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Enteral Nutrition in Sepsis - Less or More?

Current nutrition guidelines uniformly recommend using enteral nutrition (EN) as first-line nutrition therapy, starting early within 24-48 hours after ICU admission.[1,2,3] Early EN has several non-nutritional benefits such as supporting the immune and metabolic responses as well as preserving gut integrity.[4] However, it is still less clear what the optimal dose of EN should be, particularly during the first week of illness, and whether specific subgroups of critically ill patients respond differently to the amount of EN.

Three recent prospective-randomized studies[5,6,7] have compared full EN to intentional underfeeding or trophic nutrition, i.e. provision of small volume EN aiming to produce positive local effects on gastrointestinal mucosa and beneficial systemic effects.[8] None of these studies showed an effect on mortality but reported more gastrointestinal complications with the full EN feeding strategy. Based on these studies, the updated Surviving Sepsis Campaign (SSC) guidelines[9] suggest avoiding mandatory full caloric feeding and using low dose EN in the first week of ICU stay (evidence grade 2B). This recommendation contradicts the 2013 Canadian Critical Care Nutrition Clinical Practice Guidelines that recommend optimizing dose of EN and not using an initial strategy of trophic feeds for 5 days[10] (see **Table 1**). Their recommendation, intended for all ICU patients, not just septic patients, was based on multiple randomized trials and large-scale observational studies in heterogeneous critically ill patients.[11,12,13]

Table 1: Comparison of the SSC and Canadian guidelines

Topic	Key points of SSC guidelines on EN	Key points of Canadian guidelines on EN
Early vs. Delayed Nutrient Intake	• Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose **within the first 48 hours** after a diagnosis of severe sepsis/septic shock (grade 2C).	• **Early EN (within 24-48 hours following admission to ICU) is recommended** in critically ill patients. • When starting EN in critically ill patients, **strategies to optimize delivery of nutrients (starting at target rate, higher threshold of gastric residual volumes, use of prokinetics and small bowel feedings) should be considered.**
Trophic vs. Full Feeds	• **Avoid mandatory full caloric feeding** in the first week but rather **suggest low dose feeding (e.g., up to 500 calories per day)**, advancing only as tolerated (grade 2B).	• In patients with Acute Lung Injury, **an initial strategy of trophic feeds for 5 days should not be considered.**

In view of these current contradictory recommendations and given the paucity of prospective randomized clinical trials in septic patients, we conducted a secondary analysis of our large international nutrition database to evaluate the effect of energy and protein intake on clinical outcomes in a cohort of critically ill septic patients.[14] Only those patients who were receiving exclusively EN were included to preclude possible confounding effects of parenteral nutrition (PN) on the amount of nutrition as PN has a treatment effect different and distinct from EN.[15,16]

What are the main findings of our large observational study?

A total of 2270 medical patients with sepsis and/or pneumonia were analyzed. Patients received a mean amount of 1057 kcal/d (14.5 kcal/kg/day) and 49 g protein/day (0.7 g/kg/d) by EN alone.[14] **Table 2** summarizes patient characteristics and clinical outcomes.

Table 2. Characteristics and clinical outcomes of study patients

Number of Patients	**Total** , N=2270
Age, years (SD)	61.7 (17.0)
BMI, mean (SD)	27.6 (8.3)
BMI, n (%)	
<24	1039 (45.9)
25-29	594 (26.2)
30-40	463 (20.4)
>40	169 (7.5)
APACHE II score, mean (SD)	23.9 (7.9)
Length of ICU stay (days), median [IQR]	11.5 [6.9-21.4]
Length of mechanical ventilation (days), median [IQR]	8.4 [4.6-19.2]
Mortality % (60 day)	30.5

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In a statistical model, we demonstrated that an increase of 1,000 kcal was associated with reduced 60-day mortality (odds ratio 0.61; 95% confidence intervals (CI) 0.48–0.77, $P < 0.001$) and more ventilator free days (VFDs) (2.81 days, 95% CI 0.53–5.08, $P = 0.02$).[14] An increase of 30 g protein per day was also associated with lower mortality (odds ratio 0.76; 95% CI 0.65–0.87, $P < 0.001$) and increase in VFDs (1.92, 95% CI 0.58–3.27, $P = 0.005$). The beneficial effect of improved nutrition on outcome persisted when estimated only for those patients with a prolonged ICU stay of at least 8 days.

More is better - Challenging the updated Surviving Sepsis campaign guidelines!

Our results challenge the recommendation of the updated Surviving Sepsis Campaign guidelines[9]. Our patient population was different to the 3 studies on which this weak recommendation is mainly based. The study by Arabi et al.[5] only included a limited number of septic patients (72 of total 240 patients). Similar to the smaller phase 2 study[6], the largest, so-called EDEN trial[7] included a select sample of patients with acute lung injury that were relatively young (mean age 52 years), well-nourished and fairly obese (average BMI of around 30) whereas our population was older (average age 62 years) and almost half of the patients had a low to normal BMI. In a prior analysis, Alberda and colleagues[17] demonstrated that patients with a BMI from 25-35 may not be sensitive to differing amounts of EN, at least with respect to mortality, whereas a mortality reduction was associated with receiving more EN in patients with BMI <25 and >35. A further point is that the average duration of ICU stay in the EDEN study was 5 days compared to 11 days in our study. To the extent that early targeted EN is particularly relevant in patients with longer length of stay, this may further explain the discordant results, especially because the beneficial effect of improved EN remained in patients staying at least 8 days in the ICU.

In summary, different studies with different methods studying different patients are causing confusion. However, the patient population in our observational study reflected a rather high nutrition risk group that may be harmed by prolonged underfeeding. Until further trials elucidate the effect of intentional underfeeding (trophic feeds) on high nutrition risk patients, we recommend that this practice of 5 days of intentionally underfeeding NOT be used in septic patients. Our findings are consistent with the Canadian clinical practices guidelines for the overall ICU population that do not recommend trophic feeds or intentional undernourishment.[10]

Key messages

- A closer to recommended daily calorie and protein intake by EN within the first week of ICU stay was associated with shorter duration of mechanical ventilation and lower mortality in critically ill septic patients.
- Our results suggest that a nutritional intake that better approximates the energy and protein target by EN in the early disease phase improves outcome through a prevention of energy and protein deficit
- Our findings contradict the current Surviving Sepsis Campaign that recommend the use of low dose rather than full EN in septic patients.

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