g/kg/d, respectively. Soybean oil-based fat emulsion was provided daily as a separate infusion and was dosed to provide 30% of the nonprotein calories. EN (tube feeding and oral diet) was utilized, as indicated, and the amount of PN was proportionally decreased. Tube feeding formulas were not GLN- or arginine-enriched. The study PN was continued up to 28 days or discontinued when the patient received >50% of caloric intake goal via EN for a consecutive 48-hour period. Patients were randomized to receive standard PN (STD-PN) utilizing conventional amino acids, or GLN-supplemented PN (GLN-PN) utilizing 20% alanyl-GLN-dipeptide (0.5 g/kg/d) and conventional amino acids (1 g/kg/d). The groups were similar in baseline characteristics and daily nutrient intakes via PN and EN. There were no differences between the STD-PN and GLN-PN groups for the total number of new health care-associated infections or 6-month cumulative mortality. Adverse events and other clinical outcomes were similar between groups.

The results of this study are disappointing given the existence of published research in critically ill patients that have suggested metabolic and clinical benefits of PN supplemented with GLN. This study was a rigorous attempt to minimize heterogeneity by controlling variability between groups, such as maintaining tight blood glucose control, ensuring nearly identical intake of protein and calories between groups, and excluding patients with malignancy, burns, trauma, shock, or significant renal/hepatic dysfunction. The GLN dosing regimen used appeared to provide an adequate amount based on achieving significantly increased and sustained plasma GLN levels above control levels for 14 days, while other studies

have been criticized for not achieving this. It may be plausible that the lack of effect of GLN was due to the administration of the dipeptide GLN compound versus the individual amino acid GLN formulation; however, further research regarding therapeutic equivalency of the GLN formulations is warranted. Other recent double-blind randomized controlled trials have failed to consistently demonstrate clinical benefits of GLN-supplemented PN in medical/surgical ICU patients using intention-to-treat analysis.^{38,57-59} It is important to note that GLN-supplemented PN appears to be safe and was not associated with an increase in adverse events. There may be a subset of critically ill patients who benefit from GLN-supplemented PN, but available evidence does not support its use in the surgical intensive care unit patient at this time.

Conclusion

With the large volume of publications pertinent to nutrition support therapy and appearance in a variety of journals, it is extremely difficult for the pharmacist engaged in nutrition support practice to stay current with the literature. We have identified what the author participants consider to be the “most important” papers from the primary literature to pharmacy nutrition support practice and provided an additional list of pertinent guidelines, consensus, and recommendation papers from various organizational groups. Although only those highest ranked articles by a majority consensus were discussed, other publications may be important depending on the patient population and the role of the pharmacist at a specific institution. It is recommended that informed pharmacists, engaged in nutrition support therapy, be familiar with those articles that are applicable to their clinical practice. Despite omission from the “most important” articles collection by this group, it is also suggested that the list of other articles in the supplemental online document also be reviewed in an effort to identify those publications that are pertinent to the reader’s practice.

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