Protein Delivery in the Critically Ill Patient

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Objectives

- Discuss rationale for adequate protein delivery in critically ill patients
- Present barriers to providing adequate protein
- Discuss potential solutions for improving protein delivery to critically ill patients

Hospital Malnutrition

- ~1/3 of patients malnourished on hospital admission
  - If left untreated, 2/3 will further decline
- ~1/3 of patients become malnourished during hospitalization

Tappenden KA, et al. JPEN 37:482-497

Hospital Malnutrition

Adverse Effects on Patient :

Morbidity

Mortality

Hospital Length of Stay

Metabolic Comparisons

	Starvation	Stress
REE	↓	↑↑
RQ	↓	↑
Primary Fuels	Fat	Mixed
Glucagon	↑	↑
Insulin	↓	↑
Gluconeogenesis	↓	↑↑↑
Blood Glucose	↓	↑↑
Ketogenesis	↑↑	↓
Plasma Lipids	↑	↑↑
Protein Synthesis	↑	↑↑
Proteolysis	↑	↑↑↑
Urine Nitrogen Loss	↑	↑↑↑

Clinical Consequences Metabolic Stress

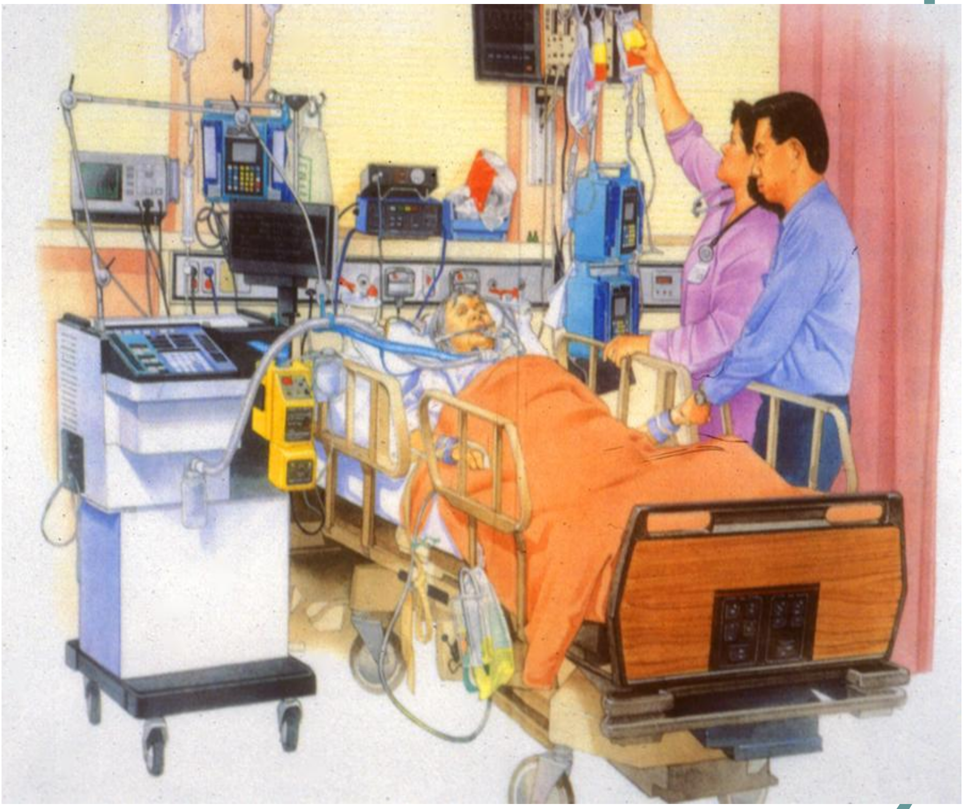
- Hypermetabolism
- Hypercatabolism
  - 12 to 35 gm Nitrogen/day (75-129 gm protein)
- Hyperglycemia
- Peripheral Insulin resistance (~50% ↓)
- Fluid & electrolyte changes

Clinical Consequences of Protein Catabolism

- ↓ Visceral proteins
- ↑ Acute phase proteins
- ↓ Coagulation capacity
- Impaired immune response/ ↑ Infection rate
- Impaired wound healing
- Altered gut function
- Skeletal muscle wasting
- ↓ Muscle function / ↑ Weakness
  - Inhibits sufficient cough, prolongs vent need

Contributors to Protein Loss

- Metabolic insult
- Paralyzing agents
- Sedation
- Bed rest
- Inotropic support



Protein Mass Loss in Critical Illness
Who is affected?

- ICU short stay (24-48 hr)
  - LBM loss minimal effect on outcome
- Severe Sepsis (1)
  - First 10 d - 67% from skeletal muscle
  - > 10 d – from viscera
  - 1.8 kg of protein
- Blunt trauma (2)
  - First 15 d – 70% from skeletal muscle
  - 0.5 kg of protein in 8 days
- Critical surgical illness (3)
  - Large nitrogen losses
  - Not much cardiac mass and function loss

1. Plank, et al. Ann Surg 228:146, 1998
2. Monk, et al. Ann Surg 223:395, 1996
3. Hill, et al. Ann Surg 226:191, 1997

Protein Turnover in Critical Illness

- Increased protein breakdown
  - (25-127%)
- Increased whole body protein synthesis
  - (16-47%), varies between tissues
  - Acute phase response, wound repair, immune response, etc)
- Negative protein balance
- Increased amino acid flux from periphery to liver

Obled, et al. Curr Opin Clin Nutr Metab Care 5:189, 2002

Energy Intake on Patient Outcome

- Negative energy balance = negative effects on outcome in ICU patients
  - Increased infectious complications (1)
- Meta-analysis (2)
  - Early EN = Reduced:
    - Infection risk
    - Hospital LOS
- Meta-analysis (3) – inconclusive
- Studies with energy intake on protein mass & turnover vary
  - disease type, nutritional status, type of feeding

1. Villet, et al. Clin Nutr 24:502, 2005
2. Marik, Zaloga. CCM 29:2264, 2001
3. Wasiak, et al. Cochrane Database Syste Rev 3, CD005489, 2006

Energy Intake on Patient Outcome Summary

- Nutritional support may limit, but not stop loss of body protein mass in Critical Illness

Protein Intake on Patient Outcome?

Table 1 Overview of relevant studies with protein delivery and outcome in mechanically ventilated critically ill patients.

	EPaNIC	TICACOS	SWISS	EDEN trial (Pilot-200 points)	EDEN trial (Full MCT-1000 points)	Arabi trial	Alberda International Critical Care Nutrition Survey	Weijs Dutch trial	Allingstrup trial (Danish)
ICU LOS (Median)	3.5 days	12 days	ICU LOS >5 days			13.1	12	19	8
Hospital LOS (Median)	15	25				68.7	24.2	39	
Mech. vent days (Median)	2	10.75		5.6 days (mean vent days in survivors)		11.9	9.0	17	
Mortality									
ICU	6.2%	25.4%				19.6		20.4	22.5%
Hospital	10.65%	38.3%		21%		36%		34.4%	
Post-discharge	11.2%	47%	23%		22.7%	38.6%	29.1%		
BMI (mean, unless indicated)	51.6% pts from 25–35	28.45	26.15	28.7	30	28.5	<25, >35 for optimal benefit of calorie delivery	26	25.6
Protein delivery	<60 g per day- both groups	Study-76 g per day (~1.0 g/kg per day)		Full energy – 54 g per day	Not reported in article	Full feed – 43.6 g per day	Recommended	Protein + energy target- 89 g per day (1.31 g/kg per day)	Mean protein delivery by group:
	(Mean: 0.8 g/kg after 3 days)	Cont-53 g per day (0.68 g/kg per day)		Trophic-11 g per day (1st 7 days then ~50 g per day)	~0.6–0/8 g/kg per day in full feeding group and after 7 days in both groups	Underfed – 47.5 g per day	1.5–2.0 g kg per day	Energy target- 78 g per day (1.06 g/kg per day)	High protein- 1.46 g/kg per day
				~ 0.8 g/kg per day for both groups after 7 days	[Personal communication- T. Rice (primary author)]	(Mean: ~0.6 g/kg per day for both groups)		No target = 67 g per day	Medium protein- 1.06 g/kg per day
								(0.83 g/kg per day)	Low protein-0.79 g/kg per day
Clinical benefit of SPN or additional calorie/protein delivery	(–)	(+) – Mortality	(+) – Infection	(–)	(–)	(–)	(+) – Mortality	(+) – Mortality hazard for reaching protein and energy target	(+) – Mortality hazard for increased protein delivery

More limited data for the Swiss trial due to only abstract data being available. EDEN trials utilized ICU-free, Hospital-free, and Mech. vent-free days as outcome measures so more limited comparison data are available. EPaNIC, Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients.

Weijs and Wischmeyer. Curr Opin Clin Nutr Metab Care, 16:194, 2013

Arabi Trial

- RCT permissive underfeeding (60-70%) energy target vs target feeding (90-100%)
- Harris-Benedict equation + stress factors
- Actual energy intake
  - 59% (1067 kcal) vs 71% (1252 kcal)
- Protein intake: 0.6 g/kg/d
- No difference:
  - Mortality: ICU, 28-day, 180-day
  - ICU LOS, infection rate
- Difference: Hospital mortality with permissive underfeeding

Arabi, et al. Am J Clin Nutr 93:569, 2011

EDEN Trial

- PRT, ALI patients (age: 52 yr)
- Average BMI: 30
- Trophic vs full feeding first 6-days intervention
- Actual energy intake:
  - 25% (400 kcal) vs 80% (1300 kcal) target
  - Attained Study day 1 (pts included within 72hr intubation)
- Actual protein intake: 0.6-0.8 g/kg/day
- No Difference:
  - Mortality: 60-day, ventilator-free days, infection rate
- Less GI complaints trophic feeds
- Summary: 25% energy target during first 6-days doesn’t affect outcomes vs 80% energy target
- Received ~50% protein needs, were likely not deficient in LBM

Rice, et al. JAMA, 307:795, 2012

Allingstrup, et al Trial

- Observational study (n=113)
- Critically ill septic patients
- Energy & protein via indirect calorimetry and nitrogen excretion
- Protein provided as: 0.8, 1.0, 1.4 g/kg/d
- Reduction in:
  - Mortality with increased protein
  - Energy no effect

Allingstrup, et al. Clin Nutr 31:462, 2012

Alberda Trial

- ICU patients with mechanical ventilation >72 hrs (n=2772, 165 ICUs)
  - Inverse relationship between odds of mortality and total calories received
  - Benefited BMI <25 and >35
  - Feeding +1000 kcal nearly halved odds of 60-day mortality (p=.014)
- Similar results with feeding additional 30gm of protein
- ? LBM critical for ICU outcomes
- **BMI <25 and >35 insufficient LBM reserves to optimally survive ICU stay without more aggressive energy and protein provision?**

Alberda, et al. Int Care Med 35:1728, 2009

Summary

- Energy target may not be most important nutritional target to meet
- Difficult to determine effect of energy versus protein
- Administration of amino acids or protein improves total body protein mass and protein turnover in critical illness
- Doses of 1.2-1.5 g/kg body weight/day

Guidelines

- SCCM/ASPEN
    - 25-30 kcal/kg/day, Protein: 1.2-2.0 g/kg/day
  - Obesity
    <u>Energy</u>
    - 60-70% target energy requirements

    <u>Protein</u>:
    - BMI 30-40, ≥2.0 gm/kg IBW/day
    - BMI >40, ≥2.5 gm/kg IBW/day
- ESPEN
    - 20-25 kcal/kg/d [first 72-96 hr], then up to 25-30 kcal/kg/d
    - No mention of protein enterally, parenteral 1.3-1.5 g/kg/d IBW
- European Society of Intensive Care Medicine
  - Cautions against > 1.8gm/kg/d
- American Burn Association
  - Protein varies: 1.5-3.0 gm/kg/d

What's the Reality??

Failure to Provide Adequate Nutrition *WHY?*

- Worldwide survey (1)
  - Energy and protein delivery ~45-55% of prescribed
- Poor volitional intake
- Financial concerns
- Advanced stage of disease
- Low priority
- Lack of knowledge or screening
- Controversial clinical outcomes

1. Sinuff t, et al. JPEN, 34:660, 2010

Weight and LBM Loss During Hospitalization *WHY??*

- Metabolic stress and consequences
- No nutrition intervention – procedures, overlooked
  - EN commonly fails to achieve >50% protein goal
- Pain (general, abdominal)
- Incontinence
- Nausea, vomiting
- Depression
- Feeding difficulties
- Unpalatable foods, altered feeding schedules
- Inadequate Diets

Diet Order

- Pt made NPO upon admission
  HD 3 – diet ordered
  HD 5 – NPO for OR
  POD 4 (HD 9) same diet for 3 days
  - **Clear Liquid Diet with Restrictions**: No concentrated sweets, low sodium
- Patient received
  - Low sodium broth
  - Sugar-free jello
  - Diet soda
  - Unsweetened coffee and tea

Table 1. Protein Intake Inspired by Recent Prospective Nutrition Studies in the Intensive Care Unit.

Studies	Protein Intake in Control Group	Protein Intake in Study Group
Van den Berghe et al,[9] g/kd/d	0.85	0.80
Rice et al,[10] g/d	11	54
Arabi et al,[11] g/d	47.5	43.6
Singer et al,[12] g/d (g/kg/d)	53 (0.68)	76 (1)
Heidegger et al,[13] g/d	56	79
Casaer et al,[14] g/d	<60	<60
Weijs et al,[8] g/d	67	89

Adapted from Singer and Pichard.[25]

Singer and Cohen, JPEN, 37:294, 2013

What’s Happening?

- Main target nutrition prescriptions on *energy* requirements
- Protein intake secondary target
- If enteral formulas provide energy target, many not meeting protein target
- Lack of ability to evaluate nitrogen needs
  - ? Choose markers according to main aims of AA provision
  - Ex: if LBM is targeted – dual-energy x-ray absorptiometry, bioimpedance, magnetic resonance imaging measurements
  - Ex: glutamine supplementation – oxidative stress, glutathione measurement

What Can Be Done?

- Collaboration amongst multiple clinical disciplines
- Protocols
  - High protein feedings
  - Supplement protein until energy targets met
- Add protein supplements:
  - to low protein diets (ex: Clear Liquids)
  - Until oral diet fully tolerated
- Use liquid protein supplements to provide oral medications [Med-Pass]

Summary

- Malnutrition not just energy deficiency
- Protein key macronutrient for improving patient outcomes
- Important to maximize delivery early and maintain
- Interdisciplinary approach
- Education and awareness key to success

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