Editorial

Editorial on "enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)"

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The benefits of early enteral nutrition (EN) support have been well established in critically ill patients. Early nutrition intervention, commencing within 24 hours of admission, has been associated with a decrease in mortality and infection complications compared to more delayed standard care nutrition support (1,2). While EN helps to promote gut mucosal proliferation, maintain gut integrity and decrease bacterial translocation which is proposed to cause spontaneous bacteremia in critically ill patients, parenteral nutrition (PN) has been considered a risk factor for increased infections in these patients. Meta-analysis studies comparing EN to PN found that PN was associated with higher rate of infectious complications, catheter-related infections and a prolonged hospital course (3-5). Result from the EPaNIC study by Casaer *et al.* showed that the early introduction of supplemental PN with EN resulted in significant more ICU infections, an increased duration of mechanical ventilation, higher rates of cholestasis, and increased hospital costs (6). Post hoc analysis showed that early supplementation of PN together with higher macronutrients resulted in delayed recovery (7). As a consequence, after the publication of EPaNIC study, a dramatic decline in PN prescriptions worldwide was noted in the cross-sectional Nutrition day study (unpublished data), a phenomenon probably not just coincidence.

More recently, the adverse effects of PN have been further explored. Overfeeding, over-dosing of intravenous lipids, and infectious complications are three major links between PN and adverse outcomes. Better practice of central venous catheter care has improved during the past decades. Retrospective data showed that the lowest mortality risk in critically ill patients was achieved when calories were provided at 70% of resting energy expenditure (REE) (8). Recognition of effect of overfeeding in critically ill patients has changed both clinical practice and study planning. The EAT-ICU trial showed no difference in outcome when 60% or 90% of measured REE was achieved during first 7 days in ICU (9), stressing the fact that when overfeeding is avoided, no complications related to nutrition therapy are observed. Many recent studies comparing EN with PN in the era of "optimal calorie" intake have shown that early nutrition support is beneficial regardless of the route (10,11). Studies from 1983–2014 showed that PN was associated with increased infection complication only when patients in the PN arm received more calorie than those in the EN arm, but when calories were provided for EN or PN in similar amounts, the difference in infectious complications was no longer observed (12). This has been nicely shown again in the NUTRIREA-2 trial where PN was found not to be harmful when given in optimized amounts. The results are also in line with 2 recent studies which compared EN to PN (10,11).

Should the significantly higher gastrointestinal side effects noted in the EN group in the NUTRIREA-2 study be of concern? Due to the large population recruited for the trial, even small differences can be statistically significant. The incidence of diarrhea reported was 36% and 33% in the EN and PN groups, respectively. More episodes of vomiting were observed in the EN group. Considering that gastroparesis is not infrequent in severely ill patients, early PN may help to decrease the rate of vomiting in the setting of shock. However, it should be noted that this did not translate into an increase in ventilator-associated pneumonia.

The most disturbing outcome from this study is related to the prevalence of bowel ischemia. Most of the literature has described a prevalence of this life-threatening condition at less than 1% despites vasopressor use (13). Currently available nutritional guidelines state that vasopressor infusion is not a contraindication for the initiation of EN (14-16). In daily clinical practice, physicians usually start EN in shock patients when hemodynamic stability has been achieved and there is no requirement for ongoing titration of vasopressors. Since no clear guidelines exist as to what constitutes a dose of vasopressor as being too high to start EN, the definition of this "high dose" vasopressor is often subjective. One retrospective study showed that at a vasopressor dose >17.5 ug of norepinephrine equivalent per minute, over 50% of patients tolerated EN safely (13). Rai *et al*. found no difference in the ability to achieve nutritional goals between patients with or without septic shock (17). The available evidence therefore suggests that the provision of EN during vasopressor infusion is possible and appears to be safe.

Why did the NUTRIREA-2 study report an incidence of bowel ischemia 2 to almost 10 times higher than that reported in the literature? The recently published study, the CALORIES trial, for example, reported an incidence of bowel ischemia of 0.9% in the EN group (10). First, participants in the NUTRIREA-2 trial were more severely ill than the former study (mean SOFA score 11 *vs.* 9.5 in NUTRIREA-2 and CALORIES study, respectively). Fewer patients in the EN group of the CALORIES trial received vasopressors as compared to the NUTRIREA-2 study (85% *vs*. 100%, respectively). Initiation of EN might aggravate injury to the gut in under-resuscitated patients. Besides, gut hypoperfusion may be present even in the absence of overt systemic sign of shock (18). One prospective cohort found that lactate levels of >2 mmol/L at the time of EN initiation was significantly associated with intestinal necrosis [HR =4.1; (95% CI, 1.4–11.5); P=0.01] (19). In Table 1 of the NUTRIREA-2 study, the mean norepinephrine dose and mean lactate levels were reported but did not reflect the exact daily administration. During the first 7 days of the study, safety concerns led to a requirement to demonstrate lactate level <2 mmol/L before EN initiation in the PN group but not in EN group. Secondly, the rapid progression to the target EN goal in this study may not be tolerated by these patients. PN is generally superior to EN in the ability to achieve caloric goals since the provision of EN is significantly and often negatively influenced by the patient's gastrointestinal condition. The amount of EN delivered when signs of feeding intolerance occurs should be considered as the "limit" of EN at that time so that early EN may not achieve the total energy target (16). The gap between the caloric goal and calories delivered by EN should be filled by supplemental PN. However, the aim of the study to explore the effects of different routes of nutrition support did not allow supplemental PN in the first 7 days in the EN group, which may have allowed for a significant calorie gap in the EN group when faced with feeding intolerance. It is possible that the study team had to make an extra effort to ensure the delivery of the same amount of calories received in the EN group as by the PN group in order to avoid the confounding effect caused by different amount of calorie delivered between group. Patients in EN group might be forcefully fed beyond what their GI condition allowed during splanchnic hypoperfusion. This might be evidenced by the comparable amount of calories delivered to patients in both groups during first few days of the study, and significantly higher rates of prokinetic usage and incidence of vomiting in EN group. Thirdly, the study does not mention safety monitoring in detail during EN delivery. When patients elicit any signs of gastrointestinal failure (20) before day 8, EN should be stopped or reduced. Attempts to clearly document any deterioration arising during EN administration should be performed, such as the demonstration of persistent hyperlactatemia, which was found to be a risk factor for developing non-occlusive mesenteric ischemia (21), or even intra-abdominal pressure monitoring in patients with intraabdominal pathology (16), before making a decision whether to continue with EN. If the decision is made to stop EN, supplemental PN should be administered to close the gap between the calorie goal and that delivered at any point of time, not only after day 8 of admission. All of these strategies might help to reduce the incidence of bowel ischemia. Last but not least, this

finding may stress the possibility that EN is actually harmful to patients with organ failures. A previous study by the same group reported an increase mortality rate in patients with shock in the presence of renal, and liver failure who received early EN (11). The mortality rate of mesenteric ischemia in this trial was 75% which is in line with other reported series (22-24).

The NUTRIREA-2 study supports the finding that PN is as safe as EN when it is delivered according to recognized practice regardless of the patient's nutritional status. However, this should not influence physicians to prescribe PN instead of EN just to avoid the adverse gastrointestinal events noted in this study. As mentioned above, the magnitude of the differences may not be clinically relevant enough to favor PN over EN. With comparable outcomes, EN is much less costly than PN. The practice of early EN should still be encouraged for mechanically ventilated patients with shock. Close monitoring of EN tolerance while it is slowly titrated is warranted in order to avoid possible serious adverse events. The increasing evidence that PN does not lead to deleterious outcomes as shown in the past should make physicians more comfortable with prescribing early PN, either as exclusive treatment, where the administration of EN is not possible or contra-indicated, or supplementally, when the calorie target cannot be achieved by EN alone. The goal should always be to provide our patients with the optimal amount of calories in order to achieve better outcomes.

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Footnote

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References

1. Doig GS, Heighes PT, Simpson F, et al. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med 2009;35:2018-27.
2. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001;29:2264-70.
3. Braunschweig CL, Levy P, Sheean PM, et al. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr 2001;74:534-42.
4. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med 2005;33:213-20; discussion 260-1.
5. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med 2005;31:12-23.
6. Casaer MP, Mesotten D, Hermans G, et al. Early versus Late Parenteral Nutrition in Critically Ill Adults. N Engl J Med 2011;365:506-17.
7. Casaer MP, Wilmer A, Hermans G, et al. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247-55.
8. Zusman O, Theilla M, Cohen J, et al. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care 2016;20:367.
9. Allingstrup MJ, Kondrup J, Wiis J, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med 2017;43:1637-47.
10. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371:1673-84.
11. Reignier J, Darmon M, Sonneville R, et al. Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study. Intensive Care Med 2015;41:875-86.
12. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117.
13. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. JPEN J Parenter Enteral Nutr 2013;37:641-51.
14. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006;25:210-23.
15. McClave SA, Taylor BE, Martindale RG, et al. 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.). JPEN J Parenter Enteral Nutr 2016;40:159-211.
16. Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 2017;43:380-98.
17. Rai SS, O'Connor SN, Lange K, et al. Enteral nutrition for patients in septic shock: a retrospective cohort study. Crit Care Resusc 2010;12:177-81.
18. Bruns BR, Kozar RA. Feeding the Postoperative Patient on Vasopressor Support: Feeding and Pressor Support. Nutr Clin Pract 2016;31:14-7.
19. Nuzzo A, Maggiori L, Ronot M, et al. Predictive Factors of Intestinal Necrosis in Acute Mesenteric Ischemia: Prospective Study from an Intestinal Stroke Center. Am J Gastroenterol 2017;112:597-605.
20. Reintam Blaser A, Jakob SM, Starkopf J. Gastrointestinal failure in the ICU. Curr Opin Crit Care 2016;22:128-41.
21. Lim JY, Kim JB, Jung SH, et al. Risk factor analysis for nonocclusive mesenteric ischemia following cardiac surgery: A case-control study. Medicine (Baltimore) 2017;96:e8029.
22. Dahlke MH, Asshoff L, Popp FC, et al. Mesenteric ischemia--outcome after surgical therapy in 83 patients. Dig Surg 2008;25:213-9.
23. Ryer EJ, Kalra M, Oderich GS, et al. Revascularization for acute mesenteric ischemia. J Vasc Surg 2012;55:1682-9.
24. Leone M, Bechis C, Baumstarck K, et al. Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. Intensive Care Med 2015;41:667-76.

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