

ICU Protein requirements – where are we up to?

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Overview

- Current ANZ practice
- EFFORT PROTEIN
- NUTRIREA-3
- (Refeeding related hypophosphatemia)
- PRECISE
- TARGET PROTEIN
- ESPEN and ASPEN guidelines
- Thoughts

Protein prescription in ANZ - survey

- 67 responses from Dietitians
- Most aimed for 1.2-1.5g protein/kg BW/day based on ESPEN guidelines
 - thought their recommendations achieved approximately 60-80% of prescriptions.
- Barriers to feeding included fasting periods, avoiding energy overfeeding, and GI intolerance.

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* Simpson F, Doig GS. The relative effectiveness of practice change interventions in overcoming barriers to change: a survey of 14 hospitals with experience implementing evidence-based feeding guidelines. J Eval in Clinical Practice.

* Effect of evidence-based feeding guidelines on mortality in critically ill adults. JAMA 2008; 300 (23).

Protein prescription in ANZ

- Observational study of 120 patients across 5 ICU's
 - Mechanically ventilated adult patients anticipated to receive EN for ≥ 24 hours
- Estimated protein requirements were 1.46 ± 0.55 g/kg IBW/day
- Actual protein delivery:
 - 0.85 ± 0.35 g/kg IBW/day (EN)
 - 0.88 ± 0.35 g/kg IBW/day (EN, TPN, protein supplements)

Protein delivery ≥ 1.2 g/kg IBW/day on 29% of total study days/pt.

EFFORT PROTEIN

- 85 ICUs across 16 countries - 1301 patients.
- $\geq 2.2\text{g/kg}$ protein vs $\leq 1.2\text{g/kg}$ protein/day (ASPEN guidelines)

Note: Able to achieve protein targets in any combination of EN/TPN/IV amino acids/ or EN protein supplement

EFFORT PROTEIN

- 85 ICUs across 16 countries - 1301 patients.
- $\geq 2.2\text{g/kg}$ protein vs $\leq 1.2\text{g/kg}$ protein/day (ASPEN guidelines)
- Nutritionally high risk (one or more)
 - BMI $\leq 25\text{kg/m}^2$ or $\geq 35\text{kg/m}^2$
 - Moderate to severe malnutrition (local definitions)
 - Frail (clinical frailty scale ≥ 5 via proxy)
 - Sarcopenia (SARC-F score ≥ 4 via proxy)
 - Mechanically ventilated and continue for >4 days
- $>18\text{yrs}$
- Primary outcome: time to discharge alive from hospital up to 60 days post ICU
 - Secondary outcome: 60-day mortality

Heyland DK, Patel J, Compher C et al. 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; 401:568-76.

EFFORT PROTEIN

- Methodology:
 - Allocation: Centralised web-based randomisation, allocated 1:1. Permuted blocks of 2, 4, 8.
 - Blinding: Patients blinded, staff unblinded
 - Follow-Up:
 - N=1329 patients – 1301 included - 2.1% excluded (n=28).
 - Primary Outcome: 645/659 (high protein) vs 656/670 (usual protein)
 - Secondary outcome (60-day mortality): 644/645 (high protein) vs 653/656 (usual protein)

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EFFORT PROTEIN

- Methodology:
- **Note:** Initial study aimed for 4,000 patients but due to COVID-19 and volunteer nature of trial, revised to at least 1200.
- Lots of pre-specified subgroup analyses
 - Baseline mNUTRIC score (0-4 vs 5-9)
 - BMI >30kg/m²
 - Trauma
 - Sepsis
 - *AKI*
 - Age
 - *APACHE II Score, SOFA score*

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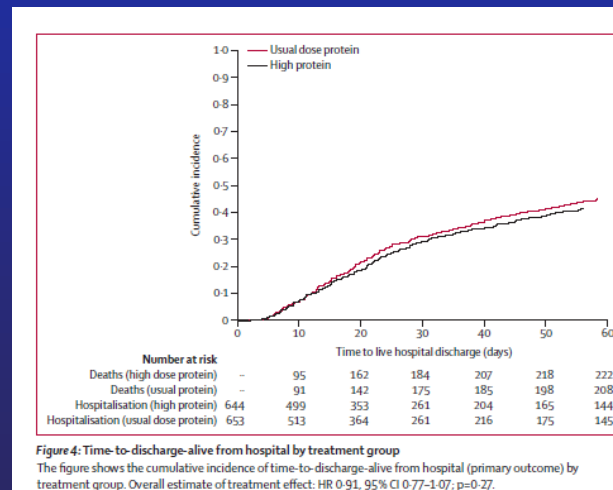
EFFORT PROTEIN

- Process measures:
- Feeds started within 96 hrs of ICU admission/mechanical ventilation
- Feeds continued for up to 28 days or death or transition to oral diet
- **Prescribed vs Actual protein intake:** $\geq 2.2\text{g/kg protein}$ vs $\leq 1.2\text{g/kg protein/day}$
 - Mean $1.6\text{g/kg/day protein}$ vs Mean $0.9\text{g/kg/day protein}$
 - Similar energy intake (14.7kcal/kg/d vs 13.2kcal/kg/d)
- *82% of patients classified as medical admissions*
- *APACHE II score 21*

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EFFORT PROTEIN

- Outcome measures:
- Time to discharge alive:
 - 46.1% (high protein) vs 50.2% (usual protein), HR 0.91 (95% CI 0.77-1.07, P=0.27).
- 60-day mortality rate:
 - 34.6% (high protein) vs 32.1% (usual protein).



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EFFORT PROTEIN

- Outcome measures:
 - Subgroup effect:
 - Higher protein arm could be harmful in patients with:
 - AKI (Stage 1-3)
 - Higher SOFA score (≥ 9) at study baseline
- for both time to discharge alive and 60-day mortality, c/w usual protein dose.

Figure S2 – Subgroup Analysis Based on Effect on Time-to-Discharge-Alive from Hospital

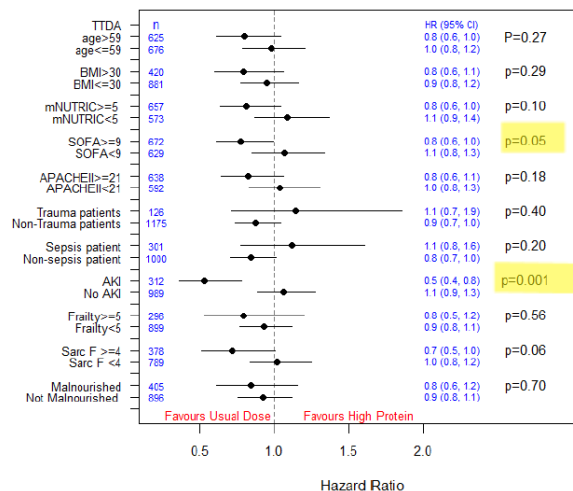
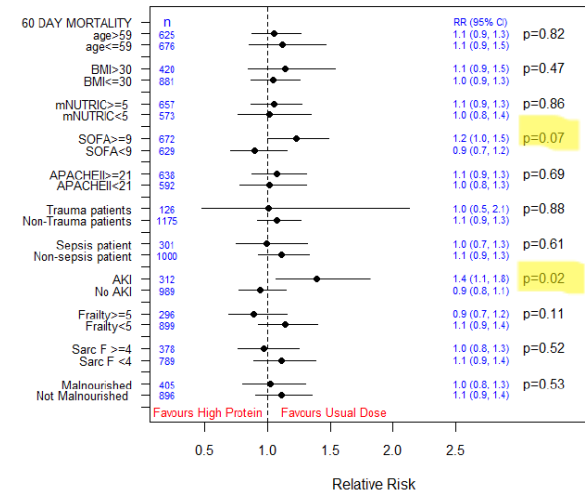


Figure S3 – Subgroup Analysis Based on Effect on 60-day Mortality



EFFORT PROTEIN

- Outcome measures:
- Subgroup effect:
- Higher protein arm could be harmful in patients with:
 - AKI (Stage 1-3)
 - Higher SOFA score (≥ 9) at study baselinefor both time to discharge alive and 60-day mortality, c/w usual protein dose.
- The high protein arm also had significantly higher urea levels by 2.1mmoles/L (c/w usual protein) arm.

EFFORT PROTEIN

- “Our findings do not support the prevailing notion that mechanically ventilated patient who are older, obese, more severely ill, frail, malnourished, or sarcopenic benefit from higher protein dose. In contrast, higher protein dosing could be harmful in patients with greater severity of illness”..

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- “In conclusion, prescribing 1.2g/kg/day (ASPEN lower end) or 1.3g/kg /day (ESPEN 2019) and striving to achieve 80% of what was prescribed seems like a reasonable and safe approach for all critically ill patients”.

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- “In conclusion, prescribing 1.2g/kg/day (ASPEN lower end) or 1.3g/kg /day (ESPEN 2019) and striving to achieve 80% of what was prescribed seems like a reasonable and safe approach for all critically ill patients”.
- “Delineating which subgroups of critically ill patients (e.g. those with burns, trauma, obesity or recovering from surgery) that could benefit from higher doses of protein requires more research to define the optimal dose and timing of administration”.

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EFFORT PROTEIN – post hoc analysis

- “In critically ill patients, what is the association between pre-existing malnutrition and time to discharge alive and does high protein treatment modify this association?” .
 - Diagnosis of malnutrition collected at study baseline: unintentional weight loss and reduced food intake prior to admission, muscle wasting or calf circumference, history of chronic malabsorption and BMI <18.5kg/m². Information from patient, primary caregiver, medical records or clinical assessments.
- Conclusion: malnutrition was associated with slower time to discharge alive, but high protein treatment did not modify the association.

EFFORT PROTEIN – 2nd post hoc analysis

- **Hypothesis:** That higher urea values over time could explain the potential harmful effects of higher doses of protein.
 - By day 6 median urea was 2.1mmol/L higher (high protein group) increasing to 3mmol/L higher by day 12. A two-fold increase in urea was associated with an increased risk of death at 30 days (adjusting for age, SOI, RRT, AKI).
- Increased risk of death in the higher protein arm of EFFORT PROTEIN was thought to be mediated by increase urea cycle activity.
- “Serum urea should be taken into consideration when initiating and continuing protein delivery in critically ill patients”.

NUTRIREA-3

- 61 French ICUs.
 - 3036 patients randomised and analysed
 - ~70% of patients had some pre-existing illness at ICU (12% had CRF)
 - *83% of patients were categorised as medical admissions, SOFA score 10*

NUTRIREA-3

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 - 3036 patients randomised and analysed
- Adults receiving IMV + vasopressor support for shock*
- Early feeding (within 24hrs of intubation or ICU admission)

Reignier J, Plantefevre G, Mira J-P et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel group trial. Lancet Respiratory Medicine 2023; 11(7):602-612.

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- Adults receiving IMV + vasopressor support for shock*
- Early feeding (within 24hrs of intubation or ICU admission)
- **Targets for the first 7 days*:**
 - 6kcal/kg/day and 0.2-0.4g/kg/day protein ('low' group) vs. 25kcal/kg/day and 1-1.3g/kg/day (standard care)
- Obese patients fed to BMI of 30.
- Underweight BMI <18.5kg/m² fed to ½ sum of Ideal+ actual body weight

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- Obese patients fed to BMI of 30.
- Underweight BMI <18.5kg/m² fed to ½ sum of Ideal+ actual body weight
- **Target from day 8 onwards:** 30kcal/kg/day +1.2-2g/kg/day protein

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NUTRIREA-3

- 2 primary outcomes:
 - All cause day 90 mortality
 - Time to readiness for ICU discharge:
 - no longer in need of, or at risk of needing IMV
 - no longer in need of, or at risk of needing vasoactive support
 - no agitation or consciousness alteration requiring close monitoring and management and;
 - no severe acute metabolic or haematological disorder requiring close monitoring and management

NUTRIREA-3

- **Methodology:**
 - Allocation: Web-based randomisation, allocated 1:1, permuted blocks of variable sizes.
 - Blinding: No blinding of physicians and nurses to volume of EN/TPN feedings
 - **Follow-Up:**
 - No LTF.
 - All cause 90 day mortality: (absolute difference -1.6%; 95% CI -5% to 2%), $P=0.41$
 - Time to ICU-discharge readiness: 8 days (5-14) in low group vs. 9 days (5-17) in standard group (HR 1.12; 95% CI 1.02 to 1.22, $P=0.015$)

Reignier J, Planteveve G, Mira J-P et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel group trial. *Lancet Respiratory Medicine* 2023; 11(7):602-612.

NUTRIREA-3 – primary/secondary outcomes

663 Table 3: Outcomes

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	Low group (n=1521)	Standard group (n=1515)	Absolute difference (95% CI)	Hazard Ratio (95% CI)	p value
Primary outcomes					
Day-90 mortality, n patients/total (%)	628/1521 (41.3)	648/1515 (42.8)	-1.5 [-5.0 to 2.0]		0.41
Time to ICU-discharge readiness, median [IQR] ^a	8.0 [5.0–14.0]	9.0 [5.0–17.0]		1.12 [1.02–1.22]	0.015
Secondary outcomes					
Day-28 mortality, n patients/total (%)	504/1519 (33.2)	533/1515 (35.2)	-2.0 [-5.4 to 1.4]		0.24
ICU mortality, cumulative incidence, %	29.6	32.7		0.89 [0.78–1.00]	0.051
Hospital mortality, cumulative incidence, %	32.2	34.5		0.93 [0.83–1.05]	0.24
ICU length of stay ^b , days, median [IQR]	9 [5–15]	10 [6–17]			
Acute-care hospital length of stay ^b , days, median [IQR]	21 [12–38]	22 [14–39]			
Time to weaning from vasopressor support, days, median [IQR]	3.0 [2.0–4.0]	3 [2.0–4.0]		1.07 [0.99–1.15]	0.054
Time to MV weaning, days, median [IQR]	5.0 [2.0–11.0]	6.0 [3.0–12.5]		1.12 [1.03–1.22]	0.007
Received dialysis, cumulative incidence, %	30.1	31.9		0.93 [0.82–1.05]	0.25
Infections, cumulative incidence, %					
ICU infection ^c	15.3	17.5		0.85 [0.71–1.01]	0.06
VAP	11.2	10.9		0.98 [0.79–1.21]	0.82
Bacteraemia	4	5.5		0.73 [0.53–1.01]	0.06
CVC infection	1.5	1.9		0.81 [0.48–1.37]	0.44
UTI	0.72	0.77		1.2 [0.54–2.67]	0.66
Soft-tissue infection, n patients	7	5			
Other infection	1.7	2.4		0.78 [0.48–1.28]	0.33
Gastrointestinal events, cumulative incidence, %					
Vomiting	20.2	25.5		0.77 [0.67–0.89]	<0.001
Diarrhoea	28.9	33.3		0.83 [0.73–0.94]	0.004
Constipation	27.8	28.7		0.97 [0.86–1.10]	0.64
Bowel ischaemia	0.9	1.8		0.50 [0.26–0.95]	0.03
Acute colonic pseudo-obstruction, n patients	8	2			
Liver dysfunction^d, cumulative incidence, %	61.7	65.8		0.92 [0.86–0.99]	0.032

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NUTRIREA-3

	Low group (n=1521)	Standard group (n=1515)	Hazard Ratio (95% CI)	p value
Clinical management				
Intubation to feeding (h), median [IQR]	16.7 [10.6–21.6]	17.0 [10.8–21.8]		
Feeding route, n (%)				
Patients receiving EN only	932 (61.6)	846 (56.0)		
Patients receiving PN only	358 (23.7)	349 (23.1)		
Patients receiving PN then EN	208 (13.8)	296 (19.6)		
Neither EN nor PN	14 (0.9)	21 (1.4)		
Daily intakes, median [IQR]				
Calories, kcal/kg/24 h ^a	7.4 [5.8–9.5]	22.0 [17.5–24.9]		
Protein, g/kg/d	0.2 [0.2–0.3]	0.9 [0.7–1.0]		
Fluids (L), median [IQR]	11.1 [6.1–16.4]	17.2 [9.7–23.4]		
Gastrointestinal events, cumulative incidence, %				
Vomiting	14.2	21.3	0.64 [0.54–0.76]	<0.001
Prokinetic drug therapy	13.1	20.9	0.60 [0.51–0.72]	<0.001
Constipation ^b	23.8	23.9	0.99 [0.87–1.13]	0.92
Diarrhoea	19.1	22.9	0.81 [0.69–0.95]	0.008
Blood parameters				
Glucose, mmol/L, median [IQR]				
Daily highest	11.6 [9.6–14.5]	13.7 [11.2–17.1]		<0.001
Daily lowest	4.8 [3.9–5.7]	5.0 [4.1–5.8]		0.002
Insulin, cumulative incidence, %	63.1	77.7	0.74 [0.70–0.80]	<0.001
Hypoglycaemia ^c , cumulative incidence, %	6.0	4.9	1.24 [0.91–1.69]	0.17
Lactate, daily highest, g/L, median [IQR]	2.8 [1.8–5.2]	3.0 [2.0–5.6]		0.003
Lactate normalisation, cumulative incidence, % ^d	86.5	84.1	1.09 [1.02–1.16]	0.01
Bilirubin, daily highest, µmol/L, median [IQR]	16.0 [10.0–33.0]	15.0 [10.0–32.0]		0.22
ALAT, daily highest, IU/L, median [IQR]	65 [33–174]	77 [36–218]		0.008
ASAT, daily highest, IU/L, median [IQR]	98 [46–288]	110 [50–345]		0.016
Hypokalaemia, cumulative incidence, % ^e	58.6	58.9	0.97 [0.89–1.06]	0.48
Hypophosphataemia, cumulative incidence, % ^f	53.6	61.3	0.83 [0.76–0.91]	<0.001
Other treatments, cumulative incidence, %				
Prone position	13.4	17.2	0.77 [0.64–0.92]	0.005
Dialysis	26.9	27.2	0.99 [0.86–1.12]	0.82

Reignier J, Plantefevre G, Mira J-P et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel group trial. *Lancet Respiratory Medicine* 2023; 11(7):602-612.

Refeeding related hypophosphatemia

- 13 ICUs across ANZ - 339 patients
 - ~65% medical admissions, APACHE II score 18, 91% mechanically ventilated
 - stratified by BMI and enrolment serum phosphate

Doig GS, Simpson F, Heighes PT, Bellomo R et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. Lancet Respiratory Medicine Dec 2015 3(12):943-52.

Refeeding related hypophosphatemia

- Adult patients who had a phosphate drop of at least 0.16mmoles/L to <0.65mmoles/L within 72hrs of feeding to receive pragmatic standard nutrition support vs. protocolised Caloric restriction
 - standardised phosphate management protocol

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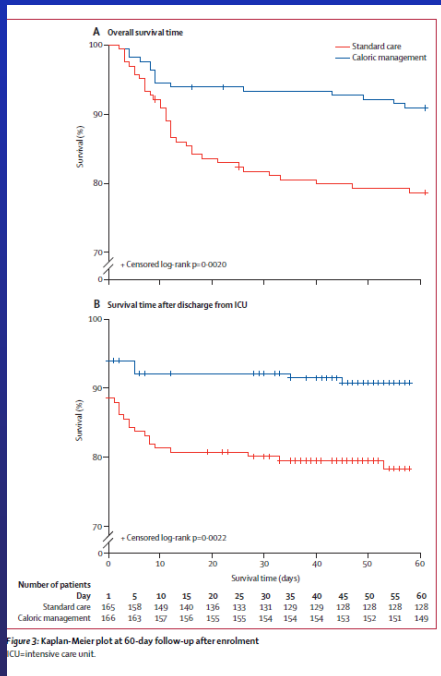
- Adult patients who had a phosphate drop of at least 0.16mmoles/L to <0.65mmoles/L within 72hrs of feeding to receive pragmatic standard nutrition support vs. protocolised Caloric restriction
 - standardised phosphate management protocol

Caloric management protocol:

- 20kcal/hr for at least 48 hours
- If >0.71mmoles phosphate then:
 - slow return to normal (40kcal/24h, 60kcal/24h, 80% goals for 24hrs then goal – IF no further phosphate drops

Refeeding related hypophosphatemia

- Primary outcome: number of days alive after ICU discharge at day 60 (P=0.19)
 - more patients alive at Day 60 (P=0.002) and;
 - overall survival time was increased (P=0.002) but
 - increased HLOS (21.7 days vs 27.9 days, P=0.003)



Doig GS, Simpson F, Heighes PT, Bellomo R et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. Lancet Respiratory Medicine Dec 2015 3(12):943-52.

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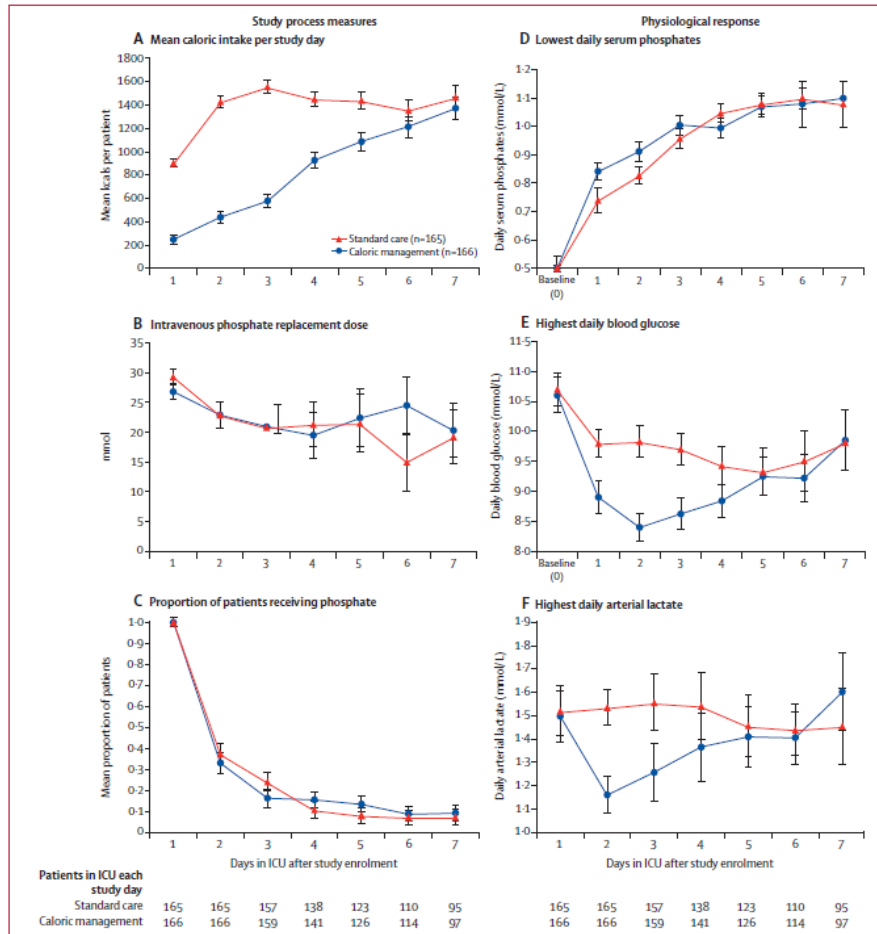


Figure 2: Study process measures and physiological responses in patients. Error bars show 95% CIs for mean differences between groups at each timepoint. ICU=intensive care unit.

	Standard care (n=165 patients)	Caloric management (n=166 patients)	Risk difference (95% CI)	p value
Vital status (% alive)				
ICU discharge status	150/165 (91%)	157/166 (95%)	3.7% (-5.3 to 12.7)	0.20
Hospital discharge status	135/165 (82%)	151/166 (91%)	9.2% (0.7 to 17.7)	0.017
Day 60 status	128/163 (79%)*	149/164 (91%)*	12.3% (3.9 to 20.7)	0.002
Day 90 status	128/163 (79%)*	143/164 (87%)*	8.7% (0.04 to 17.0)	0.041
Length of stay (days)				
ICU	10.0 (9.2 to 10.9)	11.4 (10.5 to 12.4)	1.4 (-0.42 to 3.5)	0.14
Hospital	21.7 (20.0 to 23.5)	27.9 (25.7 to 30.3)	6.2 (2.0 to 11.2)	0.003
Quality of life and physical function scores† (n responses available for analysis)				
RAND-36 general health	53.4 (22.6; n=124/128)	46.0 (26.0; n=136/143)	-7.5 (-13.4 to -1.5)	0.014
ECOG performance status	1.3 (1.0; n=125/128)	1.5 (1.1; n=135/143)	0.18 (-0.08 to 0.43)	0.18
RAND-36 physical function	47.3 (35.0; n=123/128)	40.9 (33.4; n=135/143)	-6.4 (-14.8 to 2.0)	0.13

Data are n/N (%), mean (95% CI), and mean (SD), unless otherwise stated. ICU=intensive care unit. RAND=the RAND Corporation.† ECOG=Eastern Collaborative Oncology Group. *Four patients could not be contacted after hospital discharge (two in the standard care and two in the caloric management group). †Reported by survivors at day 90 interview.

Table 2: Vital status, length of stay, and quality of life interviews

	Standard care (165 patients)	Caloric management (166 patients)	Risk difference (95% CI)	p value
Catheter*	4 (2%)	4 (2%)	0.0% (-10.7 to 10.7)	1.00
Catheter tip*	4 (2%)	4 (2%)	0.0% (-10.7 to 10.7)	1.00
Surgical wound	4 (2%)	1 (0.6%)	-1.8% (-12.5 to 8.9)	0.21
Bloodstream	8 (5%)	2 (1%)	-3.6% (-7.1 to 0.0)	0.06
Abdominal	1 (0.6%)	0	-0.6% (-1.8 to 0.6)	0.50
Clinically significant UTI†	1 (0.6%)	0	-0.6% (-1.8 to 0.6)	0.50
Airway or lung†	52 (32%)	35 (21%)	-10.4% (-19.8 to -1.1)	0.0342
CPS probable pneumonia	34 (21%)	25 (15%)	-5.5% (-13.8 to 2.7)	0.20
CPS confirmed pneumonia	22 (13%)	14 (8%)	-4.9% (-11.6 to 1.2)	0.16
Any major infection¶	27 (16%)	13 (8%)	-8.5% (-15.5 to -1.6)	0.0187

Data are n (%), unless otherwise stated. UTI=urinary tract infection. CPS=clinical pulmonary infection score. *Venous or arterial catheters. †New or worsening infiltrates and consolidation plus positive respiratory tract culture of likely pathogen sampled on the day of, day before, or day after onset of new or worsening infiltrates and consolidation. ‡CPS ≥6 plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic bronchoalveolar lavage fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72 h after starting a new antibiotic regimen. §CPS ≥6 (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable causative agent from an uncontaminated specimen (ie, blood, pleural fluid, transstracheal aspirate, or transthoracic aspirate); from respiratory secretions of a likely pathogen that does not colonise the upper airways (eg, Mycobacterium tuberculosis, Legionella species, influenza virus, or Pseudomonas aeruginosa); of a possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, bronchoalveolar lavage, or protected specimen brush); or of a positive serology. ¶Attributable excess case mortality >15%.

Table 3: New infections noted in patients after study enrolment

Doig GS, Simpson F, Heighes PT, Bellomo R et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. *Lancet Respiratory Medicine* Dec 2015 3(12):943-52.

PRECISE

- 10 hospitals (Belgian and Dutch).
 - **935 patients randomised. Primarily medical patients**
- Inclusion criteria: Invasive ventilation, expected 3 days or more.
 - Note: Patients with renal failure eligible except if not eligible for dialysis

Bels JLM, Thiessen S, van Gassek RJJ et al. Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator initiated double blind multicentre parallel group randomised controlled trial in Belgium and the Netherlands. The Lancet, 2024: 404:659-69.

PRECISE

- 10 hospitals (Belgian and Dutch).
 - **935 patients randomised.**
- Inclusion criteria: Invasive ventilation, expected 3 days or more.
- Aim: 2.0g/kg/day protein vs 1.3g/kg/day protein +25kcal/kg while in ICU (maximum 90 days)
 - Actual body weight, or fed to BMI 27kg/m²
 - **Actual 1.87g/kg/day vs 1.19g/kg/day and 19kcal/day**

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- Primary outcome: EuroQoL 5 dimension 5-level at 30/90/180 days

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PRECISE

- **Methodology:**
- Web based randomisation, variable block sizes (8,12), stratified by centre
- Blinding of all participants, staff, investigators, outcome assessors, data analysts, DSMB
- Follow-up for primary outcome N=935.
 - 430/465 (92.5%) standard protein (60g/L) vs 419/470 high (89.1%)
high protein arm (100g/L)

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PRECISE

- **Primary outcome:** EQ-5D-5L was lower in the high protein arm (1.87g/kg /day) c/w the standard care (1.19g/kg /day) arm (P=0.031) at 180 days
- In patients allocated to the high protein (1.87g/kg /day) arm:
 - There was a higher incidence of GI intolerance in the higher protein arm (P=0.030)
 - Significantly greater use of prokinetics
 - Significantly longer duration of stay in rehab.
 - Post-hoc analysis showed significantly longer time-to-discharge-alive (P=0.043)
- *72% regarded as medical admissions, APACHE II score 22 (SOFA 10)*

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PRECISE

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- Pre-planned *exploratory analysis* favoured standard EN protein amongst most subgroups for both EQ-5D-5L and mortality

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- Pre-planned *exploratory analysis* favoured standard EN protein amongst most subgroups for both EQ-5D-5L and mortality
 - Use of high protein was most unfavourable in females and patients with a medical admission
 - *No unfavourable effects on patients with AKI or MOF at time of ICU admission (note: admission classification in PRECISE trial vs in EFFORT PROTEIN patients monitored for 7 days for definition of AKI/MOF).*

Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator initiated double blind multicentre parallel group randomised controlled trial in Belgium and the Netherlands. The Lancet, 2024; 404:659-69.

PRECISE

- Authors conclusion:
 - caution is warranted when dosing nutritional protein in critically ill patients. Further research should aim to clarify protein requirements in different subgroups and in different phases of critical illness”.

Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator initiated double blind multicentre parallel group randomised controlled trial in Belgium and the Netherlands. The Lancet, 2024; 404:659-69.

TARGET PROTEIN

- 8 ICUs across ANZ. 3397 patients (ITT) via cRCT
- Two commercially available isocaloric EN feeds with differing protein (100g/L vs 63g/L)
- 3 pre-specified subgroups:
 - Invasive ventilation vs. none
 - >70 years vs. <70 years
 - BMI $\geq 35\text{kg/m}^2$ vs. $< 35\text{kg/m}^2$
- Later added:
 - Patients with AKI vs. without AKI (EFFORT PROTEIN)
- Primary outcome: number of days free of the index hospital and alive at day 90

Summers MJ, Chapple LS, Karahalios A, Bellomo R, Chapman MJ, Ferrie S et al. Augmented enteral provision during critical illness. The TARGET Protein randomized controlled trial. JAMA 2025; 334(4):319-328.

TARGET PROTEIN

- Process measures:
 - EN commenced a median of 19 hrs from ICU admission
 - EN feeding continued for 87hrs (higher protein) vs. 84hrs (usual protein)
 - Median volume of EN delivered/calendar day was 696mls (404-951mls) in higher protein arm vs. 676mls (405-957mls) in usual protein
 - EN all feeding days:
 - 14 (9,19) kcal/kg IBW high protein vs. 14 (8,19) kcal/kg IBW usual protein arm
 - Protein 1.12 (0.71,1.53) g/kg IBW high protein vs. 0.69 (0.4,0.95) usual protein arm

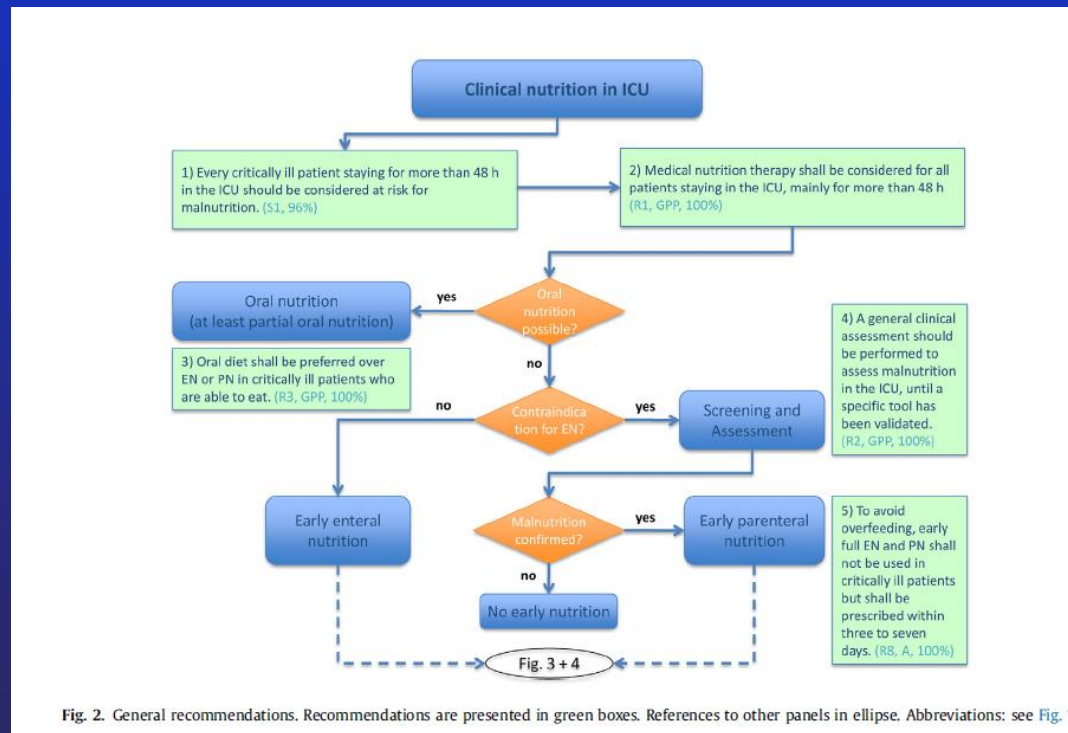
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TARGET PROTEIN

- Primary outcome: number of days free of the index hospital and alive at day 90
 - 62 (0-77) days in high protein vs. 64 (0-77) days, $P=0.46$
- ~64% medical admissions. APACHE II scores 19.

ESPEN - ICU protein requirements

- During critical illness, 1.3g/kg protein/day can be delivered progressively
- Achieve goals progressively and not before 48-72 hours



Singer P, Blaser AR, Berger MM et al. ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clinical Nutrition 2023; 1671-1689.

ASPEN - ICU protein requirements

- ASPEN: “We cannot make new recommendations at this time beyond the 2016 suggestion for 1.2-2.0g/kg/day” protein
- Feed between 12 and 25kcal/kg in the first 7-10 days of ICU stay.

Systematic review and meta-analysis

- 23 RCTs
- 3303 patients
- Search date to 29/5/2023
- Higher (1.49 ± 0.48) vs. lower (0.92 ± 0.30) g/kg/day protein dose did not significantly improve clinical outcomes
 - In the AKI subgroup, higher protein significantly increased mortality (RR 1.42, 95% CI 1.11-1.82, $I^2=0\%$, NNH=7) ³
 - Higher protein delivery also significantly increased serum urea (mean difference 2.31mmoles/L, 95% CI 1.64-2.97, $I^2=0\%$) ⁷

My thoughts

- Higher protein feeding does not appear to improve clinical outcomes

* Doig GS, Simpson F, Heighes et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. Lancet Respiratory Medicine Dec 2015 3(12):943-52.

*Wischmeyer PE, Bear DE, Berger MM et al. 2023. Personalised nutrition therapy in critical care. 10 expert recommendations. Crit Care 27.

* Finfer S, Chittock DR, Su SY et al. Intensive versus conventional glucose control in critically ill patients. NEJM 2009; 360(13):1283-97.

* Adigbli D, Hammond N. 2024. A patient level meta-analysis of intensive glucose control in critically ill adults. NEJM

My thoughts

- Clinical heterogeneity
- Route of nutrition therapy
- Goals vs actual: what was *received*
- Outcomes:
 - Should we be looking at different outcomes
 - Should we be looking at different time points
- Other interventions in combination with nutrition: early mobilisation

* Stoppe C, Hill A, Christopher KB et al. Toward precision in nutrition therapy. CCM 2025; 53(2) e429-440.

* McClave SA, Miller KR, Martindale RG. Elusive guidance to dosing of protein in critical illness. Curr Op Crit Care 2025; 31: 379-386.

My thoughts

- Individualised nutrition therapy
 - ‘Start low go slow’ – NUTRIREA-3/‘Refeeding’
 - Urea
 - Phosphate 😊
 - Blood glucose levels (NICE-SUGAR)
 - Lactate levels
 - Adjust protein feeding if not for RRT
 - Continually reassess the patient

* Doig GS, Simpson F, Heighes et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. Lancet Respiratory Medicine Dec 2015 3(12):943-52.

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Questions?

Post-hoc subgroup analysis of Nephro-protect study.

- Nephro-protect Study:
- Multicentre 16 hospital, ANZ RCT.
- Adult critically ill patients expected to stay >2 days
- Daily supplement of up to 100g IV amino acids to achieve a total protein intake of 2g/kg/day or standard care.
- Primary outcome was duration of renal dysfunction in ICU (adjusted for time at risk)
- 474 patients randomized (235 to standard care, 239 to IV amino acid therapy)

Zhu R, Allingstrup MJ, Perner A et al. The effect of IV amino acid supplementation on mortality in ICU patients may be dependent on kidney function: Post hoc subgroup analysis of a multicentre randomized trial. Crit Care Med 2018; 46: 1293-301.

Doig GS, Simpson F, Bellomo R et al. Intravenous amino acid therapy for kidney function in critically ill patients: A randomized controlled trial. Intensive Care Med 2015; 41:1197-1208.

Post-hoc subgroup analysis of Nephro-protect study.

- Nephro-protect Methodology:
- Centralised randomisation via Webserver
- Blocks of variable sizes with random seeds
- Stratified within site by BMI and high risk of renal dysfunction (APACHE II variable, creatinine increase over the previous 24h by at least 20% to over 120 micromoles/L)
- Intervention was not blinded

Zhu R, Allingstrup MJ, Perner A et al. The effect of IV amino acid supplementation on mortality in ICU patients may be dependent on kidney function: Post hoc subgroup analysis of a multicentre randomized trial. Crit Care Med 2018; 46: 1293-301.

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Post-hoc subgroup analysis of Nephro-protect study.

- **Nephro-protect primary outcome:**
- Covariate adjusted analysis revealed no difference between groups with regards to duration of renal dysfunction (RR 10.7, 95% CI 0.69-1.64, P=0.78)
- Amino acid arm had significantly improved eGFR (treatment group x time interaction, P=0.004)
- Amino acid arm had significantly increased daily urine output (+300ml/day, 95% CI 145-455ml/day, P=0.0002)

Zhu R, Allingstrup MJ, Perner A et al. The effect of IV amino acid supplementation on mortality in ICU patients may be dependent on kidney function: Post hoc subgroup analysis of a multicentre randomized trial. Crit Care Med 2018; 46: 1293-301.

Doig GS, Simpson F, Bellomo R et al. Intravenous amino acid therapy for kidney function in critically ill patients: A randomized controlled trial. Intensive Care Med 2015; 41:1197-1208.

Post-hoc subgroup analysis of Nephro-protect study.

- **Post-hoc subgroup analysis:**
- There was a significant interaction between baseline kidney function and supplementation with amino acids (p value for interaction =0.026).
 - Subgroup of patients with normal kidney function at randomization: study amino acid group were less likely to die before study day 90 (Covariate adjusted RD -7.9%, 95% CI -15.1 to -0.7, P=0.034), and in these patients there was an increase in eGFR (repeated measures treatment x time interaction P=0.009)
 - Subgroup of patients with baseline kidney dysfunction, a significant effect on mortality was not found (Covariate adjusted RD -0.6%, 95% CI -16.2 to 15.2, P=0.95),

Zhu R, Allingstrup MJ, Perner A et al. The effect of IV amino acid supplementation on mortality in ICU patients may be dependent on kidney function: Post hoc subgroup analysis of a multicentre randomized trial. Crit Care Med 2018; 46: 1293-301.

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Refeeding related hypophosphatemia

	Standard care (n=165 patients)	Caloric management (n=166 patients)
Age (years)	61 (16)	59 (16)
Sex		
Female	61 (37%)	73 (44%)
Male	104 (63%)	93 (56%)
APACHE II score ²²	18 (6)	18 (6)
Mechanically ventilated	150 (91%)	152 (92%)
BMI (kg/m ²)		
Mean	28 (6.7)	28 (7.3)
<18 kg/m ²	5 (3%)	6 (4%)
SGA		
Musclewasting	13 (0.7)	14 (0.8)
Fat loss	14 (0.7)	15 (0.8)
Risk factors for refeeding-related hypophosphatemia		
Calories per h (EN, PN, and glucose) at time of enrolment (kcal/h)	69 (20)	68 (19)
Total caloric intake (EN, PN, and glucose) 24 h before enrolment (kcal)	1188 (533)	1180 (526)
Days since feeding started in ICU	1.4 (0.7)	1.3 (0.7)
Days in ICU before enrolment	2.4 (1.2)	2.3 (1.2)
Days in hospital before enrolment	4.0 (4.3)	4.0 (4.8)
Serum phosphate at study entry (mmol/L)	0.5 (0.1)	0.5 (0.1)
Serum potassium at study entry (mmol/L)	3.9 (0.5)	3.9 (0.5)
Lowest blood glucose in previous 24 h (mmol/L)	7.4 (1.7)	6.9 (1.5)
Highest blood glucose in previous 24 h (mmol/L)	10.7 (32.8)	10.6 (32.7)
Lowest serum albumin in previous 24 h (g/L)	25.4 (65.8)	25.0 (65.7)
Maximum insulin infusion rate (units per h)	5.6 (4.3)*	5.0 (3.8)†
Semipermanent (surgically placed) feeding tube	11 (7%)	19 (12%)
History of high alcohol intake‡	22 (13%)	18 (11%)
Distal loop diuretic (administered in previous 24 h)	57 (35%)	41 (25%)
Long term or high dose corticosteroids	8 (5%)	9 (5%)
Respiratory alkalosis§	35 (21%)	33 (20%)
Creatinine (µmol/L)	84 (47)	84 (43)
Chronic health states		
Immunocompromised	11 (7%)	13 (8%)
Respiratory disease¶	10 (6%)	9 (5%)
Cardiovascular disease¶	5 (3%)	3 (2%)
Hepatic cirrhosis¶	3 (2%)	6 (4%)
Chronic dialysis¶	0	0
Insulin dependent diabetes	14 (8%)	7 (4%)

(Table 1 continues on next page)

	Standard care (n=165 patients)	Caloric management (n=166 patients)
(Continued from previous page)		
Source of admission to ICU		
Operating room	60 (36%)	57 (34%)
Emergency department	38 (23%)	50 (30%)
Hospital ward	31 (19%)	25 (15%)
Other hospital	30 (18%)	30 (18%)
Transfer from ICU	4 (2%)	4 (2%)
ICU readmission	2 (1%)	0
Admission type		
Medical	105 (64%)	108 (65%)
Emergency surgery	42 (26%)	36 (22%)
Elective surgery	18 (11%)	22 (13%)
APACHE III admission diagnosis ²³		
Respiratory	40 (24%)	51 (31%)
Gastrointestinal	24 (15%)	28 (17%)
Cardiovascular or vascular	29 (18%)	25 (15%)
Sepsis	7 (4%)	10 (6%)
Neurological	30 (18%)	20 (12%)
Trauma	23 (14%)	27 (16%)
Metabolic	6 (4%)	2 (1%)
Haematological	0	0
Orthopaedic surgery	0	0
Renal	1 (0.6%)	0
Other	5 (3%)	3 (2%)
Data are n (%), or mean (SD). APACHE=acute physiology and chronic health evaluation; scores range from 0 to 71; APACHE scores have a significant non-linear relationship with the risk of death (higher scores suggest more severe disease, associated with a higher risk of death); scores greater than 37 have been associated with a greater than 99.9% risk of subsequent death in-hospital. BMI=body-mass index. SGA=subjective global assessment of nutritional status; grades musclewasting and fat loss into four categories: no obvious loss, mild loss, moderate loss, and severe loss. EN=enteral nutrition. PN=parenteral nutrition. ICU=intensive care unit. *Of 61 patients. †Of 51 patients. ‡Defined as five or more standard drinks a day at least three times per week for men, and four or more standard drinks a day at least two times a week for women. §Defined as arterial power of hydrogen (pH) greater than 7.45 and arterial partial pressure of carbon dioxide less than 38 mm of mercury. ¶Defined by APACHE II criteria. ²²		
Table 1: Baseline characteristics		

Doig GS, Simpson F, Heighes PT, Bellomo R et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel group, multicentre, single-blind controlled trial. *Lancet Respiratory Medicine* Dec 2015 3(12):943-52.

Protein in ICU?

- Muscle loss in ICU is substantial
- Protein synthesis is blunted in ICU
- Muscle loss continues post ICU admission
- Loss of muscle is a key driver in intensive care unit acquired weakness (ICUAW)
- ICUAW linked with:
 - physical disability
 - increased health resources
 - increased health care costs

* Herridge MS, Tansey CM, Matte A et al. Functional disability 5 years after acute respiratory distress syndrome. NEJM 2011; 364(14): 1293-304.

* Batt J, Herridge MS, dos Santos CC. From skeletal muscle weakness to functional outcomes following critical illness: A translational biology perspective. Thorax 2019; 74: 1019-1098.