Proteine im Fokus

Der Patient auf der Intensivstation

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Inselspital Bern, 19. Juni 2019

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG Hôpitaux Universitaires Genève

Nutrition support in the ICU

- Detection + Correction + Prevention of protein calorie malnutrition
- Less negative nitrogen balance
- Optimizing metabolism in the crit. ill
- Reducing morbidity & rehabilitation

Malnutrition & poor outcome in critically ill patients

Picture by M. Donnier/Soins Intensifs-HUG, 2013

Malnutrition 20-40%

- **Incidence of complications↑**
- **Infections & MOF ↑**
- **Time on MV ↑**
- **Mortality ↑**
- **ICU & hospital LOS ↑**
- **Costs ↑↑↑**

Kyle et al., Clin Nutr 2006; 25:727-35
Martin et al., Can Med Ass J 2004; 170:197-204
Morgensen et al., Crit Care Med 2015;43:2605-15

Critical illness

➡ **disease requiring treatment in ICU**

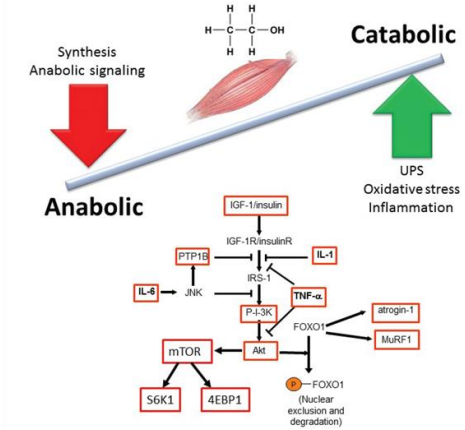
Catabolic critical illness:

life-threatening condition created by overwhelming infection (sepsis), trauma, or other kinds of severe tissue injury.

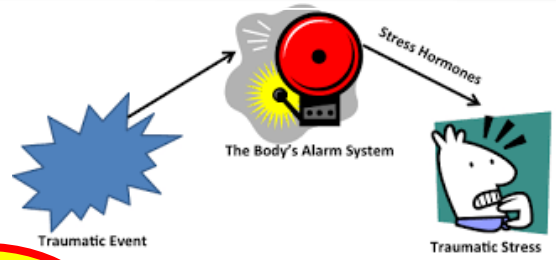
- systemic inflammatory response to major injury
- coordinated cytokine-, hormone- and nervous system-mediated phenomenon
- alters temperature regulation and energy expenditure
- invokes neuroendocrine and hematologic responses
- changes the synthesis and disposition of certain proteins in the body

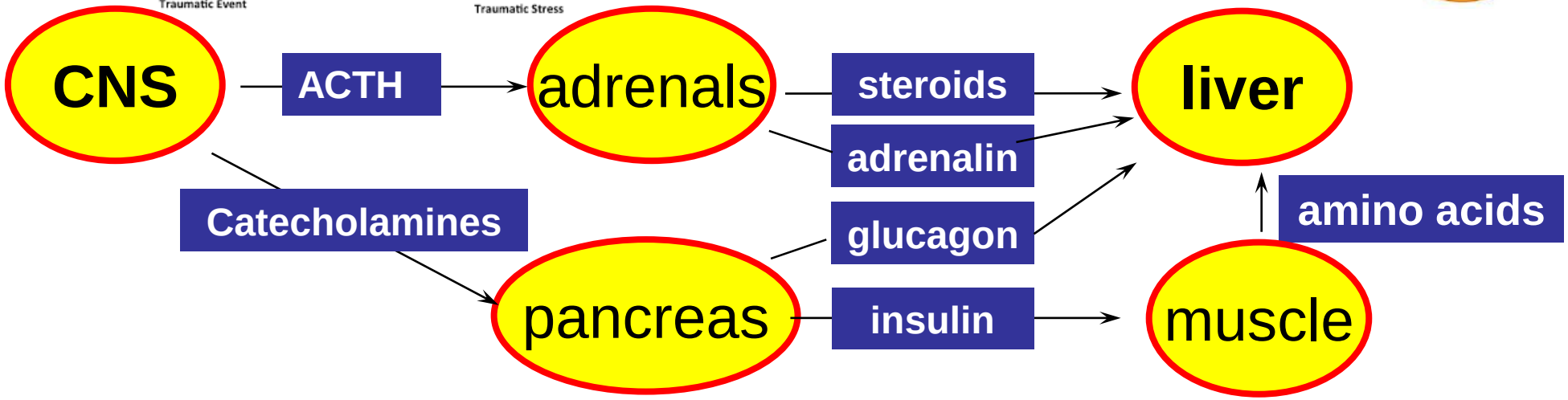
- **protein-catabolic response**

➡ **stimulates muscle protein catabolism +++**



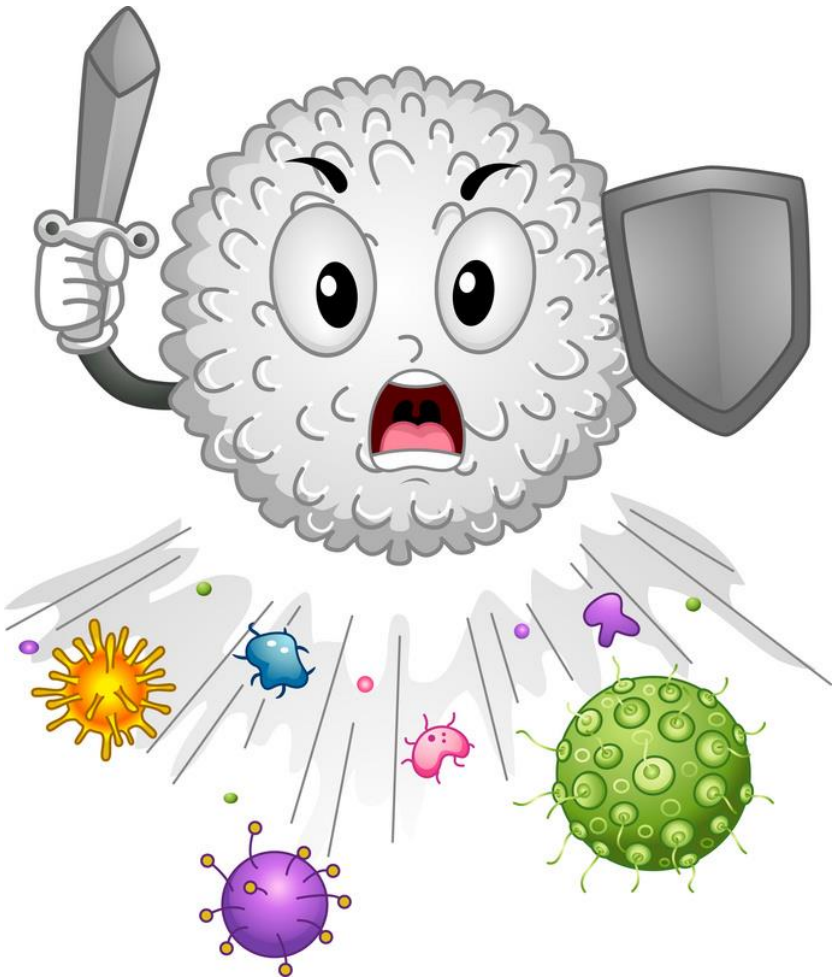
Metabolic response to stress





- **Hypermetabolism** ⇒ **Catabolism**
- **Altered Glucose Metabolism** ⇒ **Hyperglycemia**
  - -peripheral insulin resistance
  - -stimulation of hepatic gluconeogenesis
- **Sodium & water retention** ⇒ **Positive fluid balance**
- **↑ Lipolysis/lipid oxidation** ⇒ **Major body fuel**
- **Protein depletion: multifactorial** ⇒ **Depletion +++**

The role of nutrition in critical illness?



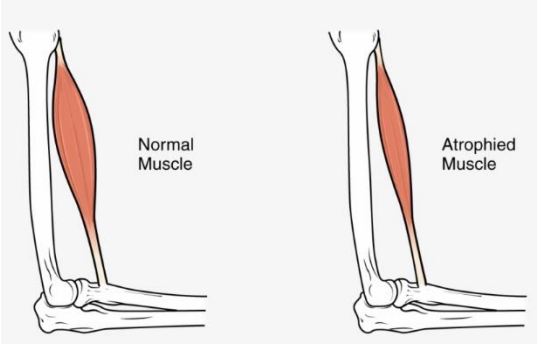
Systemic inflammation

- anorexic effect -> no food intake
- increased muscle protein catabolism
- increased body protein loss
- increased energy expenditure.

Consequences:

=> severe muscle atrophy

=> adipose tissue stores ↓



Protein a crucial macronutrient in catabolic critical illness

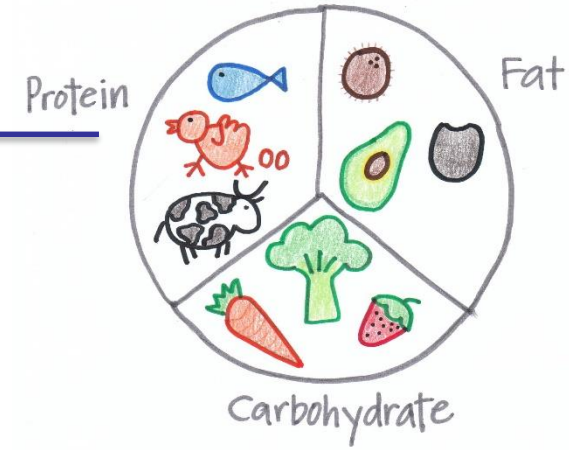
Only one **protein store** in the body => **skeletal muscle**

Rapid & severe **muscle atrophy in catabolic critical illness** even in healthy young adults with initial normal muscle mass.

Generalized **muscle atrophy at ICU admission** in the critically ill (including obese)

- old age, disuse muscle atrophy
- pre-existing protein-energy malnutrition
- more vulnerable to the critical illness

Catabolic critical illness protein requirements

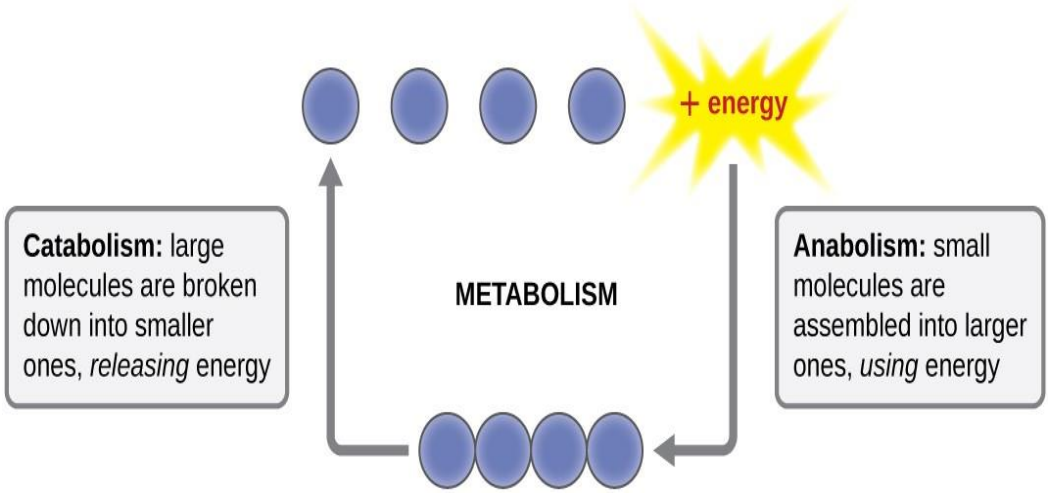


Protein = essential nutrient

Protein turnover

Proteolysis

Protein synthesis



Endogenous amino acid catabolism ↓
if dietary protein deprivation
but: not below a protein minimum or obligatory nitrogen (N) excretion rate
Adaptive regulation by incorporation of exogenous amino acids into body protein

Energy & protein requirements during critical illness

Energy-protein requirements depend on disease state & nutritional status

- Energy & protein provision to prevent body wasting in critical clinical conditions:
  - critical illness
  - severe malnutrition
  - body composition (e.g. obesity)
- Re-gain of muscle mass & energy stores during stabilized convalescent period

3 different phases in critical illness

Days 1-2

"EBB phase"

Acute Phase

Early Period

Metabolic instability

Days 3-7

Acute Phase

Late Period

"FLOW phase"

Metabolic instability +/-

Anabolism

Late Phase

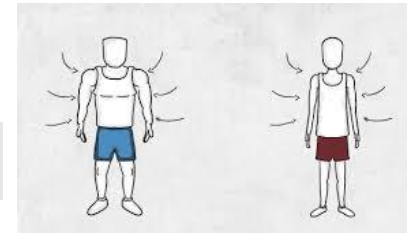
Rehabilitation

Or

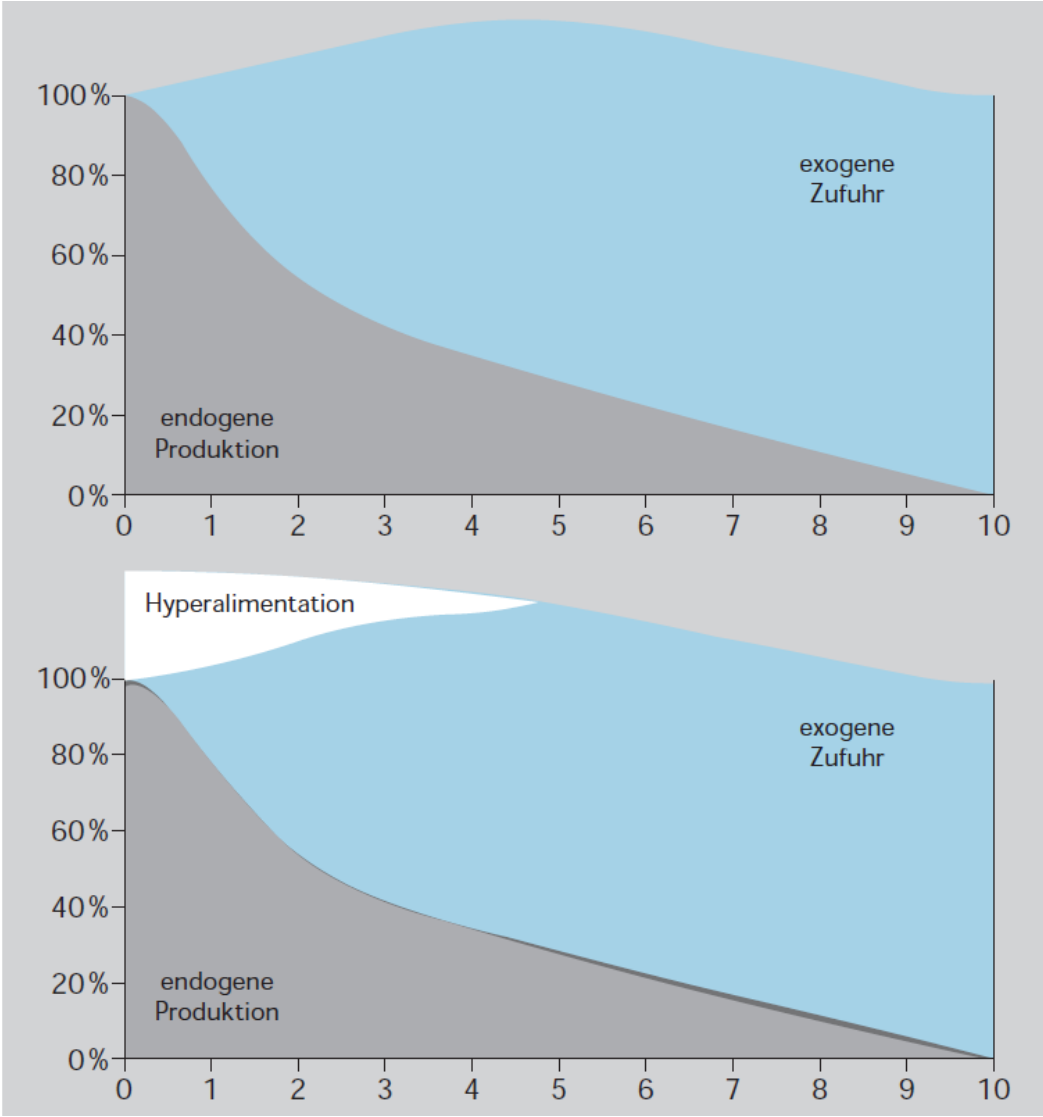
Chronic Phase

Catabolism

Muscle wasting +++



Energy from endogenous & exogenous substrates in the critically ill patient



Acute Phase (72 -96h):
utilisation of endogenous substrates (endogenous lipolysis & proteolysis)

➔ Risk of “overfeeding”

Ockenga J. et al., Aktuel Ernährungsmed 2012; 37: 22–27

Overfeeding as well as underfeeding are deleterious

Dr Heinrich Hoffmann (1809-1894) *« **Der Struwwelpeter »** 1858*

Nutrition support in the ICU

What is the optimal amount of protein for the critically ill patient ???

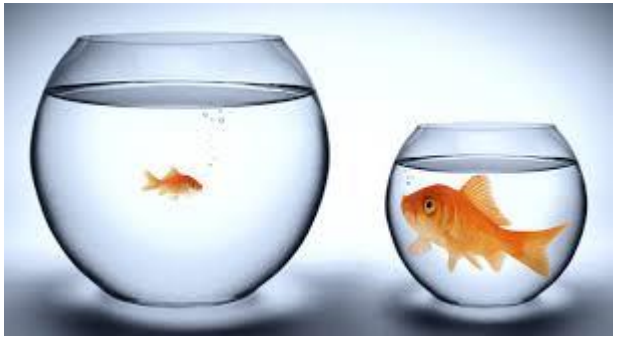
Energy & protein requirements for the critically ill

- Calorie & protein assessment is often inaccurate in the critically ill

- The right amount & the right composition of nutritional support for individual needs of the critically is a difficult art

Heidegger CP et al. Curr Op Crit Care 2008 ; 14:408-14

How much protein for the critically ill ?



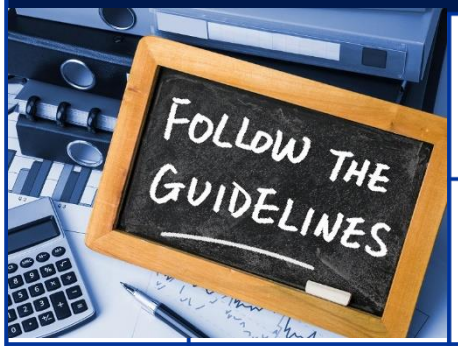
Society of Critical Care Medicine &
American Society for Parenteral and Enteral Nutrition
1.2-2.0 g protein/kg/d

European Society for Clinical Nutrition and Metabolism
1.3 g/kg protein equivalent/d

DGEM Guideline
1.0 to 1.2 g/kg protein or amino acids/d

International Guidelines – Protein Recommendations

Tabelle 1. Übersicht über die Proteinempfehlungen für nicht adipöse Patienten in den einzelnen Leitlinien



			Proteindosis (g/kg KG)		AS-Dosis (g/kg KG)	
		Steigerung	Start	am Ende der Akutphase	generell	Einschränkung
2016	ASPEN	nein		**1,2 -2,0**	n.a.	
2018	ESPEN	ja	n.a.	**1,3**	+?	
2018	DGEM	ja	0,75	**1,0**	+0,2	
2018	DGEM (Minderheitenvotum)	ja	<0,8	**≥1,2**	± 0,0	**bei nicht septischen Patienten**

KG = aktuelles Körpergewicht, AS = Aminosäuren

Kreymann KG et al., Aktuelle Ernährungsmedizin in press

Clinical Nutrition 38 (2019) 48–79

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a, *], Annika Reintam Blaser [b, c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

Summary: Clinical questions (25) with recommendations (57) & 358 ref.

- Patients at risk
- How to assess nutritional status of an ICU patient
- How to define the amount of energy to provide
- When to start & how to progress in the administration of adequate nutrition support
- The route to choose
- Special conditions of ICU patients: sepsis, polytrauma, abd. surgery, obesity

?

Amount & nature of carbohydrates, fat and **protein** - glutamine and omega-3 FA

!

High protein intake vs low protein intake?

NB

Improved outcome: mortality/infections?

How should you define protein targets?

In adult critically ill patients, does high protein intake compared to low protein intake improve outcome (↓ mortality, ↓ infections) ?

Recommendation	Grade
During critical illness, **1.3 g/kg protein** equivalents per day **progressively** -> benefits from observational studies but RCTs less conclusive -> **Optimal timing is unclear! -** only retrospective studies **URGENT NEED of well conducted RCTs !**	**0** 91%
Statement 3 **Physical activity** may improve the beneficial effects of nutritional therapy -> preventing anabolic resistance -> ↓ morbidity & improving the level of activity	**Consensus** 82% agreement

Hypothesis:

Optimal protein targets change over time in the ICU & high protein intake is only beneficial if not associated with overfeeding.

Highglights of Changes

Assessment of EE & Caloric Intake

- Strong recommendation for indirect calorimetry (IC)
- Isocaloric nutrition when IC measurements
- Avoidance of use of predictive equations
- Hypocaloric nutrition (<70%) if use of predictive equations
- Avoidance of early full EN & PN during first 3 ICU days
- After day 3 : ↑ caloric delivery up to 80-100% of measured EE

Parenteral Nutrition

- Delayed start of progressive PN on day 3-7 (except in severely malnourished)
- No PN until all strategies to maximize EN tolerance attempted

Protein Intake:

- **1.3 g/kg/d** for all ICU patients
- **No parenteral GLN** in unstable/complex ICU patients (liver & renal failure)

Evidences from Clinical Studies

OBSERVATIONAL

RANDOMIZED

JPEN
Journal of Parenteral & Enteral Nutrition

Optimal Protein and Energy Nutrition decreases mortality in mechanically ventilated, critically ill patients: A Prospective Observational Cohort Study

Table 3. Relationship Between Nutrition Therapy and Intensive Care Unit, 28-Day, and Hospital Mortality[a]

	Protein and Energy Target	Energy Target
Model 0[b]		
Intensive care unit	0.91 (0.64–1.31), P = .626	1.03 (0.86–1.25), P = .733
28 d	**0.59 (0.40–0.88), P = .010**	0.90 (0.74–1.09), P = .291
Hospital	**0.76 (0.58–0.99), P = .041**	0.93 (0.81–1.08), P = .339
Model 1[c]		
Intensive care unit	0.79 (0.54–1.17), P = .242	0.99 (0.81–1.20), P = .886
28 d	**0.51 (0.33–0.78), P = .002**	0.84 (0.68–1.03), P = .085
Hospital	**0.70 (0.53–0.94), P = .017**	0.91 (0.79–1.06), P = .233
Model 2[d]		
Intensive care unit	0.72 (0.48–1.09), P = .116	0.98 (0.80–1.19), P = .834
28 d	**0.40 (0.26–0.64), P < .001**	**0.79 (0.64–0.97), P = .024**
Hospital	**0.62 (0.46–0.84), P = .002**	0.89 (0.77–1.04), P = .137

- 886 consecutive patients (2004-10)
- Nutrition guided by indirect calorimetry: >1.2 g protein /kg
- Cumulative intakes during mechanical ventilation

=> Significant decrease in 28d mortality !!!

Weijs PJM. et al., JPEN 2012;36:60-68

THE LANCET

The Lancet, 2 February 2013; 381 (9864): 385-393

Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial

Claudia Paula Heidegger, Mette M Berger, Séverine Graf, Walter Zingg, Patrice Darmon, Michael C Costanza, Ronan Thibault, Claude Pichard

Early EN (24 h)

+

SPN from day 4 to 8 after ICU admission

for optimisation of the protein- energy target by PN
when EN is insufficient after day 3 **adjusted by IC measurements**

improves clinical outcome in critically ill patients!

- **Nosocomial infections ↓** (22%)
- **Antibiotic use ↓** (2 days)
- **Mechanical ventilation ↓** (1day)

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Mean protein delivery during intervention (Day 4 to Day 8)

Intention–to-treat analysis (n=305)

Parameter	SPN (n=153)	EN (n=152)	p - value
Protein delivery (g/kg/IBW/day)	1.2 ± 0.2	0.8 ± 0.3	< 0.0001

*Mean ± SD, Student t-test

Heidegger CP et al., Lancet 2013;381 (9864): 385-393

CARING FOR THE
CRITICALLY ILL PATIENT

JAMA®
The Journal of the American Medical Association

ONLINE FIRST

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

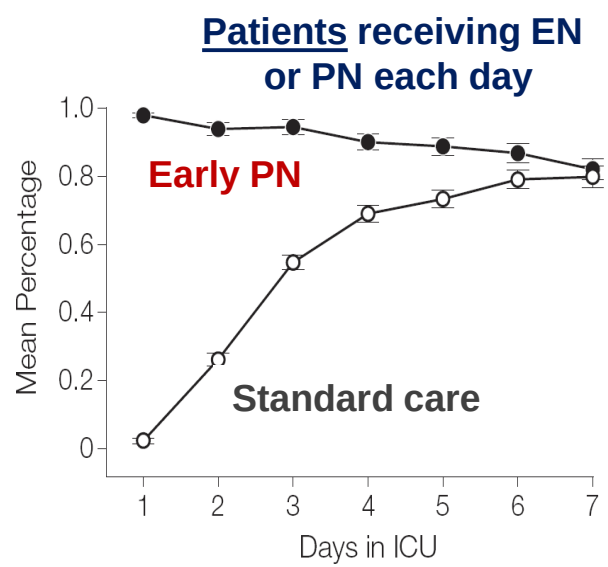
- **1.372 Australian patients with a temporary contraindication to EN**
- **Patients randomized within 24 hours of ICU admission to receive either standard care or early PN**
- **Primary endpoint: 60-day mortality**

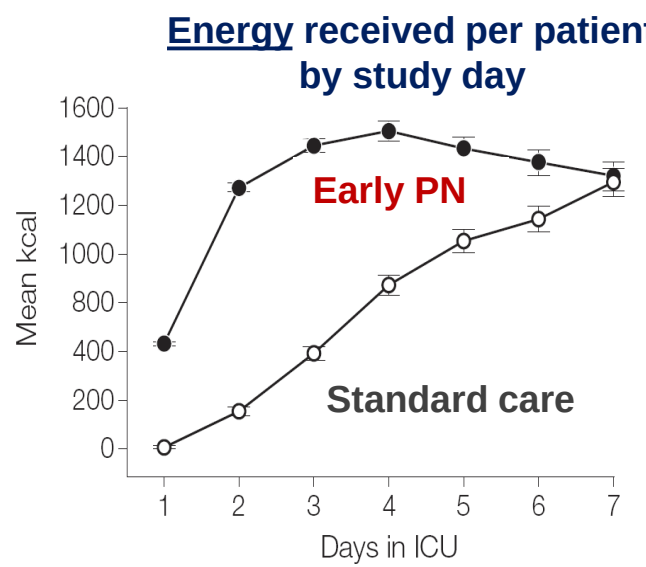
Best Route

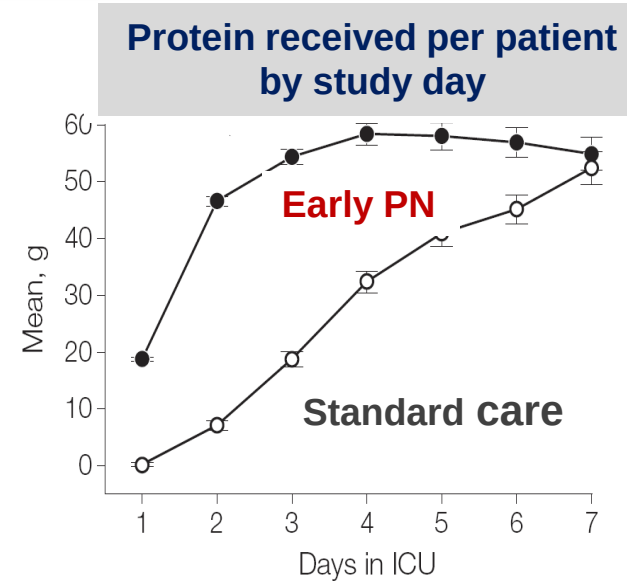
Doig G. et al., JAMA 2013;309(20):2130-2138

The Early PN Trial in critically ill patients(n=1372)

Nutrition delivery over the first 7 ICU days







Day-60mortality did not differ significantly:
standard care 22.8% vs 21.5% for early PN

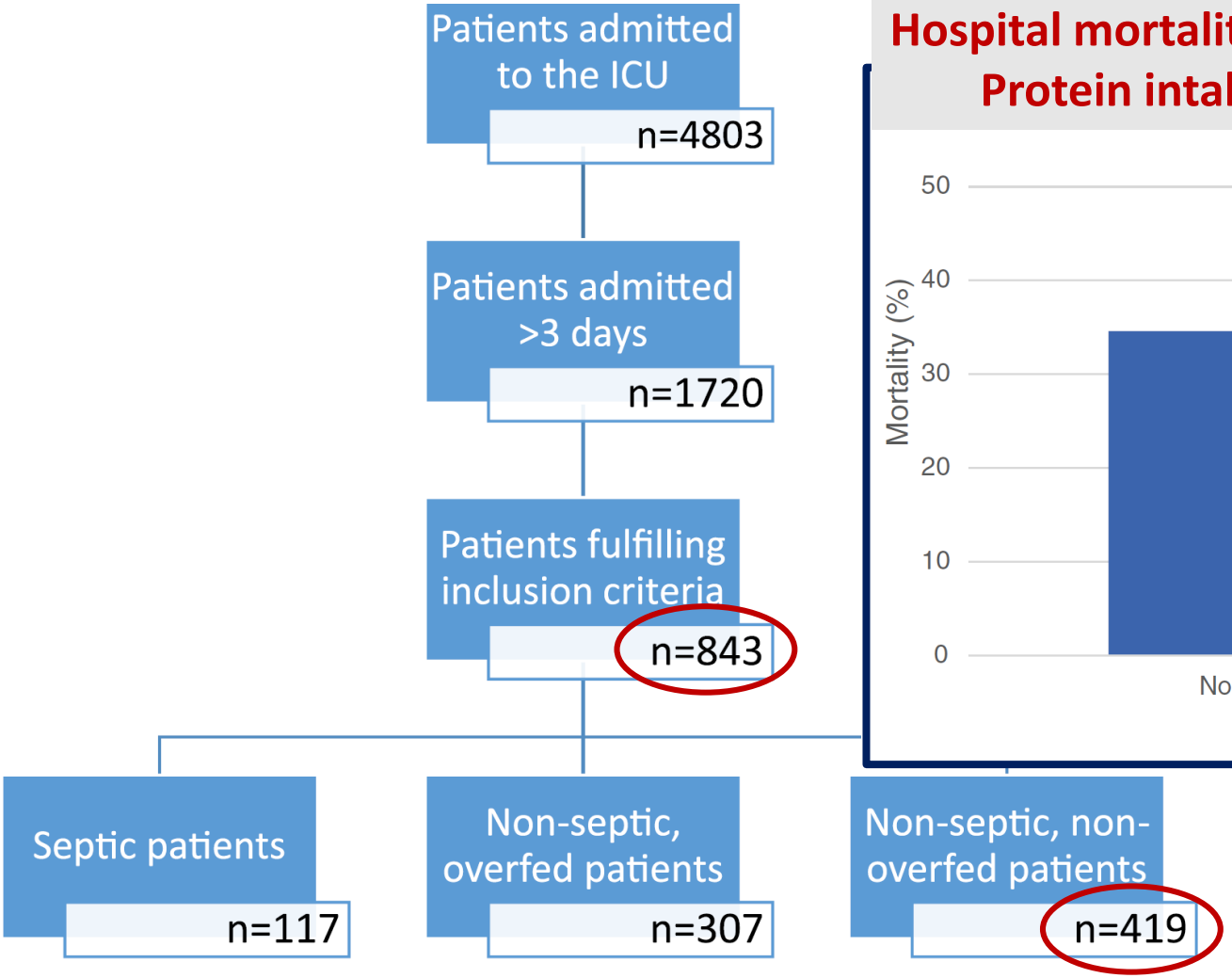
Outcome benefits for the early PN-group

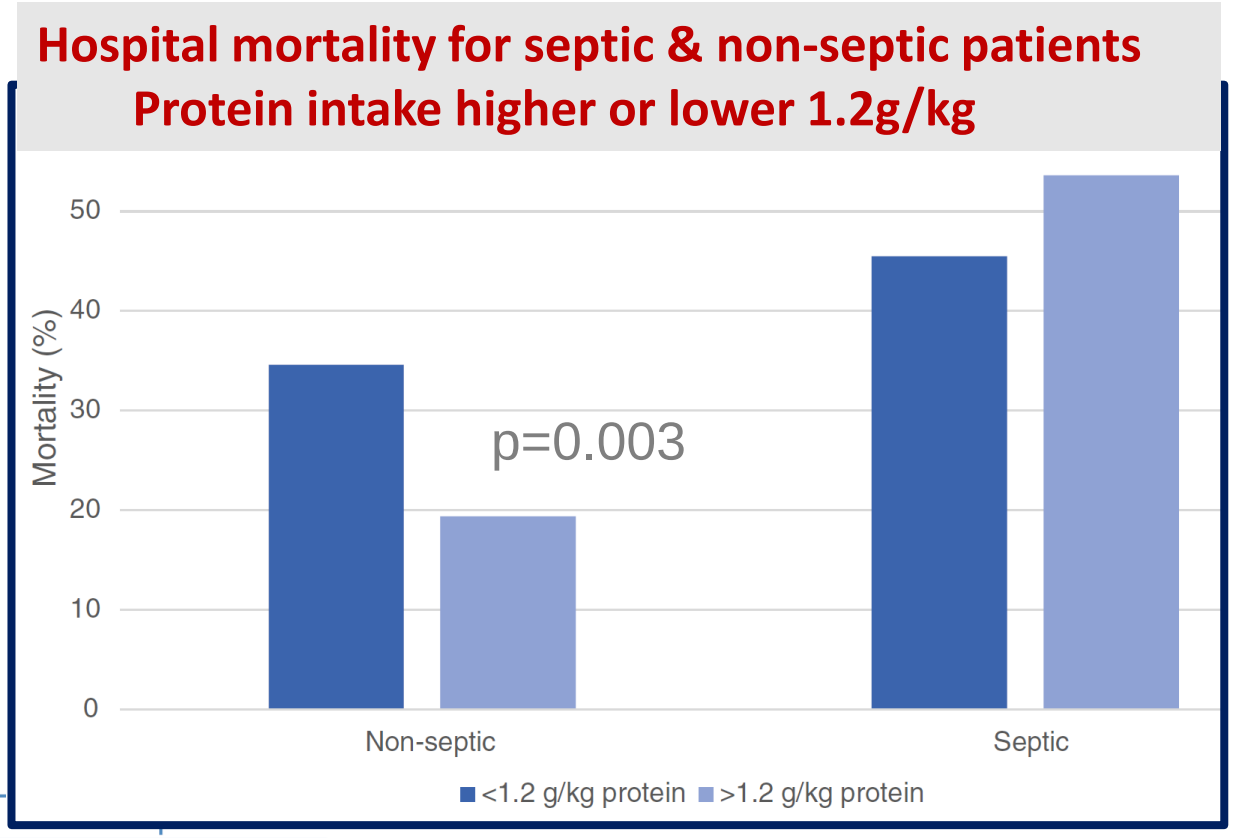
- Need for mechanical ventilation ↓ (-0.47 days per 10 pat-ICU days; p=0.01)
- Quality of life RAND-36 health status score: better maintenance of muscle mass

Doig G. et al., JAMA 2013;309(20):2130-2138

CRITICAL CARE

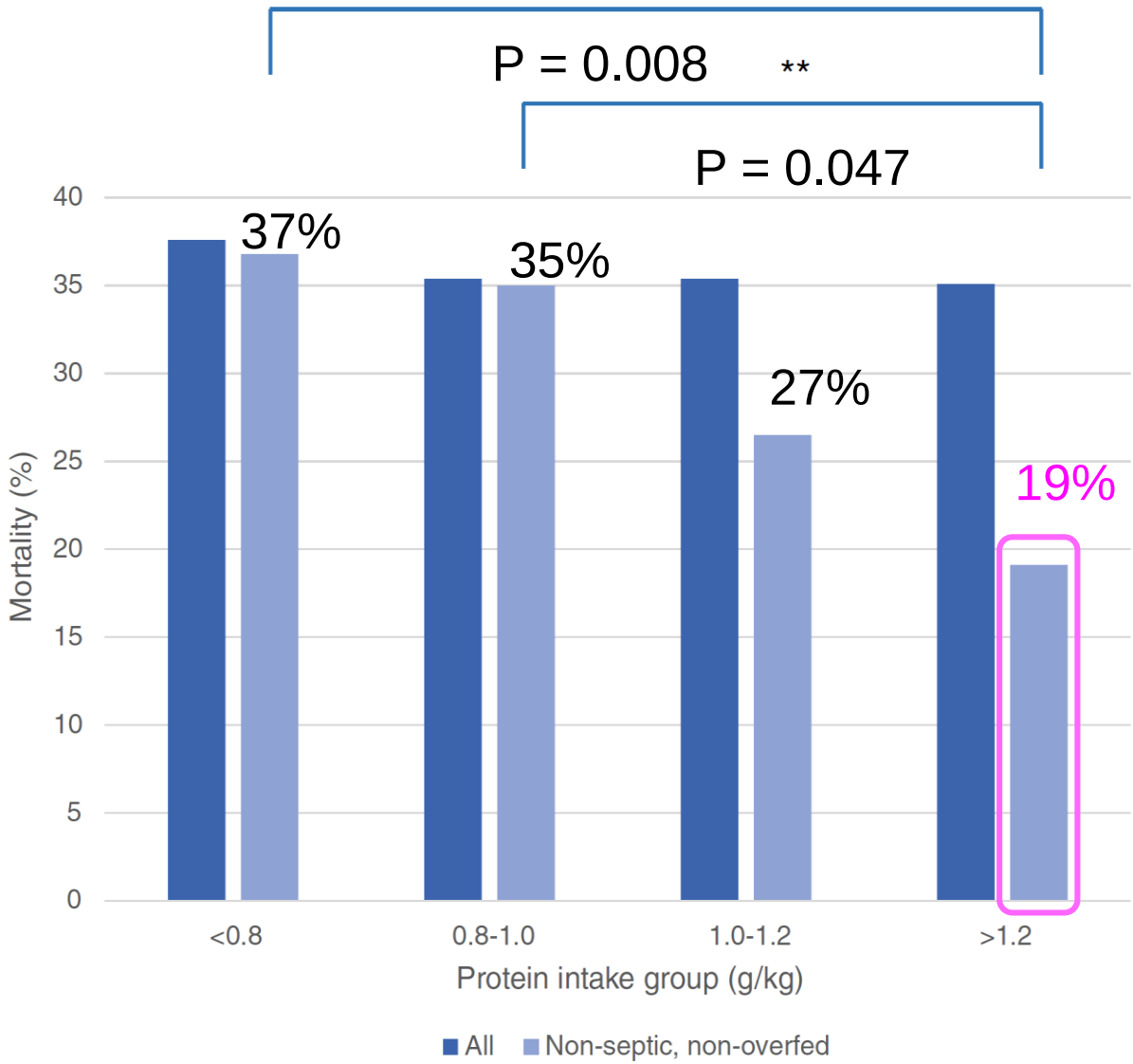
Early high protein intake (≥1.2 g/kg/d on day4) associated with ↓mortality & energy overfeeding with ↑mortality in non-septic mechanically ventilated critically ill patients





Weijs PJM et al., Crit Care 2014;18:701

Hospital mortality: patients per protein intake group & all non-septic, non-overfed patients per protein intake group



In non-septic, non-overfed critically ill patients (n = 419)

=> **early high protein intake** was associated with ↓**mortality**

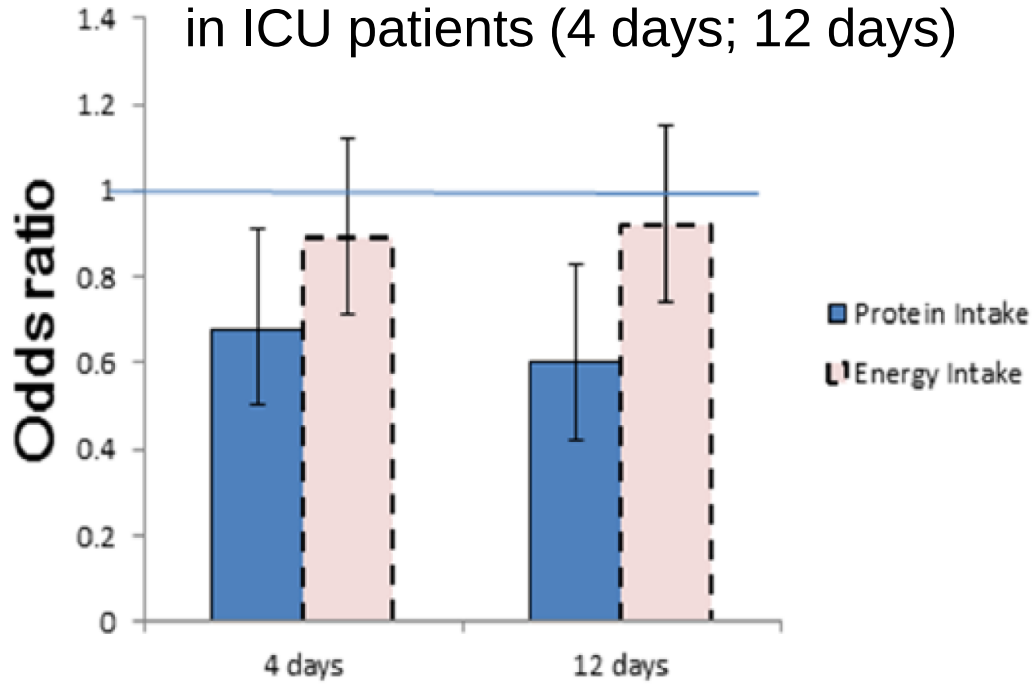
=> **early energy overfeeding** (>110% of measured EE) over the first 4 days of ICU stay with ↑**mortality**

Weijs PJM et al., Crit Care 2014;18:701

Clinical outcomes related to protein delivery in a critically ill population

A multicenter, multinational observation study

Odds of mortality by protein and energy intake in ICU patients (4 days; 12 days)



80% of protein target (mean 1.0 g/kg/d) + ↑ energy intake compared to protein target <80% (mean 0.5 g/kg/d)

Better Survival & Functional Outcome !

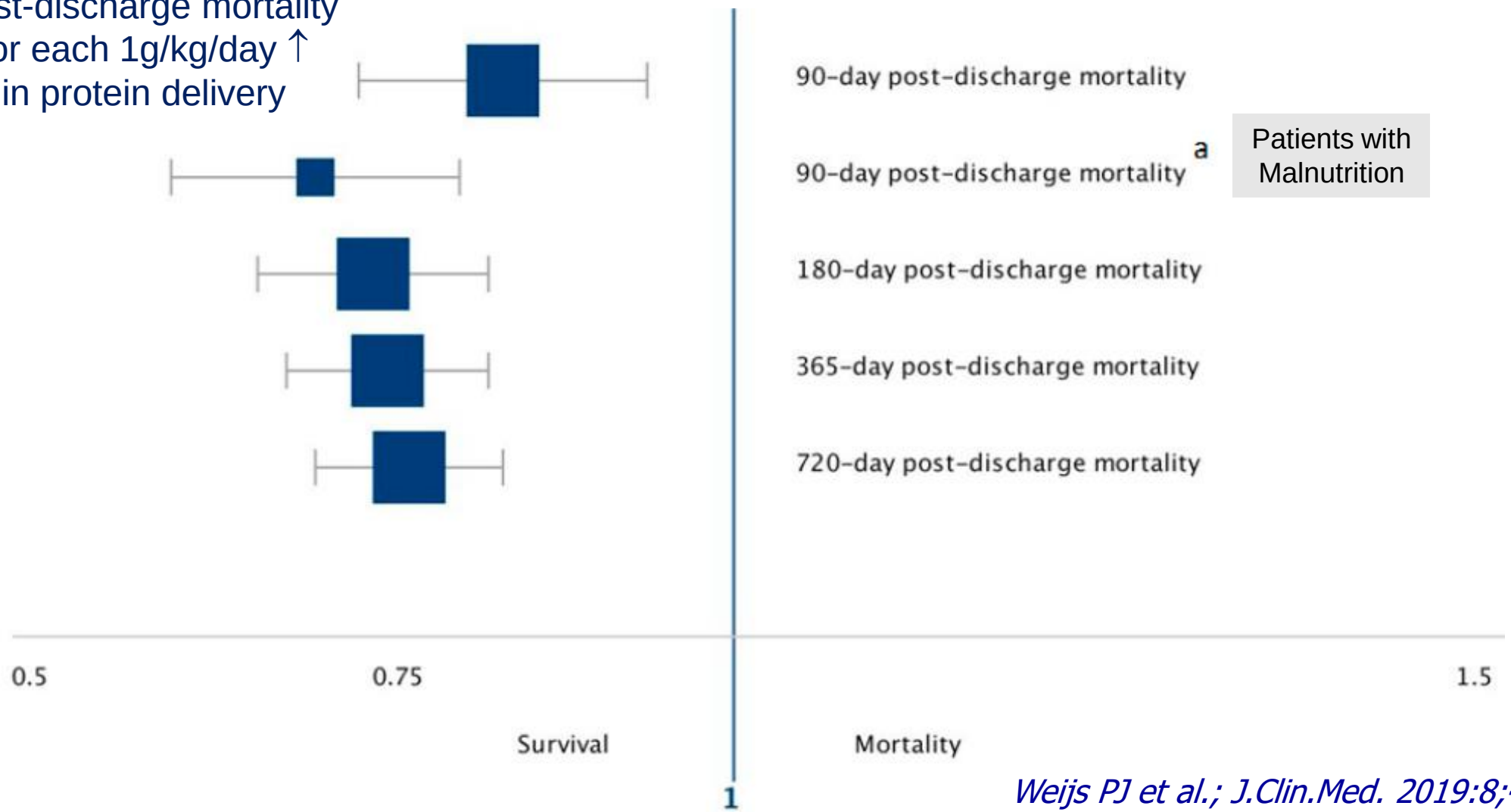
Nicolo M et al. JPEN 2016; 40:45-51

Journal of *Clinical Medicine*

Protein Intake, Nutritional Status & Outcomes in ICU Survivors

A Single Center Cohort Study

Post-discharge mortality for each 1g/kg/day ↑ in protein delivery



Patients with Malnutrition

Weijs PJ et al.; J.Clin.Med. 2019:8;43

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Original article

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, *]

Design: retrospective observational study (2011-2015)

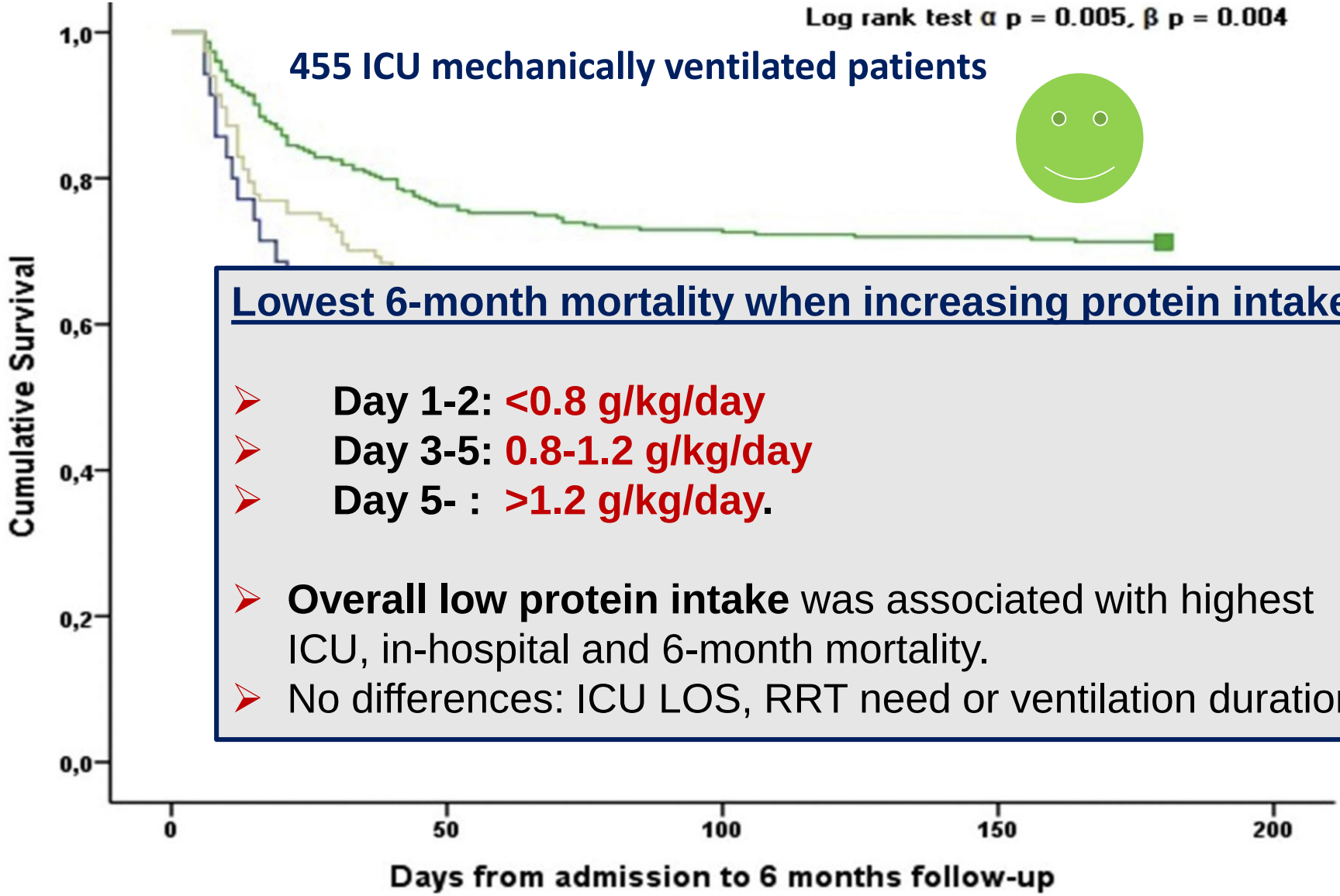
Method: **ICU mechanically ventilated patients for at least 7 days**

3 protein intake categories: **1) < 0.8 g/kg/day**
2) 0.8 -1.2 g/kg/day
3) >1.2 g/kg/day

Endpoint: 6 month mortality

Koekkoek C. et al., Clinical Nutrition 38 (2019) 883-890

The PROTINVENT retrospective study: 6 month survival



Lowest 6-month mortality when increasing protein intake

- **Day 1-2: <0.8 g/kg/day**
- **Day 3-5: 0.8-1.2 g/kg/day**
- **Day 5- : >1.2 g/kg/day.**

- **Overall low protein intake** was associated with highest ICU, in-hospital and 6-month mortality.
- No differences: ICU LOS, RRT need or ventilation duration

Koekkoek C. et al., Clinical Nutrition 38 (2019) 883-890

Observational studies

- Time dependence of the protein dose
- Protein ≥1,2 g/kg/d => mortality↓ after D4-6
  but: increase starting <0.8 g/kg on D1

- Energy input ≅ 80% of the REE during this period
- Septic patients: ↓ protein dose in the early phase
  but ↑↑↑ protein dose in the recovery phase

Achieving protein targets without energy overfeeding in critically ill patients: A prospective feasibility study

Design: prospective feasibility study

Methods: **20 mechanically ventilated non septic patients**

-> High protein-to-energy ratio nutrition (first 4 ICU days)

EN formula: protein-to-energy ratio 82g/1000 kcal (1000 ml)

-> Nutritional prescription was 90% of measured EE

Primary endpoint:

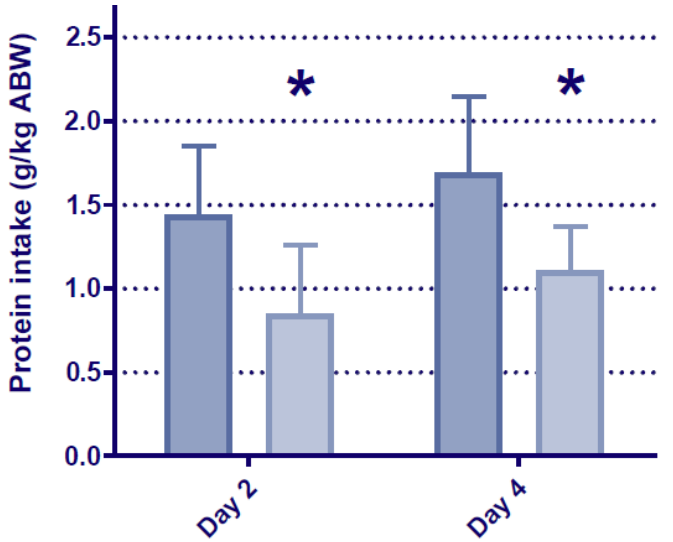
Patients (%) with protein target of 1.2 g/kg ideal BW on day 4

Other endpoints:

- comparison of nutritional intake to matched historic controls
- plasma amino acid concentrations
- gastro-intestinal tolerance and plasma urea concentrations

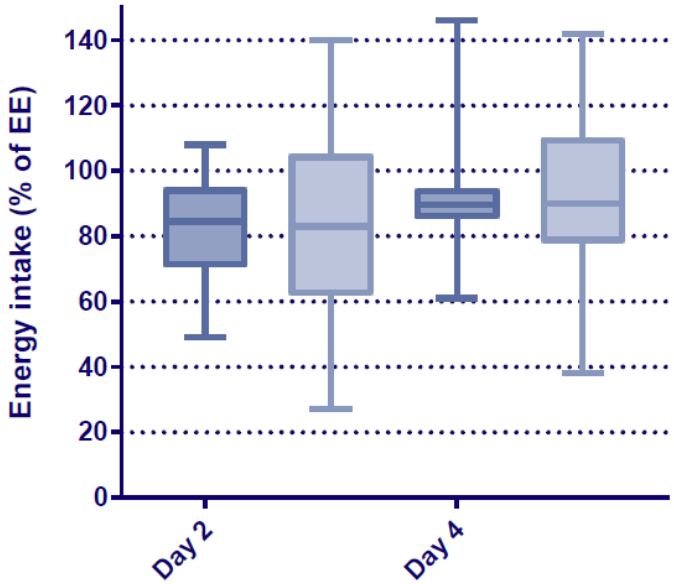
Looijaard W. et al., Clin Nutr 2018 in press

Achieving protein targets without energy overfeeding in critically ill patients: A prospective feasibility study



Study patients (n=20)

Control patients (n=23)



Results:

Protein target of 1.2 g/kg IBW on day 4: 19 patients

95% vs 65% in historic controls (p=0.024)

Mean plasma concentrations of all essential amino acids increased significantly from baseline to day 4

Predefined gastro-intestinal tolerance was good

Limitations

- Small number; no randomization
- Only 4 days use (tolerability during longer use?)

Looijaard W. et al., Clin Nutr 2018 in press

Evidences from Clinical Studies

OBSERVATIONAL

RANDOMIZED

Protein dosage:18 Randomized Controlled Trials

			Patienten	Dauer		verglichene AS/Protein Dosis		
Jahr	Autor	Patienten	(N)	(Tage)	Applikation	(g/kg/Tag)		(g/kg/Tag)
1980	Alexander	Kinder mit Verbennungen	18	42	oral	**3,9**	vs.	3,2
1982	Smith	Gastroent. chirurgische Patienten	30	14	i.v.	**2,3**	vs.	1,7
1983	Serog	Verbrennungen	24	12	enteral	**4,0**	vs.	2,1
1983	Shaw	Mangelernährte Patienten	10	16	i.v.	**2,3**	vs.	1,1
1985	Clifton	Kopfverletzungen	20	7	enteral	**2,6**	vs.	1,5
1985	Twyman	Kopfverletzungen	21	10	enteral	**2,2**	vs.	1,5
1987	Greig	Septische Patienten	9	6	i.v.	**1,2**	vs.	2,3
1989	Rees	EE bedürftige Patienten	118	≥5	enteral	**106-83 g/d**	vs.	71 g/d
1990	Larsson	Verbrennungen/Polytrauma	39	8	i.v.	**1,9-0,6**	vs.	0,0
1991	Pitkänen	Sepsis/Polytrauma	50	2	i.v.	**1,5**	vs.	0,6
1993	van der Heijden	Kritische Kranke, mechanisch beatmet	15	5	i.v.	**1,8**	vs.	1,2
2003	Scheinkestel	Kritisch Kranke mit kont. Hämofiltration	50	6	i.v.	**1,5-2,5**	vs.	2,0
2007	Singer	Kritisch Kranke mit noNV*	14	4	i.v.	**150 g/d**	vs.	75 g/d
2013	Rugeles	Kritisch Kranke	80	≥4	i.v.	**1,4**	vs.	0,8
2016	Ferrie	Kritisch Kranke	119	10	i.v.	**1,1**	vs.	0,9

- 15 / 18 studies (83%) better results with higher protein dosage
- More effective protein dosage
  - ≥ 1.3 g/kg/day - 14 studies (93%)
  - ≥ 1.5 g/kg/day - 11 studies (73%)

Primary outcome
Nitrogen balance !

Kreymann KG et al., Aktuelle Ernährungsmedizin in press

Randomized controlled trials

- No evidence for optimal protein dosage
- Nitrogen balance = outcome parameter
- Urgent need of new studies with relevant outcome parameters !

- The optimal protein dose for all patients will not exist => individual protein loss !
- New studies should include patient groups with defined protein loss.
- Kidney function appears to have a major influence on the protein effect.

EDITORIAL Open Access

Route, early or energy? … Protein improves protein balance in critically ill patients

Pet

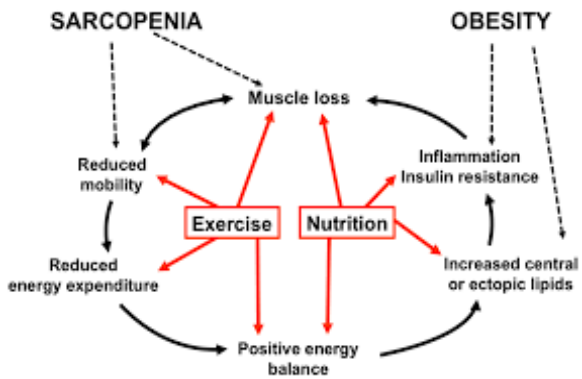
nt muscle loss

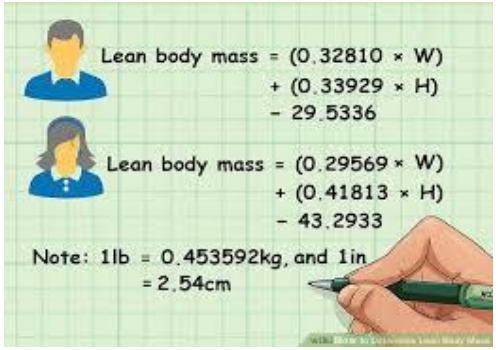
Further studies
RCTs &
post-hoc
observational studies

Weijs P. Critical Care (2018) 22:91

Tailoring Metabolic & Nutrition Therapy in ICU to individual patient's needs

Lean Body Mass (LBM) assessment



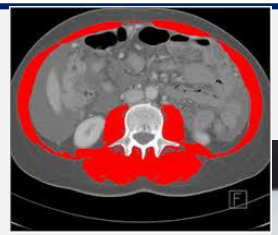


EXERCISE & Nutrition Therapy

Measuring and monitoring lean body mass in critical illness

Wilhelmus G.P.M. Looijaard[a,b,c], Jeroen Molinger[d,e], and Peter J.M. Weijs[a,b,f,g]

KEY POINTS

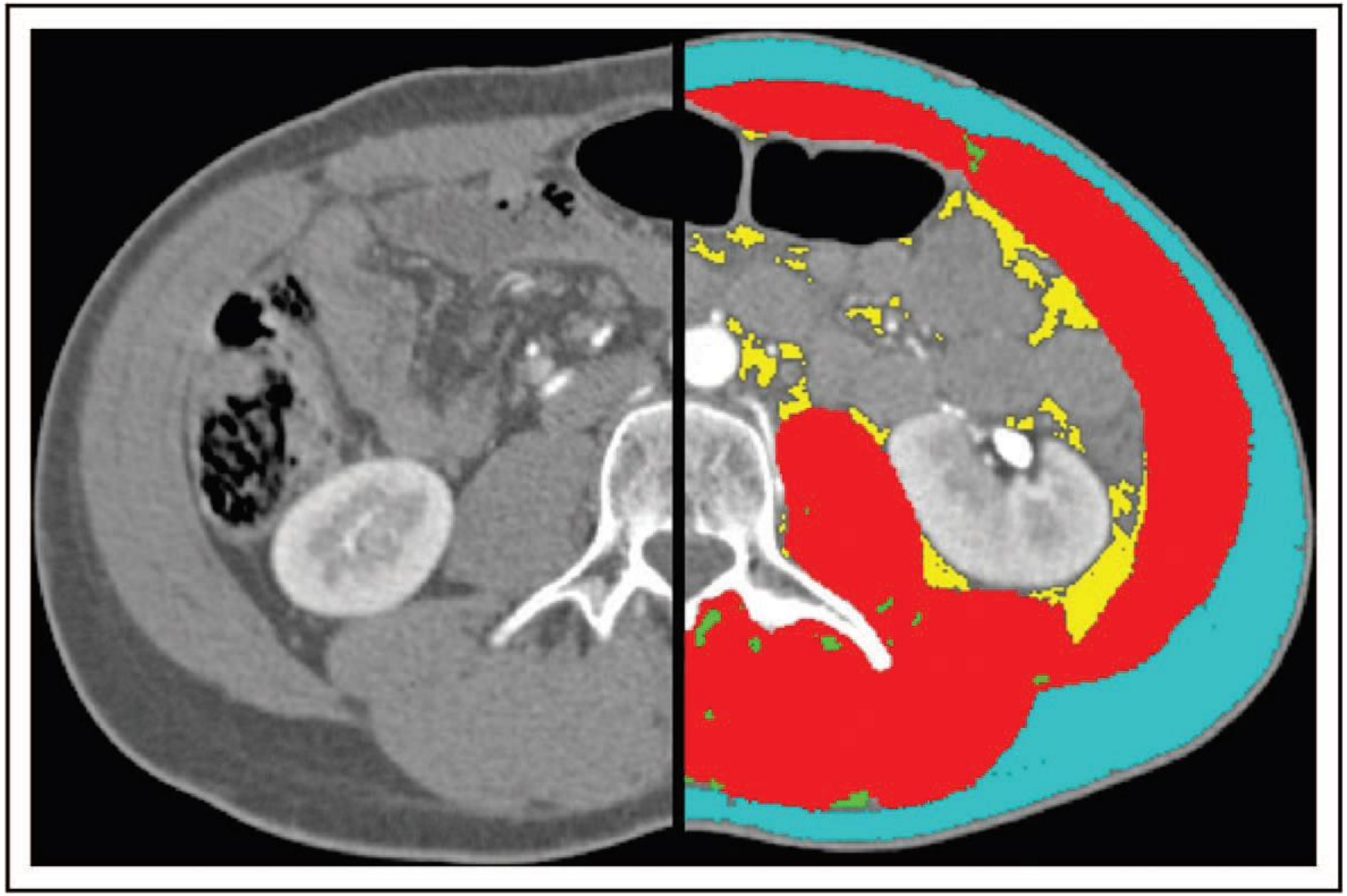


- **CT-scan analysis**
- **Musculoskeletal ultrasound**
- **Bioelectrical impedance analysis (BIA)**
  => tools to measure & monitor lean body mass

- **CT-scan analysis & BIA**
  => screening and identifying patients at risk
- **Musculoskeletal US and BIA**
  => monitoring/ follow-up measurements

Looijaard W. et al., Curr Opin Crit Care 2018, 24:241

CT-scan at the level of the 3rd lumbar vertebra (L3)



Muscle

Adipose tissue sc

Adipose tissue visc.

Adipose tissue intermusc

Looijaard W. et al., Curr Opin Crit Care 2018, 24:241

Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial

*Stefan J Schaller, Matthew Anstey, Manfred Blobner, Thomas Edrich, Stephanie D Grabitz, Ilse Gradwohl-Matis, Markus Heim, Timothy Houle, Tobias Kurth, Nicola Latronico, Jarone Lee, Matthew J Meyer, Thomas Peponis, Daniel Talmor, George C Velmahos, Karen Waak, J Matthias Walz, Ross Zafonte, Matthias Eikermann, for the International Early SOMS-guided Mobilization Research Initiative**

- Multicentre, international RCT (2011-2015)
- 200 patients to receive standard treatment (control; n=96) or intervention (n=104)
  => **Early, goal-directed mobilisation**
- 3 month follow -up

Early, goal-directed mobilisation

-> improved patient mobilisation throughout SICU admission

-> shortened patient length of stay in the SICU

-> improved patients' functional mobility at hospital discharge

Effective in preventing anabolic resistance !

Schaller SJ et al., Lancet 2016; 388: 1377–88

ICU nutritional plan priorities

Amount of nutrition
- Use indirect calorimetry
- Avoid under- and overfeeding

Nutrition risk assessment
- ICU specific tool
- Identify highest risk patients

Route of nutrition
- Early EN whenever possible
- SPN when EN fails to meet energy needs (risk patients)

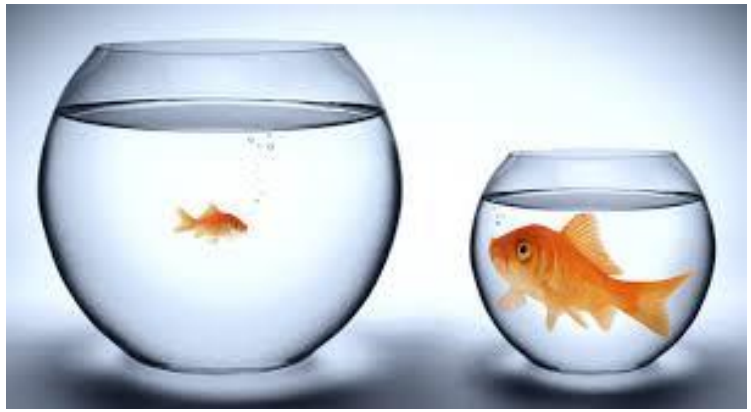
Benefit > Risk

Monitoring
- Daily reassessment & adjustments
- Laboratory data, clinical status, fluid status

Nutritional components
- Energy (balanced fat & CHO)
- Protein 1.3g/kg/d
- Micronutrient, vitamins

adapted from Singer P. ,Curr Op Clin Nutr 2013 to ESPEN 2018

Conclusions



- **Malnutrition & protein deficit are frequent in ICU patients & worsen outcome**
- **Early EN (first 24h)**
- **Avoid under- & overfeeding!**
- **Indirect calorimetry for energy assessment**
- **Stepwise advance of protein delivery**
  < 0.8g/kg/d during acute phase (Day 1)
  ↑↑ 1.3 g/kg from Day 4-6 (ESPEN 2018)
- **Cave ! Septic patient**
- **New solutions (↑ protein / ↓ calories)**
- **Lean body mass assessment (CT/US/BIA)**
  => best basis for protein dosage

- **Don't forget all other rehabilitation tools & therapies !!!**

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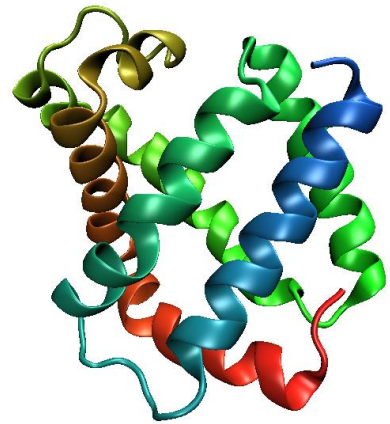
Thank you for your attention



Hippocrates 400 BC

« In all maladies, those who are well nourished do best. It is bad to be very thin and wasted. »

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