Guest Editorial

“New” Indications for Parenteral Nutrition

Rachel E. Wilkinson, PharmD,* and Roland N. Dickerson, PharmD, BCNSP*

Meeting nutritional goals and improving nutrition status are associated with a decrease in morbidity and mortality for hospitalized patients.^{1–3} Enteral nutrition (EN) is the preferred method for nutrition support therapy; however, it can sometimes be difficult to achieve optimal protein and energy goals due to gastrointestinal feeding intolerance or contraindications for its use. Parenteral nutrition (PN) is the alternative route of nutrition therapy. Historically, the use of PN has been associated with increased morbidity, primarily as infectious complications, when compared to EN.⁴ Although these complications are often related to the presence of a central venous catheter combined with the components of parenteral nutrition, they may also be due to overfeeding.^{5,6} Through advances in nutrition support therapy, the “clinical outcomes and complications gap” between EN and PN is closing.

In February 2016, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient were released; they suggest a less restricted use of PN.⁷ The guidelines recommend that PN be initiated as soon as possible after intensive care unit (ICU) admission if patients have contraindications to EN and are severely malnourished or at “high nutrition risk.” They also recommend that supplemental PN be initiated in at-risk patients after 7 to 10 days if patients are not able to meet at least 60% of energy and protein requirements.⁷ The nutrition risk screening (NRS 2002) score⁸ or the nutrition risk in the critically ill (NUTRIC) score⁹ (without serum interleukin-6 concentration) should be used for defining who is at high nutrition risk. These tools take into consideration both nutrition status and disease severity, unlike previous methods that only define one or the other. This new recommendation from the consensus authors is in contrast to the 2009 guidelines that indicate PN

should not be given to [all] patients that are unable to receive EN within the first 7 days and to reserve supplemental PN for patients unable to meet 100% of caloric goal after 7 to 10 days.¹⁰

The literature supporting these revisions and a less restricted use of PN largely stems from recent publications that suggest that PN is a safe alternative for EN.^{11–14} One of the first large meta-analyses of 26 randomized controlled trials (RCTs) that indicated no difference in mortality for use of PN when compared to EN was published in 1998.¹⁵ This meta-analysis also demonstrated a trend toward reduced complications overall, specifically in malnourished patients.¹⁵ Limitations of this meta-analysis prevented the results from being widely adopted; however, recent studies^{11–14} support these findings.

Heidegger and coworkers conducted an RCT assessing outcomes in 305 patients receiving EN plus supplemental PN versus EN alone.¹⁴ Patients who were receiving inadequate nutrition therapy from EN alone (defined as <60% of energy goals) and who were expected to stay in the ICU longer than 5 days and survive longer than 7 days, were randomized to 1 of the 2 feeding groups on day 4 of admission. The investigators found an increase in the achievement of energy and protein targets with supplemental PN as well as a significant decrease in the number of nosocomial infections per patient (from 38% to 27%).¹⁴

Another RCT, published soon after the Heidegger trial, evaluated outcomes in 1,372 critically ill patients who were given early PN (within 24 hours of admission) due to contraindications to EN versus “standard” care where initiation of PN was given early (29% of group), was delayed (27%), or was not given (41%).¹¹ Although the investigators found no significant mortality benefits of early PN, those who received early PN had fewer days of mechanical ventilation, less muscle wasting, and less loss of body fat. There was no difference in infectious complications, suggesting lack of a detrimental effect of early PN.

*Department of Clinical Pharmacy, University of Tennessee College of Pharmacy and Department of Pharmacy and Nutrition Support Service, Regional One Health, Memphis, Tennessee. Corresponding author: Roland N. Dickerson, PharmD, BCNSP, University of Tennessee College of Pharmacy, 881 Madison Avenue, Suite 345, Memphis, TN 38163; e-mail: rdickerson@uthsc.edu

The largest recent trial enrolled nearly 2,400 patients to receive either PN or EN within 36 hours of admission and continued for 5 days. There was no difference in infection rate or mortality, with the added benefit of decreased hypoglycemia and vomiting in the PN group.¹³ A major criticism of this study is that only about a third of patients from each group actually received goal nutrition intake according to the protocol. The PN group received marginally more calories and protein than the EN group, but what they received was still far from goal. Therefore, the conclusion of this study can only be made from the perspective of an underfed setting. These results during underfeeding support the concept that overfeeding may have played a role in the negative outcomes associated with PN (since PN is unlikely to be withheld compared to EN with gastric feeding intolerance) in some of the earlier PN versus EN studies.⁵

Lastly, a systematic review and meta-analysis of 18 RCTs was published in 2016 comparing the impact of EN versus PN on clinical outcomes.¹² While no difference in mortality or overall hospital length of stay was realized, there was a significant decrease in infectious complications (relative risk [RR], 0.64; 95% CI, 0.48-0.87) and ICU length of stay for the EN group. This effect was more pronounced in the subgroup of RCTs in which the PN group received significantly more calories than the EN group, while no effect was seen in trials in which EN and PN groups had a similar caloric intake. Although this study may initially appear to conflict with the previous recent studies indicating no difference in infectious complications or length of stay between EN and PN, the authors detailed that the observed differences in the EN and PN groups may be explained by the potential benefit of avoiding overfeeding (with EN) rather than the enteral route of nutrition therapy itself.¹² Although this explanation may be plausible, it should be acknowledged that a bevy of literature has focused on the immunologic role of the gastrointestinal tract and the role of provision of intraluminal nutrients in the pathophysiology of infectious complications during critical illness. In essence, it is still arguable whether past studies indicating potential superiority of EN over PN was due to overfeeding complications associated with PN or due to modulation of intestinal function and structure, particularly gut-associated lymphoid tissue, with EN.

We would be remiss if we did not mention important conflicting data. One study that refutes the 2016 guideline recommendations was an RCT of 4,640

patients who received initiation of PN either early (within 48 hours of ICU admission) or late (after 8 days of ICU admission).⁴ Patients with late initiation of PN had a 6% increase in the likelihood of being discharged alive earlier from the ICU and hospital, although mortality for both groups was similar. Patients in the late initiation PN group had fewer ICU infections (23% vs 26%) and less biochemical evidence of cholestasis, days of mechanical ventilation, and renal replacement therapy.⁴ However, this trial has been largely criticized for the patient population and the employed protocols.¹⁶ The severity of illness of the patients enrolled is questionable, because the majority of patients were admitted for an elective surgery and had an average ICU length of stay of 3 to 4 days. Furthermore, patients may not have received adequate amounts of PN to make conclusions. Patients in the early PN group received 1 to 2 days of PN while only about 25% in the late group received PN at all. Additionally, provision of PN during the first 2 days of this study was not PN, but only hypertonic dextrose (without amino acids, lipids, etc). Finally, the patients' blood glucose was managed with continuous intravenous insulin infusion utilizing a blood glucose concentration goal of 80 to 110 mg/dL, which has been shown to be unsafe for most patients.¹⁷ Given the limitations of this study, it is difficult to apply these results to the general critical care population.

The gap is closing regarding outcome detriments between EN and PN. Recent literature supports the safe use of PN as a substitute for EN (when EN is contraindicated or when EN delivery is inadequate) with no difference in the incidence of infections. The current guidelines recommend initiation of PN as soon as possible after ICU admission if patients have a contraindication to EN and are severely malnourished or at high nutrition risk.⁷ Supplemental PN should be initiated after 7 to 10 days if patients are not able to meet at least 60% of energy and protein requirements. However, it is also suggested that, in the patient at low nutrition risk, exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible.⁷ The recommendation of the older 2009 guidelines that suggest PN should not be given to *[all]* patients that are unable to receive EN within the first 7 days and to reserve supplemental PN for patients unable to meet 100% of caloric goal after 7 to 10 days¹⁰ should be abandoned.

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