

## Timing of the initiation of parenteral nutrition in critically ill adults

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### Background

Critical illness in hospitalized patients induces anorexia: an inability to eat suitably, predisposing to nutritional deficit, weakness, infections, increased duration of mechanical ventilation, delayed recovery and death [1]. To date, whether artificial nutritional support improves outcomes for critically ill patients is unclear. Enteral nutrition is associated with fewer complications than parenteral nutrition, and is less expensive [2], but enteral nutrition alone does not often achieve caloric targets. Combining parenteral and enteral nutrition could prevent nutritional deficit. However, this strategy may carry the risk of overfeeding, which has been associated with complications such as liver dysfunction [3]. Current clinical practice guidelines for nutritional support in critically ill patients are largely based on expert opinion, and differ substantially across continents, in particular about the timing to start parenteral nutrition. The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends the commencement of parenteral nutrition within 2 days after admission to the intensive care unit (ICU) for patients who cannot be adequately fed enterally [4], while the American and Canadian guidelines recommend early initiation of enteral nutrition, but suggest starting parenteral nutrition after a week in patients who are not malnourished at baseline [5].

### Summary

Casaer and coworkers [6] in a randomized, multicenter trial, compared an early to a late initiation of parenteral nutrition in adults admitted to the ICU who were not malnourished at baseline [body-mass index (BMI) of  $\geq 17$ ] in order to supplement insufficient enteral nutrition. The primary end points were the number of days spent in ICU (for survivors and non-survivors), and the time to discharge from the ICU. In 2,312 patients, parenteral nutrition was initiated within 48 h after ICU admission, whereas in 2,328 patients, it was not initiated before the eighth day from admission. The median stay in the ICU was 1 day shorter in the late-initiation group than in the early-initiation group (3 vs. 4 days, respectively,  $P = 0.02$ ), which was reflected in a relative increase of 6.3% of the likelihood of earlier discharge alive from the ICU [hazard ratio 1.06, 95% confidence interval (CI), 1.00–1.13,  $P = 0.04$ ]. Considering the secondary outcomes, patients in the late-initiation group had fewer health assistance related infections (22.8 vs. 26.2%,  $P = 0.008$ ), a lower incidence of cholestasis (32.6 vs. 38.4%,  $P < 0.001$ ), a reduction in the proportion of patients requiring more than 2 days of mechanical ventilation (36.3 vs. 40.2%,  $P = 0.006$ ), a median reduction of 3 days in the duration of renal replacement therapy (7 vs. 10 days,  $P = 0.008$ ) and a reduction in mean health care costs of €1,110 as compared with the early-initiation group (€16863 vs. €17973,  $P = 0.04$ ). The safety outcomes (in-hospital mortality rates, survival at 90 days, rates of nutrition-related complications) were similar in the two groups, but hypoglycaemia was more common in the late-initiation group patients (3.5 vs. 1.9%,  $P = 0.001$ ). Although enteral nutrition was initiated if possible in the majority of patients, the post hoc subgroup analyses including patients for whom early enteral nutrition was contraindicated showed the same results.

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The authors conclude that late initiation of parenteral nutrition compared with early initiation is associated with faster recovery and fewer complications.

### Strength of the study

- The study addresses a relevant clinical problem.

### Weakness of the study

- The length of ICU stay cannot be properly considered a clinically important end point. Although the reduction of 1 day of ICU stay has definitely some importance from an economic point of view, the clinical implication of this observation is not completely clarified by this study.
- The day of ICU discharge was evaluated by treating physicians who were not blinded to the treatment arm, which might have led to a detection bias.
- The high percentage of post-operative patients (81%) may have selected a study population that is not truly representative of patients commonly admitted to the ICU for acute critical disease (low external validity). Furthermore, malnutrition at baseline was an exclusion criteria, further limiting the generalizability of results.

### Question marks

- Patients who were assigned to the early-initiation group received increasing doses of intravenous 20% glucose solution for the first 2 days, and started parenteral nutrition on day 3. When enteral nutrition or oral nutrition covered the calculated caloric goal, parenteral nutrition was reduced and eventually stopped. Stated that in “early initiation group” median ICU stay was only 4 days, it would be interesting to know how many patients received effective parenteral nutrition and for how long.
- Data and evidence about nutrition are lacking for medical patients admitted to general wards. Although

results from this study are not directly transferable to non-ICU patients, it might be interesting to argue about how far these data can be applied to those patients, who are usually older.

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### Clinical bottom line

This study shows that late initiation of parenteral nutrition to achieve caloric goals is not associated with worse outcomes than early initiation in ICU patients who were not malnourished at admission. Therefore, parenteral nutrition should not be a concern at least in the first week of ICU stay, if patients receive enteral nutrition whenever possible and adequate aminoacid and vitamin supply.

**Conflict of interest** None.

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