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Letter to the Editor

Primum non nocere in early nutrition therapy during critical illness: Balancing the pros and cons of early very high protein administration

To the Editor,

We thank doctors Pitta, Campos and Cunha for their interest in and response to our PROTINVENT study [1].

The aim of the PROTINVENT study was to address whether timing of protein intake was relevant in ICU patients requiring prolonged mechanical ventilation. The baseline characteristics (*i.e.* the characterization of the study population) of the entire study group are depicted in table 1 of the original article, including age, type of disease (surgical emergency, surgical or medical), disease severity (APACHE II, SOFA score) and BMI. Furthermore, multivariable analysis was performed correcting for Body Mass Index, mNUTRIC-score, ICU admission year, admission categories (surgical/medical), nutritional route, time to start feeding and caloric adequacy. In addition, the timing of this retrospective study was extensively described in the method section and table 2 of the original article [1]. The study period started at ICU admission, patients were only included when they were invasively mechanically ventilated within 48 h from ICU admission and the median time to start feeding was 5.5 h [IQR 2.8–14.4].

Ideally nutritional therapy is personalized for every individual ICU patient. However, personalizing nutritional therapy based on baseline characteristics was not the aim of our study. Moreover, by creating additional subgroups (*i.e.* decreasing the number of patients per group) the validity of the results will decrease, potentially leading to overestimation of the effects studied. As can be found in the discussion and unanswered questions section of the original article, we have stated that prospective research is warranted to confirm the findings from our hypothesis generating study, and that analysis of the observed effect in different subgroups may be valuable [1].

Questions were raised regarding the larger number of patients in the intermediary group in many analyses we provided. This uneven distribution over groups is due to the target protein intake in the study population, which was derived from the international (ASPEN) guidelines, recommending 1.5 g/kg/day in patient with a BMI <27 kg/m^2, correction to BMI 27 kg/m^2 for a BMI 27–30 kg/m^2, and 2.0 g/kg/day ideal body weight (IBW) in patients with a BMI of 30–40 kg/m^2 and 2.5 g/kg/day IBW in BMI > 40 kg/m^2, respectively [2]. From observational studies it is known for long that protein targets are hard to achieve (for many reasons), resulting in lower actual protein intakes or percentage of target achieved [3]. Since very high (intact)-protein enteral feeds have become available recently - after the study period -, achievement of protein targets has become easier [4].

Furthermore, as described in the method section of the original article, the study population was divided in three protein categories for analysis. Table 2 of the original article provides a more elaborate characterization of the feeding parameters of the study population, including 5 protein intake categories (<0.5 g/kg/day, 0.5–0.8 g/kg/day, 0.8–1.0 g/kg/day, 1.0–1.2 g/kg/day, and >1.2 g/kg/day). These were not the categories used for analysis, but only described to provide a deeper insight in our study population. For analysis patients were categorized into three groups: < 0.8 g/kg/day (including those receiving < 0.5 g/kg/day), 0.8–1.2 g/kg/day (i.e. 0.8–1.0 g/kg/day and 1.0–1.2 g/kg/day) and >1.2 g/kg/day [1].

Finally, as is stated in the method section of the original article "All deaths in the Netherlands are registered in the municipal personal records database of the Dutch government. When date of death was not registered the patient was presumed alive." [1] In addition, also all deaths of people with a Dutch nationality are registered in this database.

Therefore, foreigners who were not residing in the Netherlands 6 months after their ICU treatment may have been erroneously assumed to be alive. We found only one patient fulfilling this criterion, and we are confident that this will not have influenced our results significantly.

1. Primum non nocere

Controversy regarding optimal targets, outcome measures and timing of protein delivery in critically ill patients remains [5].

The ASPEN guidelines (2016) advise early initiation of EN within 24–48 h in the critically ill patient based on a meta-analysis of 21 RCTs comparing early vs delayed EN (early EN = < 48 h) showing a significant reduction in mortality and infectious morbidity [6]. These results were in line with previous meta-analysis by Heyland (early EN = < 48 h) [7], Marik (early EN = <36 h) [8] and Doig (early EN = < 24 h) [9]. No distinction between caloric and protein intake is made regarding time of initiation. In addition, the ASPEN guidelines advise efforts to provide >80% of estimated or calculated goal energy and protein within 48–72 h with protein targets of 1.2–2.0 g/kg actual body weight [6].

However, in the more recent ESPEN guidelines (2018) progressive delivery of 1.3 g/kg protein is advised. Protein targets are based on evidence from observational studies and RCTs, observational studies reporting beneficial effects of total high protein delivery during ICU admission (lower mortality and infectious complications) while RCTs are inconclusive.

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Additionally, progressive delivery is advised as optimal timing of protein intake remains unclear with several studies reporting harm of high protein intake in the first days of ICU admission [10].

In addition, previous studies regarding protein intake in critical illness, including our own, have mainly focused on mortality and little on muscle function, relevant functional outcomes and quality of life [11]. At present it is not clear what the effects of nutrition, in particular very high early protein administration, on muscle protein gain are.

Proteins are important during critical illness, as also demonstrated in the PROTINVENT study, as the low protein intake group (<0.8 g/kg/day during the first week) encountered the lowest likelihood of survival, however early very high protein intake does not seem to confer the opposite effect. The best effect was seen when proteins were advanced to high targets over several days.

Therefore, balancing the pros and cons and until more information is available from RCTs addressing the dose and timing of protein in early critical illness, we suggest to be cautious with very high protein intakes in the first days of ICU admission, and to follow the recommendations from the recent ESPEN guidelines to progressively advance energy and protein to target in early critical illness. Similar to other areas of critical care therapy we have to be aware of the importance that when striving for gold we have to avoid a false start [12], and the first adagium in medicine is: Primum non nocere, do no harm!

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W.A.C. Koekkoek
Department of Intensive Care Medicine, Department of Internal Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716, Ede, the Netherlands
E-mail address: koekkoekk@zgv.nl.

A.R.H. van Zanten*
Head of ICU & Research, Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, the Netherlands

* Corresponding author. Fax: +31 318 43 41 16.
E-mail address: zantena@zgv.nl (A.R.H. van Zanten).

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