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EDITORIAL

Optimal timing, dose and route of early nutrition therapy in critical illness and shock: the quest for the Holy Grail

Jean Reignier[1*], Arthur R. H. Van Zanten[2] and Yaseen M. Arabi[3]

Most recent clinical practice guidelines on nutritional support in the intensive care unit (ICU) recommend that critically ill patients should receive early feeding (within 24–48 h after ICU admission), via the enteral route (enteral nutrition; EN) when feasible, and with an ultimate caloric goal of 25–30 kcal/day [1]. Meeting these conditions has been shown to be associated with reduced risk of nosocomial infectious and non-infectious complications, and also with decreased length of stay and mortality [2]. Conversely, guidelines recommend postponing or withholding early EN (EEN) in patients with hemodynamic instability [1–3]. Indeed, these patients are at high risk of impaired splanchnic perfusion and subsequent bacterial translocation or gut ischemia [4]. However, withholding EN in patients with shock may lead to delayed EN, subsequent severe underfeeding and further reduction in barrier function. Both conditions have been shown to be associated with poor outcome. Thus, whether EEN may have beneficial or deleterious effects in patients with shock, remains highly controversial [5].

In an article recently published in *Intensive Care Medicine*, Ohbe et al. addressed the safety of EEN in patients with severe cardiogenic or obstructive shock, requiring venoarterial extracorporeal membrane oxygenation (VA-ECMO) [6]. The authors designed a multicenter retrospective study, using data from a Japanese national database covering almost 90% of tertiary emergency hospitals in Japan. The main hypothesis was that EEN might have deleterious effects on outcome in these specific patients, compared to delayed EN. Of 179,821 mechanically ventilated patients treated with noradrenaline for cardiogenic or obstructive (pulmonary embolism, cardiac tamponade and aortic dissection) shock, 1769 patients were treated with VA-ECMO during more than 2 days and were included in the study. The acuity of illness was severe: 68% of the patients had pre-ECMO cardiac arrest, and 63% died during hospital stay. Ischemic heart disease was the main cause of shock. No patients with septic shock were included. In total, 220 patients (12%) received EN within 2 days after the initiation of VA-ECMO and were classified as the EEN group. A careful statistical analysis using marginal structural models with inverse probability of treatment weighting was used to account for time-varying confounders that may be associated with the decision to initiate EEN. Compared to delayed EN, EEN was associated with reduced hospital and 28-day mortality. There was no difference in incidence of bowel ischemia and nosocomial pneumonia when both groups were compared.

Whether or not EEN may be protective in severely hemodynamically unstable patients with cardiogenic or obstructive shock unresponsive to conventional therapies

*Correspondence: jean.reignier@chu-nantes.fr
[1] Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire Hotel-Dieu, Université de Nantes, 30 Bd. Jean Monnet, 44093 Nantes Cedex 1, France
Full author information is available at the end of the article

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is particularly relevant. These patients are at high risk of impaired splanchnic perfusion, intolerance to EN and gut ischemia [2, 7]. Data reported by Ohbe et al. are in line with previous observational studies indicating the safety of EN in patients with ECMO (VA and VV), and with another study using a similar design in mechanically ventilated patients with shock [8–10]. However, interpretation of the results of this study should take into account its several important limitations. First of all, despite the large number of patients included, the multicenter design and the statistical analysis limiting confounding factors, the retrospective design precludes strong conclusions on causal relationships between EEN and the outcome data observed. Recent history of nutritional support in the ICU has taught us that data obtained from observational studies were sometimes not confirmed in RCTs, and even opposite findings may be encountered [11]. Second, EEN was defined as EN started within 2 days after starting VA-ECMO. This definition does not comply with guidelines or previous large RCTs, which define EEN as EN started within 24–48 h after ICU admission or intubation [1, 2]. Moreover, in the current study, centers did not record the exact time between intubation and the initiation of EN, and only ranges of 24 h were provided. In total, 8.5% of the patients had ECMO started 2 days or more after intubation. Third, prescription and delivery of nutritional support in participating ICUs were not standardized at all. The incidence of enteral feeding intolerance (EFI) and management of EFI were not recorded. The amounts of nutrients received by patients were not reported. Furthermore, criteria for bowel ischemia were not predefined. Finally, despite the use of marginal structural models, the influence of unmeasured confounders cannot be excluded. These study limitations suggest a large risk of bias and preclude definitive conclusions on the impact of "early EN" in this specific patient group.

Nutrition therapy in the ICU comprises a complex decision-making process which includes the route of feeding, the dose of nutrients, and the timing of administration. Recent RCTs have shown no differences in survival and nosocomial infections in patients receiving early parenteral nutrition (PN) compared to early EN [12, 13]. However, compared to early PN, EEN was associated with more bowel ischemia when studied in patients with shock [13]. Other RCTs did not demonstrate the superiority of "standard" caloric goals compared to trophic feeding and permissive underfeeding [14, 15]. An observational study on mechanically ventilated patients with shock suggested that early nutrition, but not the route and the dose, have an impact on survival [13]. These data are in line with the most recent meta-analysis showing no difference between early EN and PN, but reduced mortality and lower incidence of pneumonia with early compared to delayed EN [16]. The debate of the optimal timing to commence nutrition in critically ill patients is thus clearly on the table. In the future, studies on the best timing of nutritional support in the ICU should use "standard" definitions of EEN. Moreover, it seems advisable to also better define "delayed EN", which is not just a start after a predefined delay in daily clinical practice, but after clinical relevant endpoints such as the withdrawal of cardiovascular support or achieving a predefined level of hemodynamic stability. Thus, the optimal cut-off used to define "delayed" EN may even be later than the definition now commonly used to define delayed EN, and may differ from patient to patient. Using different cut-offs to define delayed and EEN may also confer larger differences in effects observed on outcomes, and, thus, better definitions could facilitate future more rigorous and convincing data. Future studies on this topic should also be performed in the settings of well-defined management protocols for nutrition therapy, to limit bias and to circumvent pitfalls in the analysis of the results obtained [11].

In conclusion, Ohbe et al. provide new data suggesting that the best timing for nutrition therapy is probably "early" in critically ill patients with severe circulatory failure. However, the study has limitations mainly related to its retrospective design. Moreover, it strongly underlines the need for future carefully designed RCTs to provide high-level evidence on how to initiate EEN in high-risk critically ill patients. How nutritional therapy is provided may have an impact on the outcome of critically ill patients. Therefore, let's prove it!

Author details
[1] Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire Hotel-Dieu, Université de Nantes, 30 Bd. Jean Monnet, 44093 Nantes Cedex 1, France. [2] Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, The Netherlands. [3] King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS) and King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia.

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References

1. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM,

Sacks GS, Roberts PR, Compher C, Society of Critical Care M, American Society of P, Enteral N (2016) 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 (ASPEN). Crit Care Med 44:390–438
2. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, Fruhwald S, Hiesmayr M, Ichai C, Jakob SM, Loudet CI, Malbrain ML, Montejo Gonzalez JC, Paugam-Burtz C, Poeze M, Preiser JC, Singer P, van Zanten AR, De Waele J, Wendon J, Wernerman J, Whitehouse T, Wilmer A, Oudemans-van Straaten HM, Function EWGoG (2017) Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 43:380–398
3. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
4. Rokyta R Jr, Matejovic M, Krouzecky A, Novak I (2003) Enteral nutrition and hepatosplanchnic region in critically ill patients—friends or foes? Physiol Res 52:31–37
5. Thibault R, Pichard C, Wernerman J, Bendjelid K (2011) Cardiogenic shock and nutrition: safe? Intensive Care Med 37:35–45
6. Ohbe H, Jo T, Yamana A, Matsui H, Fushimi K, Yasunaga H (2018) Early enteral nutrition for cardiogenic or obstructive shock requiring venoarterial extracorporeal membrane oxygenation: a nationwide inpatient database study. Intensive Care Med. https://doi.org/10.1007/s00134-018-5319-1
7. Reintam Blaser A, Poeze M, Malbrain ML, Bjorck M, Oudemans-van Straaten HM, Starkopf J (2013) Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med 39:899–909
8. Berger MM, Revelly JP, Cayeux MC, Chiolero RL (2005) Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. Clin Nutr 24:124–132
9. Pettignano R, Heard M, Davis R, Labuz M, Hart M (1998) Total enteral nutrition versus total parenteral nutrition during pediatric extracorporeal membrane oxygenation. Crit Care Med 26:358–363
10. Reignier J, Darmon M, Sonneville R, Borel AL, Garrouste-Orgeas M, Ruckly S, Souweine B, Dumenil AS, Haouache H, Adrie C, Argaud L, Soufir L, Marcotte G, Laurent V, Goldgran-Toledano D, Clec'h C, Schwebel C, Azoulay E, Timsit JF (2015) 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 41:875–886
11. Arabi YM, Casaer MP, Chapman M, Heyland DK, Ichai C, Marik PE, Martindale RG, McClave SA, Preiser JC, Reignier J, Rice TW, Van den Berghe G, van Zanten AR, Weijs PJ (2017) The intensive care medicine research agenda in nutrition and metabolism. Intensive Care Med 43:1239–1256
12. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM (2014) Trial of the route of early nutritional support in critically ill adults. N Engl J Med 371:1673–1684
13. Reignier J, Boisrame-Helms J, Brisard L, Lascarrou J, Ait Hssain A, Anguel N, Argaud L, Asehnoune K, Asfar P, Bellec F, Botoc V, Bretagnol A, Bui H, Canet E, Da Silva D, Darmon M, Das V, Devaquet J, Djibre M, Ganster F, Garrouste-Orgeas M, Gaudry S, Gontier O, Guerin C, Guidet B, Guitton C, Herbrecht J, Lacherade J, Letocart P, Martino F, Maxime V, Mercier E, Mira J, Nseir S, Piton G, Quenot J, Richecoeur J, Rigaud J, Robert R, Rolin N, Schwebel C, Sirodot M, Tinturier F, Thévenin D, Giraudeau B, Le Gouge A (2017) Enteral versus parenteral early nutrition in ventilated adults with shock: a multicentre, randomised trial (NUTRIREA-2). Lancet 391:133–143
14. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P (2012) Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 307:795–803
15. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Afesh L, Permi TTG (2015) Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med 372:2398–2408
16. Tian F, Heighes PT, Allingstrup MJ, Doig GS (2018) Early enteral nutrition provided within 24 h of ICU admission: a meta-analysis of randomized controlled trials. Crit Care Med 46:1049–1056