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ESPEN LLL Course
Topic 18 - Nutritional Support in Intensive Care Unit Patients

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Lifelong Learning Programme

Protein Needs and Optimal Administration

Module 18.2

Pierre Singer, MD
Critical Care Department and Institute for Nutrition Research
Rabin Medical Center, Beilinson Hospital
Tel Aviv University, Israel

Learning objectives:

- Protein metabolism in the critically ill
- Higher protein intake increases whole protein content in the body
- What is the best protein intake during the early or late period of the acute phase and in the post acute phase for PICS or rehabilitation
- No strong evidence for high protein administration (more than 1.3 g/kg/d) in ICU patients
- Disease specific protein therapy for trauma, renal or frail and elderly patients

Daily protein turnover in individual organs

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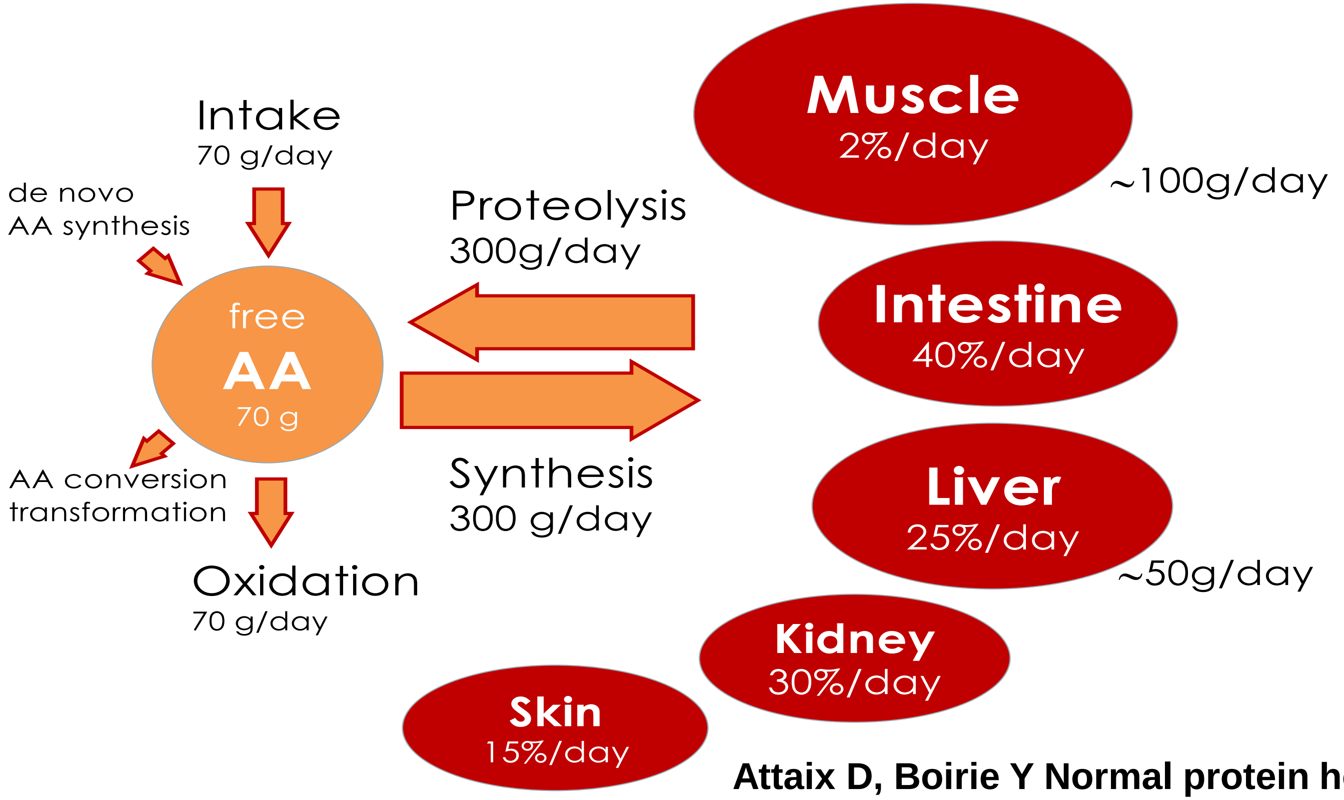
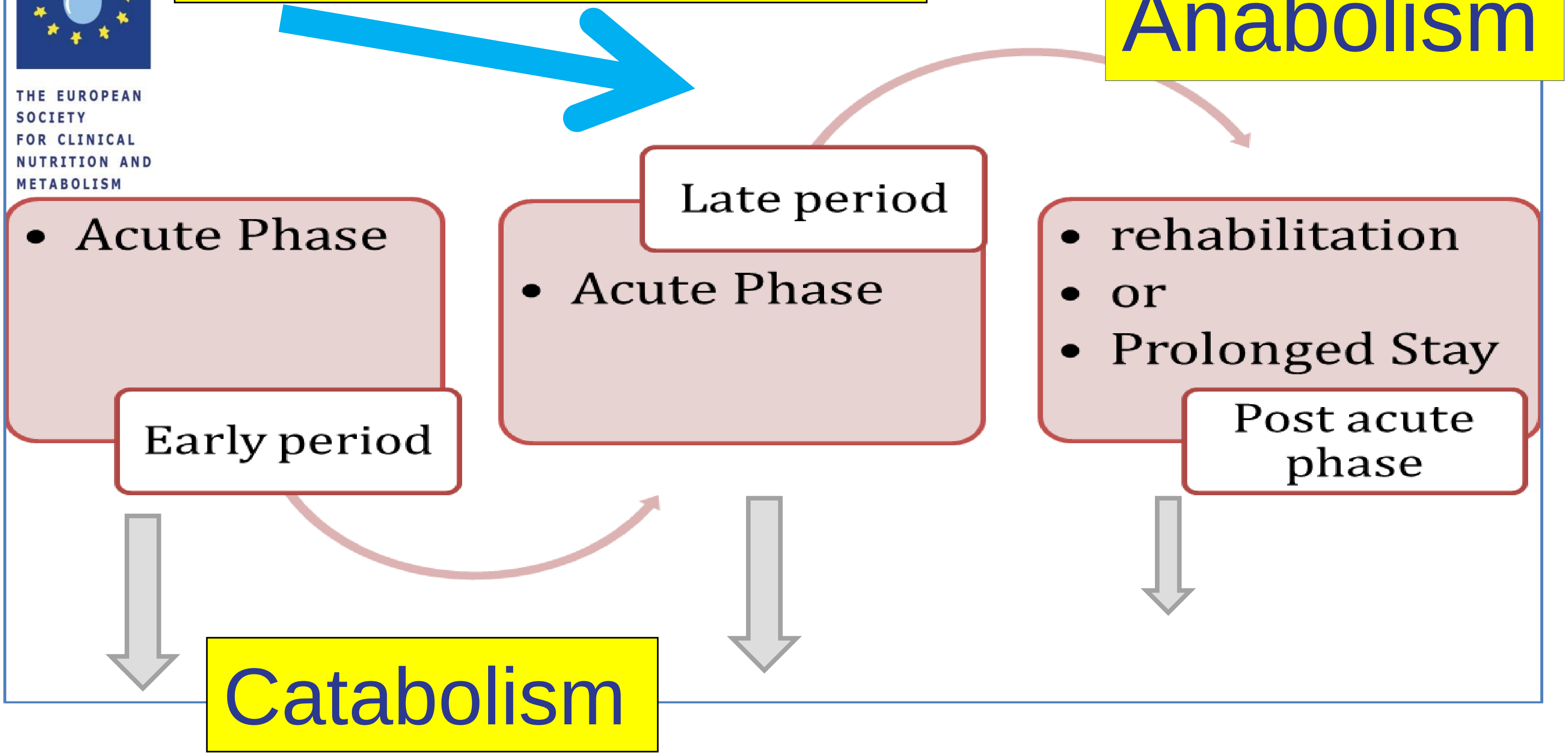


Attaix D, Boirie Y Normal protein homeostasis

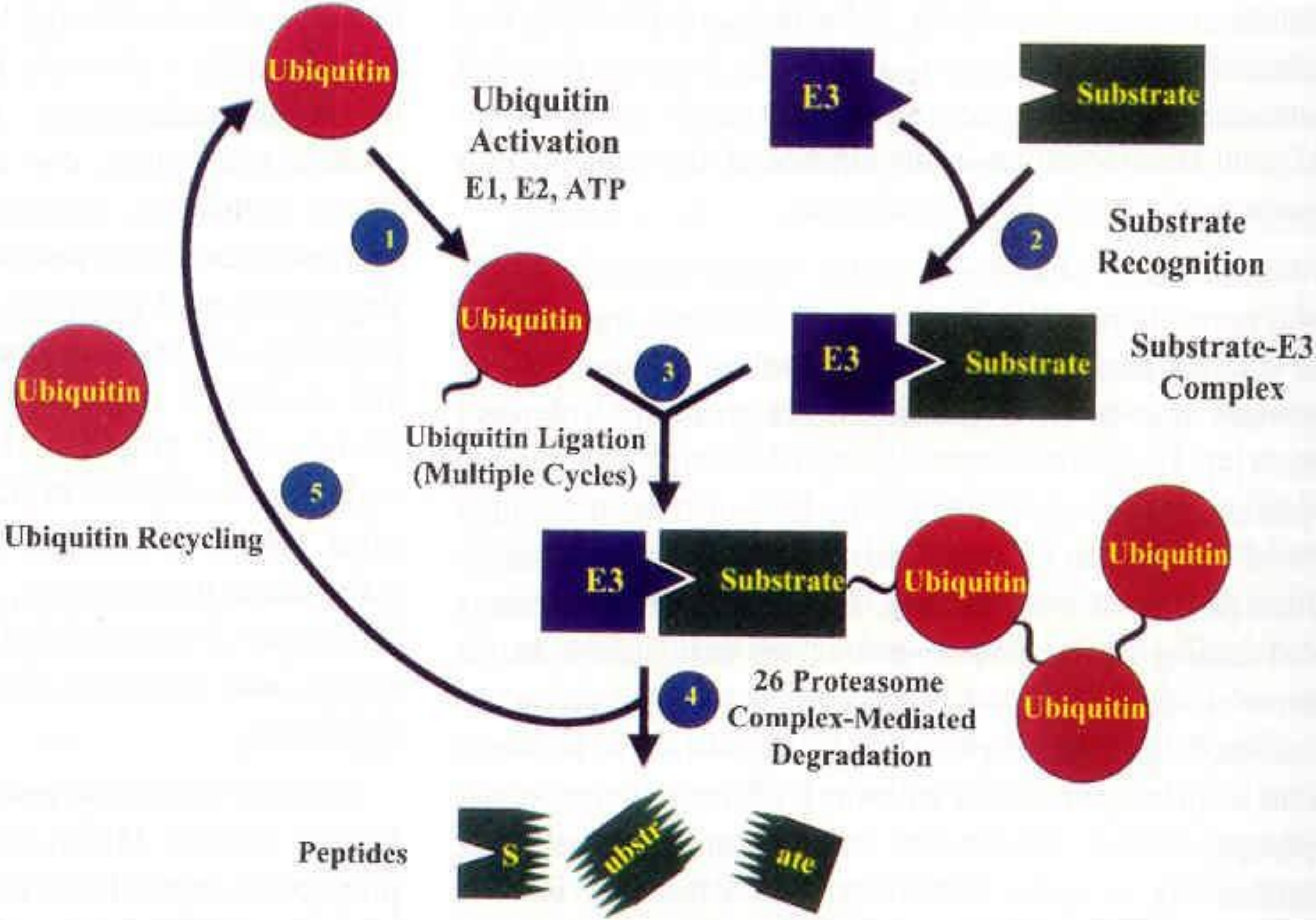
Organs with a large turnover may be susceptible to decreased free amino-acids. Some organs are prioritized in acute illness.

Proteolysis for substrate endogenous production



Singer et al: ESPEN Guidelines: Nutrition in ICU. Clin Nutr 2019

The Ubiquitin Proteolytic Pathway



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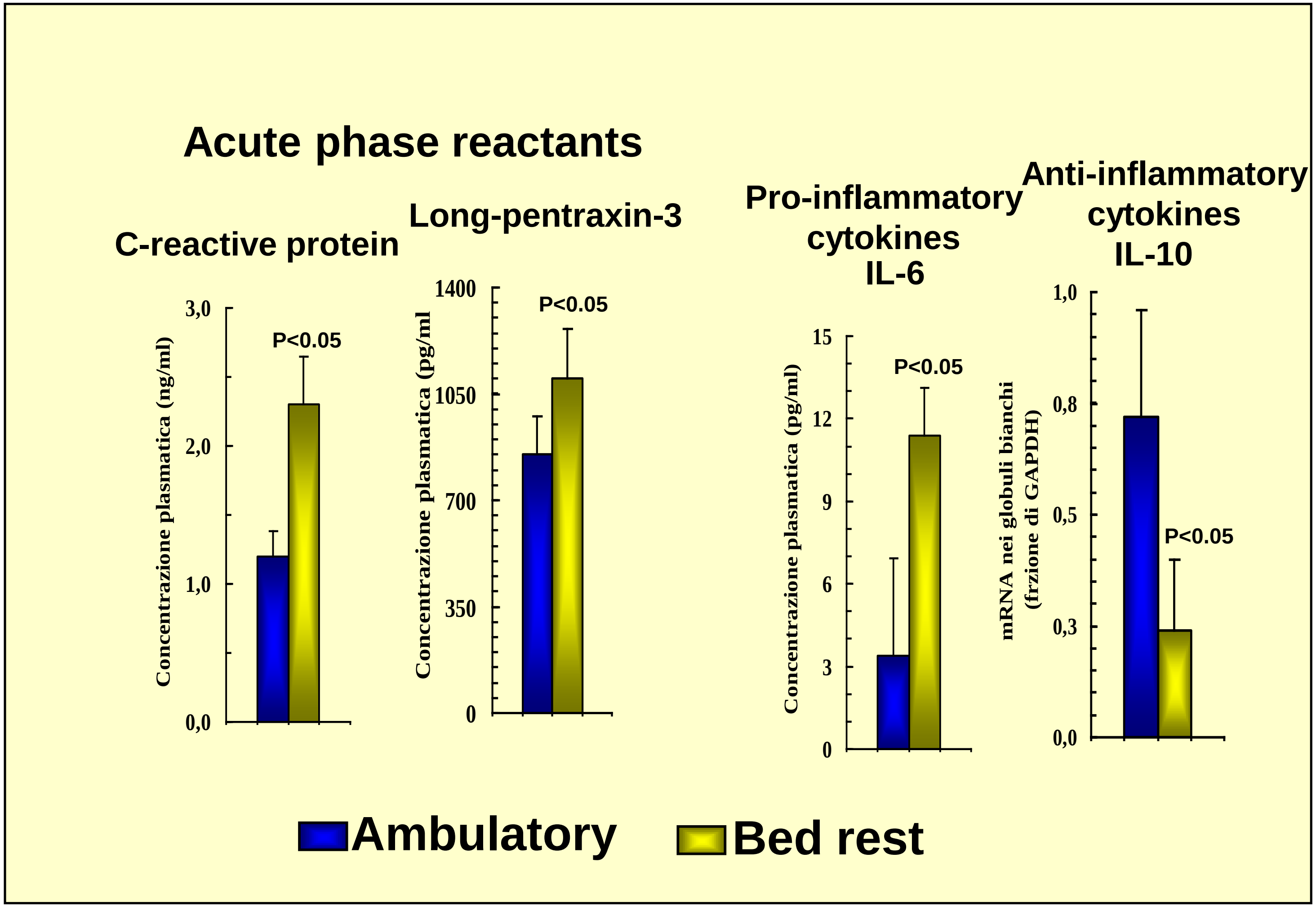
EFFECTS OF 2-WEEK BED REST ON INFLAMMATORY MEDIATORS IN HEALTHY YOUNG VOLUNTEERS



J Clin Endocrinol Metab 2008

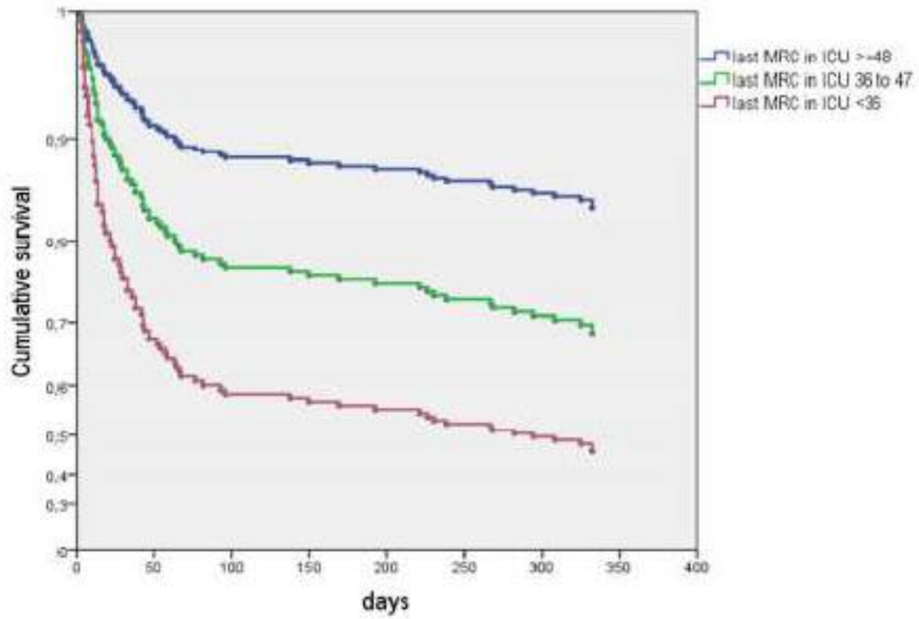
Clinical consequences of protein and muscle loss

Acute Outcomes and 1-Year Mortality of Intensive Care Unit–acquired Weakness

A Cohort Study and Propensity-matched Analysis

Greet Hermans[1,2], Helena Van Mechelen[2], Beatrix Clerckx[2,3], Tine Vanhullebusch[2], Dieter Mesotten[2,3], Alexander Wilmer[1], Michael P. Casaer[2,3], Philippe Meersseman[1], Yves Debaveye[2,3], Sophie Van Cromphaut[2,3], Pieter J. Wouters[2,3], Rik Gosselink[4], and Greet Van den Berghe[2,3]

AJRCCM 2014

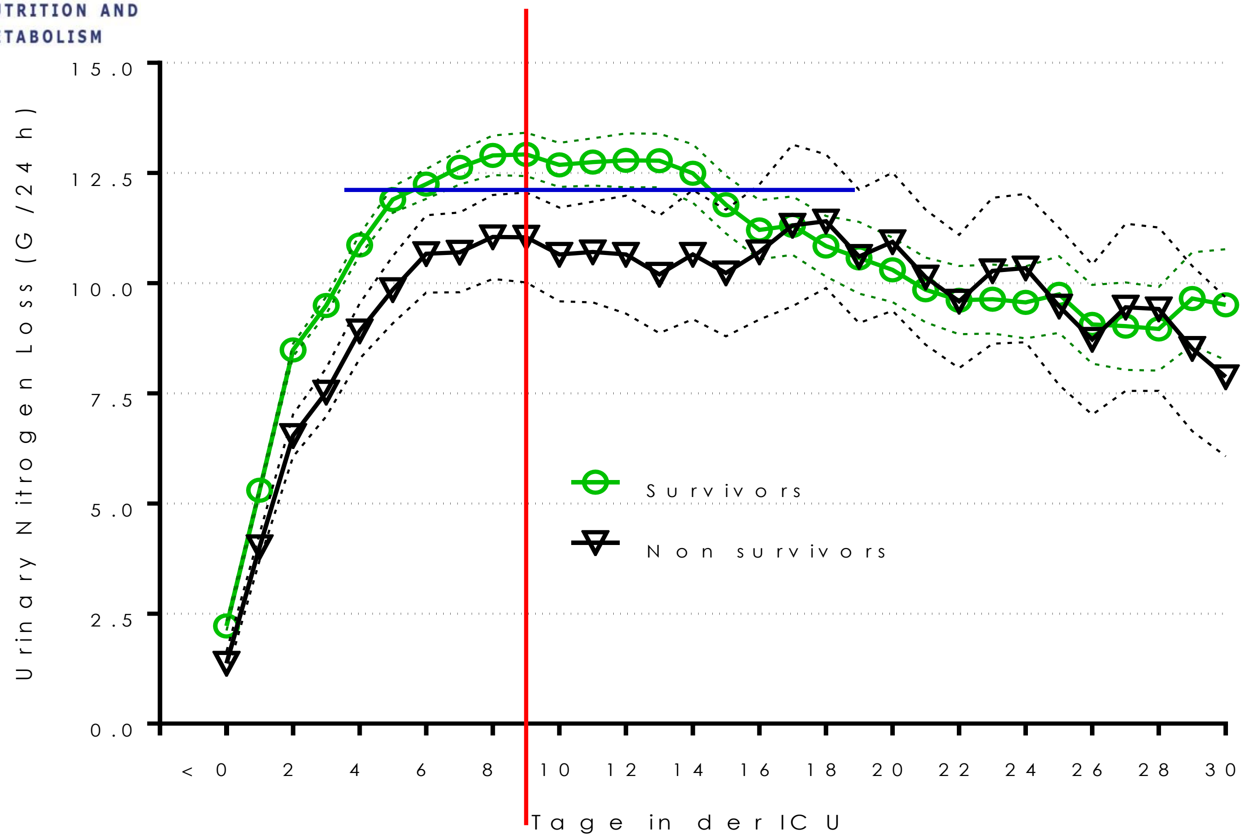


1-year mortality: 31% vs. 17 %; (P = 0.015)

Assessment

- Nitrogen output
- FFM through bioeletrical impedance
- Ultra sound
- CT
- MRI
- Stable isotopes
- Biopsy

Nitrogen Loss



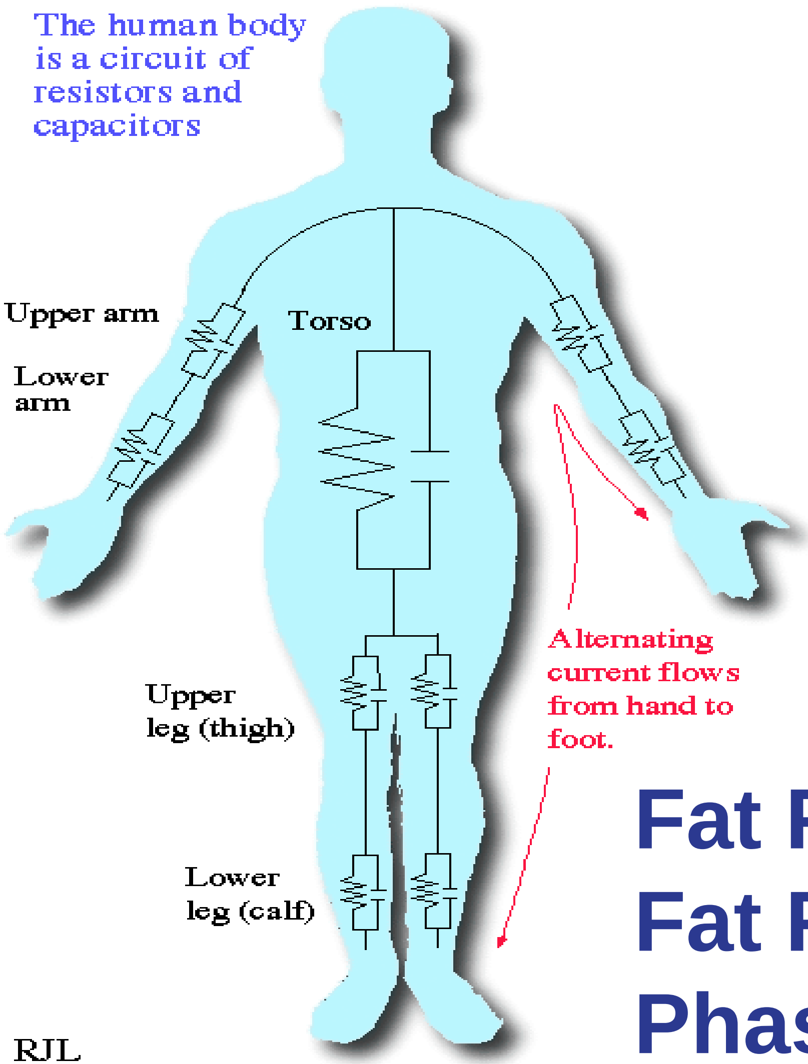
Factors:

- Weight +0.5g/10kg
- Height +0.4g/10cm
- Age- 1.4g 60a - 1.8g 80a
- Gender (f) - 1.2g
- Death - 1.0g
- BMI no effect
- Time in ICU !!!
- **Baseline 12g/day**

N: 5527 2001-2014 Hospital Mortality 8.5% LOS 8 days

From M Hiesmayr

Bioelectrical Analysis



Fat Free Mass
Fat Free Mass Index FFMI
Phase Angle

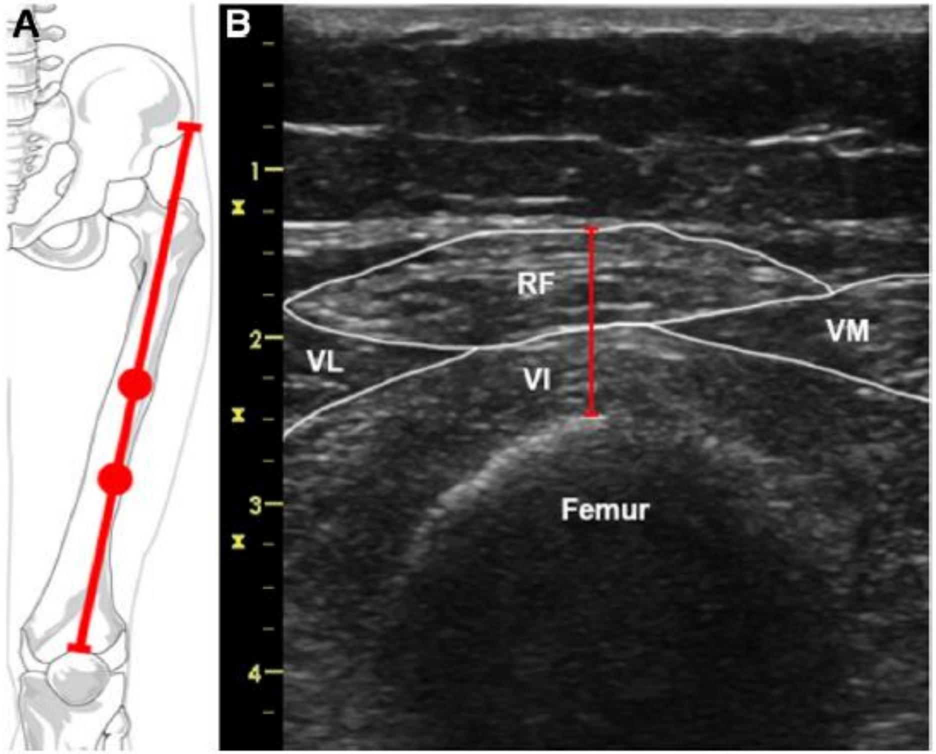


Fig. 1 Ultrasound assessment of the *quadriceps femoris* muscle thickness. **a** Anatomical diagram locating the "midpoint" and the "two-thirds" measurement sites. From *Wikimedia Commons*. **b** Transverse ultrasound section made by linear probe at the midpoint site. RF: *rectus femoris*; VL: *vastus lateralis*; VM: *vastus medialis*; VI: *vastus intermedius*

Pardo *et al. BMC Anesthesiology* (2018) 18:205

Wischmeyer P, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care 2015; 19: S6

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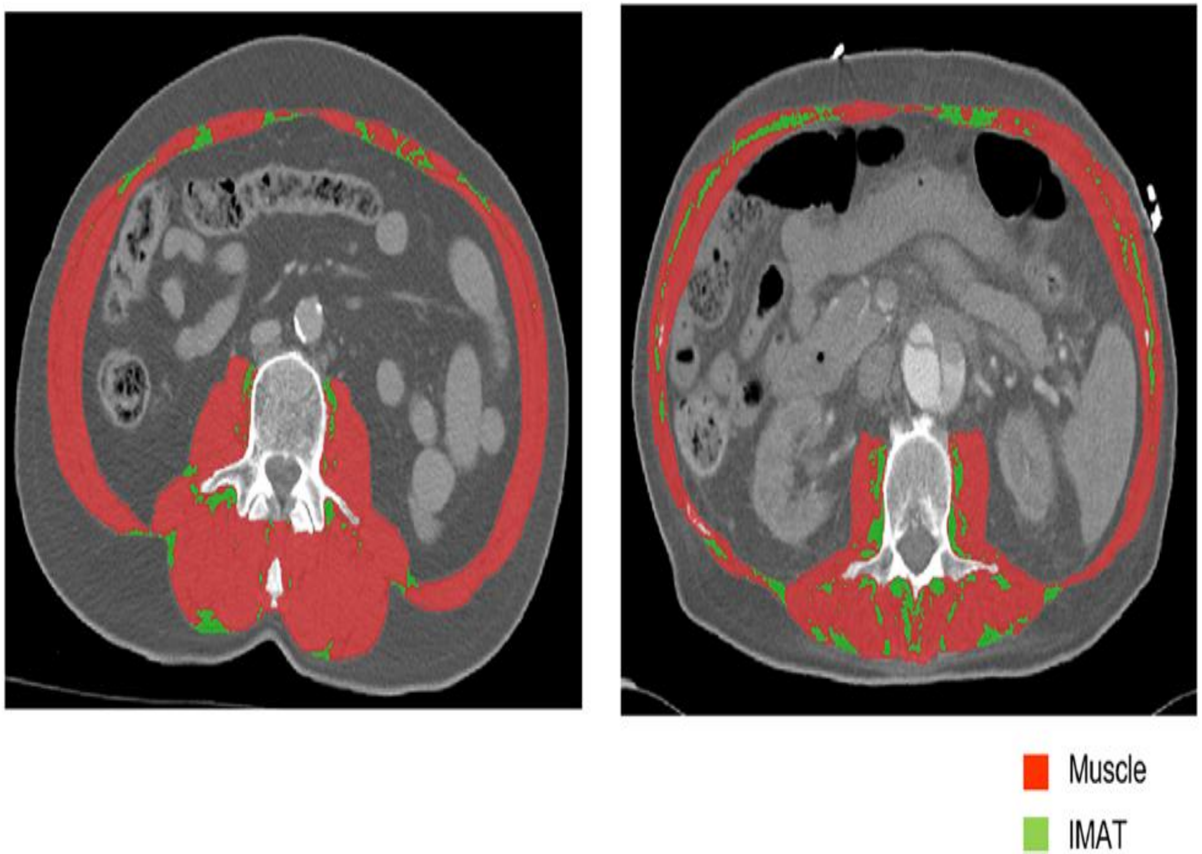
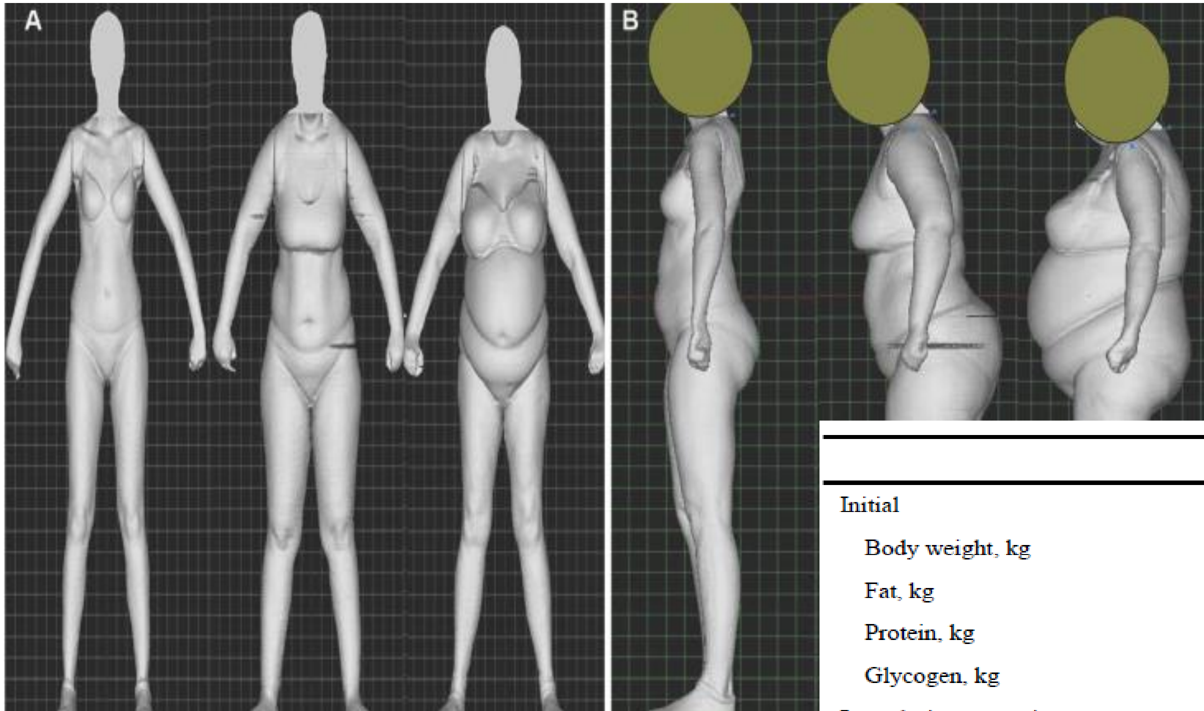


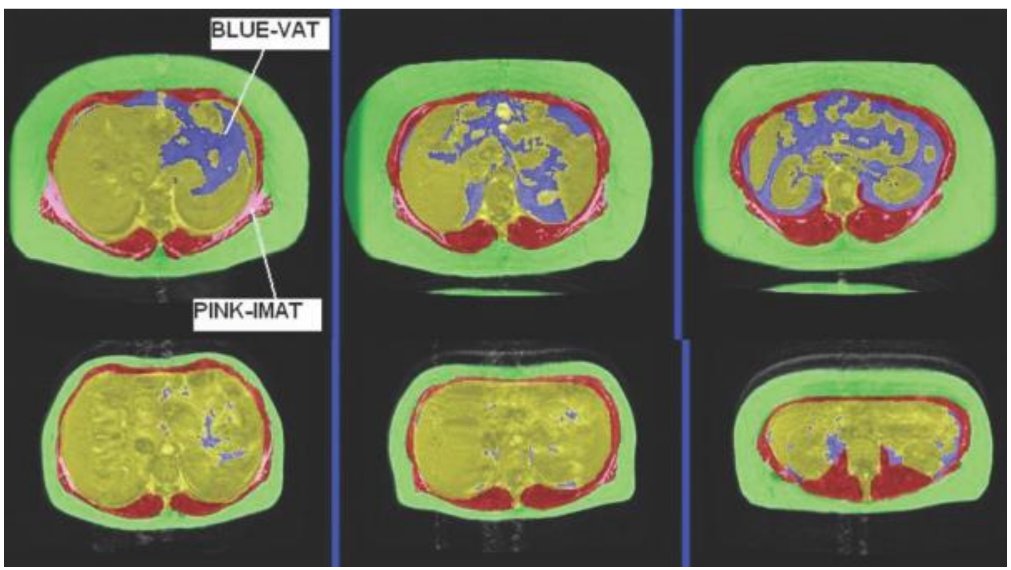
Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients

Looijaard *et al. Critical Care* (2016) 20:386



MRI

Gallagher DeLegge,,
JPEN 2011; 35: 21S



	Lean Man	Obese Man
Initial		
Body weight, kg	70	140
Fat, kg	9.0	61.5
Protein, kg	12.2	15.7
Glycogen, kg	0.3	0.4
Loss during starvation		
Weight (% of initial)	38.0	69.0
Weight, kg	26.6	96.6
Fat, kg[a]	8.0	61.5
Protein, kg[b]	4.6	8.1
Glycogen, kg	0.3	0.4
Available energy during starvation, kcal (%)		
Fat	75,200 (77.6)	568,700 (93.8)
Protein	20,400 (21.1)	36,000 (5.9)
Glycogen	1260 (1.3)	1680 (0.3)
Total	98,860 (100.0)	606,380 (100.0)
Mean daily total energy expenditure, kcal/d[c]	1500	2260
Survival time, d	65	270

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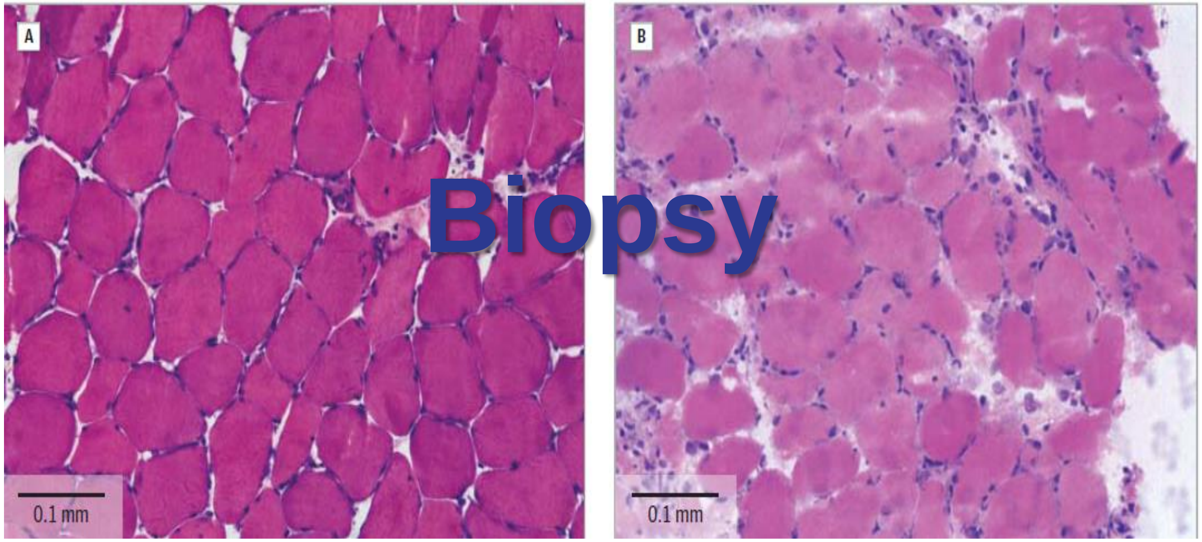
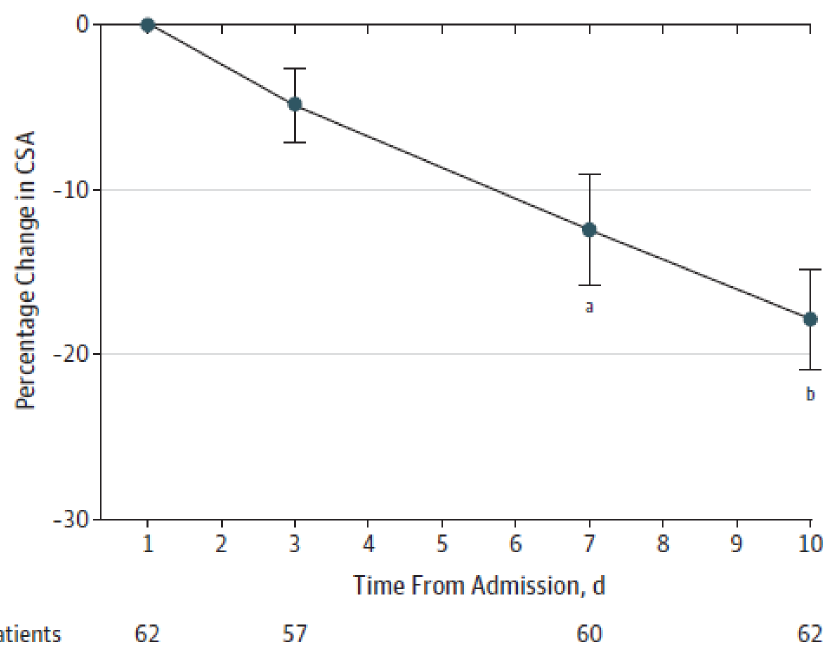


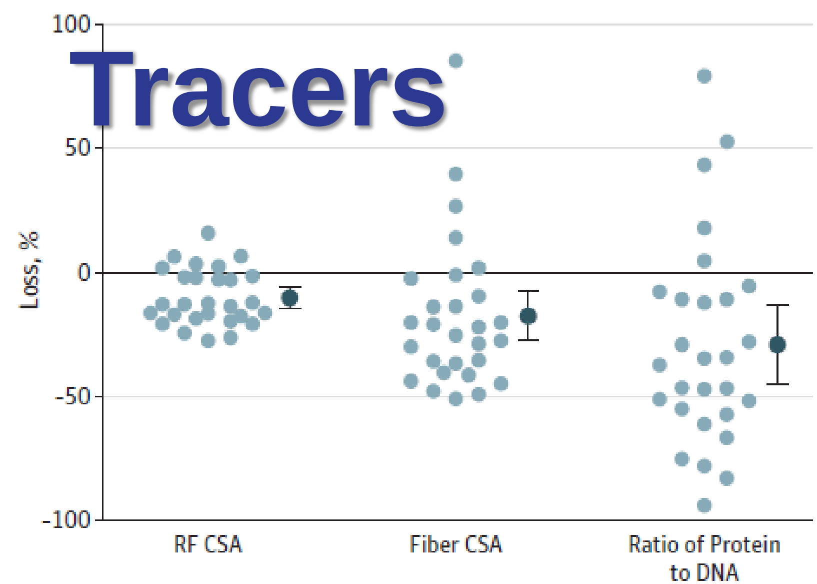
Biopsy

A Change in rectus femoris (RF) cross-sectional area (CSA) over 10 d



B Measures of muscle wasting in patients assessed by all 3 measures on both day 1 and day 7 (n = 28)

Tracers



JAMA. 2013;310(15):1591-1600..

Evidence for protein administration

- Observational studies
- PRCT and meta analysis
- Guidelines

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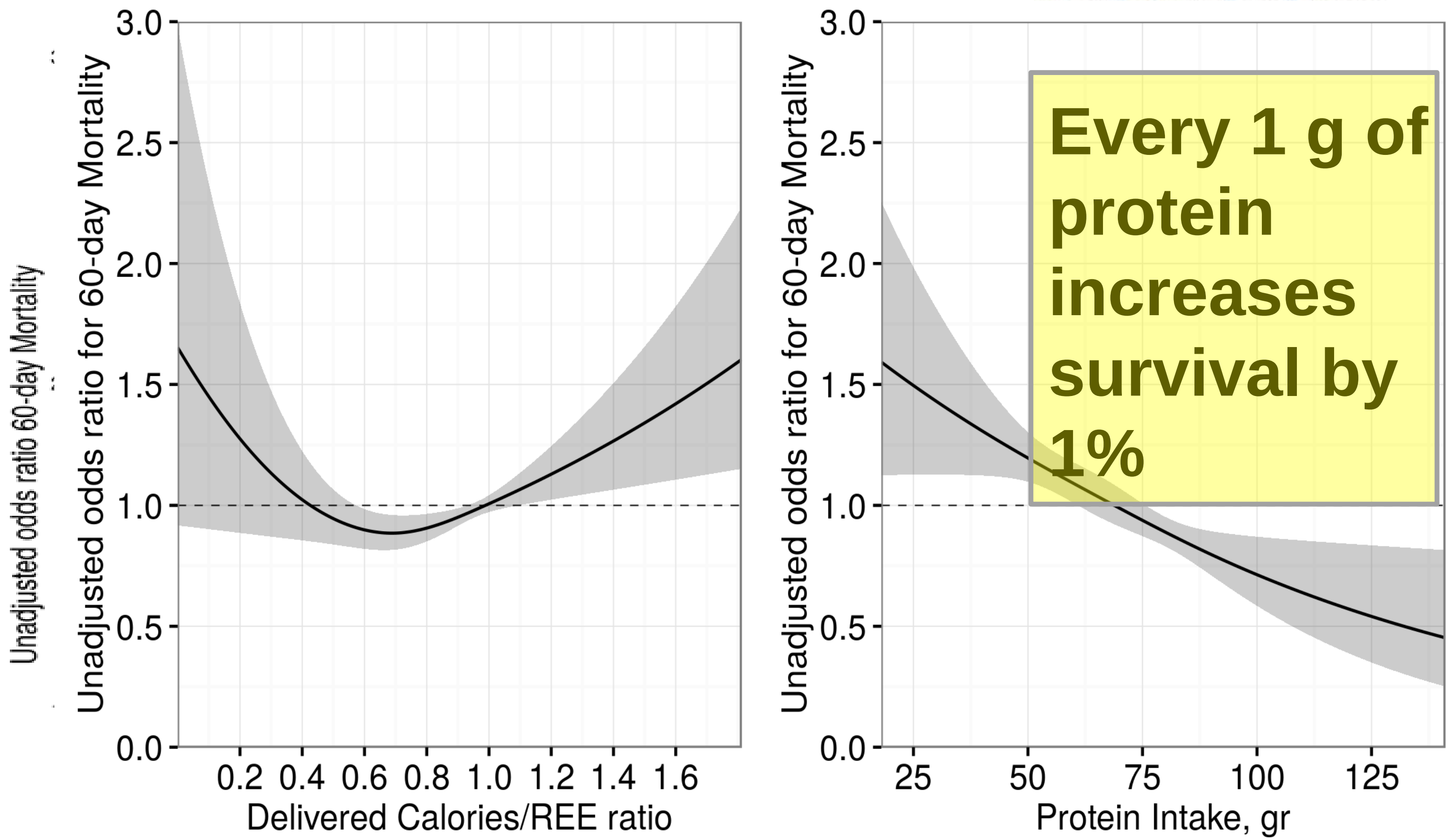

Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study

Oren Zusman[1*], Miriam Theilla[2,3], Jonathan Cohen[2,4], Ilya Kagan[2], Itai Bendavid[2] and Pierre Singer[2,4]

Crit Care 2016

Study or Subgroup	High Dose Events	High Dose Total	Low Dose Events	Low Dose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	0.9%	1.00 [0.07, 13.87]	1985
Rugeles 2013	11	40	12	40	12.5%	0.92 [0.46, 1.83]	2013
Doig 2015	42	236	47	235	42.3%	0.89 [0.61, 1.29]	2015
Ferrie 2016	12	59	9	60	9.6%	1.36 [0.62, 2.98]	2016
Allingstrup 2017	30	100	32	99	34.8%	0.93 [0.61, 1.40]	2017
Total (95% CI)		**445**		**444**	**100.0%**	**0.94 [0.74, 1.21]**	
Total events	96		101				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.93$, df = 4 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 0.46 (P = 0.65)

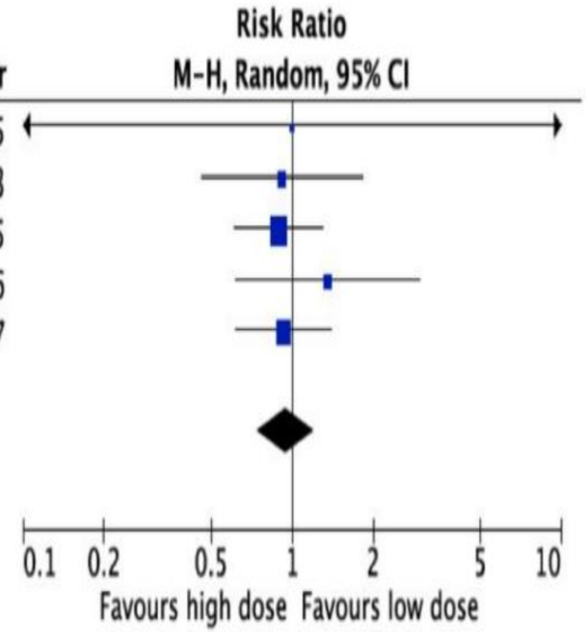

Figure 1. Meta-analysis of five randomized trials of high vs. low dose protein administration in the critically ill: effect on overall mortality.

Should We Prescribe More Protein to Critically Ill Patients?

Nutrients 2018, *10*, 462;

Daren K. Heyland [1,2,3,*], Renee Stapleton [4] and Charlene Compher [5]

What to do to improve outcome and preserve muscles?

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- Give more?

- Give early?

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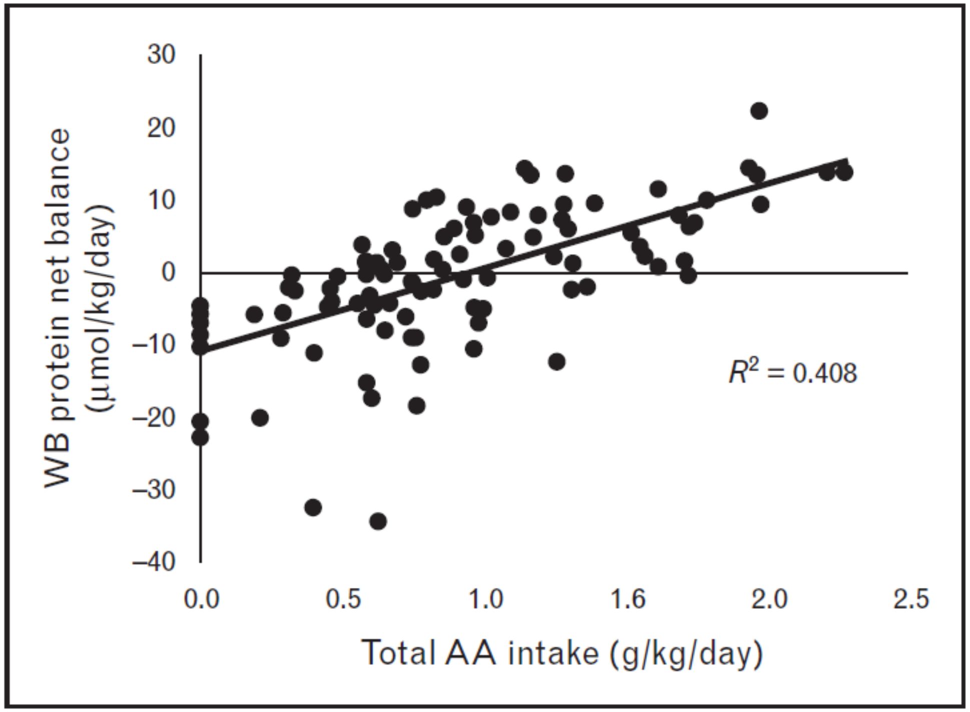


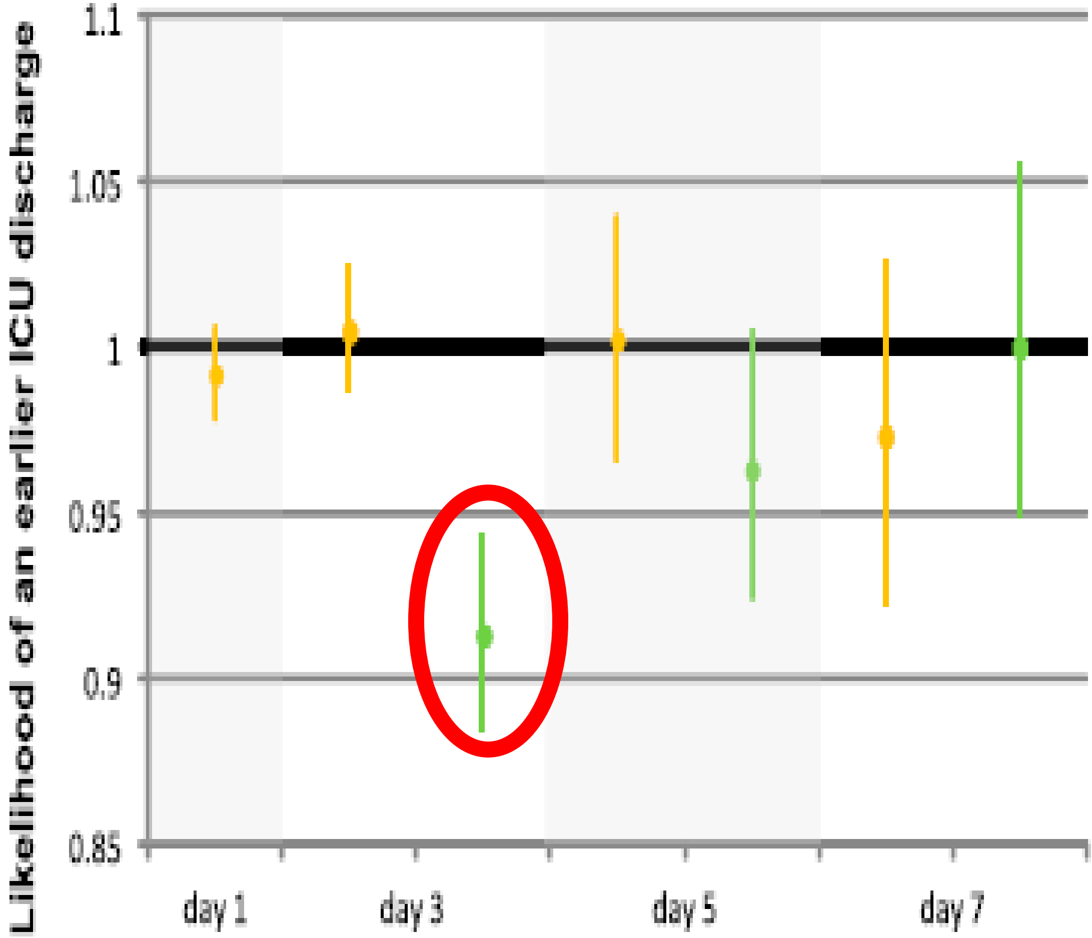
FIGURE 1. Protein balance in relation to amino acid intake in critically ill patients treated in the ICU from four different studies. Whole-body protein balance was measured using isotopically labeled phenylalanine. (Reproduced with

CURRENT OPINION

Does feeding induce maximal stimulation of protein balance?

Felix Liebau, Åke Norberg, and Olav Rooyackers

Casaer, Wilmer, Hermans, *et al.*: Early Nutrition in the ICU: Less Is More



- Increase in mortality?

Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial. A post hoc analysis. Am J Respir Crit Care Med 2013; 187: 247–255.

What is early?

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- The timing: starting during the first 72 hours, regardless of the dose?
- The amount: Early and plenty: up to 1 g/kg/d within 72 hours

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Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study

W.A.C. (Kristine) Koekkoek [a, 1], C.H. (Coralien) van Setten [a, 1], Laura E. Olthof [a], J.C.N. (Hans) Kars [b], Arthur R.H. van Zanten [a, *]

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Clinical Nutrition

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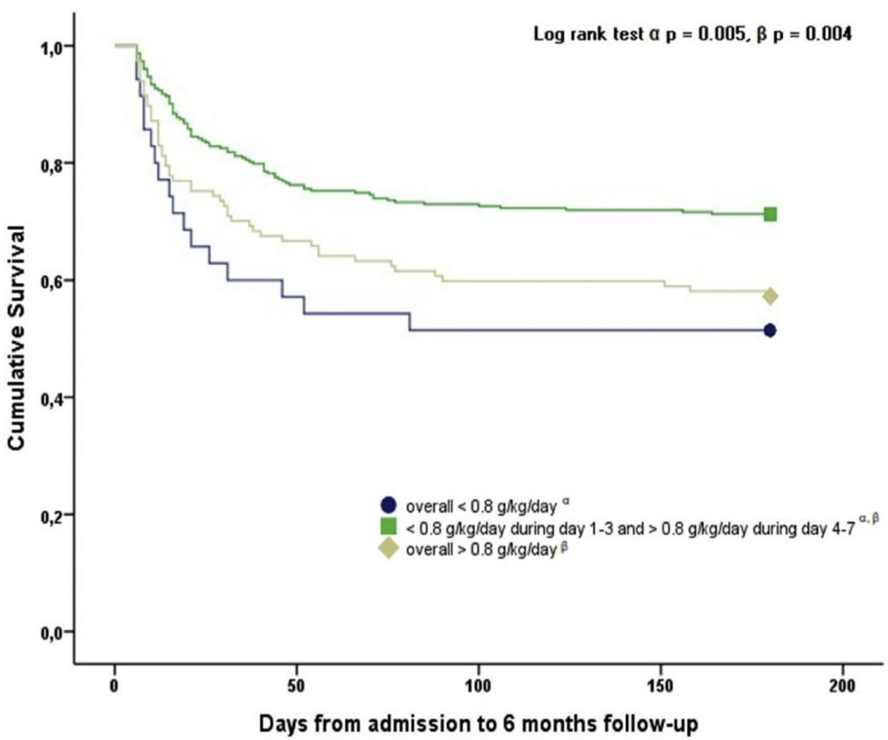
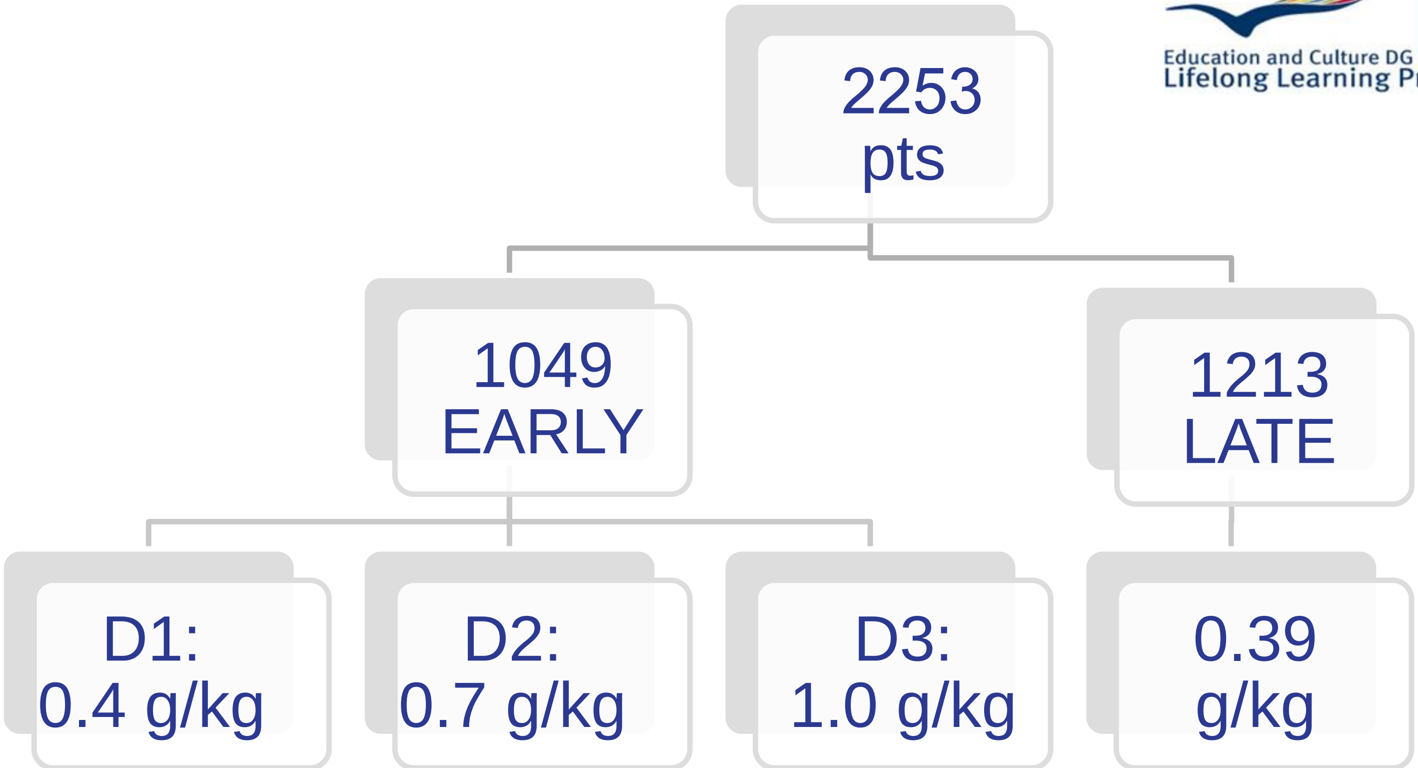
W.A.C. Koekkoek et al. / Clinical Nutrition xxx (2018) 1–8



Cox Proportional Hazard Model Analysis: Average protein intake during day 1–3 and day 4–7 and 6-month mortality comparing protein intake categories.

Average protein intake	N	B	Hazard Ratio	95% CI	p-value
Days 1–3					0.019
$<0.8\ g{*}kg^{-1}{*}day^{-1}$	338	Reference			
$>0.8\ g{*}kg^{-1}{*}day^{-1}$	117	0.208	1.231	1.040–1.457	0.016
Days 4–7					0.008
$<0.8\ g{*}kg^{-1}{*}day^{-1}$	40	0.473	1.605	1.178–2.186	0.003
$0.8–1.2\ g{*}kg^{-1}{*}day^{-1}$	164	−0.335	0.716	0.558–0.917	0.008
$>1.2\ g{*}kg^{-1}{*}day^{-1}$	251	Reference			

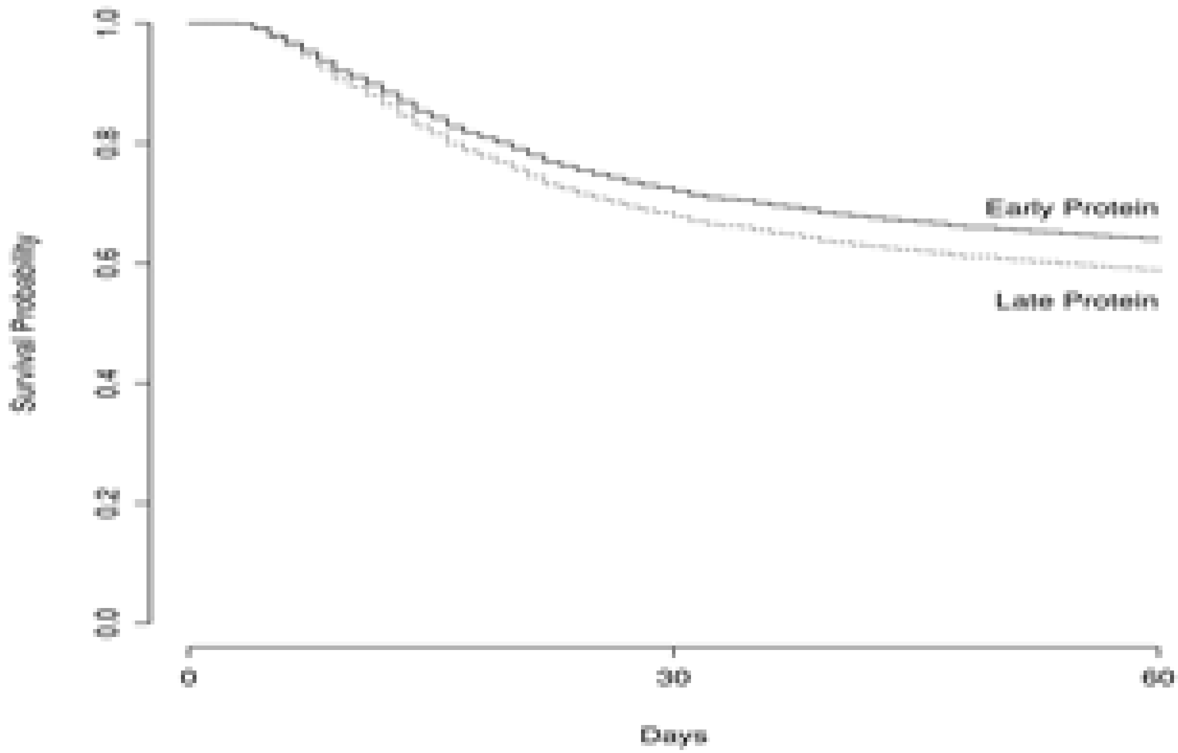


nutrients
MDPI

Article

Early Administration of Protein in Critically Ill Patients: A Retrospective Cohort Study

Itai Bendavid [1,2,*,†], Oren Zusman [2,3,†], Ilya Kagan [1,2], Miriam Theilla [1,4], Jonathan Cohen [1,2] and Pierre Singer [1,2]



60 days mortality: **36% in early** and **43% in late** protein administration ($p<0.001$ for difference) Cox analysis: HR 0.84, 95% CI 0.72- 0.98, $p=0.01$

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High protein intake > 2 g/kg/day Recommended like in cancer, burns, …

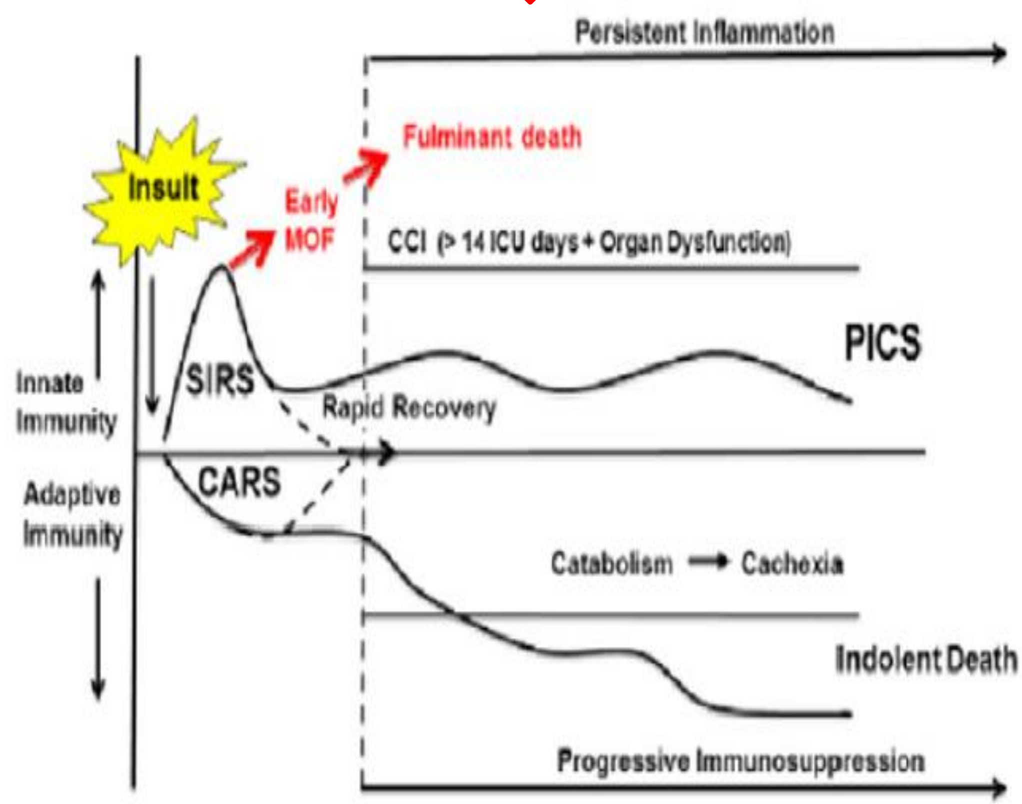

Figure 1

Nutrition Support for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome

Nutr Clin Pract. 2017; 32: 121S–127S

Frederick A. Moore, MD[1], Stuart Phillips, PhD[2], Craig McClain, MD[3], Jayshil J. Patel, MD[4], and Robert Martindale, MD, PhD[5]

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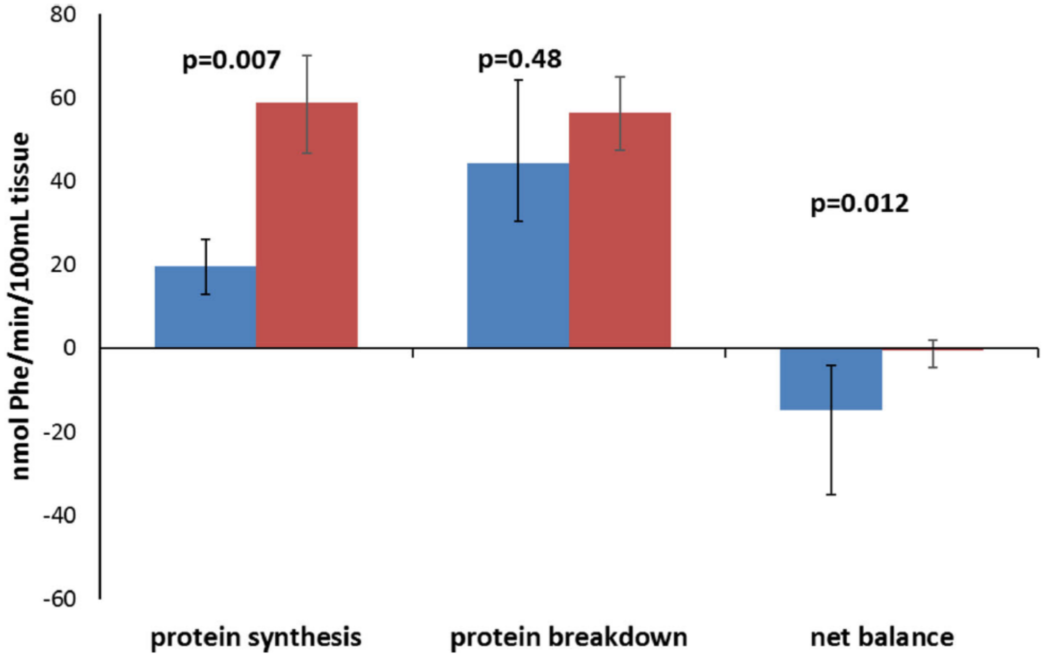

Fig. 2 Skeletal muscle mixed protein turnover in long-staying intensive care unit patients ($n = 20$). Measurements in the period days 10–20 (*blue bars*; $n = 10$) are compared with those in the period days 30–40 (*red bars*; $n = 9$). Data are given as medians (quartiles). The p values are given for nonparametric comparisons between the two time periods

An attenuated rate of leg muscle protein depletion and leg free amino acid efflux over time is seen in ICU long-stayers

Critical Care (2018) 22:13

Lena Gamrin-Gripenberg[1,2], Martin Sundström-Rehal[1,2], Daniel Olsson[3], Jonathan Grip[1,2], Jan Wernerman[1,2] and Olav Rooyackers[1,2*]

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Intermediate conclusions

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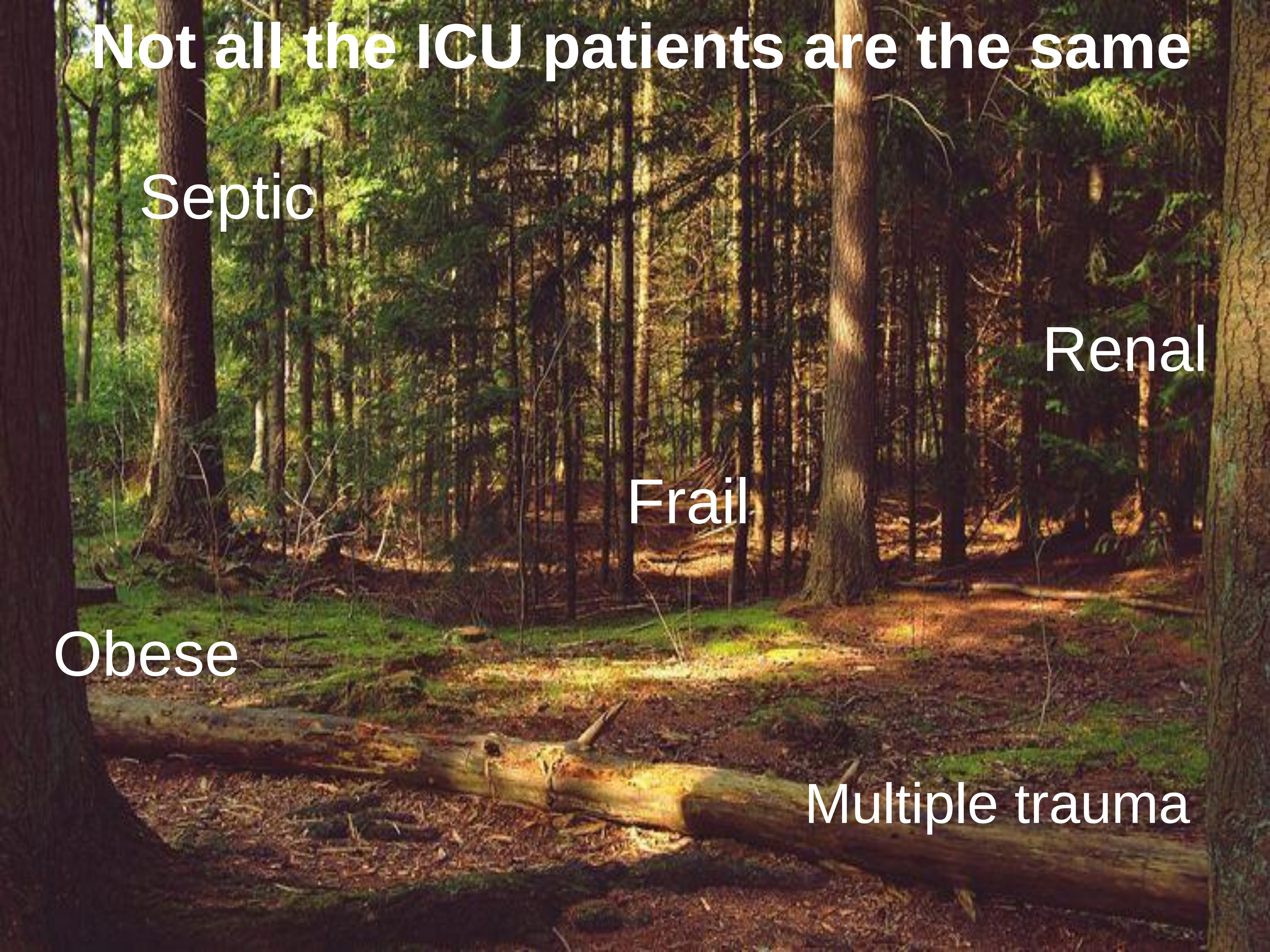
- Most of the patients do not receive enough protein intake
- Early progressive administration of energy AND protein may be beneficial, but remain to be demonstrated
- Late protein administration seems beneficial


Not all the ICU patients are the same
Septic
Renal
Frail
Obese
Multiple trauma

Obese patients

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- Provide 60 – 70% of target energy needs
- At least 2gm/kg ideal body weight of protein
- Pro – improves insulin sensitivity
  - prevents hypercapnea, fluid retention
  - weight loss BUT NOT PRIMARY OBJECTIVE
- Con – higher rates of infection
  - poorer outcomes with negative energy balance
- **ASPEN/SCCM – endorses hypocaloric feeding in obese patients**
- **ESPEN propose to measure IC and N2 excretion to guide medical nutritional therapy**

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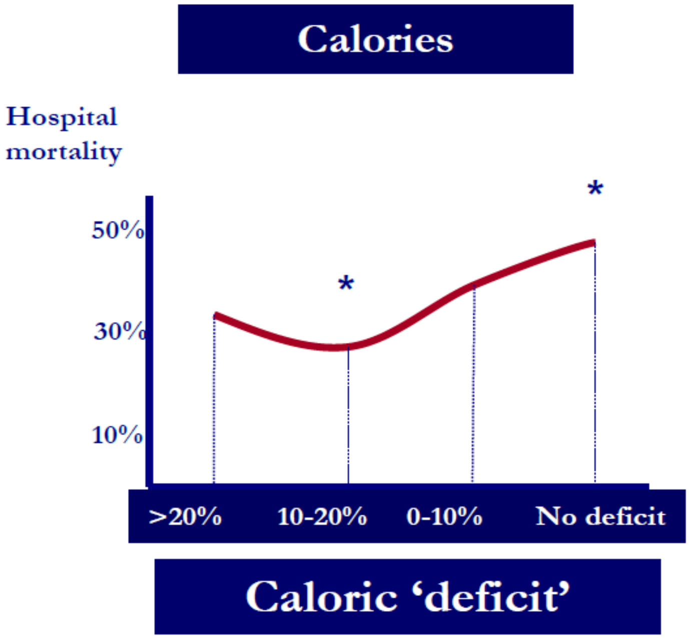
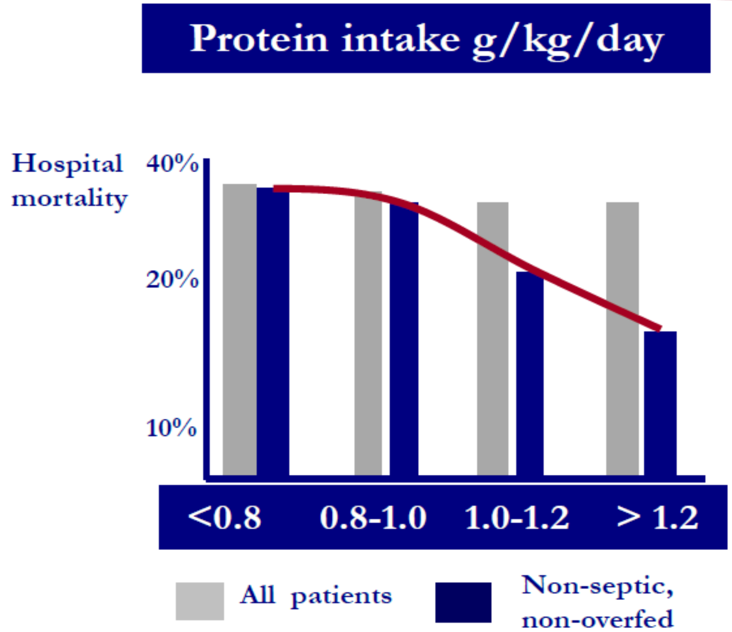
Day 4





More energy **and** *more protein* **had opposite effects**

Weijs P, Looijaard, W, Beishuizen A, Girbes AR, Oudemans-van Staaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care 2014; 18:701

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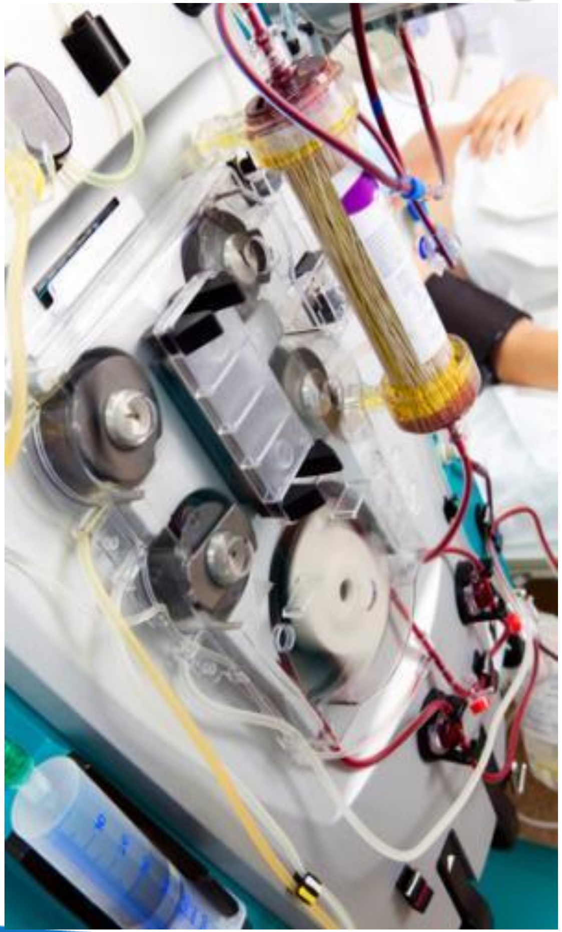
The Acute Kidney Injury patients



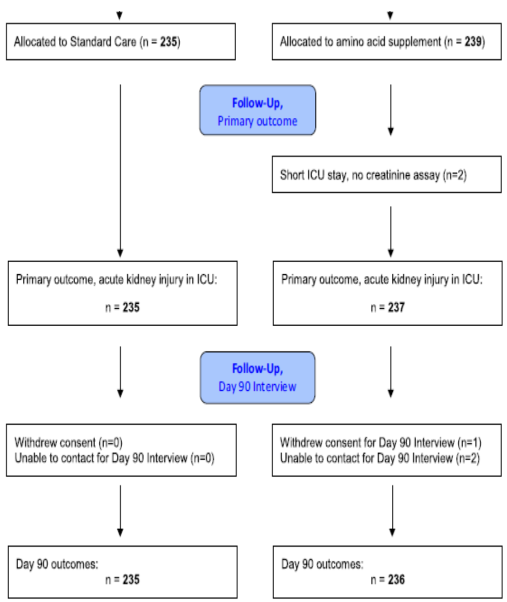
Protein losses during CRRT

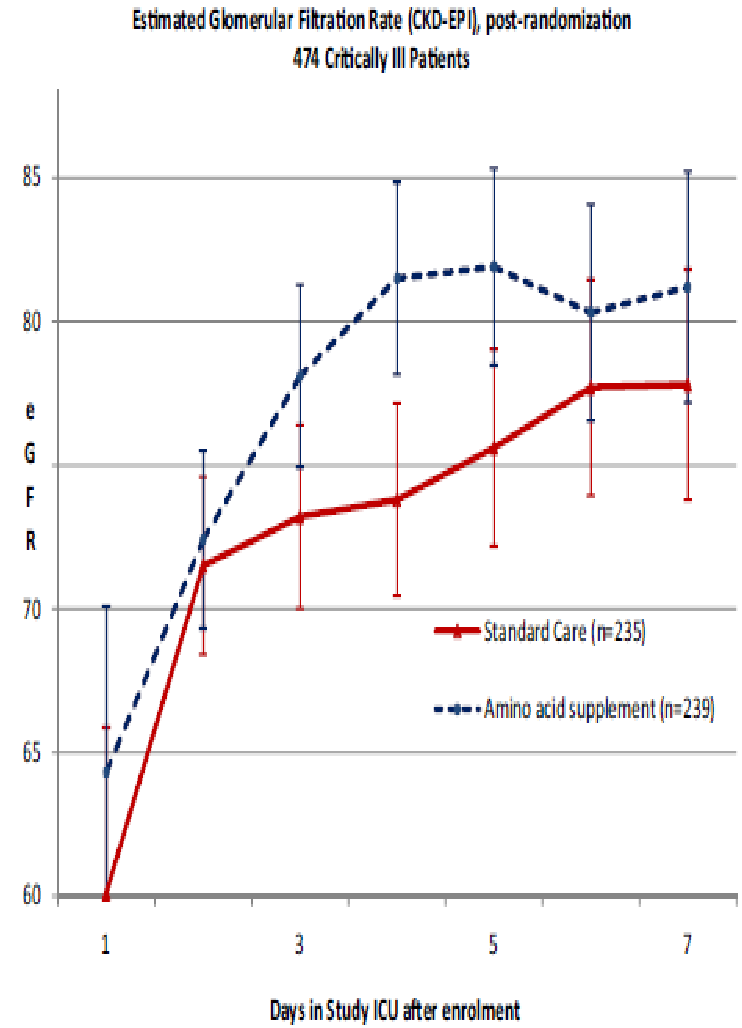
- Molecular weight of AA; 140 Da and lost during CRRT
- AA lost: 7.9 g/24h with flow 1000 mL/h and 2.4 g/24 with flow 500 mL/h
- Lost more during ultrafiltration
- Convection increases loss by 1.2 to 7.6 g/d
- Diffusion inducing catabolism
- **All together loss of amino acids: 10-15 g/day**

Chua HR, Baldwin I, Fealy N, Naka T, Bellomo R. Amino acid balance with extended daily diafiltration in acute kidney injury. Blood Purif 2012; 33:292-99.

Gordon S. Doig
Fiona Simpson
Rinaldo Bellomo
Philippa T. Heighes
Elizabeth A. Sweetman
Douglas Chesher
Carol Pollock
Andrew Davies
John Botha
Peter Harrigan
Michael C. Reade

Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled tria





Intensive Care Med 2015; 41: 1197-1208

Table 3 Tertiary outcomes: mortality, length of stay, and quality of life

Mortality	Standard care (235 patients)	Amino acid supplement (239 patients)	Risk difference (exact 95 % CI)	Exact *P* value
ICU discharge mortality, % (*n*/N)	12.8 % (30/235)	11.7 % (28/239)	−1.05 % (−10.1 to 7.8)	0.78
Hospital discharge mortality, % (*n*/N)	18.3 % (43/235)	15.5 % (37/239)	−2.28 % (−11.7 to 6.3)	0.46
Day 90 mortality, % (*n*/*N*)	20.0 % (47/235)	17.8 % (42/236)[a]	−2.20 % (−11.1 to 6.9)	0.56

Length of stay	Standard care (235 patients)	Amino acid supplement (239 patients)	Difference (95 % CI)	*P* value
ICU stay (days), mean (95 % CI)	10.7 (10.0 to 11.5)	11.6 (10.8 to 12.5)	0.91 days (−0.62 to 2.68)	0.26
Hospital stay (days), mean (95 % CI)	24.8 (23.0 to 26.6)	26.0 (24.2 to 28.0)	1.3 days (−2.2 to 5.3)	0.49

Quality of life and physical function (reported by survivors at day 90 interview)	Standard care (188 survivors)	Nephro-protect (194 survivors)	Difference (95 % CI)	*P* value
RAND-36 General Health, mean (SD) *(n responses available for analysis)*	52.8 (25.9) (*n* = 180)	50.5 (27.2) (*n* = 192)	2.3 (−3.1 to 7.7)	0.41
ECOG Performance Status, mean (SD) *(n responses available for analysis)*	1.18 (1.0) (*n* = 181)	1.31 (1.0) (*n* = 192)	−0.13 (−0.34 to 0.07)	0.21
RAND-36 Physical Function, mean (SD), *(n responses available for analysis)*	53.2 (33.0) (*n* = 180)	47.7 (33.7) (*n* = 192)	5.5 (−1.31 to 12.3)	0.11
Requiring RRT at day 90, % *(n/N responses available for analysis)*	0.5 % (1/183)	0.0 % (0/191)	−0.5 (−10.7 to 9.6 %)	0.49

Table 2 Secondary renal outcomes

Secondary renal outcomes	Standard care (235 patients)	Amino acid supplement (239 patients)	Difference (95 % CI)	*P* value
Volume received, mean (SD) *mL per ICU day*	2232 (905)	2612 (857)	380 mL (221 to 539)	<0.0001
Urine output, mean (SD) *mL per ICU day*	2009 (845)	2309 (872)	300 mL (145 to 455)	0.0002

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The Effect of IV Amino Acid Supplementation on Mortality in ICU Patients May Be Dependent on Kidney Function: Post Hoc Subgroup Analyses of a Multicenter Randomized Trial

Critical Care Medicine:2018 ; 46:1293-1301

Ran Zhu, MD[1]; Matilde J. Allingstrup, PhD[1,2]; Anders Perner, PhD[2]; Gordon S. Doig, PhD[1]; for the Nephro-Protective Trial Investigators Group

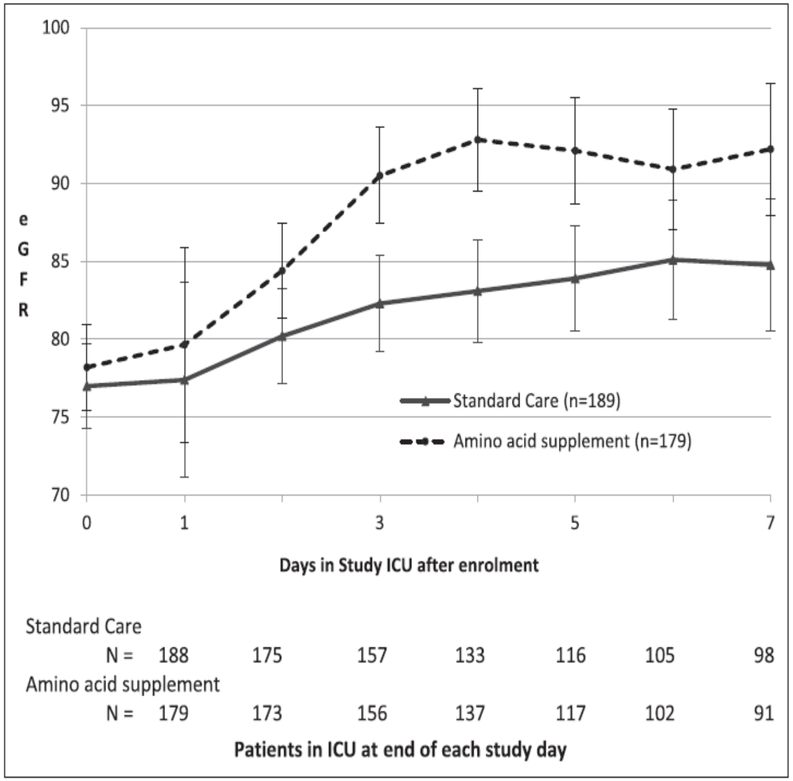
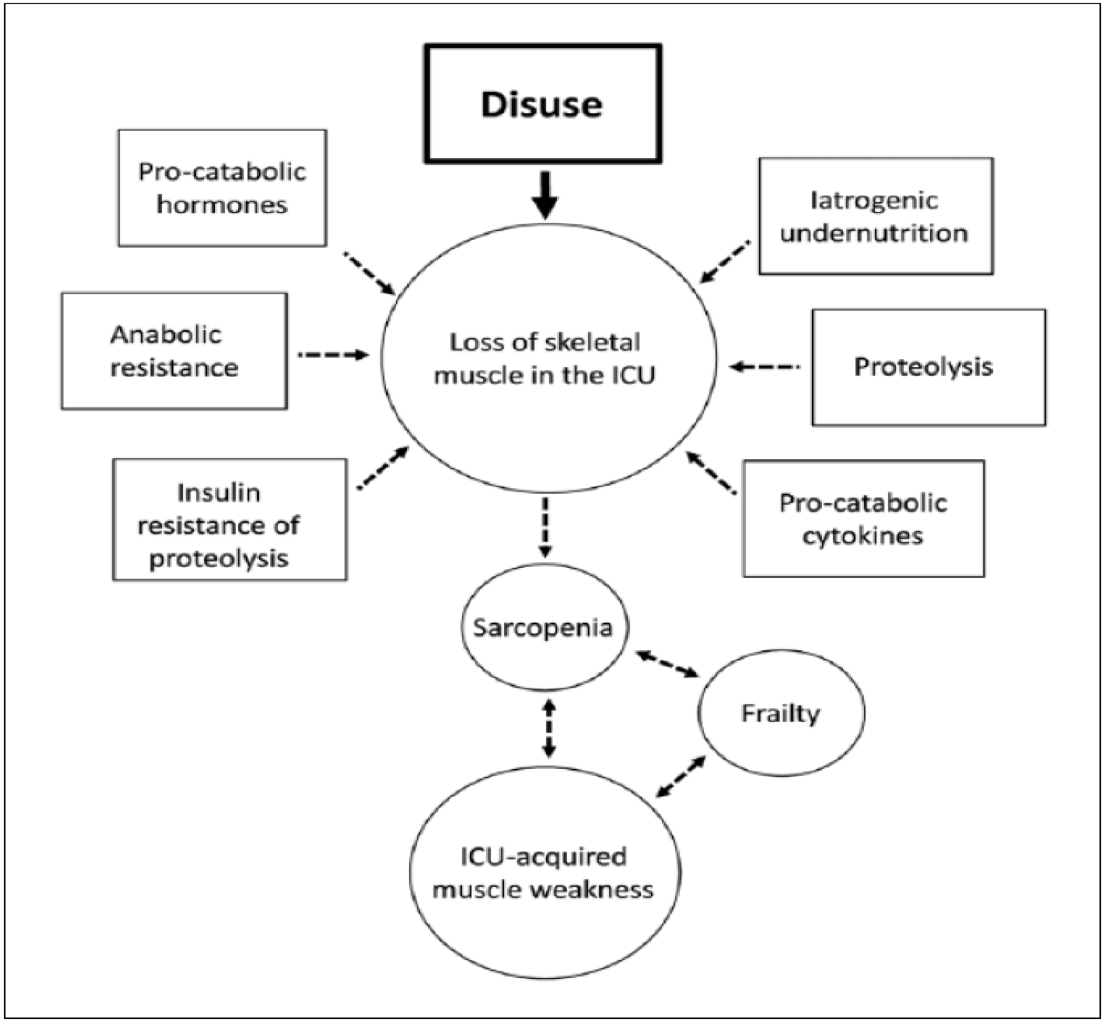


TABLE 3. Mortality, Length of Stay, and Health-Related Quality of Life

Outcome	Standard Care	Amino Acid Supplement	Difference (95% CI)	p
Subgroup with "no" baseline kidney dysfunction and "no" baseline risk of progression of AKI				
	189 patients	179 patients		
Deaths before study day 90, % (n/N)	21.2% (40/189)	14.2% (25/176)[a]	−7.9% (−15.1 to −0.7)	0.0341[b]
ICU stay (d), mean (95% CI)	10.6 (9.8–11.5)	11.5 (10.6–12.5)	0.87 d (−0.86 to 2.89)	0.35
ICU discharge mortality, % (n/N)	12.7% (24/189)	10.0% (18/179)	2.6% (−7.6 to 12.8)	0.51[c]
Hospital stay (d), mean (95% CI)	23.7 (21.9–25.8)	25.3 (23.3–27.5)	1.5 d (−2.3 to 6.0)	0.45
Hospital discharge mortality, % (n/N)	19.6% (37/189)	11.7% (21/179)	−7.8% (−15.0 to 0.0)	0.045[c]
RAND-36 general health, mean (SD) (n/N responses available for analysis)	53.5 (25.4) (143/149)	49.5 (26.7) (149/151)	−4.0 (−10.0 to 2.0)	0.19
ECOG performance status, mean (SD) (n/N responses available for analysis)	1.17 (1.0) (143/149)	1.35 (1.0) 149/151	0.17 (−0.05 to 0.40)	0.14
RAND-36 physical function, mean (SD) (n/N responses available for analysis)	52.5 (32.8) (142/149)	46.3 (33.5) (149/151)	−6.2 (−13.8 to 1.5)	0.11
Survivors requiring RRT at day 90, % (n/N)	0.7% (1/144)	0.0% (0/149)	−0.7 (−12.2% to 10.8%)	0.49[c]

The frail and the older



Protein Turnover and Metabolism in the Elderly Intensive Care Unit Patient

Stuart M. Phillips, PhD[1]; Roland N. Dickerson, PharmD[2]; Frederick A. Moore, MD[3]; Douglas Paddon-Jones, PhD[4]; and Peter J. M. Weijs, PhD[5,6]

Nutrition in Clinical Practice
Volume 32 Supplement 1
April 2017 112S–120S

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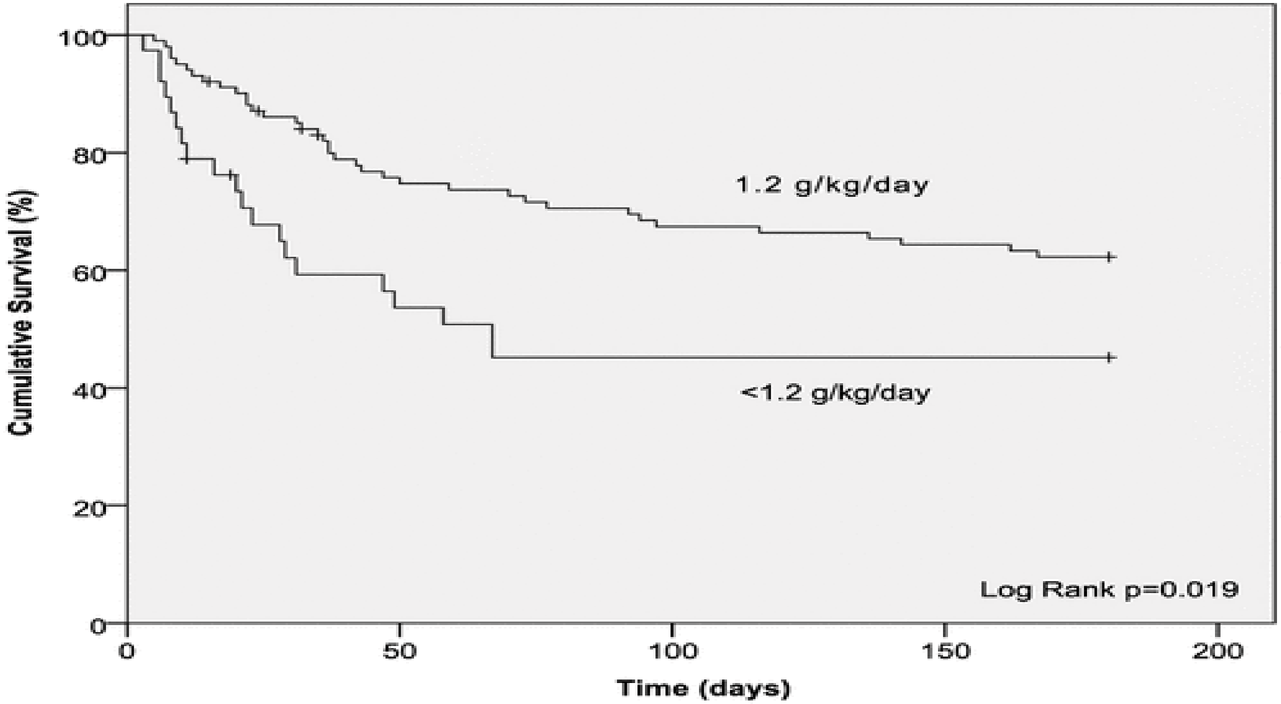
Adequate Protein Nutrition Support Modifies 6-Month Mortality Risk of Low Muscle Mass in Critically Ill Patients



Wilhelmus G. P. M. Looijaard; Ingeborg M. Dekker;
Heleen M. Oudemans-van Straaten; Peter J. M. Weijs

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Addition of exercise to nutrition in the ICU

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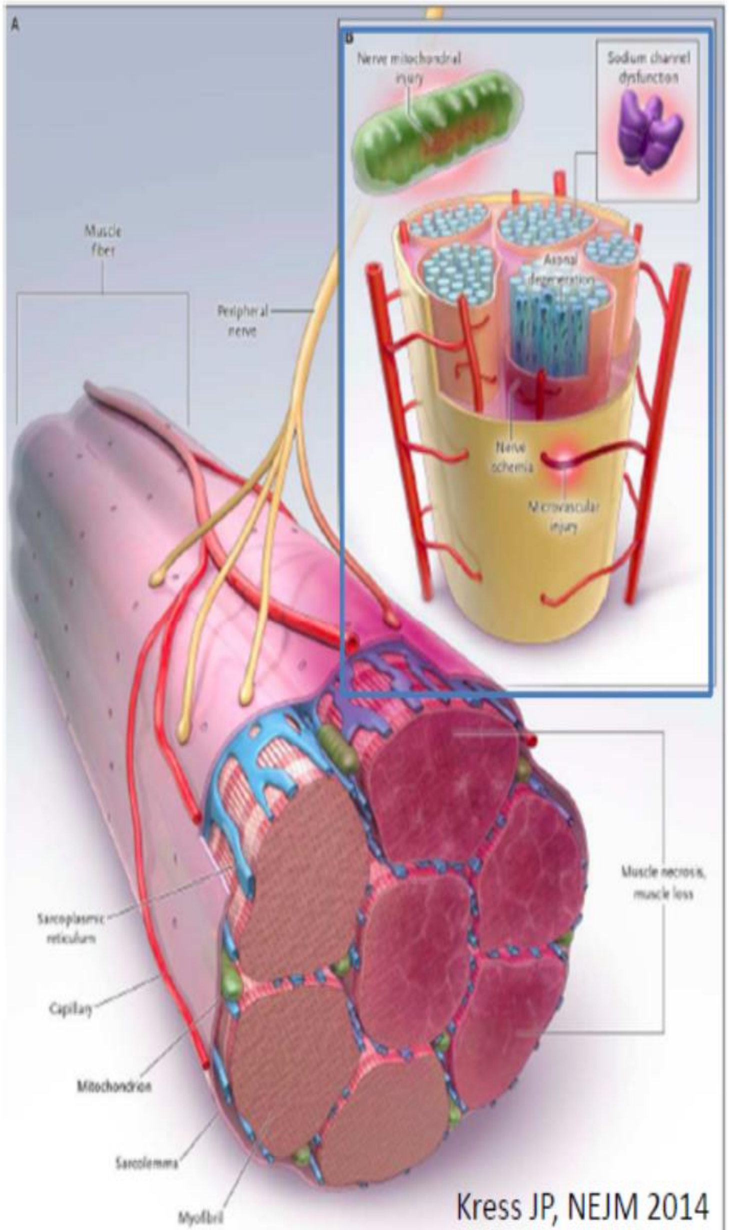

Kress JP, NEJM 2014

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Exercise-Induced Skeletal Muscle Remodeling and Metabolic Adaptation: Redox Signaling and Role of Autophagy

Elisabetta Ferraro,[1] Anna Maria Giammarioli,[2] Sergio Chiandotto,[3] Ilaria Spoletini,[1] and Giuseppe Rosano[1,4]

ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 1, 2014

MyHC type	Metabolism	Mitochondrial density Citrate synthase SDH Time to peak tension Energy efficiency Endurance capacity	LDH	Shortening velocity	Fatigue resistant	Color Myoglobin	CSA	Force production
Type I	Oxidative	High	Low	Slow twitch	Resistant	Red High	Small	Weak
Type IIa	Oxidative Glycolitic	Intermediate	Intermediate	Fast twitch	Resistant	Low red Intermediate	Large	Intermediate
Type IIx/d	Glycolitic	Low	High	Fast twitch	Fatigable	White Low	Large	Strong
Type IIb	Glycolitic	Low	High	Fast twitch	Fatigable	White Low	Large	Strong

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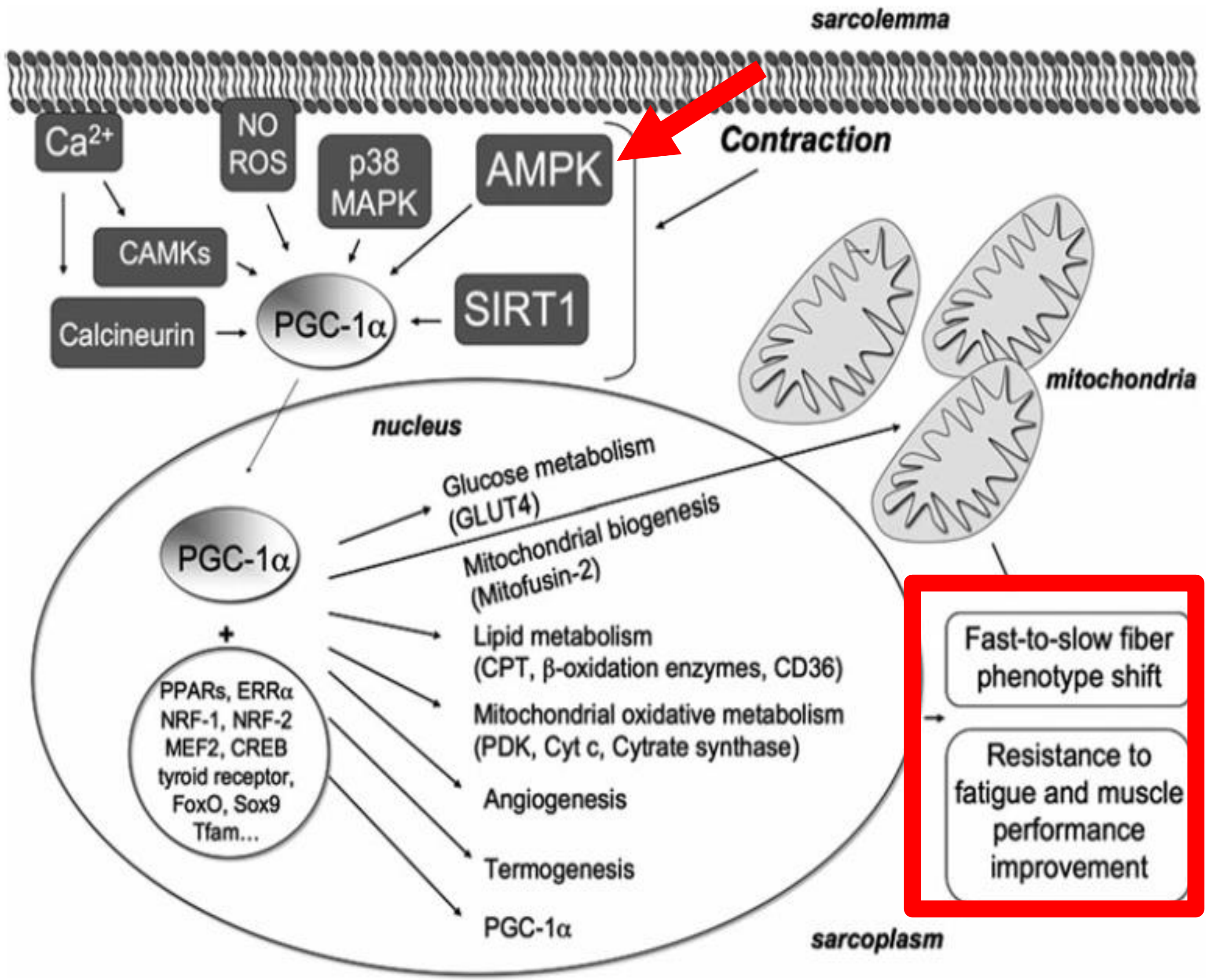

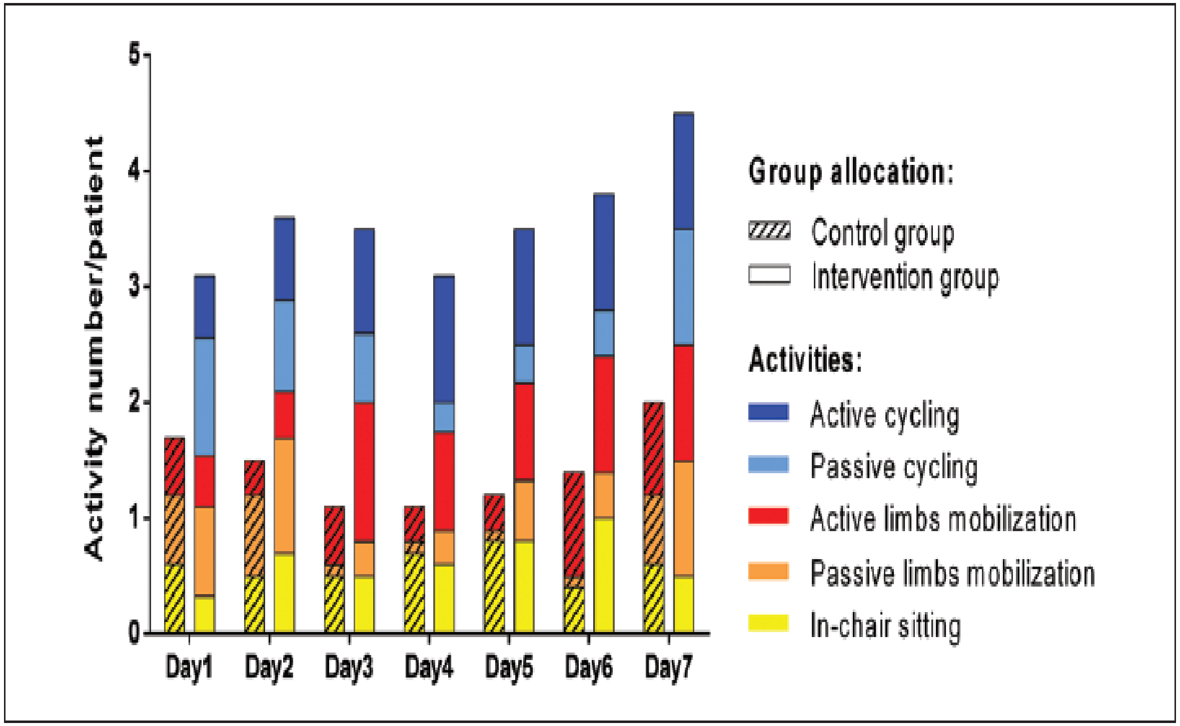

Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial

Cheryl E. Hickmann, PT, PhD[1]; Diego Castanares-Zapatero, MD, PhD[1]; Louise Deldicque, PhD[2]; Peter Van den Bergh, MD, PhD[3]; Gilles Caty, MD, PhD[4]; Annie Robert, PhD[5]; Jean Roeseler, PT, PhD[1]; Marc Francaux, PhD[2]; Pierre-François Laterre, MD[1]

Intensive Care Med 2017

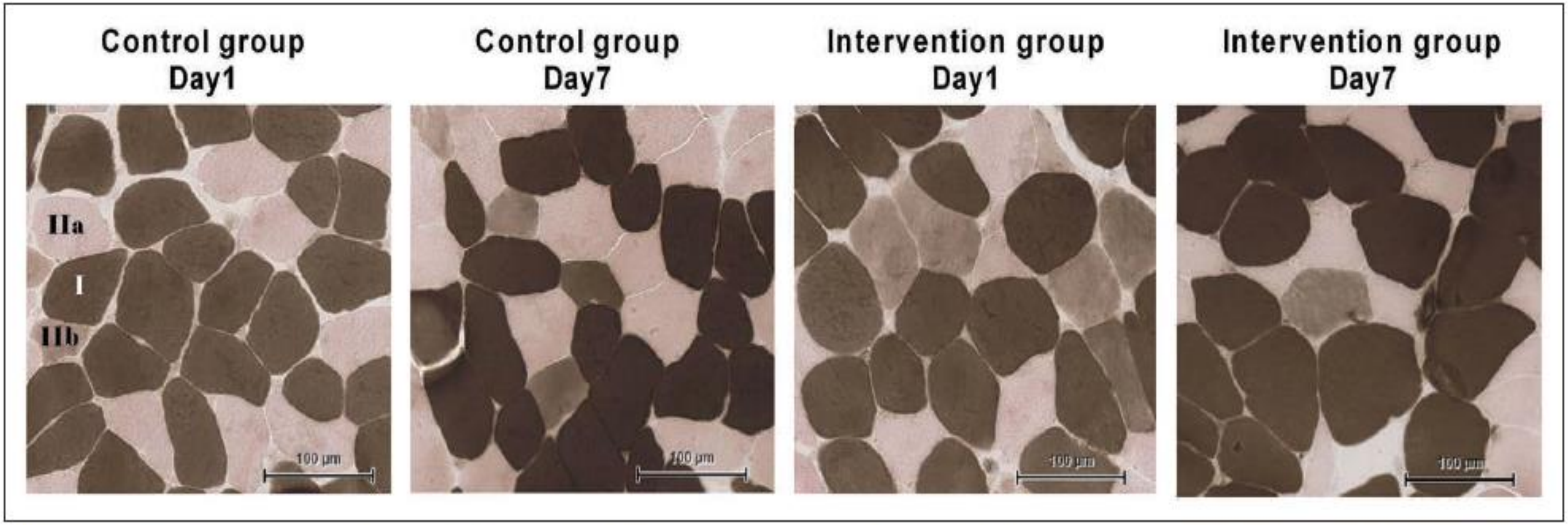

Figure 3. Muscle fiber cross-sectional area changes by group. Skeletal muscle sections stained with adenosine triphosphatase pH 4.50; *black* fibers correspond to type-I fibers; *gray* fibers are type-IIb fibers and; *pink* fibers correspond to type-IIa.

TABLE 2. Changes in Cross-Sectional Area by Groups

	Control Group (*n* = 9), Mean ± SD		Intervention Group (*n* = 8), Mean ± SD		
Fiber Type	Day 1	Day 7	Day 1	Day 7	p^b
All fibers types (µm^2)	3,603 ± 1,284	2,629 ± 1,174[a]	3,448 ± 1,993	3,770 ± 1,473	0.01
Type I fibers (µm^2)	4,236 ± 1,379	3,135 ± 1,103[a]	4,250 ± 1,977	4,678 ± 1,189	0.02
Type-IIa fibers (µm^2)	3,949 ± 1,447	2,744 ± 1,260[a]	2,574 ± 856	2,920 ± 745	0.003
Type-IIb fibers (µm^2)	2,624 ± 1,243	2,006 ± 1,286[a]	2,082 ± 1,083	2,576 ± 948	0.04

In adult critically ill patients, does high protein intake compared to low protein intake improve outcome?

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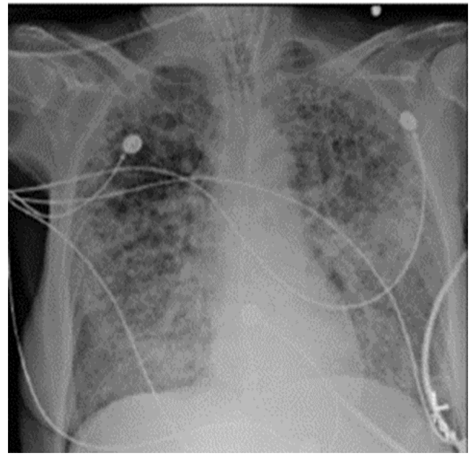
- 1.3 g protein /kg per day should be delivered progressively during critical illness.
- Grade of recommendation: O - (91%) agreement
- Exercise can be suggested.

Singer et al: ESPEN Guidelines: Nutrition in ICU. Clin Nutr 2019

Conclusions



- Different diseases react differently to protein administration
- Requirements adapted to weight, age, metabolic status: not a unique recommendation!
- High amount of protein is needed (1.3 g/d) and some patients may need more and some less
- Exercise may decrease protein catabolism