Protein requirements from health to ICU (short version)

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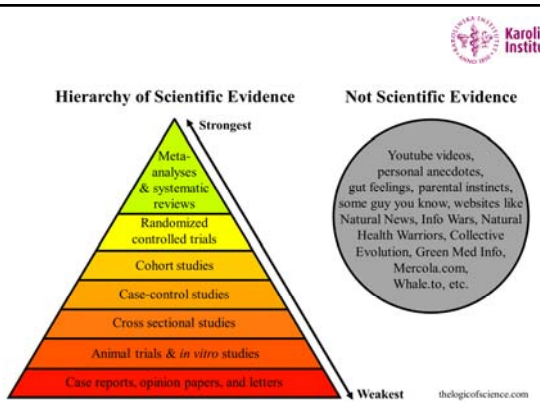
Norsk Selskap for Klinisk Ernæring, Oslo 2017

Disclosure

- Payed lectures for Fresenius-Kabi, Baxter, Nestlé and Nutricia
- Consultant Fresenius-Kabi



Outline

- Protein metabolism
- Methods to study protein metabolism in humans
- Protein requirements in health
- Protein requirements in the elderly
- Protein requirements in disease
- Protein metabolism and requirement in the ICU

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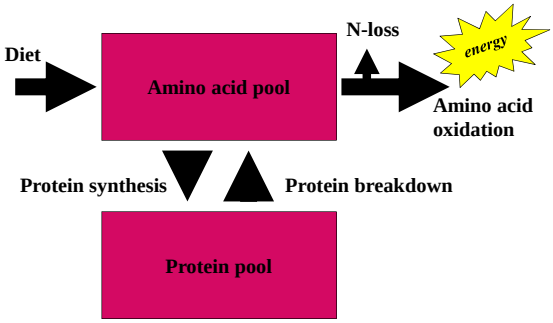
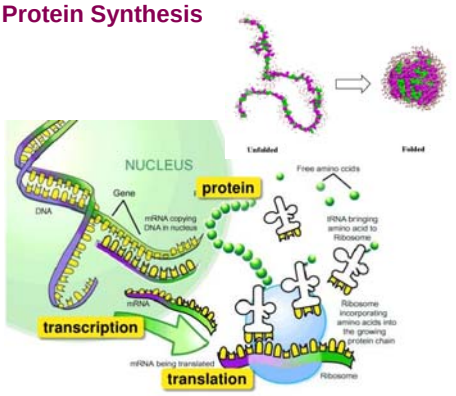
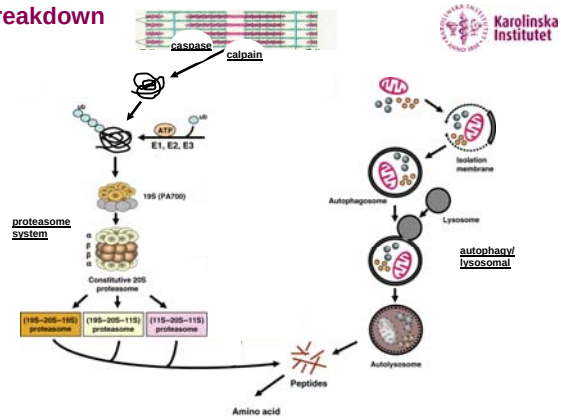
Protein Turnover



Protein Synthesis

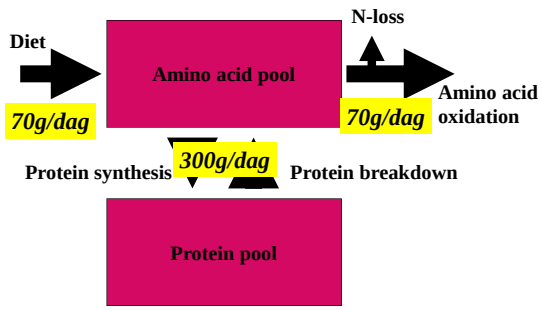


Breakdown

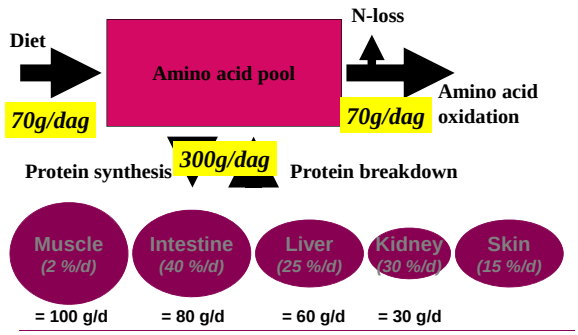


Adapted from Luo H et al. Cardiovasc Res 2009

Protein Turnover



Protein Turnover



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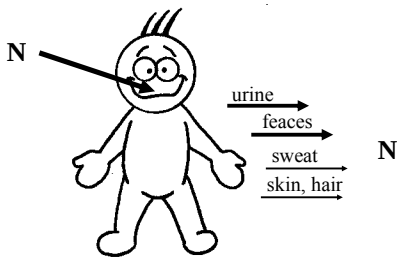
Determining protein requirements

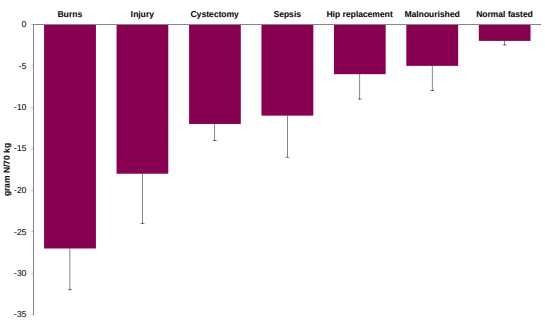
- **RCT with**

- Biochemical/physiological outcomes:
  - Nitrogen balance
  - Muscle or lean body mass
  - Protein turnover

- Clinical outcomes:
  - mortality,
  - quality of life,
  - muscle function

Nitrogen balance measurements





Elwyn et al, Crit Care Clin 1987

Nitrogen balance measurements LIMITATIONS

- Accurate collection of all intakes and excretions needed
- Needs long measurement periods (days)
- Might need longer adaptation times
- Other losses possible (N_2 gas)
- Kidney and liver failure will influence measurements

- Only balance, no turnover

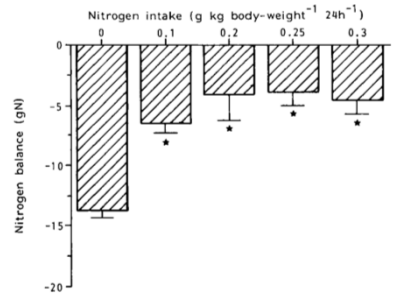
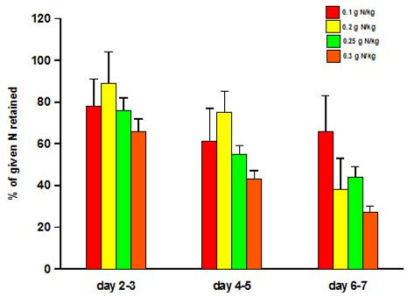


Figure 1 *Mean (s.e.m.) daily nitrogen balance on days 2–8 after severe trauma. The groups receiving nitrogen are compared with the group with no nitrogen intake.* * $P < 0.001$

Larsson et al, Br J Surg 1990



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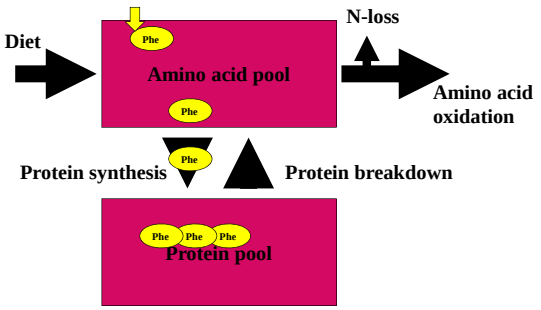
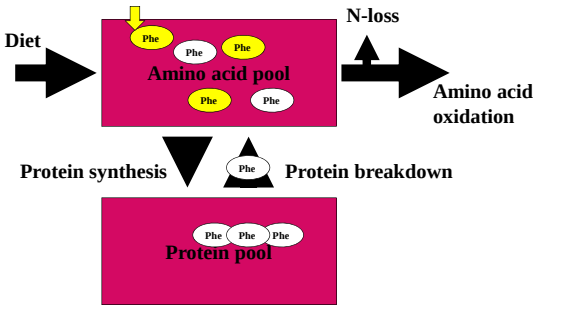
Protein Turnover Measurements



Protein Turnover Measurements



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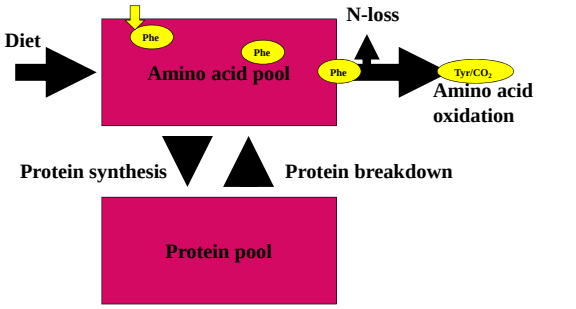
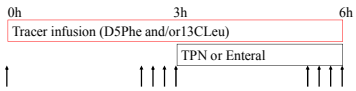


How we practically do this?



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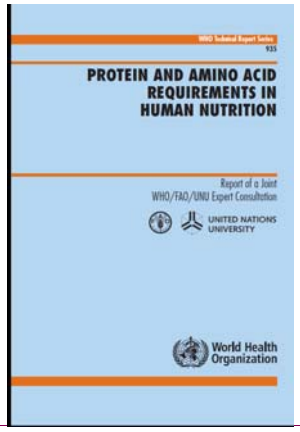

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British Journal of Nutrition (2012), **108**, S3–S21
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Identifying recommended dietary allowances for protein and amino acids: a critique of the 2007 WHO/FAO/UNU report

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(Submitted 30 August 2011 – Final revision received 14 November 2011 – Accepted 6 January 2012)

> Within this conceptual framework the minimum protein requirement (MPR) is defined as: *the lowest level of dietary protein intake that will balance the losses of nitrogen from the body, and thus maintain the body protein mass, in persons at energy balance with modest levels of physical activity, plus, in children or in pregnant or lactating women, the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*

Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults[1–3]

William W Rand, Percy L Pellett, and Vernon R Young

Karolinska Institutet

All studies from WHO report 1985 + Medline search

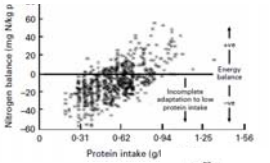
↓

Healthy and nitrogen balance (27 studies; 411 subjects)

↓

Individual data and ≥ 3 levels (19 studies; 271 subjects)

Identifying recommended dietary allowances for protein and amino acids: a critique of the 2007 WHO/FAO/UNU report



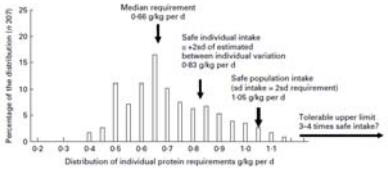


Table 47
Safe level of protein intake for infants, children and adolescent boys and girls

	Boys			Girls		
Age (years)	Weight [a] (kg)	Safe level of protein intake[b] (g/kg/day)	Safe level of protein intake (g/day)	Weight[a] (kg)	Safe level of protein intake[b] (g/kg/day)	Safe level of protein intake (g/day)
0.5	7.8	1.31	10.2	7.2	1.31	9.4
1	10.2	1.14	11.6	9.5	1.14	10.8
1.5	11.5	1.03	11.8	10.8	1.03	11.1
2	12.3	0.97	11.9	11.8	0.97	11.4
3	14.6	0.90	13.1	14.1	0.90	12.7
4–6	19.7	0.87	17.1	18.6	0.87	16.2
7–10	28.1	0.92	25.9	28.5	0.92	26.2
11–14	45.0	0.90	40.5	46.1	0.89	41.0
15–18	66.5	0.87	57.9	56.4	0.84	47.4

[a] WHO reference values (7).
[b] From Tables 33a and 33b.

Table 48
Extra protein requirements for pregnancy and lactation

	Safe intake (g/day)	Additional energy requirement (kJ/day)	Protein:energy ratio
Pregnancy trimester			
1	1	375	0.04
2	10	1200	0.11
3	31	1950	0.23
Lactation			
First 6 months	19	2800	0.11
After 6 months	13	1925	0.11

Biological value protein

Protein Source	Biological Value
Egg, whole	93.7
Milk	84.5
Fish	76.0
Beef	74.3
Soybeans	72.8
Rice, polished	64.0
Wheat, whole	64.0
Corn	60.0
Beans, dry	58.0

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In the previous report (*8*), four nitrogen balance studies in elderly people were reviewed: the one such study included in the meta-analysis, and three others. Taken together these studies were inconsistent and the report concluded that the safe intake of protein should not be lower than 0.75 g/kg per day for older adults and the elderly. Two studies have specifically addressed the question of the extent of any age-related changes in protein requirements, with studies on both younger and older subjects (*71, 72*). No differences were identified and the study design does not allow a requirement value to be predicted with any confidence. A 30-day balance study aimed to test the adequacy of the safe allowance (0.8 g/kg, *73*) showed zero nitrogen balances for the group as a whole, even though the study involved energy intakes that may well have been inadequate. Thus none of these published studies provides convincing evidence that protein requirement of elderly people differs from the protein requirement for younger adults.

Table 10
Estimation of nitrogen requirement in healthy adults

Source of data	Factor	Number of points	Median slope	Median intercept[a]	Median requirement[a]
Individuals	All	235	0.47	−48.1	104.6
		95% CI	(0.44, 0.50)	(−51,−45)	(101, 110)
Climate	Temperate	154	0.45	−45.3	102.8
	Tropical	81	0.50	−51.9	113.3
	***P*-value**		**0.20**	**0.011**	**0.047**
Age	Young	221	0.48	−49.4	103.9
	Old	14	0.31	−36.7	130.5
	***P*-value**		**0.003**	**0.025**	**0.401**
Sex	Male	181	0.46	−49.4	109.3
	Female	54	0.47	−43.1	91.4
	***P*-value**		**0.47**	**0.20**	**<0.001**
Diet	Animal	64	.46	−48.8	104.0
	Vegetable	77	.47	−49.4	106.7
	Mixed	94	.48	−46.6	104.2
	***P*-value**		**0.62**	**0.81**	**0.62**

Special Article

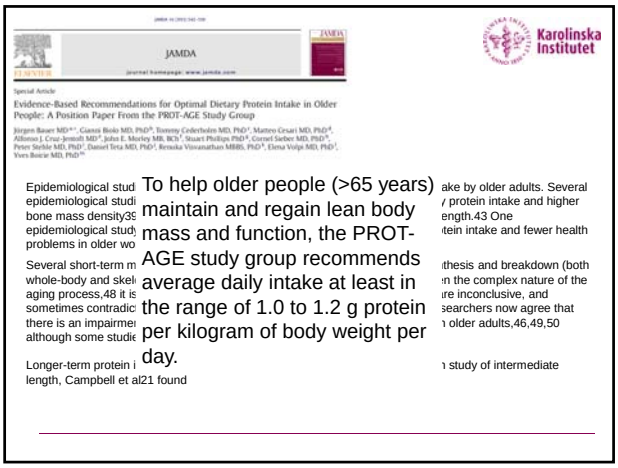
Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group

Jürgen Bauer MD[a,*], Gianni Biolo MD, PhD[b], Tommy Cederholm MD, PhD[c], Matteo Cesari MD, PhD[d], Alfonso J. Cruz-Jentoft MD[e], John E. Morley MB, BCh[f], Stuart Phillips PhD[g], Cornel Sieber MD, PhD[h], Peter Stehle MD, PhD[i], Daniel Teta MD, PhD[j], Renuka Visvanathan MBBS, PhD[k], Elena Volpi MD, PhD[l], Yves Boirie MD, PhD[m]

Epidemiological studies and clinical trials support the need for higher protein intake by older adults. Several epidemiological studies have found a positive correlation between higher dietary protein intake and higher bone mass density; slower rate of bone loss; and muscle mass and strength. One epidemiological study showed a positive association between higher dietary protein intake and fewer health problems in older women.

Several short-term metabolic studies investigated the differences in protein synthesis and breakdown (both whole-body and skeletal muscle) between younger and older adults. Given the complex nature of the aging process, it is not surprising that the combined results of these studies are inconclusive, and sometimes contradictory, for the fasted state. In the fed state, however, most researchers now agree that there is an impairment of the muscle protein anabolic response to meal intake in older adults, although some studies found no difference between older and younger adults

Longer-term protein intake studies in older adults are scarce. In one intervention study of intermediate length, Campbell et al found



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Epidemiological studi ake by older adults. Several epidemiological studi / protein intake and higher bone mass density35 ength.43 One epidemiological study tein intake and fewer health problems in older wo

Several short-term m thesis and breakdown (both whole-body and skel n the complex nature of the aging process,48 it is re inconclusive, and sometimes contradic searchers now agree that there is an impairme older adults,46,49,50 although some studie

Longer-term protein study of intermediate length, Campbell et al21 found

To help older people (>65 years) maintain and regain lean body mass and function, the PROT-AGE study group recommends average daily intake at least in the range of 1.0 to 1.2 g protein per kilogram of body weight per day.

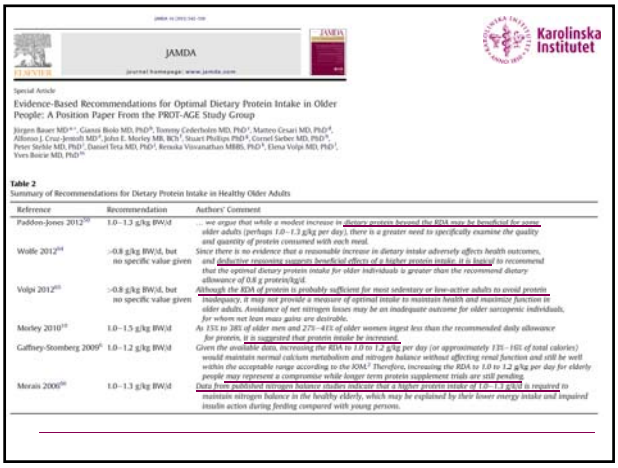

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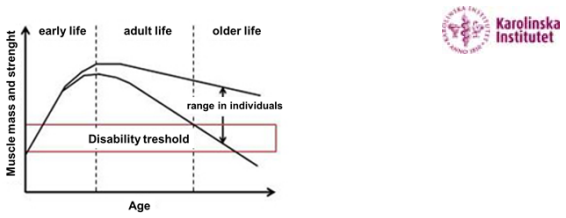
Table 2
Summary of Recommendations for Dietary Protein Intake in Healthy Older Adults

Reference	Recommendation	Authors' Comment
Paddon-Jones 2012[30]	1.0–1.3 g/kg BW/d	*... we argue that while a modest increase in dietary protein beyond the RDA may be beneficial for some older adults (perhaps 1.0–1.3 g/kg per day), there is a greater need to specifically examine the quality and quantity of protein consumed with each meal.*
Wolfe 2012[84]	>0.8 g/kg BW/d, but no specific value given	*Since there is no evidence that a reasonable increase in dietary intake adversely affects health outcomes, and deductive reasoning suggests beneficial effects of a higher protein intake, it is logical to recommend that the optimal dietary protein intake for older individuals is greater than the recommend dietary allowance of 0.8 g protein/kg/d.*
Volpi 2012[85]	>0.8 g/kg BW/d, but no specific value given	*Although the RDA of protein is probably sufficient for most sedentary or low-active adults to avoid protein inadequacy, it may not provide a measure of optimal intake to maintain health and maximize function in older adults. Avoidance of net nitrogen losses may be an inadequate outcome for older sarcopenic individuals, for whom net lean mass gains are desirable.*
Morley 2010[19]	1.0–1.5 g/kg BW/d	*As 15% to 28% of older men and 27%–41% of older women ingest less than the recommended daily allowance for protein, it is suggested that protein intake be increased.*
Gaffney-Stomberg 2009[6]	1.0–1.2 g/kg BW/d	*Given the available data, increasing the RDA to 1.0 to 1.2 g/kg per day (or approximately 13%–16% of total calories) would maintain normal calcium metabolism and nitrogen balance without affecting renal function and still be well within the acceptable range according to the IOM.[5] Therefore, increasing the RDA to 1.0 to 1.2 g/kg per day for elderly people may represent a compromise while longer term protein supplement trials are still pending.*
Morais 2006[86]	1.0–1.3 g/kg BW/d	*Data from published nitrogen balance studies indicate that a higher protein intake of 1.0–1.2 g/kg/d is required to maintain nitrogen balance in the healthy elderly, which may be explained by their lower energy intake and impaired insulin action during feeding compared with young persons.*

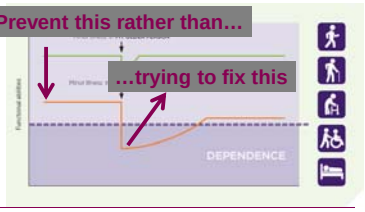
Do elderly need more protein?

- From a **scientific point of view**, I do not see the convincing evidence

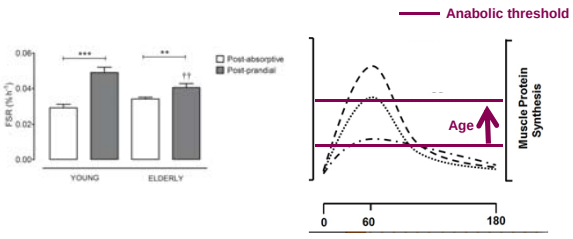


Prevent this rather than…

…trying to fix this



Anabolic resistance



Wall et al, Plos One 2015

Do elderly need more protein?

- NO, from a **scientific point of view**, since I do not see the convincing evidence
- YES, from a **general health perspective**, since it might have a benefit for some elderly (frail, chronic disease) but it certainly doesn't harm

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Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. ▸ Several high-quality studies with consistent results ▸ In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ▸ One high-quality study ▸ Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. ▸ One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. ▸ Expert opinion ▸ No direct research evidence ▸ One or more studies with very severe limitations

Source: GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 1 (modified by the EBM Guidelines Editorial Team)


Clinical Nutrition

ESPEN guidelines on chronic intestinal failure in adults

Disease	Recommendation	Evidence
Intestinal failure	We recommend that the protein and energy requirements for CIF patients be based on individual patient characteristics (e.g. intestinal absorptive capacity as estimated by gastrointestinal anatomy and/or underlying disease) and specific needs (e.g. acute illness, protein malnutrition), and that the adequacy of the regimen is regularly evaluated through clinical, anthropometric, and biochemical parameters.	Very Low
	We do not suggest the routine addition of individual amino acids (glutamine, cysteine, taurine) in the parenteral formula to decrease complications in adults on HPN.	Low
	Many stable patients on HPN are satisfactorily maintained on pre-scriptions that provide 0.8 -1.4 g of protein	


Clinical Nutrition

ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis

Disease	Recommendation	Evidence
CF	The European Food Safety Authority (EFSA) recommends a population reference intake (PRI) of 0.83 g of protein/kg body weight per day in adults. Protein needs are likely to be higher for individuals with CF compared to non-CF individuals, i.e., 20% or more of macronutrient intake, consistent with protein intake needs for individuals with other inflammatory diseases	-


Clinical Nutrition

ESPEN endorsed recommendations: Nutritional therapy in major burns

Disease	Recommendation	Evidence
Burn injury	Protein requirements, are higher than in other categories of patients, and should be set around 1.5-2.0 g/kg in adults and 1.5-3 g/kg/day in children.	Very Low (D)
	Glutamine. Currently, it is therefore difficult to recommend a precise dose, a route, or duration of administration.	
	Currently, there is no evidence in the literature to recommend arginine supplementation in burn patients.	

Parenteral nutrition

Disease		Amount	Evidence
Acute Renal Failure	Conservative therapy, mild catabolism	0.6–0.8 (max. 1.0) g/kg/d	Low (C)
	Extracorporeal therapy, moderate catabolism	1.0–1.5 g/kg/d	Low (C)
	CCRT, severe hypercatabolism	Up to maximum 1.7 g/kg/d	Low (C)
Surgery (peri-operative)		1.5 g/kg ideal body weight	Moderate (B)
Oncology		Recommendations range between a minimum amino acid supply of 1 g/kg/day and a target of 1.2–2 g/kg/day	(Very Low (D))

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Critical illness

Disease	Amount	Evidence
ESPEN (2009)		
ASPEN (2016)		

Critical illness

Disease	Amount	Evidence
ESPEN (2009)	When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight per day in conjunction with an adequate energy supply	Moderate (B)
ASPEN		

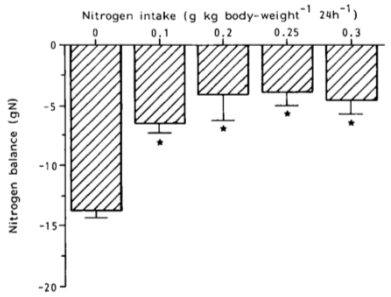


Figure 1 *Mean (s.e.m.) daily nitrogen balance on days 2–8 after severe trauma. The groups receiving nitrogen are compared with the group with no nitrogen intake.* * $P < 0{\cdot}001$

Larsson et al, Br J Surg 1990

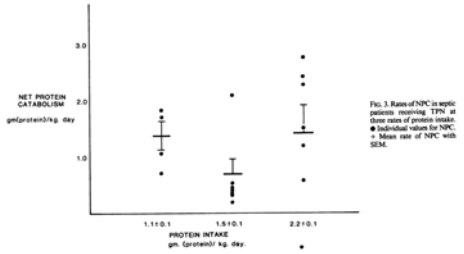


Fig. 3. Rates of NPC in septic patients receiving TPN at three rates of protein intake. ● Individual values for NPC. + Mean rate of NPC with SEM.

Shaw et al, Ann Surg 1987

Critical illness

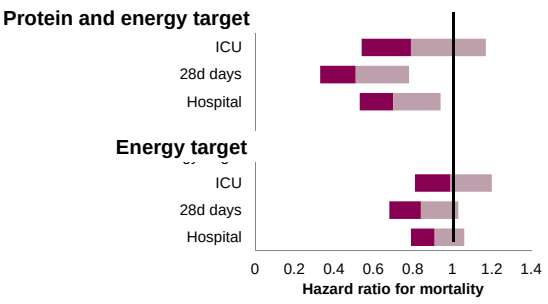
Disease	Amount	Evidence
ESPEN (2009)	When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight per day in conjunction with an adequate energy supply	Moderate (B)
ASPEN	Protein requirements are expected to be in the range of 1.2–2.0 g/kg actual body weight per day	Very low (D)

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

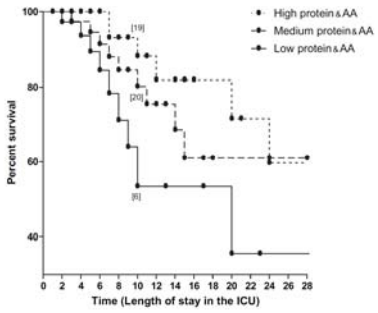
	Protein and Energy Target	Energy Target
Model 0[b]		
Intensive care unit	0.91 (0.64–1.31), $P = .626$	1.03 (0.86–1.25), $P = .731$
28 d	**0.59 (0.40–0.88), $P = .010$**	0.90 (0.74–1.09), $P = .291$
Hospital	**0.76 (0.58–0.99), $P = .041$**	0.93 (0.81–1.08), $P = .339$
Model 1[c]		
Intensive care unit	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), $P = .137$

[a]Presented as hazard ratio (95% confidence interval). Bold font indicates significance ($P < .05$).
[b]Unadjusted.
[c]Adjusted for sex, age, body mass index, diagnosis, hyperglycemic index, and Acute Physiology and Chronic Health Evaluation II score.
[d]Additionally adjusted for time to energy target and use of parenteral nutrition.

Weijs et al, JPEN 2012



Weijs et al, JPEN 2012



Allingstrup et al, Clin Nutr 2012

Intervention studies

Appropriate protein provision in critical illness: a systematic and narrative review[1–3]

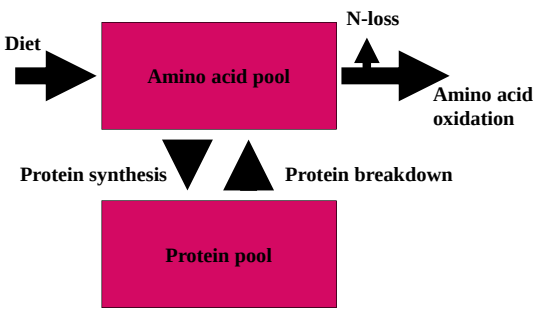
L. John Hoffer and Bruce R Bistrian

Am J Clin Nutr 2012;96:591–600. Printed in USA. © 2012 American Society for Nutrition

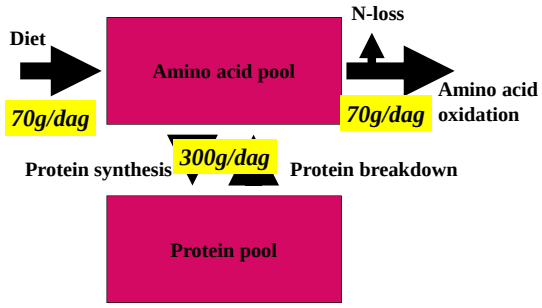
Total nr studies	13
Randomized	4
Nitrogen balance	12
Turnover	3
Body composition	1
Amino acid profiles	1
Outcome	2

Results: The limited amount and poor quality of the evidence preclude conclusions or clinical recommendations but strongly suggest that 2.0–2.5 g protein substrate · kg normal body weight^{-1} · d^{-1} is safe and could be optimum for most critically ill patients. At the

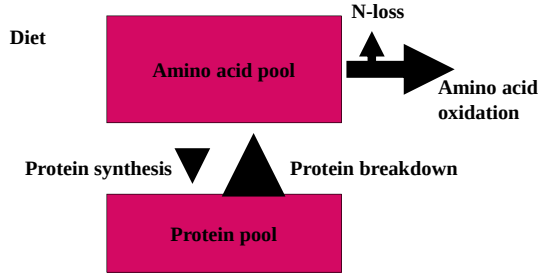
Protein Turnover



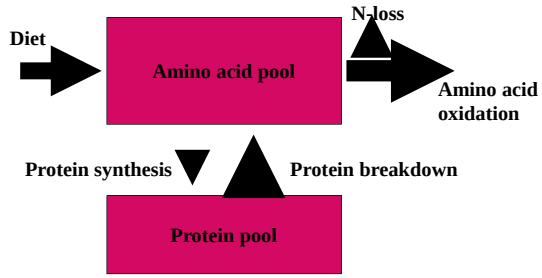
Protein Turnover



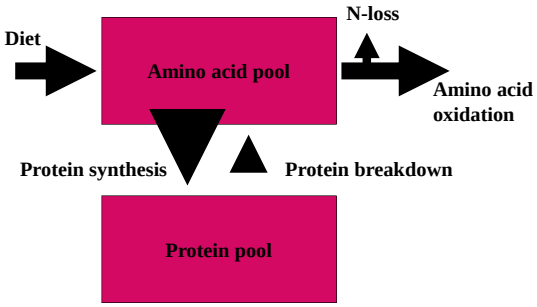
Protein Turnover with critical illness

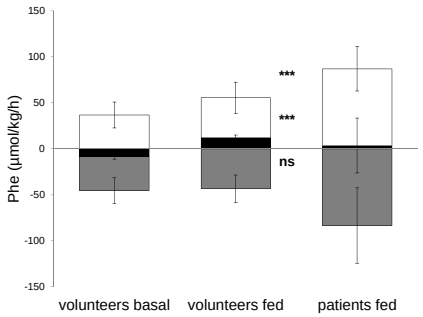


Protein Turnover with critical illness

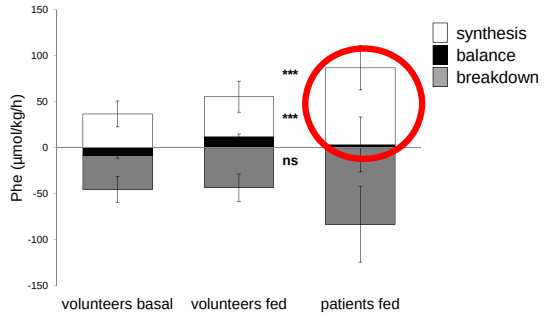


Protein Turnover with critical illness

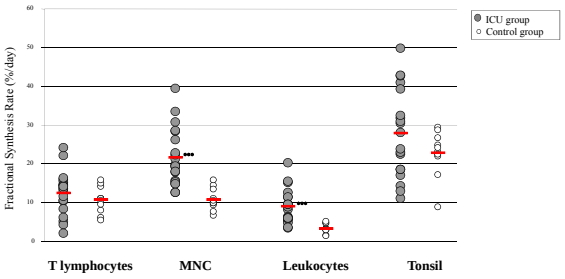




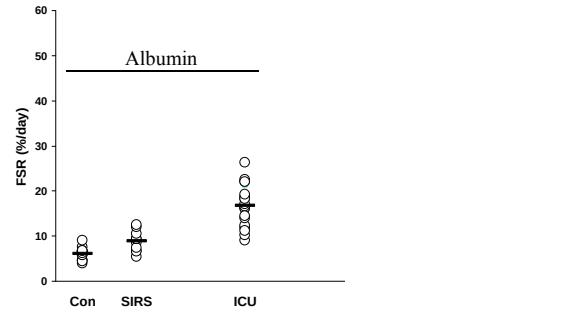
Rooyackers et al, Clin Nutr 2014



Rooyackers et al, Clin Nutr 2014

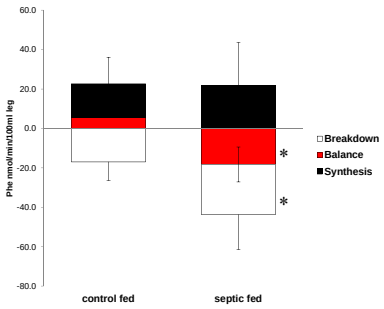


Januskiewicz et al, J Clin Immun 2007

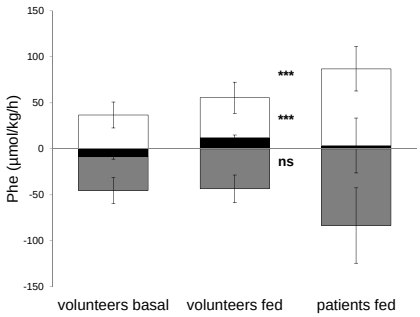


Barle et al, ICM 2001, Clin Sci 2006

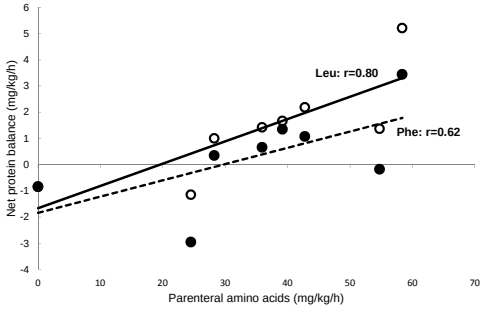
Rooyackers et al, Clin Nutr 2014



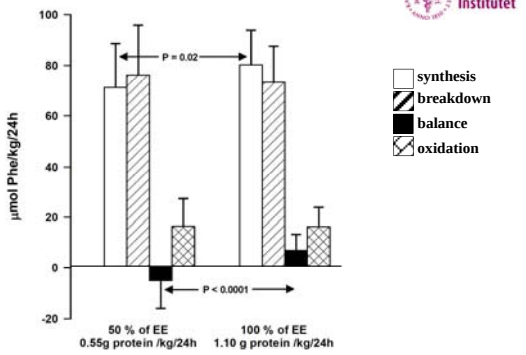
Klaude et al, Clin Sci 2011



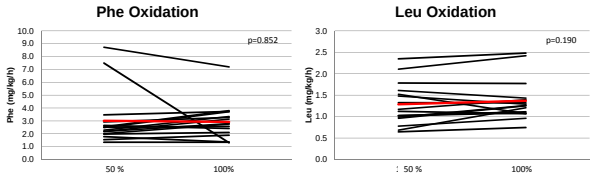
Rooyackers et al, Clin Nutr 2014



Rooyackers et al, Clin Nutr 2014

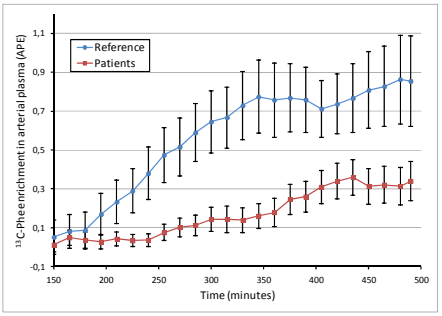


Berg et al, Crit Care 2013

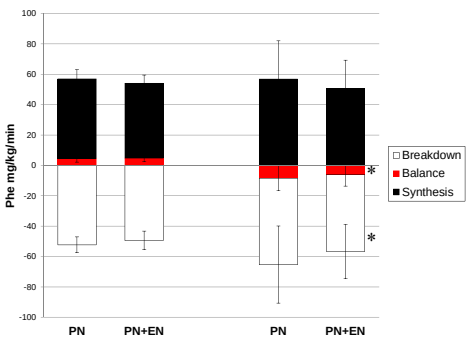


Berg et al, Crit Care 2013

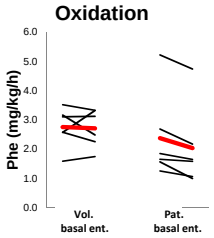
^{13}C Phe enrichment in arterial plasma



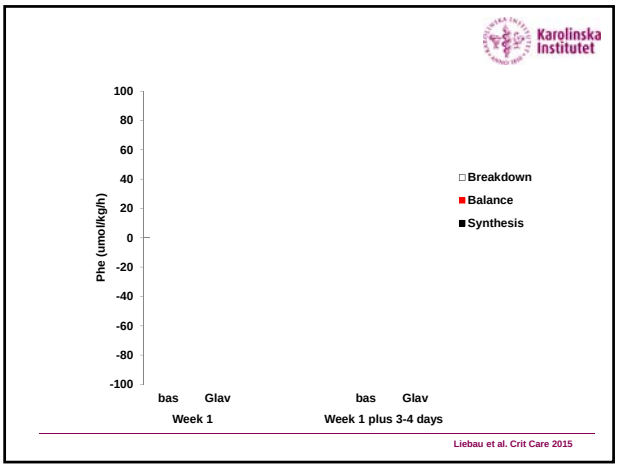
Liebau et al., AJCN 2015

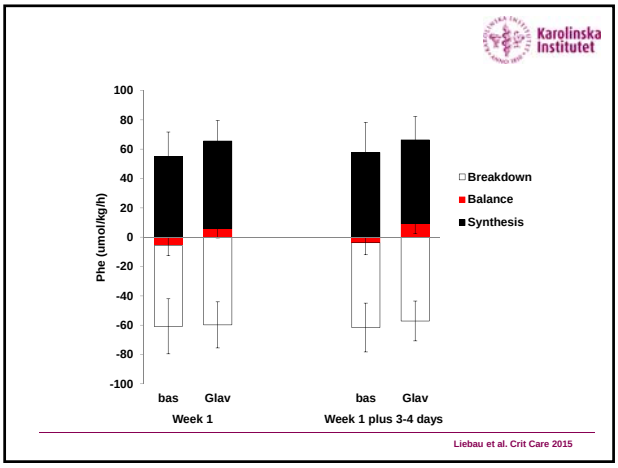


Liebau et al., AJCN 2015



Liebau et al., AJCN 2015


Karolinska Institutet
100
80
60
40
20
0
-20
-40
-60
-80
-100
Phe (umol/kg/h)
Breakdown
Balance
Synthesis
bas
Glav
bas
Glav
Week 1
Week 1 plus 3-4 days
Liebau et al. Crit Care 2015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Phe (umol/kg/h)
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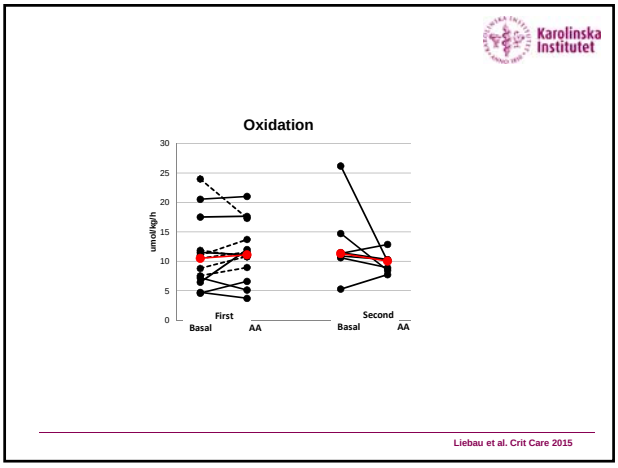
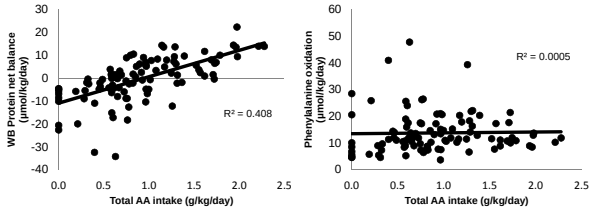
Week 1 plus 3-4 days
Liebau et al. Crit Care 2015


Karolinska Institutet
Oxidation
30
25
20
15
10
5
0
umol/kg/h
First
Basal
AA
Second
Basal
AA
Liebau et al. Crit Care 2015

Protein turnover and feeding



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Protein requirements from health to ICU

- Healthy >0.8 g/kg/day
- Elderly 1.0-1.2 g/kg/day
- Disease Depends on disease but in general acute disease are recommended to get bit more: >1.0 g/kg/day
- ICU 1.3-1.5 g/kg/day
- Burn 1.5-2.0 g /kg/day

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