Editorial

More and sooner, but not necessarily better

Piyagarnt Vichayavilas[1], Katja Gist[2], Jon Kaufman[2]

[1]Department of Clinical Nutrition, Children's Hospital Colorado, Aurora, CO, USA; [2]The Heart Institute, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Correspondence to: Piyagarnt Vichayavilas. Department of Clinical Nutrition, Children's Hospital Colorado, 13123 E. 16th Ave, Box 270, Aurora, CO 80045, USA. Email: Piyagarnt.Vichayavilas@childrenscolorado.org.

Submitted May 20, 2016. Accepted for publication May 31, 2016.
doi: 10.21037/jtd.2016.06.73
View this article at: http://dx.doi.org/10.21037/jtd.2016.06.73

Critically ill children have generalized nutrition compromise. The timing of parenteral nutrition (PN) initiation has been under debate in both adults and children. A recent report of a multi-national randomized control trial in children demonstrated clinical superiority of delaying initiation of parental nutrition, and was associated with improved clinical outcomes and a lower rate of infection. In this editorial, we discuss our communication with the authors and our experience in a large cardiac intensive care unit (CICU) in the United States where improved nutrition delivery, and early PN, has improved weight-for-age z-score (WAZ) but has not shown any difference in length of hospital stay or reduced ventilator times.

Neonates, infants, and some children with critical illness have limited nutrition reserves. Cumulative protein and energy deficits have been linked to prolonged ventilator times, increased length of intensive care stay, and subsequent poor growth and anthropometric parameters (1,2). Such deficits may also have long-term deleterious effects with regards to neurodevelopment and neurocognitive performance. Providing adequate nutrition in the form of protein, calories, and macro- and micronutrients is a modifiable intervention and therapy in the pediatric ICU. This is particularly the case with the use of PN. Obvious attention must be paid to electrolytes, fluid balance, and hepatic dysfunction, and delivery often requires central venous access. Despite the need for considerable monitoring, it is common practice to use PN to bridge the gap until a child can tolerate full enteral feeds to attenuate cumulative nutrition deficit in the ICU.

A large randomized controlled trial of critically ill adults comparing early versus late PN, including over 4,000 patients, published in *NEJM* 2011, found that late PN was associated with a 6.3% increase in the likelihood of being discharged from the ICU and hospital alive. In addition, patients in the late PN group had fewer ICU infections, lower incidence of cholestasis, a decrease in the proportion of those requiring mechanical ventilation for more than 2 days, and a decrease in the duration of renal replacement therapy (3). This set the stage for a recent study from the European and Canadian pediatric critical care units revealing that critically ill children treated by withholding PN for a week as they titrated up on enteral feeds had similar outcomes: shorter PICU and overall hospital stay. They also had fewer infections, reduced duration of mechanical ventilation, and lower risk for needing renal replacement therapy (4). The need for mechanical ventilation and renal replacement therapy are both poor prognostic markers in critically ill children and associated with worse outcomes. In addition, longer days in the ICU are also associated with worse outcomes. Therefore therapies or interventions that result in a reduction of either or both of these metrics should be considered.

Contrary to routine management of initiating early PN, Fivez *et al*. presented an excellent multi-center, multi-national, prospective and randomized study, demonstrating clinical superiority of delayed PN in the pediatric population (4). It is worth noting that the study population was quite diverse, and included both medical and surgical patients, of which 15% were neonates, and 42% cardiac patients. While late PN showed improved clinical outcome, it is still unclear whether early PN is harmful to patients that rely on intravenous nutrition. In this study, 45% of patients in the early PN group were discharged from the ICU by day 4, thus reflecting a large number of patients that may not have needed PN, and 78% in the late PN

group never received treatment. For those patients that rely on PN, it is remains unclear whether delayed PN is a setback, as it can add to the iatrogenic caloric and protein deficit in the ICU. Further studies are needed to evaluate this and the development of a desperately needed pediatric and neonatal guideline for PN support.

The results of this study are provocative and unsettling. Medical history is littered with examples of provider interventions and therapies performed with the best of intentions that have been subsequently demonstrated to be harmful. Providing more and earlier nutrition would seem to be an unlikely example. However, as a number of studies have shown that increasing calories from PN do not translate to improved clinical outcomes, the conflict persists: how do we promote growth in some neonates that rely on intravenous nutrition; and perhaps, how do we do so while being judicious with the use of PN (3,5,6)?

As in most pediatric critical care units, providing adequate nutrition has been a focus of our practice. We are proud that over the last five years we have consistently been able to improve caloric and protein delivery (7). Neonates in our CICU receive early PN, and enteral nutrition when medically feasible. Nevertheless, although we have significantly increased nutrition provision, more calories and protein may not parallel clinical advantage. We continue to struggle with the question of what are clinically relevant outcomes? We could not demonstrate reduced length of hospital stay or reduced ventilator times for neonates and infants despite better nutrition delivery.

In our personal communications with the authors, they informed us that neonates who cannot be fed were not excluded as long as they were not requiring PN before admission to the PICU. This is a compelling discovery as it shows that withholding PN still holds clinical benefit in a population at highest risk of malnutrition. So far, there are no studies looking at effects of early *vs*. late PN on weight gain in infants. We know that infants and children with congenital heart disease are at risk of neurodevelopmental delay. Poor growth has been reported to have an impact on mental and psychomotor development (8). We were able to show that increase nutrition delivery attenuates the decrease in WAZ in our single-ventricle patients (7). When enteral feeding is hazardous, we question whether withholding PN for a week would pose growth and wound healing compromise to an already at-risk population awaiting surgical repair of congenital heart disease.

Interestingly, the group with delayed delivery of enteral nutrition demonstrated lower plasma levels of γ-glutamyltransferase and alkaline phosphatase, but higher levels of plasma bilirubin and higher levels of C-reactive protein. This would seem to be conflicting secondary outcomes. However, perhaps this serves to reinforce the complexity of biochemistry in the setting of critical illness, as well as the importance of clinically relevant outcomes. Biomarkers and organ specific enzymes and compounds should be analyzed, but also considered secondary outcomes compared to the number of new infections, ventilator dependence and time to discharge.

Any strategy for delaying PN should include consideration of external validity. Firstly, while the STRONG kids' questionnaire has been validated in hospitalized children, it did not include those who were critically ill (9). Secondly, 45% of patients in the early PN group were discharged from the PICU by day 4, and in most centers these patients would not be candidates for PN. Lastly, enteral nutrition delivery reached half of goal by day 8 and remained mostly unchanged thereafter, bringing attention to enteral feeding practice differences that may influence the duration of PN use. Due to these reasons, our question is whether early PN is harmful; or rather, it is early PN adding risks to those patients that never needed intravenous nutrition support to begin with? Is it the timing of PN (early *vs*. late PN), or perhaps the duration of PN (early PN group likely had longer PN exposure) that increases risks, or both. This stresses the importance of a pediatric and neonatal guideline for PN support. With that, the benefits of PN may be more evident in those patients that rely on it, and minimizing PN associated risks in those patients that do not require PN support. This will also be a framework with which other studies can evaluate practice based on standard guidelines.

It seems that in the instance of pediatric critical illness and the findings of the Leuven, Rotterdam, and Edmonton group, the more we think we are doing to help our patients the more we might be further muddying the waters.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Zhongheng Zhang (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Fivez T, Kerklaan D, Mesotten D, *et al*. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374:1111-22.

References

1. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. Clin Nutr 2004;23:1381-9.
2. Radman M, Mack R, Barnoya J, et al. The effect of preoperative nutritional status on postoperative outcomes in children undergoing surgery for congenital heart defects in San Francisco (UCSF) and Guatemala City (UNICAR). J Thorac Cardiovasc Surg 2014;147:442-50.
3. Kutsogiannis J, Alberda C, Gramlich L, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. Crit Care Med 2011;39:2691-9.
4. Fivez T, Kerklaan D, Mesotten D, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374:1111-22.
5. Cahill NE, Murch L, Jeejeebhoy K, et al. When early enteral feeding is not possible in critically ill patients: results of a multicenter observational study. JPEN J Parenter Enteral Nutr 2011;35:160-8.
6. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. Crit Care Med 2012;40:2204-11.
7. Kaufman J, Vichayavilas P, Rannie M, et al. Improved nutrition delivery and nutrition status in critically ill children with heart disease. Pediatrics 2015;135:e717-25.
8. Medoff-Cooper B, Irving SY, Hanlon AL, et al. The Association among Feeding Mode, Growth, and Developmental Outcomes in Infants with Complex Congenital Heart Disease at 6 and 12 Months of Age. J Pediatr 2016;169:154-9.e1.
9. Hulst JM, Zwart H, Hop WC, et al. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. Clin Nutr 2010;29:106-11.

Cite this article as: Vichayavilas P, Gist K, Kaufman J. More and sooner, but not necessarily better. J Thorac Dis 2016;8(8):1877-1879. doi: 10.21037/jtd.2016.06.73

