Proteine im Fokus
Der Patient auf der Intensivstation

PD Dr. med. Claudia Heidegger
Service des Soins Intensifs
Genève

Inselspital Bern, 19. Juni 2019
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

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
- Altered Glucose Metabolism
  - peripheral insulin resistance
  - stimulation of hepatic gluconeogenesis
- Sodium & water retention
- \( \uparrow \) Lipolysis/lipid oxidation
- Protein depletion: multifactorial

Catabolism

Hyperglycemia

Positive fluid balance

Major body fuel

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
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 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

Energy-protein requirements depend on disease state & nutritional status
3 different phases in critical illness

Days 1-2
- Acute Phase
  - Early Period
- Metabolic instability
- Catabolism
- Muscle wasting +++

“EBB phase”

Days 3-7
- Acute Phase
  - Late Period
- Metabolic instability +/-

“FLOW phase”

Late Phase
- Rehabilitation
  - Or
- Chronic Phase

Anabolism

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”
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 ???

ONE SIZE DOES NOT FIT ALL.
KEEP TRYING...

And eventually you will find the perfect fit.
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 ill is a difficult art

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

<table>
<thead>
<tr>
<th>Jahr</th>
<th>Organisation</th>
<th>Steigerung</th>
<th>Start</th>
<th>Proteindosis (g/kg KG) am Ende der Akutphase</th>
<th>AS-Dosis (g/kg KG) generell</th>
<th>Einschränkung</th>
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<tr>
<td>2016</td>
<td>ASPEN</td>
<td>nein</td>
<td>n.a.</td>
<td>1,2 - 2,0</td>
<td>n.a.</td>
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<tr>
<td>2018</td>
<td>ESPEN</td>
<td>ja</td>
<td>n.a.</td>
<td>1,3</td>
<td>+?</td>
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<td>DGEM</td>
<td>ja</td>
<td>0,75</td>
<td>1,0</td>
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<td>2018</td>
<td>DGEM (Minderheitenvotum)</td>
<td>ja</td>
<td>&lt;0,8</td>
<td>≥1,2</td>
<td>± 0,0</td>
<td>bei nicht septischen Patienten</td>
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</tbody>
</table>

KG = aktuelles Körpergewicht, AS = Aminosäuren

*Kreymann KG et al., Aktuelle Ernährungsmedizin in press*
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 h, 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?**

**Improved outcome: mortality/infections?**
### Recommendation

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

<table>
<thead>
<tr>
<th>Model 0</th>
<th>Protein and Energy Target</th>
<th>Energy Target</th>
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<tbody>
<tr>
<td></td>
<td>0.91 (0.64–1.31), P = .626</td>
<td>1.03 (0.86–1.25), P = .733</td>
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<tr>
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<td>0.59 (0.40–0.88), P = .010</td>
<td>0.90 (0.74–1.09), P = .291</td>
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<tr>
<td></td>
<td>0.76 (0.58–0.99), P = .041</td>
<td>0.93 (0.81–1.08), P = .339</td>
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</table>

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Protein and Energy Target</th>
<th>Energy Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.79 (0.54–1.17), P = .242</td>
<td>0.99 (0.81–1.20), P = .886</td>
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<tr>
<td></td>
<td>0.51 (0.33–0.78), P = .002</td>
<td>0.84 (0.68–1.03), P = .085</td>
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<tr>
<td></td>
<td>0.70 (0.53–0.94), P = .017</td>
<td>0.91 (0.79–1.06), P = .233</td>
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</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>Protein and Energy Target</th>
<th>Energy Target</th>
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<tbody>
<tr>
<td></td>
<td>0.72 (0.48–1.09), P = .116</td>
<td>0.98 (0.80–1.19), P = .834</td>
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<tr>
<td></td>
<td>0.40 (0.26–0.64), P &lt; .001</td>
<td>0.79 (0.64–0.97), P = .024</td>
</tr>
<tr>
<td></td>
<td>0.62 (0.46–0.84), P = .002</td>
<td>0.89 (0.77–1.04), P = .137</td>
</tr>
</tbody>
</table>

- 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 !!!
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 ↓ (1 day)
Mean protein delivery during intervention
(Day 4 to Day 8)
Intention–to-treat analysis (n=305)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SPN (n=153)</th>
<th>EN (n=152)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein delivery (g/kg/IBW/day)</td>
<td>1.2 ± 0.2</td>
<td>0.8 ± 0.3</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Mean ± SD, Student t-test

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

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

- Patients receiving EN or PN each day
- Energy received per patient by study day
- Protein received per patient by study day

Day-60 mortality 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
Early high protein intake (≥1.2 g/kg/d on day 4) associated with ↓mortality & energy overfeeding with ↑mortality in non-septic mechanically ventilated critically ill patients

$\text{Patients admitted to the ICU} \quad n=4803$

$\text{Patients admitted >3 days} \quad n=1720$

$\text{Patients fulfilling inclusion criteria} \quad n=843$

$\text{Septic patients} \quad n=117$

$\text{Non-septic, overfed patients} \quad n=307$

$\text{Non-septic, non-overfed patients} \quad n=419$

$\text{Hospital mortality for septic & non-septic patients}$

Protein intake higher or lower 1.2 g/kg

$\text{Non-septic}$

$\text{Septic}$

$p=0.003$

Weijis 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

P = 0.008  **

P = 0.047

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
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

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
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

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

**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

<table>
<thead>
<tr>
<th>Jahr</th>
<th>Autor</th>
<th>Patienten</th>
<th>(N)</th>
<th>Dauer</th>
<th>Applikation</th>
<th>verglichene AS/Protein Dosis</th>
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<tbody>
<tr>
<td>1980</td>
<td>Alexander</td>
<td>Kinder mit Verbrennungen</td>
<td>18</td>
<td>42</td>
<td>oral</td>
<td>3,9 vs. 3,2</td>
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<tr>
<td>1982</td>
<td>Smith</td>
<td>Gastroent. chirurgische Patienten</td>
<td>30</td>
<td>14</td>
<td>i.v.</td>
<td>2,3 vs. 1,7</td>
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<td>Serog</td>
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<td>12</td>
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<td>4,0 vs. 2,1</td>
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<td>Shaw</td>
<td>Mangelernährte Patienten</td>
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<td>16</td>
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<td>2,3 vs. 1,1</td>
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<td>1985</td>
<td>Clifton</td>
<td>Kopfverletzungen</td>
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<td>7</td>
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<td>2,6 vs. 1,5</td>
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<td>1985</td>
<td>Twyman</td>
<td>Kopfverletzungen</td>
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<td>10</td>
<td>enteral</td>
<td>2,2 vs. 1,5</td>
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<td>1987</td>
<td>Greig</td>
<td>Septische Patienten</td>
<td>9</td>
<td>6</td>
<td>i.v.</td>
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<td>Rees</td>
<td>EE bedürftige Patienten</td>
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<td>≥5</td>
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<td>1,5 vs. 0,6</td>
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<td>van der Heijden</td>
<td>Kritische Kranke, mechanisch beatmet</td>
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<td>i.v.</td>
<td>1,8 vs. 1,2</td>
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<td>1,5-2,5 vs. 2,0</td>
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<td>2016</td>
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<td>Kritisch Kranke</td>
<td>119</td>
<td>10</td>
<td>i.v.</td>
<td>1,1 vs. 0,9</td>
</tr>
</tbody>
</table>

- 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%

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

- Bolus protein feeding can stimulate protein synthesis.
- What about continuous (low dose per time unit) protein feeding?
- Absolute levels of protein balance?
- Where is the protein going?
- Can we change muscle mass & outcome of ICU patients with protein nutrition?
- Heterogeneous ICU population - one size does not fit all!
- Which patient might benefit from higher protein feeding?
- Patients with ↓ protein reserve (low muscle mass) may be at highest risk in ICU and may benefit more from early protein nutrition intervention.

Criticall illness - protein catabolism - important muscle loss - influences patients and clinical outcomes

Further studies - RCTs & post-hoc observational studies
Tailoring Metabolic & Nutrition Therapy in ICU to individual patient’s needs

Lean Body Mass (LBM) assessment

SARCOPENIA
- Muscle loss
- Reduced mobility
- Reduced energy expenditure
- Positive energy balance

OBESITY
- Inflammation
- Insulin resistance
- Increased central or ectopic lipids

Exercise
Nutrition

EXERCISE & Nutrition Therapy

Lean body mass = (0.32810 × W) + (0.33929 × H) - 29.5336

Lean body mass = (0.29569 × W) + (0.41813 × H) - 43.2933

Note: 1lb = 0.453592kg and 1in = 2.54cm
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
CT-scan at the level of the 3rd lumbar vertebra (L3)

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


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

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

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

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

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

Benefit > Risk

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

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

Hippocrates 400 BC