

Energy and Protein Needs in Critical Illness: Updates and New Considerations

Beth Peterson MS, RD, CSO, LDN, CNSC
UMass Memorial Medical Center
Worcester, MA

Disclosures

- Nothing to disclose

Learning Objectives

- Describe the current evidence on energy and protein delivery in critically ill adult patients.
- Discuss how this new evidence may influence clinical practice.
- Summarize these learnings with a case study example.

Current Societal Energy and Protein Guidelines for Critically Ill Patients¹⁻⁴

| | Energy Recommendations | Protein Recommendations |
|-------------|---|---|
| 2016 ASPEN | 25-30 kcal/kg actual body wt for BMI <30 11-14 kcal/kg actual body wt for BMI 30-50 22-25 kcal/kg ideal body wt for BMI >50 | 1.2-2 g/kg actual body wt for BMI <30 2 g/kg ideal body wt for BMI 30-40 2.5 g/kg ideal body wt for BMI >40 |
| 2022 ASPEN | 12-25 kcal/kg in the first 7-10 days of ICU stay | 1.2-2 g/kg |
| 2019 ESPEN* | ≤70% of measured/calculated EE in the early phase of acute illness, whereas after day 3, it should cover 80%–100% of measured EE and 70% of calculated EE | 1.3 g/kg |
| 2022 ESPEN | No change | No change |

*Preadmission dry weight for patients with BMI <30 or ideal body weight based on the patient's height calculated to BMI = 25

And Then...

The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C González, Kevin O'Reilly, Racquel Regala, Courtney Wedemire, Miguel Ibarra-Estrada, Christian Stoppe, Luis Ortiz-Reyes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

Association between urea trajectory and protein dose in critically ill adults: a secondary exploratory analysis of the effort protein trial (RE-EFFORT)

Ryan W. Haines^{1,2*}, John R. Prowle^{1,2,3}, Andrew Day⁴, Danielle E. Zudin Puthuchear^{1,2†}

Low versus standard calorie and pro ventilated adults with shock: a randomised multicentre, open-label, parallel-group trial

Jean Reignier, Gaetan Plantefeve, Jean-Paul Mira, Laurent Argaud, Pierre Asfar, Nadia Hoang-Nam Bui, Delphine Chatellier, Louis Chauvelot, Alain Combes, Christophe Cracco, Michael Darmon, Vincent Das, Matthieu Debarre, Agathe Delbove, Jérôme Devaquet, Louis-Marie Dumont, Olivier Gontier, Samuel Groyer, Laurent Guérin, Bertrand Guidet, Yannick Hourmant, Samir Jaber, Fabien Lambiotte, Christophe Leroy, Philippe Letocart, Benjamin Madeux, Julien Maizel, Olivier Martinet, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Mai-Anh Nay, Saad Nseir, Johanna Oziel, Walter Picard, Gael Piton, Jean-Pierre Quenot, Florian Reizine, Anne Renault, Jack Richecoeur, Jean-Philippe Rigaud, Francis Schneider, Daniel Silva, Michel Sirodot, Bertrand Souweine, Fabienne Tamion, Nicolas Terzi, Didier Thévenin, Guillaume Thiery, Nathalie Thieulot-Rolin, Jean-Francois Timsit, Francois Tinturier, Patrice Tirot, Thierry Vanderlinden, Isabelle Vinatier, Christophe Vinsonneau, Sebastian Voicu, Jean-Baptiste Lascarrou, Amélie Le Gouge, for the NUTRIREA-3 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS-TRIGGERSEP) Group

TICACOS international: A multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study

P. Singer^{a,*}, E. De Waele^b, C. Sanchez^c, S. Ruiz Santana^d, J.C. Montejo^e, P.F. Laterre^f, A. Soroksky^g, E. Moscovici^a, I. Kagan^a

Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands

Julia L M Bels, Steven Thiessen, Rob J J van Gassel, Albertus Beishuizen, Ashley De Bie Dekker, Vincent Fraipont, Stoffel Lamote, Didier Ledoux, Clarissa Scheeren, Elisabeth De Waele, Arthur R H van Zanten, Laura Bormans-Russell, Bas C T van Bussel, Marlies M J Dictus, Tom Fivez, Ingeborg Harks, Iwan C C van der Horst, Joop Jonckheer, Hugues Marechal, Paul B Massion, Ingrid Meex, Michelle C Paulus, Martin Rinket, Susanne van Santen, Katrien Tartaglia, Adam M Deane, Frieda Demuydt, Zudin Puthuchear, Lilian C M Vloet, Peter J M Weijs, Sander M J van Kuijk, Marcel C G van de Poll*, Dieter Mesotten*, on behalf of the PRECISE study team†

New Evidence on Energy Provisions

- Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3). *Lancet Respir Med.* (2023)⁵
- Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. *N Engl J Med.* (2018)⁶
- Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. *Intensive Care Med.* (2017)⁷
- Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open.* (2020)⁸

NUTRIREA – 3⁵

- Multicenter, pragmatic, RCT
- 3036 adults on mechanical ventilation and vasopressor support from 61 French ICUs
- Randomized to receive low (6 kcal/kg/day and 0.2-0.4 g/kg/day protein) vs standard (25 kcal/kg/day and 1.0-1.3 g/kg/day protein) feeding targets
 - Within 24 hrs of mechanical ventilation and continued until extubation, withdrawal of vasoactive drugs, death, or end of day 7
- Primary outcome: time to readiness for ICU discharge and day 90 all-cause mortality
 - Secondary outcome: secondary infections, gastrointestinal events, and liver dysfunction

NUTRIREA – 3⁵

- Actual energy received: 7.4 (5.8–9.5) kcal/kg/day vs. 22.0 (17.5–24.9) kcal/kg/day
- Actual protein received: 0.2 (0.2–0.3) g/kg/day vs. 0.9 (0.7–1.0) g/kg/day

| | Low group (n=1521) | Standard group (n=1515) | Absolute difference (95% CI) | Hazard ratio (95% CI) | p value |
|---|---------------------|-------------------------|------------------------------|-----------------------|---------|
| Primary outcomes | | | | | |
| Day 90 mortality | 628 (41.3%) | 648 (42.8%) | -1.5 (-5.0 to 2.0) | .. | 0.41 |
| Time to readiness for ICU discharge* | 8.0 (5.0 to 14.0) | 9.0 (5.0 to 17.0) | .. | 1.12 (1.02 to 1.22) | 0.015 |
| Secondary outcomes | | | | | |
| Day 28 mortality | 504 (33.2%; n=1519) | 533 (35.2%) | -2.0 (-5.4 to 1.4) | .. | 0.24 |
| ICU mortality, cumulative incidence | 29.6% | 32.7% | .. | 0.89 (0.78 to 1.00) | 0.051 |
| Hospital mortality, cumulative incidence | 32.2% | 34.5% | .. | 0.93 (0.83 to 1.05) | 0.24 |
| ICU length of stay, days† | 9.0 (5.0 to 15.0) | 10.0 (6.0 to 17.0) | .. | .. | .. |
| Acute-care hospital length of stay, days† | 21.0 (12.0 to 38.0) | 22.0 (14.0 to 39.0) | .. | .. | .. |
| Time to weaning from vasopressor support, days | 3.0 (2.0 to 4.0) | 3.0 (2.0 to 4.0) | .. | 1.07 (0.99 to 1.15) | 0.054 |
| Time to invasive mechanical ventilation weaning, days | 5.0 (2.0 to 11.0) | 6.0 (3.0 to 12.5) | .. | 1.12 (1.03 to 1.22) | 0.007 |
| Received dialysis, cumulative incidence | 30.1% | 31.9% | .. | 0.93 (0.82 to 1.05) | 0.25 |
| Infections, cumulative incidence | | | | | |
| ICU infection‡ | 15.3% | 17.5% | .. | 0.85 (0.71 to 1.01) | 0.06 |
| Ventilator-associated pneumonia | 11.2% | 10.9% | .. | 0.98 (0.79 to 1.21) | 0.82 |
| Bacteraemia | 4.0% | 5.5% | .. | 0.73 (0.53 to 1.01) | 0.06 |
| Central venous catheter infection | 1.5% | 1.9% | .. | 0.81 (0.48 to 1.37) | 0.44 |
| Urinary tract infection | 0.7% | 0.8% | .. | 1.20 (0.54 to 2.67) | 0.66 |
| Soft-tissue infection | 7 patients | 5 patients | .. | .. | .. |
| Other infection | 1.7% | 2.4% | .. | 0.78 (0.48 to 1.28) | 0.33 |
| Gastrointestinal events, cumulative incidence | | | | | |
| Vomiting | 20.2% | 25.5% | .. | 0.77 (0.67 to 0.89) | <0.001 |
| Diarrhoea | 28.9% | 33.3% | .. | 0.83 (0.73 to 0.94) | 0.004 |
| Constipation | 27.8% | 28.7% | .. | 0.97 (0.86 to 1.10) | 0.64 |
| Bowel ischaemia | 0.9% | 1.8% | .. | 0.50 (0.26 to 0.95) | 0.030 |
| Acute colonic pseudo-obstruction | 8 patients | 2 patients | .. | .. | .. |
| Liver dysfunction, cumulative incidence§ | 61.7% | 65.8% | .. | 0.92 (0.86 to 0.99) | 0.032 |

NUTRIREA - 3⁵

□ Thoughts to ponder:

□ **WHY**

□ Autophagy is a key mechanism for safeguarding cellular integrity, notably in the muscle, and therefore makes a significant contribution to recovery after severe critical illness. Increased macronutrient intakes could suppress autophagy, thereby decreasing the clearance of damaged cell components.

□ **TIMING**

□ NUTRIREA – 3 did not consider the theoretical phases of critical illness and the standard group received an AGGRESSIVE dose of nutrition within 24 hs of intubation in a very sick population of patients (mean norepi equivalent dose in both groups was 0.5 mcg/kg/min)

TARGET⁶

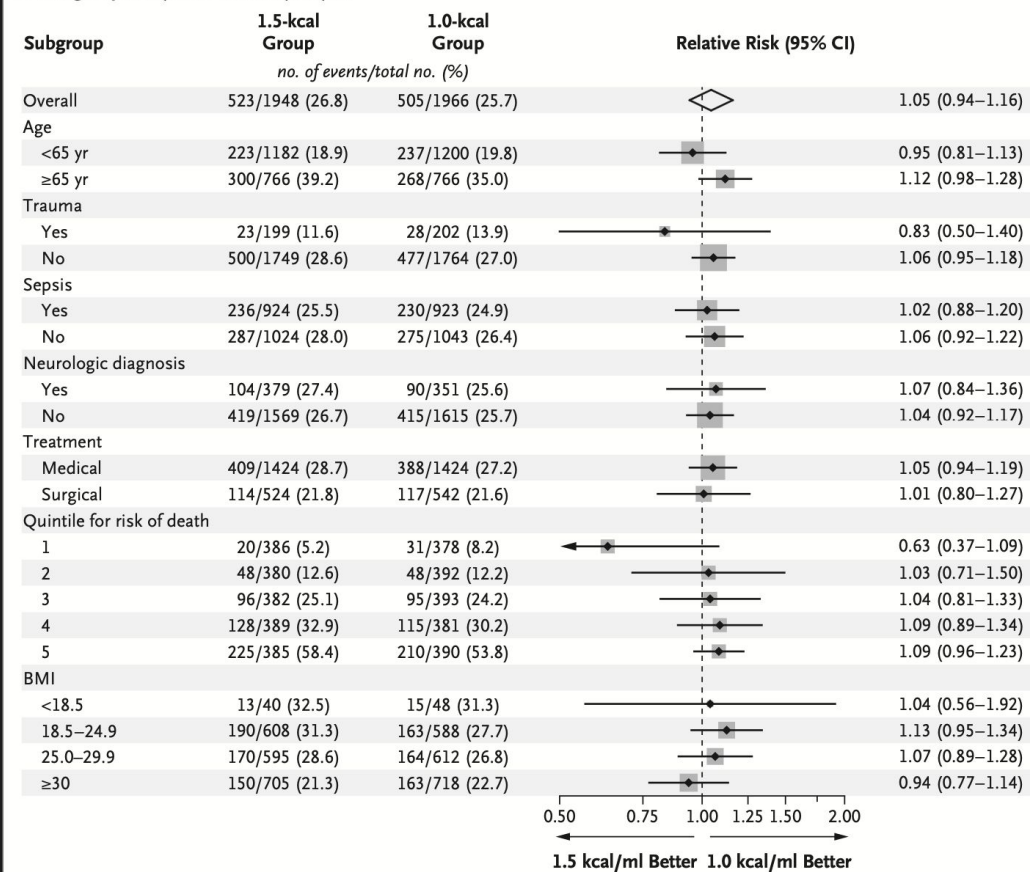
- Multicenter, double-blinded, pragmatic, RCT
- 3957 adults mechanically ventilated in 46 Australian and New Zealand ICUs who received enteral nutrition at a dose of 1 mL/kg of ideal body weight and were randomized to either a 1.5 kcal/mL energy dense formula (intervention group) or a 1 kcal/mL routine formula (control group)
- Higher calorie delivery did not affect 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 or adverse events

Table 2. Daily Nutrition Delivery up to Day 28.*

| Measure | 1.5-kcal Group (N=1971) | 1.0-kcal Group (N=1985) [†] | Difference or Relative Risk (95% CI) [‡] |
|---|-------------------------|--------------------------------------|---|
| Median time from ICU admission to commencing trial nutrition (IQR) — hr | 15.8 (7.7 to 26.3) | 15.9 (7.9 to 28.3) | -0.4 (-1.1 to 0.4) |
| Median duration of trial nutrition (IQR) — days [§] | 6.0 (3.0 to 11.0) | 6.0 (3.0 to 11.0) | 0 |
| Volume of trial nutrition delivered — ml/day [¶] | 1242±318 | 1262±313 | -20 (-40 to 0) |
| Percentage of trial target rate delivered | 81±17 | 82±16 | -1 (-2 to 0) |
| Calories delivered — kcal/day [¶] | | | |
| Trial nutrition | 1863±478 | 1262±313 | 601 (576 to 626) |
| Trial nutrition plus other sources | 1930±547 | 1407±397 | 523 (493 to 553) |
| Calories delivered — kcal/kg of ideal body weight per day [¶] | | | |
| Trial nutrition | 29.1±6.2 | 19.6±4.0 | 9.5 (9.2 to 9.9) |
| Trial nutrition plus other sources | 30.2±7.5 | 21.9±5.6 | 8.3 (7.9 to 8.7) |
| Calories delivered — kcal/kg of actual body weight per day ^{¶**} | | | |
| Trial nutrition | 23.1±7.1 | 15.6±4.8 | 7.5 (7.1 to 7.9) |
| Trial nutrition plus other sources | 23.9±7.8 | 17.4±5.5 | 6.6 (6.2 to 7.0) |
| Protein delivered [¶] | | | |
| Trial nutrition — g/day | 69.6±17.8 | 69.4±17.2 | 0.1 (-1.0 to 1.2) |
| Trial nutrition — g/kg of ideal body weight per day | 1.09±0.22 | 1.08±0.23 | 0.01 (-0.01 to 0.02) |

TARGET⁶

B Subgroup Analysis of Death by Day 90



EAT-ICU⁷

□ EAT-ICU

- Single center RCT in Denmark that fed mechanically ventilated patients (203 participants) 100% of needs based on indirect calorimetry and nitrogen balance vs standard care
- Intervention was not associated with improved physical quality of life at 6 months, mortality, rates of new organ failures, serious adverse reactions or nosocomial infections in the ICU, length of ICU or hospital stay, or days alive without life support at 90 days
- More patients in the EGDN group had severe hyperglycemia and received higher doses of insulin as compared to those who received standard care

| | | |
|---|-----------------------|------------------------|
| Energy intake, kcal/day | 1877 (1567–2254) | 1061 (745–1470) |
| Energy balance ^c , kcal/day | –66 (–157 to –6) | –787 (–1223 to –333) |
| Measured ^d protein requirement, g/kg/day | 1.63 (1.36–2.05) | 1.16 (0.89–1.62) |
| Protein intake, g/kg/day | 1.47 (1.13–1.69) | 0.50 (0.29–0.69) |
| Protein balance ^c , g/kg/day | –0.28 (–0.76 to 0.11) | –0.69 (–1.02 to –0.38) |

Merker, et al⁸

- Merker, et al
 - A secondary analysis of EFFORT, an RCT conducted in 8 Swiss hospitals (2/2014 - 2/2018) with 1950 participants (2028 patients in the initial study)
 - More nutrition in patients with higher levels of inflammation (defined as CRP >100 mg/L) was associated with higher mortality
 - Inflammation modifies metabolism/ability to use nutrients

New Evidence on Protein Provisions

- The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial. *Lancet*. (2023)⁹
- The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial. *Crit Care*. (2023)¹⁰
- Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands. *Lancet*. (2024)¹²
- High-protein intake and early exercise in adult intensive care patients: a prospective, randomized controlled trial to evaluate the impact on functional outcomes. *BMC Anesthesiol*. (2021)¹³

EFFORT Protein⁹

- Multicenter, international, pragmatic, single-blinded, RCT
- 1301 adults at high nutrition risk on mechanical ventilation from 85 ICUs in 16 countries
- Randomized to high dose protein (2.2 g/kg/day) vs. “usual” dose protein (< or =1.2 g/kg/day)
 - Within 96 hrs of mechanical ventilation and continued for up to 28 days or extubation/death
- Primary outcome: time-to-discharge-alive from the hospital within 60 days
 - Secondary outcome: 60-day mortality

EFFORT Protein⁹

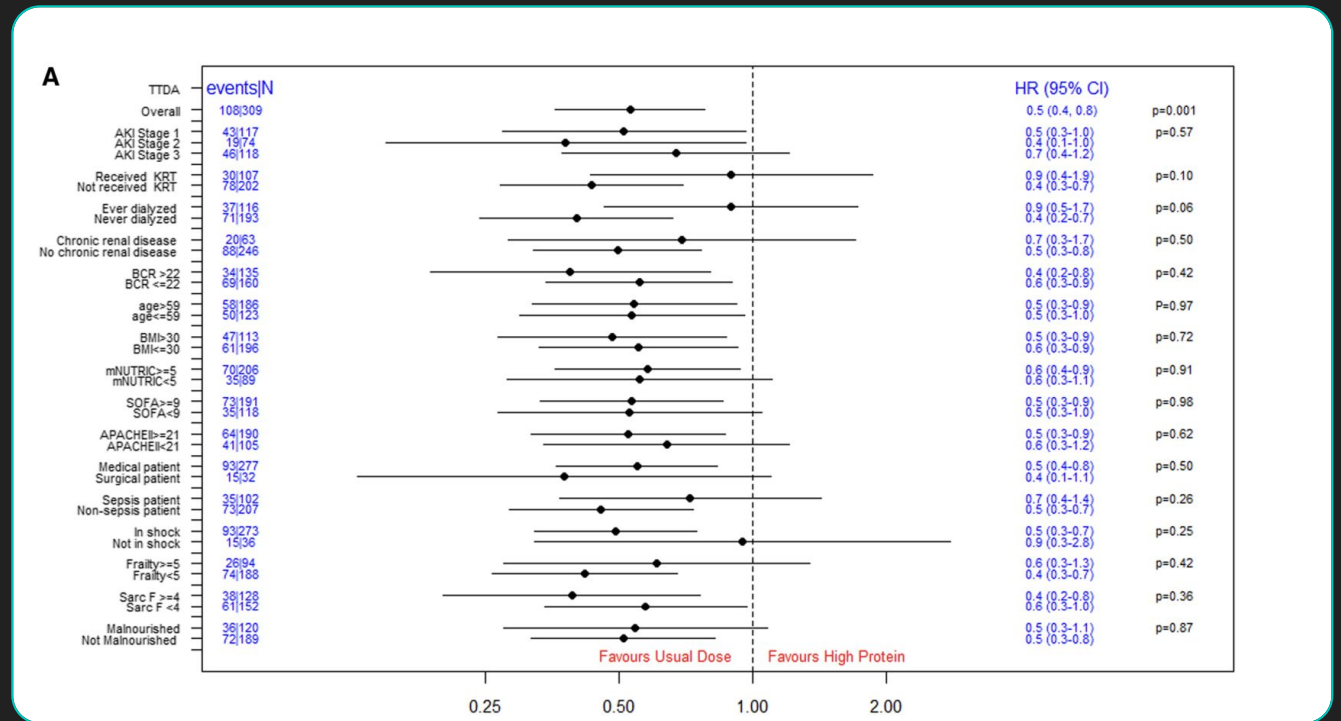
- Actual protein received: 1.6 +/- 0.5 g/kg/d vs. 0.9 +/- 0.3 g/kg/day
 - Both groups received a similar energy intake: 14.7 +/- 6.9 kcal/kg/d vs 13.2 +/- 6.4 kcal/kg/d
- Alive discharge at 60 days: 46.1% vs. 50.2% (HR 0.91)
- 60-day mortality: 34.6% vs. 32.1% (RR 1.08)
- Hospital mortality, duration of mechanical ventilation, ICU stay, and hospital stay were similar between groups

EFFORT Protein⁹

- In other words: protein dose didn't make a difference...
- EXCEPT: subgroup analysis suggested an interaction between protein dose and patients with acute kidney injury (stage 1–3) and high SOFA score (≥ 9) upon admission on both time-to-discharge-alive and 60-day mortality, **favoring the usual protein dose**

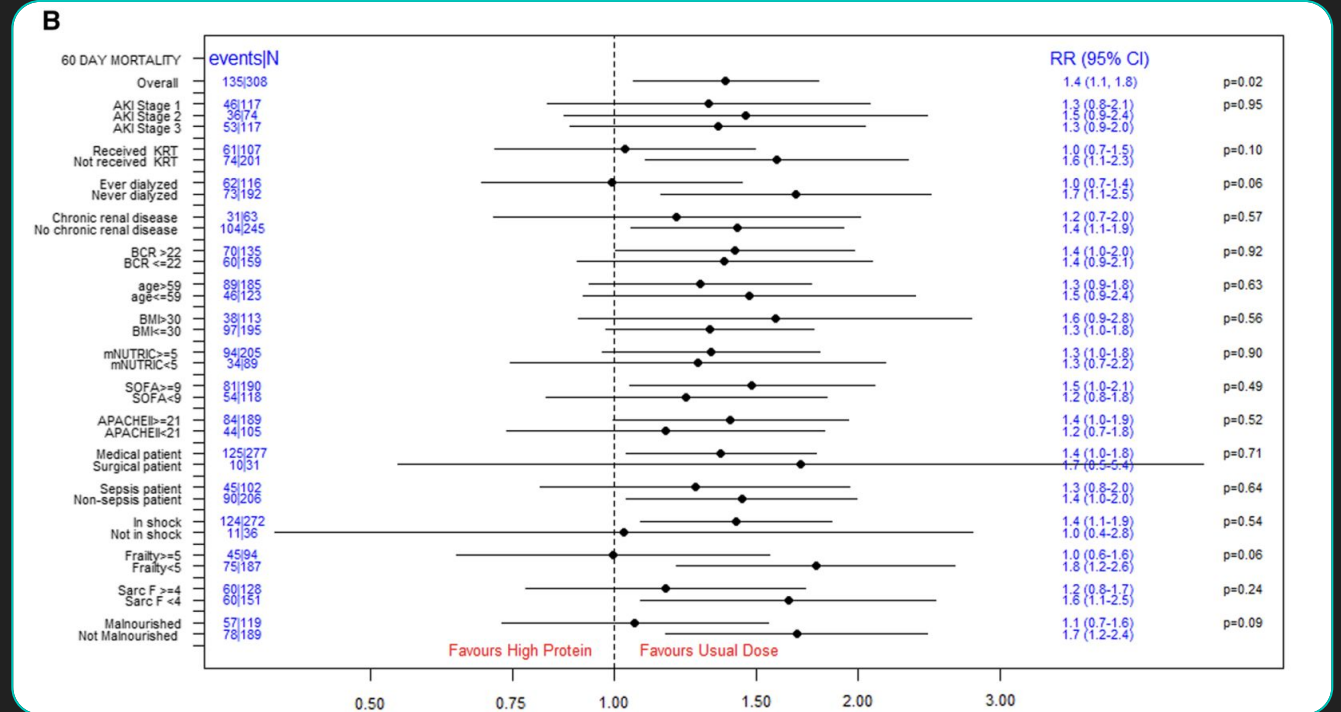
EFFORT Protein

□ The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial¹⁰



EFFORT Protein

□ The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial¹⁰



EFFORT Protein

□ Thoughts to ponder:

□ **WHY**

- In critically ill patients with AKI AA utilization is impaired and transport into muscle is reduced □ exogenously administered protein increases metabolic stress

□ **TIMING**

- EFFORT did not consider the theoretical phases of critical illness and administered the same dose throughout the 28-day study period □ what if we wait until patients are in an “anabolic phase” to provide high protein doses?
- REPLENISH (Replacing Protein via Enteral Nutrition in a Stepwise Approach in Critically Ill Patients) trial is trying to answer this question (incremental increase in protein after day 5)¹¹

□ **LONG TERM**

- Would higher protein doses improve the physical recovery of survivors of critical illness, especially if administered with exercise (even if it does not improve TTDA or mortality)?

PRECISE¹²

- Multicenter, double-blinded, pragmatic, RCT in 5 Dutch and 5 Belgian hospitals
- Protein received: 1.19 g/kg per day (0.63–1.26) in the standard protein group and 1.87 g/kg per day (0.96–2.00) in the high protein group
- High enteral protein provision resulted in:
 - Lower health-related quality of life measured by the EQ-5D-5L health utility score
 - Statistically significant increase in time-to-discharge-alive from the hospital
 - Greater incidence of GI intolerance and use of prokinetics
- High protein may be particularly harmful to females and medical patients

Azevedo, et al¹³

- Single center RCT in Brazil (3 ICUS, mix of medical, surgical, trauma)
- 181 mechanically ventilated patients randomized to either the HPE (high protein and early exercise) group or the control group
 - HPE group: higher protein intake + 2x15-min sessions of cycle ergometry/day
 - Control group: lower protein intake + standard PT care (passive and active movements at least 2x/day)



<https://www.medimotion.co.uk/motomed-movement-therapy/letto/>

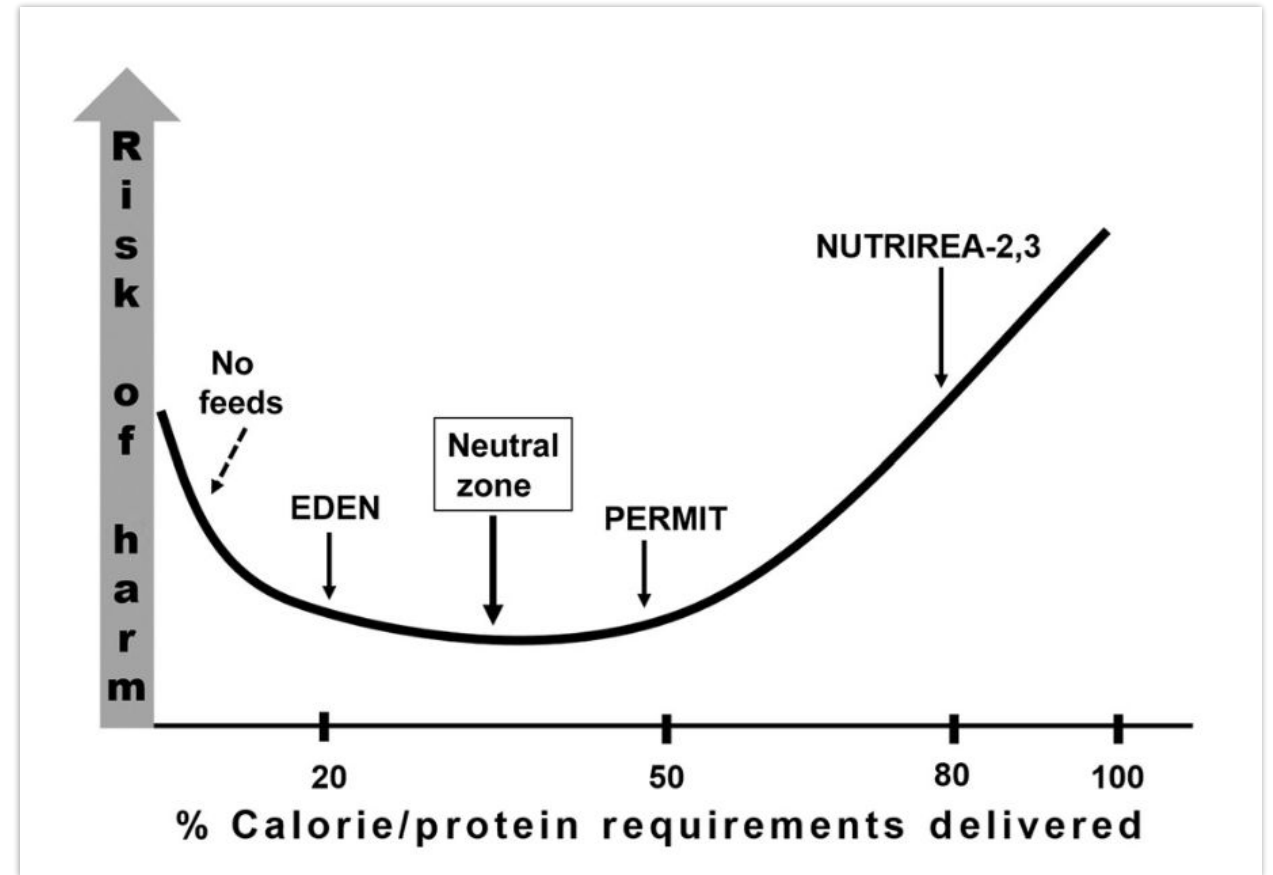
Azevedo, et al¹³

Table 3 Primary and secondary outcomes

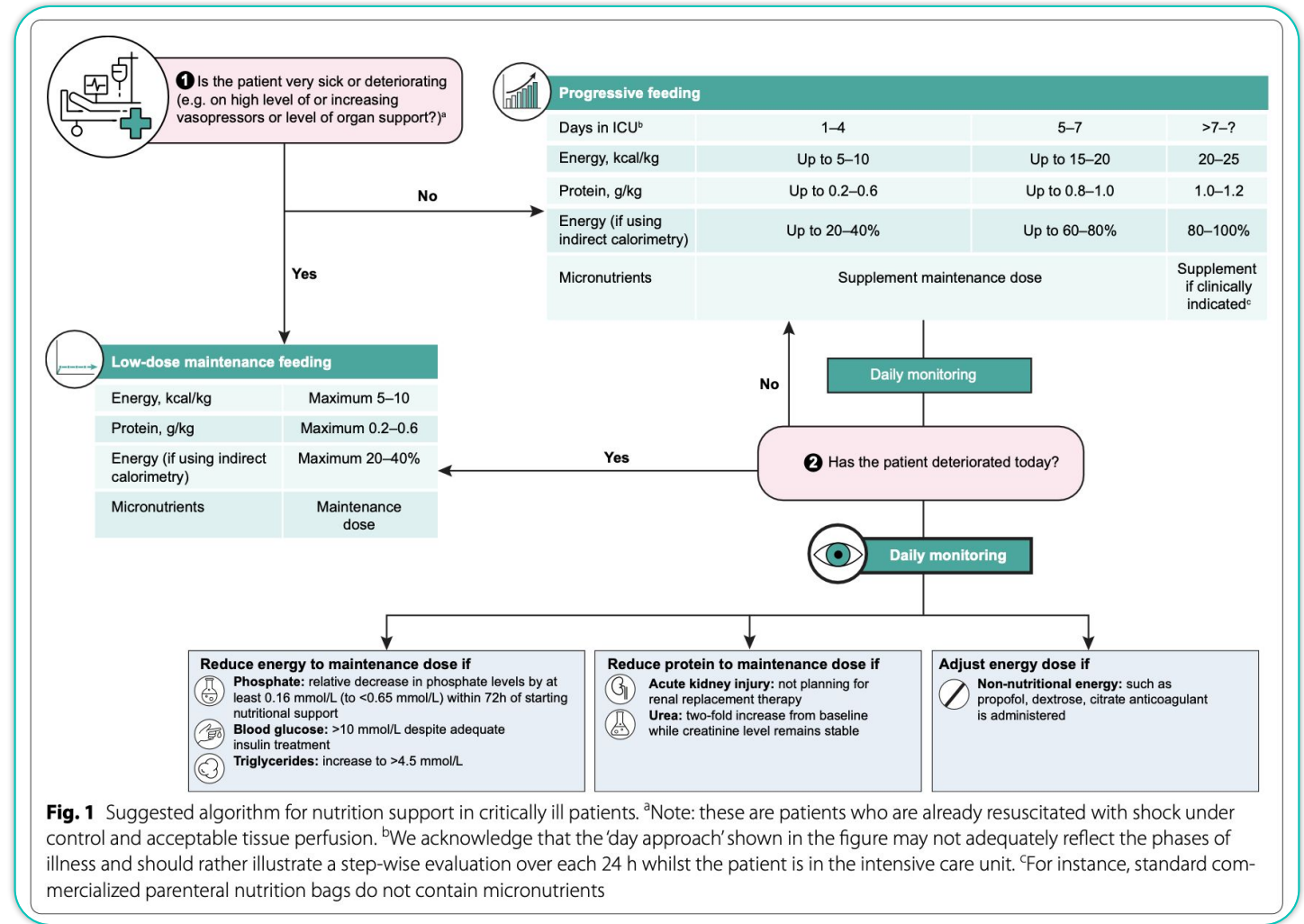
| Variable | HPE group n = 87 | Control group n = 94 | P value |
|--------------------------------|---------------------|-------------------------|---------|
| PCS score, Median (IQR) | | | |
| 3 months | 24.40 (0.00–49.12) | 0.00 (0.00–37.0) | 0,01 |
| 6 months | 33.63 (0.00–71.61) | 0.00 (0.00–55.1) | 0,01 |
| ICU-acquired weakness n (%) | 16 (29.1) | 26 (46.4%) | 0.05 |
| Length of stay, days | | | |
| Median (IQR) | | | |
| ICU | 18 (12–36) | 23 (16–36) | 0,11 |
| Hospital | 38 (18–70) | 40 (21–60) | 0,96 |
| Duration of MV, days | | | |
| Median (IQR) | 10 (5–19) | 12 (7–21) | 0,09 |
| Mortality | | | |
| n (%) | | | |
| ICU | 23 (26.4) | 41 (43.6) | 0,01 |
| Hospital | 25 (31.2) | 47 (53.4) | 0,002 |
| 6-months follow-up | 29 (33.3) | 51 (54.2) | 0.005 |

PCS physical component summary

So What Should We Do?¹⁴



So What Should We Do?¹⁵



Other Considerations

- When to feed more?
 - Biomarkers: urea to creatinine ratio (more research needed)
- Nutrition in rehab
 - The impact of a tailored nutrition intervention delivered for the duration of hospitalisation on daily energy delivery for patients with critical illness (INTENT)¹⁶
- Future Research: nutrition and exercise combined
 - Nutrition and Exercise in Critical Illness (NEXIS)
 - The Preservation of Muscle Function in Critically Ill Patients (PRESMUS)

Case Study: KS

- 52 yo male admitted 5/17 w/history of AUD, cirrhosis, COPD, and possible HFpEF who presented to OSH with respiratory distress, multiple falls at home, and hypotension, found to be in shock d/t necrotizing pancreatitis with AHRF d/t severe ARDS requiring intubation 5/17, as well as AKI and metabolic/respiratory acidosis, requiring CRRT.
- Nutrition history is sparse. His health care proxy (his brother) wasn't very sure about usual weight, weight loss, eating habits or intake, etc. He did confirm that patient was a heavy drinker, usually consuming 8 "nips" a day (roughly 9 shots). BMI = 34.5 kg/m²

Case Study: KS (day #2)

- 5/18: MD consult for tube feeding recommendations
 - Norepinephrine: 0.35 mcg/kg/min
 - Vasopressin: 2.4 units/hour
 - Other drips: cisatracurium, insulin, ketamine, versed, dilaudid
 - On CRRT
 - OG to LIS
 - Abdominal exam: firm, distended, hypoactive BS
 - Bladder pressure: 13 (c/f abdominal compartment syndrome)
 - Lactate: 8.0 mmol/L

Case Study: KS (day #5)

- 5/21
 - Norepinephrine: 0.22 mcg/kg/min
 - Vasopressin: 1.8 units/hour
 - Other drips: ketamine, versed, dilaudid; intermittently requiring boluses of rocuronium for vent dyssynchrony
 - Remains on CRRT
 - OG to LCS (output 1.5-2L daily)
 - Abdominal exam: firm, distended, hypoactive BS, no BM yet
 - Bladder pressure: 23
 - Lactate: WNL

Case Study: KS (day #7)

- 5/23
 - Norepinephrine: 0.32 mcg/kg/min
 - Vasopressin: 3.6 units/hour
 - Other drips: precedex, versed, dilaudid; still requiring boluses of rocuronium for vent dyssynchrony, eventually restarted on cisatracurium
 - Remains on CRRT
 - High protein 1 mL/kcal formula @10 mL/hr started via OG
 - Stopped 12H later
 - Abdominal exam: firm, distended, hypoactive BS, no BM yet
 - Bladder pressure: 20
 - Lactate: WNL

Case Study: KS (day #9)

- 5/25
 - Norepinephrine: 0.12 mcg/kg/min
 - Vasopressin: 1.8 units/hour
 - Other drips: precedex, versed, dilaudid, ketamine, cisatracurium
 - Remains on CRRT
 - Nasoenteric feeding tube placed, tip advanced to 3rd portion of duodenum
 - Same high protein 1 mL/kcal formula @10 mL/hr restarted
 - Abdominal exam: firm, distended, hypoactive BS, LARGE BM
 - Bladder pressure: 17
 - Lactate: WNL

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Questions

