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Permissive underfeeding or standard enteral feeding in critically ill adults

There is no significant difference in 90-day mortality between patients receiving 40–60% of their daily caloric requirements and those receiving 70–100%.
Level of evidence: 2B (low quality RCT).

Appraised by: Kerrie Aldridge, Kieran Donnelly, Andrew Johnston

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Three-part clinical question:
Patients: A diverse group of critically ill patients commenced on enteral feeding regimes within 48 h of critical care admission.
Intervention: Patients were randomised to receive either (a) Permissive underfeeding – receiving 40–60% of their calculated daily caloric requirement, or (b) standard feeding – receiving 70–100% of their calculated daily caloric requirement. Daily protein intake in both groups was targeted to 1.5 g/kg/day, and the rest of the calories came from a variety of standard, commercially available enteral feeds depending on the usual practice of the trial centres involved.
Outcomes:

1. Primary outcome: 90-day all-cause mortality.
2. Secondary outcomes: mortality in ICU, 28-day mortality, in-hospital mortality, 180-day mortality, and serial SOFA scores.
3. Tertiary outcomes: days free from mechanical ventilation, ICU-free days, hospital length of stay, hypoglycaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, transfusions of packed red cells, ICU-associated infections, feeding intolerance and diarrhoea.

The study design:

Multi-centre, prospective, unblinded randomised controlled trial (RCT) taking place between November 2009 and September 2014 at seven tertiary care centres in Saudi Arabia and Canada.

The study patients:

A total of 894 patients were randomised, from a total of 6337 assessed for eligibility. Baseline characteristics between the two groups were similar. Mean BMI was 29, and mean age 50.

Inclusion criteria: Patients aged 18–80 years old, admitted to an intensive care unit (ICU), expected to stay for at least 72 h and commenced on enteral feeding within 48 h of ICU admission.

Exclusion criteria: Lack of commitment to ongoing life support, brain death, pre-existing conditions with expected six-month mortality >50%, post-cardiac arrest, use of total parenteral nutrition, previously enrolled in the same study, pregnant, patients admitted following burns or liver transplant, and patients on 'high-dose' vasopressors.

Underfeeding group: A total of 448 patients, of which five did not receive the allocated intervention. The aim was to receive 40–60% of calculated daily caloric requirements and 1.5 g/kg/day of protein. Patients actually received a mean of 46% of caloric requirement (SD 14) and a mean of 68% of protein requirements (SD 24) (See Table 1).

Standard feeding group: A total of 446 patients, of which four did not receive the allocated intervention. The aim was to receive 70–100% of calculated daily caloric requirements and 1.5 g/kg/day of protein. Patients actually received a mean of 71% of caloric requirements (SD 22) and a mean of 69% of protein requirements (SD 25) (See Table 1).

Results: There was no significant difference found between any of the measured outcomes, including on pre-specified subgroup analysis.

EBM questions:

1. Do the methods allow accurate testing of the hypothesis? **Partly**. This was a multi-centre, RCT but was unblinded throughout, from patient enrolment to data analysis, meaning there is potential for bias. The planned caloric targets in each group (40–60% or 70–100%) meant that some patients in the underfeeding group may have had only a 10% lower intake than those in the standard feeding group, which may be too small a difference to demonstrate any real effect.
2. Do the statistical tests correctly test the results to allow differentiation of statistically significant results? **Yes.**

Table 1. Illustration of the overlap between caloric intake between the two groups.

	Standard feeding group	Underfeeding group
Calories received (kCal/day ± SD)	1299 ± 467	853 ± 257
Calories - % of calculated requirement (± SD)	71 ± 22	46 ± 14
Protein received (g/day ± SD)	59 ± 25	57 ± 24
Protien – % of calculated requirement (± SD)	69 ± 25	68 ± 24

3. Are the conclusions valid in light of the results? **No**. The authors conclude that there is no significant difference in mortality between patients receiving 40–60% on non-protein calories requirements and those receiving 70–100% of their caloric requirements, when both groups receive the full recommended amount of protein. However, patients in both groups only actually received 70% of their target protein intake. Additionally, patients in the standard feeding group received a mean of 71% of target caloric intake, with standard deviation of 22%. Whilst there was statistical difference between the two groups in terms of caloric intake ($p<0.001$) an estimated 50% of patients within the standard feed group did not meet their caloric target range of 70–100%.
4. Did results get omitted and why? **Yes.** A total of nine patients were lost to follow-up before 90 days, five from the underfeeding group, four from the full feeding group.
5. Did the authors suggest areas for further research? **No.**
6. Did they make any recommendations based on the results and were they appropriate? **No.**
7. Is the study relevant to my clinical practice? **Yes.** The study demonstrates the difficulty of achieving target caloric intake in critically ill patients even in the context of a trial. The results demonstrate no significant difference in outcomes between those in the permissive underfeeding group, but methodological problems and lack of other studies confirming this finding mean it is too early to apply these findings to clinical practice.
8. What level of evidence does this study represent? **Level 2B** (CEBM) – this is a low quality RCT.
9. What grade of recommendation can I make on the basis of this study? **B.** Made on the basis of a level 2 study.
10. What grade of recommendation can I make when this study is considered along with the other available evidence?
    B. There is one RCT from the same authors demonstrating some benefit to underfeeding in critically ill patients, but this also had limitations, and there are a number of studies demonstrating worse outcomes in patients receiving inadequate nutrition.
11. Should I change my practice because of these results? **No.** There is no evidence of benefit to permissive underfeeding from this or other studies.
12. Should I audit my practice because of these results? **No.**

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