

What should we target after TARGET?

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The Augmented versus Routine approach to Giving Energy Trial (TARGET) is the largest critical care nutrition trial ever undertaken.¹ The primary analysis of TARGET included 3957 mechanically ventilated adults from 46 Australian and New Zealand intensive care units (ICUs) who were randomly assigned to energy-dense (1.5 kcal/mL) or routine (1.0 kcal/mL) enteral nutrition, aiming for a dose of 1 mL/kg per hour using ideal body weight. Patients assigned to 1.5 kcal/mL received \approx 1900 kcal per day on average, while those assigned to 1.0 kcal/mL received \approx 1300 kcal per day on average. The increased calorie delivery with energy-dense nutrition did not affect Day 90 mortality, survival time, receipt of organ support, number of days alive and out of the ICU and hospital or free of organ support, or the incidence of infective complications. While guidelines that were written before the publication of TARGET recommend an energy intake of 25–30 kcal/kg per day (1875–2250 kcal/day for a 75 kg patient),^{2–4} clinicians might reasonably be asking themselves what they should now target when it comes to caloric intake in critically ill adults.

TARGET is the first large multicentre trial to deliver recommended goal calories using the enteral route. There is no suggestion that doing this improves patient outcomes. The results of 6-month follow-up of quality of life in TARGET are pending,^{5,6} but based on what we currently know, while achieving recommended goal calories via the enteral route is possible, there no longer appears to be any particular reason to aspire to do this.

TARGET is one of a series of trials investigating energy delivery in the critically ill that suggest that patient outcomes are similar over a very broad range of calorie delivery, at least in the early stages of an ICU admission.

The EDEN randomised trial compared initial trophic feeding for the first 6 days with full enteral feeding in 1000 patients within 48 hours of developing acute lung injury.⁷ The full feeding group received \approx 1300 kcal per day on average for the first 6 days, while the trophic feeding group received \approx 400 kcal per day. After Day 6, the care of all patients who were still receiving mechanical ventilation was according to the full feeding protocol and patients received \approx 1300 kcal per day. Notably, the full feeding group in the EDEN trial received a similar number of calories to the routine enteral nutrition group in TARGET. The reduced calorie delivery in the trophic feeding group did not alter ventilator-free days (the primary outcome) or 60-day mortality. There were also no differences in infective complications between the groups. Moreover, in survivors of the initial episode of acute

lung injury, there was no difference in physical function, survival, or multiple other secondary outcomes at 6 and 12-month follow-up.⁸

The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients Trial (PermiT) compared permissive underfeeding for up to 14 days with standard enteral feeding in 894 critically ill adults.⁹ During the intervention period, the permissive underfeeding group received \approx 800 kcal per day on average, while the standard feeding group, like the routine enteral nutrition group in TARGET, received \approx 1300 kcal per day. Again, no difference between groups was seen with respect to Day 90 mortality or ICU or hospital length of stay.

The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial compared early supplementation of enteral with parenteral nutrition (within 48 hours of ICU admission) with later initiation (after Day 7) in patients in whom caloric targets could not be met by enteral nutrition alone.¹⁰ Early initiation of parenteral nutrition resulted in goal calories being delivered sooner but was associated with delayed recovery and more complications.

In contrast, the Early Parenteral Nutrition Study, which evaluated early provision of parenteral nutrition to patients with relative contraindications to enteral nutrition, did not demonstrate an increased incidence of complications or delayed recovery with augmented calorie delivery using parenteral nutrition. Again, a difference in calorie delivery had no impact on subsequent survival.¹¹

Taken together, the data from large-scale multicentre randomised controlled trials suggest that early trophic feeding for 6 days (\approx 400 kcal/day),⁷ permissive underfeeding for 14 days (\approx 800 kcal/day),⁹ standard care feeding (\approx 1300 kcal/day),^{1,7,9} and energy-dense enteral nutrition (\approx 1900 kcal/day) result in similar patient outcomes.¹¹ In addition, early supplementation of caloric intake with parenteral nutrition does not appear to improve outcomes.^{10,11}

While trials have not comprehensively evaluated the approach of individualising calorie delivery based on measured or calculated calorie requirements, the observation that patient outcomes are similar across such a broad range of caloric delivery calls into question the notion that minor adjustments in prescribed calorie goals based on empiric calculations of energy requirements could plausibly affect important patient outcomes. In short, trials do not support a view that calorie intake is a major determinant of outcomes in heterogeneous groups of ICU patients or in several specific subgroups. Given that efforts to increase

calorie delivery do not appear to improve patient outcomes, and that early trophic feeding and permissive underfeeding appear to result in similar outcomes to standard calorie delivery, a reasonable response if one encounters difficulty achieving recommended calorie goals by the enteral route may be simply to reduce the calorie target. The benefits of strategies to increase calorie delivery such as the administration of gastric prokinetic agents and the placement of small intestinal feeding tubes must now be questioned.

When considering the current evidence base, there are several important caveats to bear in mind. First, the large pragmatic trials undertaken so far have been performed in high income countries and their findings may not apply in low income countries where malnutrition is more common.^{1,7-9,11} Even in high income countries, there is still uncertainty about the calorie target in critically ill patients with poor nutritional status at baseline; in TARGET there were relatively few patients with low body mass index.¹ In the EDEN study, patients with malnutrition at baseline were specifically excluded. Second, the pragmatic nature of these trials may not have captured all population harms or benefits that are important to patients. Third, one could speculate that calorie delivery may be unimportant early after admission to the ICU, but later, during the recovery period, increased calorie delivery may improve recovery. Finally, unless one specifically supplements protein, the intake of calories and protein by the enteral route are directly coupled so that reducing calorie targets may result in an inadvertent failure to deliver sufficient protein. The optimal dose of protein for critically ill patients is currently uncertain.¹² However, as loss of muscle mass and negative nitrogen balance are common in critically ill patients and are associated with morbidity and mortality,¹³ it is clear that evaluating protein targets is now a priority in the field of critical care nutrition.¹⁴

Competing interests

None declared.

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