Significant Published Articles for Pharmacy Nutrition Support Practice in 2014 and 2015

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ABSTRACT

Purpose: To assist the pharmacy clinician engaged in nutrition support in staying current with the most pertinent literature.

Methods: Several experienced board-certified clinical pharmacists engaged in nutrition support therapy compiled a list of articles published in 2014 and 2015 that they considered to be important to their practice. Only those articles available in print format were considered for potential inclusion. Articles available only in preprint electronic format were not evaluated. The citation list was compiled into a single spreadsheet where the author participants were asked to ascertain whether they considered the paper 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.

Results: A total of 108 articles were identified; 36 of which were considered to be of high importance. An important guideline article published in early 2016, but not ranked, was also included. The top-ranked articles from the primary literature were reviewed.

Conclusion: It is recommended that the informed pharmacist, who is engaged in nutrition support therapy, be familiar with the majority of these articles.

Key Words—consensus, enteral nutrition, guidelines, outcomes, parenteral nutrition

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Staying current with the literature is a requirement for the informed pharmacist who maintains an evidence-based clinical practice. This requirement has become more challenging to fulfill as a paradigm shift has changed the practice culture of a full-time pharmacy nutrition support specialist to a more integrated model whereby the clinical pharmacist provides pharmacotherapy services along

with nutrition support responsibilities. As a result of this change, informed clinicians are responsible for staying abreast of numerous therapeutic areas that interface with their clinical practice in addition to nutrition support therapy. Because nutrition support therapy is integrated with many divergent specialized fields (eg, medicine, surgery, pediatrics, gastroenterology, oncology, nephrology, infectious disease,

Supplementary material: The online version of this article includes the eAppendix.

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endocrinology, hepatology, transplantation, trauma, burns, home infusion, critical care, dietetics, nursing, and pharmacy), it is nearly impossible 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 their clinical practice. Additionally, it is our intent to provide an updated source of pertinent new literature since the last time this project was undertaken.¹

METHODS

To assist pharmacy clinicians engaged in nutrition support in staying current with the most pertinent literature, the primary author of this paper (R.N.D.) invited several clinical pharmacists with active involvement in pharmacy nutrition support practice and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) to provide citations of articles published from January 2014 to December 2015 that resulted in a change or affirmation of their current clinical practice or that they considered to be important for future clinical practice. Seven author participants are board-certified nutrition support pharmacists and one is a board-certified pharmacotherapy specialist. The duration of individual practice experience of the group members ranges from 4 years to more than 30 years. Members of this authorship group have advanced practice roles with direct patient care responsibilities for prescribing enteral and/or parenteral nutrition (PN), laboratory analysis, and pharmacotherapy integrated with nutrition therapy (eg, fluid and electrolytes, prokinetic drugs, insulin, antidiarrheal and laxative therapy), and some have administrative or supervisory roles with respect to nutrition support therapy. This group has a broad range of practice experiences. Most are acute care-based, but some have long-term care (home parenteral and enteral nutrition [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 principal author participant (R.N.D.) asked each member of the author participant group to provide citations published from January 2014 to December 2015 that changed or affirmed their current clinical practice or that they considered to be important for future clinical practice. 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 January 2016 or later) were not evaluated. The citation list was compiled into a single spreadsheet where the author participants were asked to denote whether they considered the paper important to nutrition support pharmacy practice. An abstract and complete citation of each paper was provided along with the scoring sheet to assist the author participants with the evaluation process in the event they could not recall the details of the paper. To insure 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 108 articles were collectively collated for initial evaluation by the authorship group. Thirty-six papers were identified as most important for pharmacy nutrition support practice as determined by a majority vote. Of the 36 publications collectively selected by the author participant group, 8 were published in *Journal of Parenteral and Enteral Nutrition*, *Nutrition in Clinical Practice*, *Critical Care Medicine*, and *Critical Care* each contributed 4 papers to the collection. Three papers each were obtained from the *New England Journal of Medicine* and *Clinical Nutrition*, for an additional subtotal of 6 papers. The remaining 10 papers were from 7 different pharmacy, nutrition, and medical journals. One guideline article, published in February 2016, was included due to its level of importance for those engaged in nutrition support of hospitalized patients. The 72 citations, not part of the finalist group, are available online as a supplement to this paper.

Individual rankings, based on relevancy to pharmacy nutrition support clinical practice according to the author participant group, are given in **Table 1**. The highest ranked articles are summarized in the discussion along with a narrative regarding their implications for pharmacy nutrition support practice.

Table 1. Rankings of significant publications for pharmacy nutrition support practice^a

First author	Title	No. of authors that indicate high importance ^b
Arabi ²	Permissive underfeeding or standard enteral feeding in critically ill adults	8
Boullata ⁹	Pancreatic enzymes prepared in bicarbonate solution for administration through enteral feeding tubes	8
van Zanten ¹²	High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: A randomized clinical trial	8
Becker ¹⁵	Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition)	7
Braunschweig ¹⁶	Intensive nutrition in acute lung injury: A clinical trial (INTACT)	7
Busch ¹⁸	Use of piggyback electrolytes for patients receiving individually prescribed vs premixed parenteral nutrition	7
Dugan ²²	Maximum tolerated osmolality for peripheral administration of parenteral nutrition in pediatric patients	7
Edmunds ²⁴	The effects of different IV fat emulsions on clinical outcomes in critically ill patients	7
Elke ²⁸	Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: Secondary analysis of a large international nutrition database	7
Grau-Carmona ³⁵	Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU lipids study	7
Guenther ³⁷	Standardized competencies for parenteral nutrition prescribing: The American Society for Parenteral and Enteral Nutrition model	7
McClave ⁷	Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)	NR
Austin ³⁹	Factors influencing <i>Candida albicans</i> growth in parenteral nutrition with and without lipid emulsion: Using an established framework to inform maximum duration of infusion policy decisions	6
Bakker ⁴⁰	Early versus on-demand nasoenteric tube feeding in acute pancreatitis	6
Blanchette ⁴¹	Standardized versus custom parenteral nutrition: Impact on clinical and cost-related outcomes	6
Dickerson ⁴²	Improved safety with intravenous insulin therapy for critically ill patients with renal failure	6
Dickerson ⁴³	Influence of aging on nitrogen accretion during critical illness	6
Harvey ⁴⁴	Trial of the route of early nutritional support in critically ill adults	6
MacKay ⁴⁵	Physical compatibility of sodium glycerophosphate and calcium gluconate in pediatric parenteral nutrition solutions	6
Mesejo ⁴⁶	Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: A prospective, open-label, blind-randomized, multicenter study	6
Tucker ⁴⁷	American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) standards of practice for nutrition support pharmacists	6

(continued)

Table 1. Rankings of significant publications for pharmacy nutrition support practice^a (CONT.)

First author	Title	No. of authors that indicate high importance ^b
Wei ⁴⁸	The association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: A multicenter cohort study	6
Zacharioudakis ⁴⁹	Antimicrobial lock solutions as a method to prevent central line-associated bloodstream infections: A meta-analysis of randomized controlled trials	6
Amrein ⁵⁰	Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: The VITdAL-ICU randomized clinical trial	5
Crosara ⁵¹	A J-shaped relationship between caloric intake and survival in critically ill patients	5
Finfer ⁵²	Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: Long-term follow-up of a subgroup of patients from the NICE-SUGAR study	5
Frazer ⁵³	Relationship between triglyceride tolerance, body mass index, and fat depots in hospitalized patients receiving parenteral nutrition	5
Grintescu ⁵⁴	The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients—A randomized-controlled clinical study	5
Jafari ⁵⁵	Parenteral immunonutrition in patients with acute pancreatitis: A systematic review and meta-analysis	5
McClave ⁵⁶	Volume-based feeding in the critically ill patient	5
Oghazian ⁵⁷	Effectiveness of regular versus glargine insulin in stable critical care patients receiving parenteral nutrition: A randomized controlled trial	5
Pawlik ⁵⁸	Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: A prospective, randomized study	5
Perry ⁵⁹	Microbial contamination of enteral feeding products in thermoneutral and hyperthermal ICU environments	5
Robinson ⁶⁰	The relationship among obesity, nutritional status, and mortality in the critically ill	5
Spasovski ⁶¹	Clinical practice guideline on diagnosis and treatment of hyponatraemia	5
Tian ⁶²	Effect of initial calorie intake via enteral nutrition in critical illness: A meta-analysis of randomised controlled trials	5
Weijjs ⁶³	Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients	5

Note: NR = not rated (included due to its level of importance despite its publication in early 2016).

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

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

A narrative regarding guideline and consensus papers was not provided. Due to its substantial level of relevance and importance to our practice, the citation for the SCCM and the A.S.P.E.N. guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patients is provided despite its being published in 2016.

DISCUSSION

1. Arabi et al. (2015). Permissive underfeeding or standard enteral feeding in critically ill adults.² The objective of this study (the PermiT trial) was to determine whether there was a difference in the 90-day mortality of 2 groups of critically ill adults: those who were provided with moderate

nonprotein calories (permissive underfeeding) while maintaining full protein provision compared to those provided with standard EN and full protein. This was a randomized controlled, unblinded trial performed in 7 tertiary centers in Saudi Arabia and Canada and included 894 critically ill, adult patients requiring enteral feeding within 48 hours of intensive care unit (ICU) admission and expected to remain in the ICU for longer than 72 hours. Patients were randomized into the permissive underfeeding group ($n = 448$) with a caloric goal of 40% to 50% of total calories or standard therapy group ($n = 446$) with a caloric goal of 70% to 100% of total calories. Caloric estimations were made through use of the Penn State equation³ for ventilator-dependent patients with a body mass index (BMI) less than 30 kg/m² or the Ireton-Jones equation⁴ for those considered obese (BMI ≥ 30 kg/m²) and for nonobese patients who were spontaneously breathing. Protein goals for both groups were calculated at 1.2 to 1.5 g/kg/day. Protein flushes were utilized to maintain similar protein intakes. Enteral feeding was continued for the duration of ICU stay or a maximum of 14 days.

Baseline characteristics of the groups were similar. The mean age of all patients was 50 years with a BMI of 29 kg/m². Seventy-five percent of all patients were medical intensive care unit (MICU), 21% nonoperative trauma, and the remainder surgical ICU (SICU). One-third of patients were admitted with severe sepsis. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were 21 and 10, respectively, for both groups indicating high severity of illness. The researchers found no statistically significant difference in 90-day mortality between the permissive underfeeding group and standard feeding group (27.2% and 28.9%, respectively; relative risk [RR], 0.94; 95% CI, 0.76-1.16). There was also no statistically significant difference in secondary or tertiary endpoints. The researchers concluded that providing moderate nonprotein calories (permissive underfeeding) and full protein intake in critically ill patients provided no benefit in mortality and overall outcomes compared to standard EN with full protein provision.

It is important to understand the implications and limitations of the PermiT trial. The lack of benefit of providing full caloric estimations to critically ill patients seen in this trial is not a new finding^{5,6};

however, caution must be taken in applying results of such studies to general ICU populations. Patients in these 3 trials were younger, predominantly MICU patients with a limited number of malnourished patients, a subset for which guidelines support the use and benefit of full feeding.⁷ Although mean caloric targets were met for both groups ($46 \pm 14\%$ of calculated caloric requirements for permissive underfeeding group and $71 \pm 22\%$ for standard enteral feeding), most would still consider both to be permissive underfeeding. The lack of meeting calculated protein goals in both groups (mean protein provision of both groups was 0.7 g protein/kg/day) of this trial is also of concern as it was well below the study design and not in line with current guideline recommendations (1.2-2 g protein/kg/day).⁷ Recent evidence points to the importance of adequate protein provision in critically ill patients over total caloric intake on clinical outcomes.⁸ This, as well as patient selection, may be responsible for the end results of this study. In summary, while it appears that for the subset of patients in the PermiT trial there is no untoward effect on 90-day mortality or clinical outcomes with permissive underfeeding, caution must be undertaken in applying this method of feeding to all ICU patients (specifically SICU, malnourished, and elderly patients) until more evidence is published.

2. Boullata et al. (2015). Pancreatic enzymes prepared in bicarbonate solution for administration through enteral feeding tubes.⁹

Patients with pancreatic insufficiency who require pancreatic enzyme replacement therapy and are unable to take medication by mouth pose a significant challenge. For those with enteral access, several techniques for administering pancrelipase using the feeding tube have been described.^{10,11} Product labeling does not include recommendations for administering pancreatic enzymes via enteral feeding tubes and cautions against the disruption of the delayed-release enteric-coated granules. However, feeding tube occlusion can occur if granules are administered intact. One recommendation has been to dissolve the enteric-coated granules (uncrushed) in sodium bicarbonate prior to administration to minimize risk of tube occlusion.¹¹

The intent of this in vitro study was to evaluate the dissolution and physicochemical effects of 4 delayed-release pancrelipase products (*Creon*, *Pancreaze*, *Ultresa*, *Zenpep*) when added to sodium bicarbonate solution. The intact contents

of each capsule were added to sodium bicarbonate (8.4%) injection 20 mL, evaluated by visual inspection, and measured for pH, relative particle count, and osmolality at 0-, 5-, 10-, 20-, and 30-minute intervals. Of note, the contents were not stirred. Direct visual inspection at 30 minutes demonstrated complete dissolution of *Creon* (24,000 lipase units), *Ultresa* (23,000 lipase units), and *Zenpep* (20,000 and 40,000 lipase units). *Pancreaze* (21,000 lipase units) and the higher doses of *Creon* (48,000 lipase units) and *Ultresa* (46,000 lipase units) did not completely dissolve 30 minutes after preparation. It is possible that larger amounts of sodium bicarbonate may be required to dissolve the higher doses of enzymes, but this was not studied. The relative particle count generally increased over time as enzymes disintegrated and osmolality increased over time as enzymes dissolved. In conclusion, the results suggest that dissolution of pancrelipase capsule contents in sodium bicarbonate solution varies with product and dose, but it can effectively be done in certain cases. Each institution should evaluate current practice patterns and formulary considerations to best determine applicability of study results. Keep in mind that dissolving the enteric coating prior to administration is done at the risk of activating enzyme prior to reaching site of action in the small bowel and compromising therapeutic efficacy. Further study is required to evaluate clinical outcome of this practice.

3. van Zanten et al. (2014). High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: A randomized clinical trial.¹²

The intent of this study (the MetaPlus trial) was to determine whether a high protein EN enriched with immune-modulating nutrients reduces the incidence of infections compared with standard high protein EN in mechanically ventilated, critically ill patients. In a randomized, double-blind, multicenter trial conducted in 14 ICUs in Europe, 1 of 2 formulas was given to 152 and 149 patients, respectively, within 48 hours of ICU admission and patients continued on the formula during their ICU stay for a maximum of 28 days. Patients were expected to require mechanical ventilation and EN for at least 3 days. There were no statistically significant differences in the incidence of new infections between groups (53%

vs 52%) or other clinical outcomes except for a higher 6-month mortality rate adjusted for age and APACHE II score in the medical subgroup (54% vs 35%; $p = .04$). The researchers concluded that the immune-modulating enteral formula did not improve infectious complications and may be harmful.

It is important to recognize that not all ICU patients are the same. Only the medical subgroup of patients in the MetaPlus study showed a difference in 6-month mortality. However, preexisting infections prior to initiation of these feedings may have confounded their findings. About two-thirds of the MICU patients had a preexisting infection prior to initiation of the enteral formulas in contrast to the surgical and trauma patient population subgroups at one-third and one-fifth, respectively. Finally, all patients received only 1 g/kg/d or less of protein despite provision of “high protein containing” enteral formulas. Unfortunately, this protein intake is inadequate for most critically ill surgical or trauma patients¹³; this may have influenced outcomes (eg, lack of clinical benefit) for these subpopulations. Congruent with the MetaPlus findings, the 2016 SCCM-A.S.P.E.N. guidelines recommend that immune-modulating formulations be avoided in MICU patients.⁷ However, the guidelines also recommend that immune-modulating formulations be considered for patients with traumatic injuries, including traumatic brain injury, and for patients undergoing major surgery where ICU admission is expected.⁷ There is a growing body of evidence supporting immune-modulating formulas for perioperative use in patients undergoing elective gastrointestinal surgery.¹⁴ In summary, this study provides strong evidence that immune-modulating formulas should not be given to MICU patients, especially if they are already infected. Extrapolation of these detrimental findings to all critically ill patients, such as surgical and trauma patients, would be inappropriate.

4. Becker et al. (2015). Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition).¹⁵

This consensus statement discusses the nutritional assessment of pediatric patients for evidence of malnutrition. It is important for all

disciplines that are engaged in nutrition therapy of the pediatric patient to be familiar with the content of this paper. The authors discuss use of *z* scores for weight for height/length, BMI for age, or length/height for age or mid-upper arm circumference as well as weight gain velocity, weight loss, deceleration in weight for length/height *z* score, and inadequate nutrient intake. They conclude that a standardized diagnostic approach will assist in the prevention and treatment of undernutrition in this vulnerable population and help to further ensure the provision of high-quality, cost-effective nutritional care.

5. Braunschweig et al. (2015). Intensive nutrition in acute lung injury: A clinical trial (INTACT).¹⁶

The investigators of this single center, randomized controlled trial studied the impact of intensive nutritional intervention versus standard nutritional therapy in 78 MICU and SICU patients diagnosed with acute lung injury who required mechanical ventilation. The mean age of all participants was 55 years, about 30% of patients in both groups were obese, and two-thirds were considered to have a normal nutritional status as assessed by subjective global assessment. Intensive nutritional intervention consisted of initiation of EN within 6 hours of hemodynamic stability, volumetric feeding to account for feeding interruptions, and oral dietary intake initiated with additional snacking options and meal tickets soon after extubation. Standard nutrition therapy consisted of a protocolized feeding algorithm whereby holding of EN occurred if the gastric residual volume exceeded 250 mL or if vomiting occurred or aspiration was suspected and, following extubation, oral diets were initiated and prescribed by the managing medical services. Calorie counts were conducted based on patient recall of meal consumption. Energy and protein goals were 30 kcal/kg/d and 1.5 g/kg/d, respectively.

Patients received 85% of goal in the intensive intervention group as opposed to 55% in the standard control group ($p < .0001$). There was no significant difference in hospital or ICU length of stay, ventilator days, or number of infections between groups. However, a marked difference in mortality (40% for the intensive therapy group as opposed to 16% for conventional therapy; $p = .17$) prompted the investigators to terminate the trial early. The investigators concluded that intensive nutritional therapy increased mortality.

The reader should be assured that the 2 populations are very similar, especially when a large difference in mortality between groups is discovered and when mortality differences of other large nutrition trials in patients with acute lung injury/acute respiratory distress syndrome are not that profound.¹⁷ It would have been useful if the researchers had provided more information about the level of illness of their patients. It also would have been helpful to know what proportion of patients were medical versus surgical, distribution of the suspected etiology for the acute lung injury (eg, sepsis, pneumonia, trauma, inhalational injury, pancreatitis), duration of ICU stay and nutrition therapy prior to enrollment in the study, and number of patients already infected prior to or at randomization. It would have been insightful for the authors to provide other therapies that were given to both groups that may have influenced feeding tolerance (eg, prone positioning, use of non-depolarizing neuromuscular blockers, vasopressors, corticosteroids, and prokinetic pharmacotherapy). Although the intensive therapy group required more insulin, details regarding the level of glycemic control were not provided. It is also unclear whether all patients received a similar type of feeding formulation as the specific formulas used were not discussed. Although there was no difference in the number of patients who received PN or number of PN days, it would have been useful to know about the timing of initiation of the PN. Differences in timing of initiation of PN may suggest early EN intolerance, which may have related to severity of illness. Finally, it would be intuitive that aggressive feeding that results in more feeding intolerance complications, hyperglycemia, and electrolyte perturbations might lead to poorer clinical outcomes; however, due to inadequate detail provided in this article, it is unclear whether these were actual patient care issues in this study.

In summary, these data suggest that intensive nutritional intervention, given to well-nourished patients with acute lung injury in the early phase of mechanical ventilation, may cause potential harm. However, current SCCM-A.S.P.E.N. guidelines recommend that either trophic or full nutrition by EN is appropriate for patients with acute respiratory distress syndrome/acute lung injury and who are expected to have a duration of mechanical ventilation for 72 hours or longer as

these 2 strategies of feeding have similar patient outcomes over the first week of hospitalization.⁷ The detrimental effect of “aggressive” or “intensive” nutrition intervention for patients with acute respiratory distress syndrome/acute lung injury as suggested by this study requires further investigation.

6. Busch et al. (2015). Use of piggyback electrolytes for patients receiving individually prescribed vs premixed parenteral nutrition.¹⁸

Commercially available premixed preparations of PN are popular in Europe as an alternative to individualized PN compounded to meet the requirements of each individual patient. These products are available with varying strengths of macronutrient and micronutrient content; however, there are few commercially available premixed PN preparations with electrolytes available in the United States. This study compared the use of supplemental intravenous piggyback (IVPB) electrolytes in patients receiving premixed PN to patients receiving individualized PN preparations. The study captured a 30-day time period when premixed PN formulations were used due to an amino acid shortage and the preceding 30-day time period when PN formulations were individually compounded. The study excluded pediatrics, significant metabolic abnormalities, and significant electrolyte abnormalities at baseline. Serum electrolyte monitoring was conducted daily during the first week of PN provision and at least 2 days per week thereafter. Patients were administered electrolyte IVPB supplementation to maintain serum potassium greater than 4 mEq/L, magnesium greater than 2 mEq/L, and phosphate greater than 3 mg/dL. Individualized PN was compounded using an automated compounding device, while the premixed PN products consisted of *Clinimix-E 4.25/10* (4.25% amino acids and 10% dextrose) and *Clinimix-E 5/15* (5% amino acids and 15% dextrose; Baxter, Deerfield, IL). The premixed PN products were not manipulated to provide any additional macronutrient or electrolyte content; however, ranitidine, insulin, multivitamin, and trace element products were manually added to each preparation as clinically appropriate. Overall, the number of daily IVPB electrolyte doses prescribed was higher in the premixed PN population when compared to the individualized PN population (13.8 ± 6.8 vs 7.03 ± 3.8 ; $p = .0001$). The premixed PN population

incurred greater patient charges for supplemental IVPB electrolytes in comparison to the custom PN population, resulting in a cost difference of \$11,855.74 for 30 days of treatment per patient.

This study provides information on the clinical appropriateness of predetermined electrolyte content in commercially available premixed preparations of PN; however, it should be pointed out that IVPB electrolyte supplementation could be ordered by any provider independent of the nutrition support team prescribing PN. In addition, the investigators did not discuss the presence or absence of any protocol utilized to correct electrolyte imbalances, which would create a standard of care for patients receiving both premixed and individualized PN. In regard to cost savings, only charges associated with IVPB electrolyte supplementation were included, not charges related to the PN formulation or supplemental IV fat emulsion. While other studies identify benefits of premixed PN in regard to cost avoidance and reduced infectious complications, it should be noted that this study provides additional data to consider when determining options for PN delivery.¹⁹⁻²¹ In conclusion, patients receiving individualized PN received less supplementation of IVPB electrolytes and greater cost avoidance in comparison to patients receiving premixed PN formulations available in the United States.

7. Dugan et al. (2014). Maximum tolerated osmolality for peripheral administration of parenteral nutrition in pediatric patients.²²

The provision of PN via peripheral veins is difficult to optimize due to the risks for phlebitis and infiltration. Solution osmolality is a critical contributing factor to these risks. Osmolality is a measure of all osmotically active particles within a liter of solution. Parenteral nutrition additives, including macronutrients and micronutrients, all contribute to the final osmolality. Meeting nutritional requirements for patients usually results in PN solutions with high osmolality, limiting the ability to use peripheral veins. A.S.P.E.N. notes a maximum osmolality of 900 mOsm/L for safe infusion via the peripheral vein based on a comprehensive review of the literature, however the grade of the recommendation was weak due to data limited by study design and small sample size.²³ Further, the majority of the available literature supporting this recommendation is based on adult patients. Due to limited data to support the

maximum tolerated osmolality via the peripheral vasculature in children, the researchers sought to evaluate the overall incidence of phlebitis and infiltration and to determine the maximum tolerated osmolality for peripheral parenteral nutrition (PPN) in pediatric patients.

This retrospective study evaluated patients 18 years of age or younger over a 2-year period who received PPN with a final osmolality less than or equal to 1,000 mOsm/L and compared them to a matched-cohort (1:1) who received PPN with a final osmolality greater than 1,000 mOsm/L. Patients were matched according to weight in order to ensure homogeneity between groups. Patients were excluded if they were older than 18 years of age or received central venous administration of PN or cyclic PN. The composite of phlebitis and infiltration was the primary outcome measure. A total of 176 patients in each group were evaluated with similar baseline demographics, with the exception of more males in the less than or equal to 1,000 mOsm/L group (68%) compared to the greater than 1,000 mOsm/L group (55%; $p = .01$). This difference did not affect the primary outcome measure. The investigators found that those patients receiving PPN in the greater than 1,000 mOsm/L group had significantly more phlebitis and infiltration compared to those in the less than or equal to 1,000 mOsm/L group (45% vs 34%, respectively; odds ratio [OR], 1.65; 95% CI, 1.07-2.54; $p = .02$). The primary outcome was not affected by being a neonate, concurrent medications, or site of PPN infusion. All patients with phlebitis (both groups) experienced this complication within 12 ± 6.5 hours from the start of the infusion. Of those experiencing phlebitis, concomitant administration of intravenous fat emulsion did not have an effect. The researchers additionally evaluated other contributing factors such as age, weight, PPN composition, and site of PPN, finding that the only risk factor that significantly contributed to phlebitis and infiltration was osmolality greater than 1,000 mOsm/L (OR, 1.67; 95% CI, 1.08-2.52; $p = .02$).

Although this study is limited by its retrospective design, it is one of the larger studies available and is strengthened by its inclusion of pediatric patients beyond the neonatal period. An important observation in this study is the high rate of phlebitis and infiltration in both groups

(approximately 40% observed occurrence). This highlights that PPN carries a significant risk for phlebitis and infiltration regardless of osmolality, stressing the importance of close monitoring and the possible need for site rotation.

8. Edmunds et al. (2014). The effects of different IV fat emulsions on clinical outcomes in critically ill patients.²⁴

Although a majority consensus could not be achieved, current clinical practice guidelines in the United States recommend withholding soybean oil (SO)-based lipid emulsion (LE) during the first week following initiation of PN in the ICU in non-malnourished patients and minimizing to 100 g/week in malnourished patients to prevent essential fatty acid deficiency.⁷ The guidelines also suggest considering the use of alternative LEs (SMOF [SO, medium chain triglycerides (MCT), olive oil (OO), and fish oil (FO)], MCT, OO, and FO) in this patient population if available. These recommendations are based primarily upon the metabolic pathway of SO-based LEs exacerbating the inflammatory immune response by serving as a precursor of arachidonic acid with subsequent production of pro-inflammatory prostaglandins and leukotrienes.²⁵ Additionally, a recent meta-analysis of FO-based LEs in ICU patients showed significantly reduced infections (RR, 0.65; 95% CI, 0.44-0.94; $p = .02$).²⁶

Unfortunately, there was no direct comparison of the different forms of LEs available internationally until publication of this study. The purpose of this prospective observational study was to determine whether there are differences in clinical outcomes with use of different LE products from an international sample of older ICU patients (mean age of 62 years or older). To enroll in the study, patients had to be in the ICU for at least 72 hours and received PN for at least 5 days with SO-based versus alternative LEs versus lipid-free PN. Nutrition-related data were collected for 12 days (unless death or ICU discharge came first). Patient groups were divided into 5 categories based on the type of LE given: (1) SO-based ($n = 223$), (2) physical mixture and structured MCT oil-based ($n = 65$), (3) OO-based ($n = 74$), (4) any FO-containing LE ($n = 19$), and (5) lipid-free PN ($n = 70$). Of the 451 patients enrolled in the study, 49% were emergency surgical admissions, 19% were elective surgery patients, and 32% were medical patients. Mean APACHE II score for the entire population

was 21. The lipid-free PN received the lowest amount of calories at 1036 kcal/day with the OO-based and FO-containing LEs receiving the highest at 1553 kcal/day and 1517 kcal/day, respectively ($p < .001$). Sixty-day mortality was highest in the MCT oil and SO-based LE groups at 31% and 28% of patients compared to 19%, 15%, and 11% for the lipid-free, OO-based and FO-based groups, respectively ($p = .034$). The median ICU length of stay was shortest in the FO and OO-based LE groups at 7 and 8 days compared to 10, 11, and 11 days for the MCT oil, SO-based, and lipid-free PN groups, respectively ($p < .001$).

While this trial showed little difference between SO-based and MCT oil-based LEs, it did report benefits in the ICU for OO-based and FO-based LEs in PN.²⁷ It should be noted that the lower number of ICU patients receiving FO-based LEs may represent a type I error with the outcomes reported, since a recent meta-analysis of FO-based LE²⁶ did not find the same results as this study. Given the observational nature of the study design, it is also unclear why certain patients were given a specific LE that may have introduced patient-LE selection bias. However, this study indicates promise for the use of FO- and OO-based LEs in ICU patients. These data warrant confirmation by future randomized, prospective controlled trials.

9. Elke et al. (2014). Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: Secondary analysis of a large international nutrition database.²⁸

The Surviving Sepsis Campaign guidelines²⁹ suggest avoiding mandatory full caloric feeding and using low-dose EN in the first week of management based on findings by prospective randomized studies.^{5,6,30} Conversely, the 2013 Canadian critical care nutrition guidelines³¹ recommend optimizing EN and not using trophic feeds for the initial 5 days based on other literature.³²⁻³⁴ Given the contradictory guideline recommendations and existing literature, the purpose of this study was to evaluate the effect of energy and protein amount given by EN on clinical outcomes in a large cohort of critically ill septic patients.

In this secondary analysis of pooled data from international nutrition studies, 2,270 patients met study inclusion criteria (diagnosis of sepsis and/or pneumonia, admitted to the ICU for at least

3 days, mechanically ventilated within 48 hours of ICU admission, only received EN). On average, EN was started within 48 hours of admission to the ICU (mean $\pm$ SD, 26.6 $\pm$ 26.4 hours). The mean intakes were 1,057 kcal/day (14.5 kcal/kg/day) and 49 g protein/day (0.7 g/kg/day). The authors reported that an increase of 1,000 kcal was associated with a reduced 60-day mortality (OR, 0.61; 95% CI, 0.48-0.77; $p < .001$) and more ventilator-free days (2.81 days; 95% CI, 0.53-5.08; $p = .02$). Similarly, an increase of 30 g protein per day was associated with a reduced 60-day mortality (OR, 0.76; 95% CI, 0.65-0.87; $p < .001$) and more ventilator free-days (1.92 days; 95% CI, 0.58-3.27; $p = .005$). The researchers concluded that achieving closer to recommended caloric and protein EN intake early in ICU admission is associated with improved clinical outcomes for critically ill septic patients.

The researchers acknowledge that their findings should be interpreted with caution. Since this was a pooled observational study, there may not be a causal relationship between delivery of energy and protein intakes closer to recommended amounts and clinical outcomes. Also, with tolerance of EN often being linked to severity of illness, it is possible that patients tolerating close to recommended amounts of calories and protein were less sick. The mean APACHE II score for study patients was 23.9, but other markers of severity of illness were not examined in the study. Consequently, reduced 60-day mortality and increased ventilator-free days may be due to patients being less sick at baseline rather than the provision of close to recommended caloric and protein intake. Additionally, the investigators intended to evaluate their study question in a cohort of critically ill septic patients, but all patients may not have been septic because patients with an ICU admission diagnosis of sepsis or pneumonia were included (45% sepsis; 55% pneumonia). Their assumption was that most mechanically ventilated patients admitted with pneumonia are septic, but this is not always true. Furthermore, patients were not categorized as sepsis or septic shock because this information was unavailable in the pooled data.

In summary, this study challenges the current Surviving Sepsis Campaign guidelines and warrants further evaluation of optimal energy and protein requirements for septic patients in the acute phase of management by more robust trials.

This study only included MICU patients, so the results cannot be extrapolated to other critically ill patients, such as surgical and trauma patients. Based on expert consensus in the absence of definitive literature, the 2016 SCCM-A.S.P.E.N. guidelines recommend the provision of trophic feeding for the initial phase of sepsis, advancing as tolerated after 24 to 48 hours to greater than 80% of target energy goal over the first week. The delivery of 1.2 to 2 g protein/kg/day is suggested.⁷

10. Grau-Carmona et al. (2015). Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU lipids study.³⁵

This article, entitled the ICU Lipids Study (sponsored by B. Braun Medical S.A.), was a prospective, multicenter, randomized, comparative double-blind trial in 17 Spanish medical/surgical ICUs of older adults (mean age of 61 years) requiring PN for approximately 9 days. Patients were randomized to receive either a 50% MCT/50% SO (control group; $n = 78$) or a 50% MCT/40% SO/10% FO (experimental group; $n = 81$) LE. The PN formulations delivered 23 kcal/kg/day including 1 g lipid emulsion/kg/day (0.1 g FO/kg/day in MCT/SO/FO group) and 1.4 g protein/kg/day. Patients were allowed to receive EN and approximately 53% in each group did, although the specific caloric amounts and protein provision from EN therapy were not reported.

The primary endpoint of this study was the prevalence of nosocomial infections (NIs) after 28 ICU days (earlier if death or ICU discharge). NIs included mechanical ventilation-associated pneumonia, bacteremia, endocarditis, mediastinitis, meningitis or ventriculitis, surgical wound infection, intra-abdominal abscess, and urinary infection. One hundred and seventy-five patients were enrolled for study; 16 withdrew for a total of 159 evaluable patients. Unfortunately, only 59 (76%) patients in the MCT/SO group and 58 (72%) patients in the MCT/SO/FO group received PN for 5 days or more as outlined in their inclusion criteria. The mean APACHE II and SOFA scores were 21 and 7, respectively, for both groups. Approximately 29% of all patients had septic shock, and the only baseline characteristic that was statistically different was the number of patients with pancreatitis (6.4% in MCT/SO vs 17.3% in MCT/SO/FO; $p = .049$). The ICU population studied was 48% medical ICU and

52% surgical ICU with 82% of patients requiring mechanical ventilation.

At least one NI occurred in 37% of the MCT/SO (control) group as compared to 21% of the MCT/SO/FO (experimental) group ($p = .04$). Antibiotic-free days were similar (1 vs 2 days; $p = .29$). These findings were consistent with those of a recent meta-analysis of FO-based LEs in ICU patients showing significantly reduced infections.²⁶ While a reduction in infectious complications support the use of the MCT/SO/FO-based PN, their data was confounded by a trending increase in ICU mortality (33% vs 21%; $p = .106$) for the FO-based PN group. These data would also infer bias toward a shorter period of time at risk for getting NIs.³⁶ Laboratory evidence of hepatic dysfunction occurred in 75% of all patients during the trial. The use of a MCT/SO/FO-based PN over an MCT/SO-based LE PN did not appear to have any difference on laboratory evidence of liver dysfunction despite conventional LE dosages.

A trending increase in greater mortality in the MCT/SO/FO-based PN, despite the statistically significant reduction in NIs, warrants caution in the routine use of this form of LE for critically ill patients. Given its unavailability in the United States, this precludes usage at this time.

11. Guenter et al. (2015). Standardized competencies for parenteral nutrition prescribing: The American Society for Parenteral and Enteral Nutrition model.³⁷

This report indicates that prescribing of PN requires that competency for prescribers from all disciplines be demonstrated using a standardized process. They describe methods to assess general nutrition competencies, provide a framework with elements for assessing PN prescribing competencies, and provide the A.S.P.E.N.-endorsed model for PN prescribing.

12. McClave et al. (2016). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).⁷

This interdisciplinary report serves as an update and expansion of the previous guidelines published by A.S.P.E.N. and SCCM in 2009.³⁸ These 2016 guidelines were based on data available up until December 31, 2013. Some of the 2009 recommendations have not changed

whereas some other areas have changed based on new literature. The article is divided into subsections: nutrition assessment, initiation, dosing, formula selection, and monitoring of tolerance and adequacy of EN, adjunctive therapy (eg, fiber, antioxidants, probiotics, glutamine) and PN indications and optimization. Considerable expansion was noted for “disease-specific” topics (eg, pulmonary, renal and hepatic failure, pancreatitis, various surgical subsets, sepsis, postoperative surgery, chronic critical illness, obesity, and end-of-life situations). This article is an essential “must read” for all clinicians engaged in nutrition support therapy.

CONCLUSION

With the volume of articles and their appearance in differing journals, it is extremely difficult for the pharmacist to stay current with studies applicable to pharmacy nutrition support practice. Although only the “top” rated papers were discussed, the other identified articles³⁹⁻⁶³ may be important to a pharmacist’s clinical practice depending on the patient population and the role of the pharmacist at a specific institution. Thus, it is recommended that the informed pharmacist, engaged in nutrition support therapy, be familiar with the majority of these articles as applicable to their clinical practice.

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