Effekt einer frühen Ernährungstherapie auf den Krankheitsverlauf von mangelernährten medizinischen Patienten: das EFFORT Projekt
(Effect of Early Nutritional Therapy on Frailty, Functional Outcomes and Recovery of Undernourished Medical Inpatients Trial)

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Malnutrition in the medical inpatient population

• Benefit of NRS Screening?
• When/in whom/how should we use nutritional therapy?

EFFORT project

• Metaanalysis and consensus treatment recommendations
• Randomized trial to study efficacy and safety
• Ancillary project

Outlook and discussion
... today you see this malnourished patient

**Acute medical condition**

- Sepsis due to pneumonia, renal function ↓
- Hyperglycemia, *acute loss of appetite*

**Chronic co-morbidities**

- Old age, chronic renal failure, diabetes
- Weight loss, low body mass index, *increased nutritional risk (NRS = 3)*

*Should this patient receive nutritional therapy?*
### 1. INITIALES SCREENING

<table>
<thead>
<tr>
<th>Frage</th>
<th>Ja</th>
<th>Nein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ist der BMI &lt; 20,5?</td>
<td>Nein</td>
<td>Nein</td>
</tr>
<tr>
<td>Hat der Patient innerhalb der letzten 3 Monate Gewicht verloren?</td>
<td>Nein</td>
<td>Nein</td>
</tr>
<tr>
<td>Verminderte Nahrungsaufnahme in der letzten Woche?</td>
<td>Nein</td>
<td>Nein</td>
</tr>
<tr>
<td>Liegt eine schwere Erkrankung vor?</td>
<td>Nein</td>
<td>Nein</td>
</tr>
</tbody>
</table>

---

**Ermittlung des Ernährungszustands**

**Schweregrad der Erkrankung**

**metabolische Stresssituation**

---

**FINALES SCREENING 2.**
Malnutrition and Mortality

Kantonsspital Aarau,
6 month observation (04/2013-10/2013)
4000 patients, ~ 30% at risk for malnutrition (NRS≥3 points)

Nutritional Risk score (NRS)

... what is the evidence for medical patients?

128 RCTs analyzed

![Graph showing nutritional risk score and clinical outcome for various diagnostic groups.](image)

**Legend:**
- **No effect**
- **Positive effect**

**Fig. 5** Nutritional risk score and clinical outcome: results for various diagnostic groups. Same data as in Figure 1 categorized according to diagnostic group. ARF: acute renal failure. Femur: femoral fracture. Misc: miscellaneous. Shaded bars, positive effect; black bars, no effect.
# Gruppierung

<table>
<thead>
<tr>
<th>MDC</th>
<th>06</th>
<th>Krankheiten und Störungen der Verdauungsorgane</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRG</td>
<td>621B</td>
<td>Adhäsiolyse am Peritoneum, Alter &gt; 3 Jahre und ohne ausserst schwere oder schwere CC oder andere Eingriffe an Darm oder Enterostoma ohne ausserst schwere CC, Alter &gt; 15 Jahre</td>
</tr>
<tr>
<td>PCCL</td>
<td>0</td>
<td>Normale Gruppierung</td>
</tr>
</tbody>
</table>

# Kostengewicht

<table>
<thead>
<tr>
<th>Basiskostengewicht</th>
<th>1.047</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effektives Kostengewicht</td>
<td>1.047</td>
</tr>
<tr>
<td>Zuschlagssatz pro Tag</td>
<td>0.071</td>
</tr>
<tr>
<td>Abschlagssatz pro Tag</td>
<td>0.544</td>
</tr>
<tr>
<td>Keine Tage sind zu- oder abschlagspflichtig</td>
<td></td>
</tr>
</tbody>
</table>

# Diagnosen

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Gültigkeit</th>
<th>Benutzt</th>
<th>CCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>K56.6</td>
<td>Sonstiger und nicht näher bezeichneter mechanischer ileus</td>
<td>Gültige Diagnose</td>
<td>Nein</td>
<td>2</td>
</tr>
<tr>
<td>Z90.4</td>
<td>Verlust anderer Teile des Verdauungstraktes</td>
<td>Gültige Diagnose</td>
<td>Nein</td>
<td>0</td>
</tr>
<tr>
<td>I10.00</td>
<td>Benigne essentielle Hypertonie: Ohne Angabe einer hypertensiven Krise</td>
<td>Gültige Diagnose</td>
<td>Nein</td>
<td>0</td>
</tr>
<tr>
<td>F32.9</td>
<td>Depressive Episode, nicht näher bezeichnet</td>
<td>Gültige Diagnose</td>
<td>Nein</td>
<td>0</td>
</tr>
</tbody>
</table>

# Prozeduren

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Gültigkeit</th>
<th>Benutzt</th>
<th>OR/NOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.59</td>
<td>Sonstige Lösung von peritonealen Adhäsionen</td>
<td>Gültige Prozedur</td>
<td>Ja</td>
<td>OR</td>
</tr>
<tr>
<td>54 21 10</td>
<td>Laparoskopie, Diagnostische Laparoskopie</td>
<td>Gültige Prozedur</td>
<td>Nein</td>
<td>OR</td>
</tr>
<tr>
<td>96.07</td>
<td>Einsetzen einer anderen (naso-) gastrischen Sonde</td>
<td>Gültige Prozedur</td>
<td>Nein</td>
<td>Weder OR noch NOR Prozedur</td>
</tr>
<tr>
<td>89.0A.32</td>
<td>Ernährungsberatung und -therapie</td>
<td>Gültige Prozedur</td>
<td>Nein</td>
<td>Weder OR noch NOR Prozedur</td>
</tr>
<tr>
<td>99.15</td>
<td>Parenterale Infusion konzentrierter Nährlosungen</td>
<td>Gültige Prozedur</td>
<td>Nein</td>
<td>NOR</td>
</tr>
<tr>
<td>88.01.10</td>
<td>Computertomographie gesamtes Abdomen</td>
<td>Gültige Prozedur</td>
<td>Nein</td>
<td>Weder OR noch NOR Prozedur</td>
</tr>
</tbody>
</table>
Mehreinnahmen von rund 20'000 CHF
… today you see this malnourished patient

Potential **benefit** of nutritional therapy?

- Strong association with adverse outcomes
- Starvation leads to catabolism and ultimately death
- High biological plausibility, “common consensus”
Cachexia due to acute disease

- Cell recycling?
- Appetite↓
- Infections?
- Anorexia
- Stress response?
- Infections
- Intestinal motility ↓
- Hyperglycemia?
- Catabolism↑
- Immune system?
- Organ dysfct?
- Inflammation?
- Insulin Resistance↑
- Hormonal response?
- Muscle mass↓
- Insulin Resistance
- TNF-α
- IL-6
- IL-1β
- Adrenal stimulation
- Increased resting metabolic rate
- CRP↑
- Albumine↓
- Decreased memory
- GLP-1↑
Autophagy in critically ill patients

Electron microscopy
- intact/swollen mitochondria
- autophagic vacuoles

Histochemistry
- eosin staining
- ubiquitin

Protein analysis
- phosphoinositide-3-kinase (PI3K) class III,
- sirtuin-1,
- protein disulfide isomerase
- glucose-related protein 78
- inositol-requiring enzyme-1
- AMP-activated protein kinase (AMPK),

What is Best Way to Reduce Caloric Deficits?

Europe

Nutritional strategy during the first week in ICU according to randomisation.

Early PN group

Late PN group

PN

EN

USA

Nutritional Target

EN

Casaer MP, Van den Berghe G, NEJM 2011;365:506
• PRCT 4640 adult ICU pts multicenter  
  Received 2009 Stoutenbeek Award for study design  
  All pts started on EN, tight glucose control

• Results

<table>
<thead>
<tr>
<th></th>
<th>Early PN (ESPEN)</th>
<th>Late PN (ASPEN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=2312)</td>
<td>(n=2328)</td>
</tr>
<tr>
<td>Infection</td>
<td>26.2%</td>
<td>22.8% *</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>4.0 d</td>
<td>3.0 d *</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>14.0 d</td>
<td>12.0 d *</td>
</tr>
<tr>
<td>Durat CRRT</td>
<td>10.0 d</td>
<td>7.0 d *</td>
</tr>
<tr>
<td>MV &gt; 2 days</td>
<td>40.2%</td>
<td>36.3% *</td>
</tr>
<tr>
<td>Hosp mortality</td>
<td>10.9%</td>
<td>10.4% (p=NS)</td>
</tr>
<tr>
<td>ICU dschg alive</td>
<td>71.7%</td>
<td>75.2%*</td>
</tr>
<tr>
<td>Healthcare cost</td>
<td>17.973 E</td>
<td>16.863 E *</td>
</tr>
</tbody>
</table>

* p<0.05

Casaer MP, Van den Berghe G, NEJM 2011;365:506
Is reaching the targets not good enough?

"VEGETARIAN" IS AN OLD INDIAN WORD FOR BAD HUNTER
Effect of Glutamine on clinical Outcomes

Effect on Mortality

RR: 0.78 (95% 0.58, 1.04)

Benefit of Antioxidants?

Effect of Antioxidant on Mortality (n=20)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AOX Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews</td>
<td>84 251</td>
<td>84 251</td>
<td>23.3%</td>
<td>1.00 [0.78, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Angstwurm</td>
<td>7 21</td>
<td>11 21</td>
<td>3.0%</td>
<td>0.64 [0.31, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Angstwurm 2007</td>
<td>46 116</td>
<td>61 122</td>
<td>17.9%</td>
<td>0.79 [0.60, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Berger '98</td>
<td>1 10</td>
<td>0 10</td>
<td>0.2%</td>
<td>3.00 [0.14, 65.90]</td>
<td></td>
</tr>
<tr>
<td>Berger 2001a</td>
<td>2 9</td>
<td>1 12</td>
<td>0.3%</td>
<td>2.67 [0.28, 25.04]</td>
<td></td>
</tr>
<tr>
<td>Berger 2001b</td>
<td>0 11</td>
<td>1 12</td>
<td>0.2%</td>
<td>0.36 [0.02, 8.04]</td>
<td></td>
</tr>
<tr>
<td>Berger 2007</td>
<td>1 11</td>
<td>1 10</td>
<td>0.2%</td>
<td>0.91 [0.07, 12.69]</td>
<td></td>
</tr>
<tr>
<td>Berger 2008</td>
<td>14 102</td>
<td>9 98</td>
<td>2.6%</td>
<td>1.49 [0.68, 3.29]</td>
<td></td>
</tr>
<tr>
<td>Crimi</td>
<td>49 112</td>
<td>76 112</td>
<td>23.5%</td>
<td>0.64 [0.50, 0.82]</td>
<td></td>
</tr>
<tr>
<td>El–Attar 2009</td>
<td>2 40</td>
<td>1 40</td>
<td>0.3%</td>
<td>2.00 [0.19, 21.18]</td>
<td></td>
</tr>
<tr>
<td>Forceville</td>
<td>14 31</td>
<td>13 29</td>
<td>5.1%</td>
<td>1.01 [0.58, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Kuikinski</td>
<td>0 8</td>
<td>8 9</td>
<td>0.2%</td>
<td>0.07 [0.00, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Manzanares 2011</td>
<td>5 15</td>
<td>7 16</td>
<td>2.0%</td>
<td>0.76 [0.31, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Mishra</td>
<td>11 18</td>
<td>15 22</td>
<td>7.2%</td>
<td>0.90 [0.56, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Nathens</td>
<td>5 301</td>
<td>9 294</td>
<td>1.4%</td>
<td>0.54 [0.18, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Porter</td>
<td>0 9</td>
<td>0 9</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preiser</td>
<td>8 20</td>
<td>6 17</td>
<td>2.3%</td>
<td>1.13 [0.49, 2.62]</td>
<td></td>
</tr>
<tr>
<td>Schneider</td>
<td>6 29</td>
<td>6 29</td>
<td>1.6%</td>
<td>1.00 [0.37, 2.74]</td>
<td></td>
</tr>
<tr>
<td>Valenta</td>
<td>19 75</td>
<td>24 75</td>
<td>6.1%</td>
<td>0.79 [0.48, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>4 33</td>
<td>9 35</td>
<td>1.4%</td>
<td>0.47 [0.16, 1.38]</td>
<td></td>
</tr>
<tr>
<td><strong>Zimmerman</strong></td>
<td>5 20</td>
<td>8 20</td>
<td>1.2%</td>
<td>0.38 [0.12, 1.21]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1242</strong></td>
<td><strong>1243</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.82 [0.72, 0.93]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**RR: 0.82 (95% 0.72, 0.93)**

Figure 1: Effects of antioxidant strategies on mortality (n = 20). AOX, antioxidants; RR, risk ratio; 95% CI, 95% confidence intervals.

Glutamine: HARMFUL

Antioxidants: NO EFFECT

Heyland, NEJM 2013;368:1489-97
Loss of appetite is one of the plausible adaptive mechanisms during the acute phase of illness.

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change".

Charles Darwin
Swiss Study Supplemental Parenteral Nutrition

• High risk Med ICU patients (n=275)
  Functional gut, expected ICU LOS>5d
  Study pts: Add PN after 3 days if <60% Measured REE
  Controls: EN alone

• Results (EN vs SPN)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>Signif</th>
</tr>
</thead>
<tbody>
<tr>
<td>New infection</td>
<td>-0.27</td>
<td>0.019</td>
</tr>
<tr>
<td>Mech vent hrs</td>
<td>-87.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>-2.70d</td>
<td>0.009</td>
</tr>
</tbody>
</table>

• Key issues:
  Wait longer to add PN (at 72 hrs)
  Only add if EN feeds <60% goal

... today you see this malnourished patient

Potential benefit of nutritional therapy?
• Strong association with adverse outcomes
• Starvation leads to catabolism and ultimately death
• High biological plausibility, “Common consensus”

Potential **harm** of nutritional therapy?
• Is loss of appetite a physiological, protective adaption of the body?
• Few clinical studies in medical inpatients: no proof of efficacy and safety
• Substrate may not be used in acute illness? Risk of complication?
Ernährungsaustonomie – ethisches Grundsatzpapier zur Ernährung der Patientinnen und Patienten im Akutspital

«..... Die Ernährungsgewohnheiten eines Menschen gelten als Grundrecht und jede Form von Ernährungssubstitution ist als therapeutische Massnahme zu werten ....»

«....Als therapeutische Massnahme hat die Ernährung in gleicher Art und Weise die Kriterien der Indikation jeder anderen medikamentösen Therapie zu erfüllen....»

R. Baumann-Hölzle, Schweizerische Ärztezeitung, 2006;87: 33
Overall hypothesis
Individualized nutritional therapy to reach nutritional targets is a cost-effective strategy to prevent complications, frailty and improve functional outcomes in acutely-ill undernourished medical inpatients

Towards the project`s general aim, 5 separate aims will be accomplished
The EFFORT Project

**aim#1**

Meta-analysis
Current evidence?

EFFORT
Schuetz P. et al, Effect of Early Nutritional Therapy in Medical Inpatients. COCHRANE protocols (2013)
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Patient type</th>
<th>N</th>
<th>Study intervention</th>
<th>Control treatment</th>
<th>Outcomes evaluated</th>
<th>Main effects of study intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somanchi, 2011</td>
<td>Adult hospitalized medical patients</td>
<td>400</td>
<td>Individualized nutritional counseling</td>
<td>Standard nutritional care</td>
<td>LOS, diagnosis coding of malnutrition cases, delays in nutritional support</td>
<td>Significant reduction in LOS with economic benefit</td>
</tr>
<tr>
<td>Starke J, 2011</td>
<td>Malnourished general medical inpatients</td>
<td>132</td>
<td>Individualized ONS</td>
<td>Standard nutritional care</td>
<td>Caloric intake, weight, vitamin levels, QoL, complications, readmission, mortality (6m)</td>
<td>Higher caloric/protein intake, less weight loss, increased QoL, fewer complications</td>
</tr>
<tr>
<td>Rüfenacht U, 2010</td>
<td>Malnourished general medical inpatients</td>
<td>36</td>
<td>Intensive nutritional counseling with ONS</td>
<td>ONS only</td>
<td>Anthropometrics, energy and protein intake, QoL questionnaire</td>
<td>Higher caloric/protein intake, QoL improvement after hospitalization</td>
</tr>
<tr>
<td>Norman K, 2008</td>
<td>Malnourished inpatients with GI disease</td>
<td>101</td>
<td>Dietary counseling with ONS over 3-month period</td>
<td>Dietary counseling without ONS</td>
<td>BMI, muscle strength, readmission, QoL</td>
<td>Improved hand grip strength and peak flow, fewer readmissions, better QoL</td>
</tr>
<tr>
<td>Gariballa SA, 2007</td>
<td>Acutely ill inpatients &gt;65y</td>
<td>445</td>
<td>400 ml ONS/d</td>
<td>Standard nutritional care plus placebo</td>
<td>Nutritional status, depression (geriatric depression questionnaire), cognitive function</td>
<td>Significant improvement in depression score after 6 month, no difference in cognitive function</td>
</tr>
<tr>
<td>Johansen N, 2004</td>
<td>Malnourished inpatients</td>
<td>212</td>
<td>Individualized nutritional therapy</td>
<td>Standard nutritional care</td>
<td>Caloric intake, LOS, complications, mortality, QoL</td>
<td>Higher caloric/protein intake, shorter LOS</td>
</tr>
<tr>
<td>Hickson M, 2004</td>
<td>Malnourished medical inpatients, &gt;65 y old</td>
<td>592</td>
<td>Nutritional counseling by health care assistants</td>
<td>Standard nutritional care</td>
<td>Weight/BMI, Barthel’s index, infection, LOS, in-hospital mortality</td>
<td>Less antibiotic use, otherwise no effect</td>
</tr>
<tr>
<td>First author, year</td>
<td>Patient type</td>
<td>N</td>
<td>Study intervention</td>
<td>Control treatment</td>
<td>Outcomes evaluated</td>
<td>Main effects of study Intervention</td>
</tr>
<tr>
<td>-------------------</td>
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</tbody>
</table>
Meta-analysis – effects on mortality - preliminary results

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RD (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.17 (-0.39, 0.05)</td>
<td>1/18</td>
<td>4/18</td>
<td>1.63</td>
</tr>
<tr>
<td>2</td>
<td>-0.05 (-0.12, 0.03)</td>
<td>2/66</td>
<td>5/66</td>
<td>8.03</td>
</tr>
<tr>
<td>3</td>
<td>-0.06 (-0.13, 0.01)</td>
<td>21/186</td>
<td>33/195</td>
<td>8.80</td>
</tr>
<tr>
<td>4</td>
<td>0.06 (-0.00, 0.12)</td>
<td>32/223</td>
<td>19/222</td>
<td>10.22</td>
</tr>
<tr>
<td>5</td>
<td>-0.01 (-0.06, 0.04)</td>
<td>31/292</td>
<td>35/300</td>
<td>11.44</td>
</tr>
<tr>
<td>6</td>
<td>0.03 (-0.04, 0.10)</td>
<td>9/108</td>
<td>6/108</td>
<td>8.85</td>
</tr>
<tr>
<td>7</td>
<td>-0.00 (-0.17, 0.16)</td>
<td>1/17</td>
<td>1/16</td>
<td>2.74</td>
</tr>
<tr>
<td>8</td>
<td>0.06 (-0.28, 0.41)</td>
<td>9/17</td>
<td>7/15</td>
<td>0.69</td>
</tr>
<tr>
<td>9</td>
<td>0.00 (-0.36, 0.36)</td>
<td>7/15</td>
<td>7/15</td>
<td>0.65</td>
</tr>
<tr>
<td>10</td>
<td>0.11 (-0.13, 0.35)</td>
<td>1/9</td>
<td>0/13</td>
<td>1.36</td>
</tr>
<tr>
<td>11</td>
<td>-0.15 (-0.40, 0.10)</td>
<td>2/17</td>
<td>5/19</td>
<td>1.28</td>
</tr>
<tr>
<td>15</td>
<td>-0.35 (-0.63, -0.07)</td>
<td>2/16</td>
<td>9/19</td>
<td>1.06</td>
</tr>
<tr>
<td>20</td>
<td>0.00 (-0.09, 0.10)</td>
<td>2/39</td>
<td>2/41</td>
<td>6.12</td>
</tr>
<tr>
<td>22</td>
<td>-0.11 (-0.36, 0.14)</td>
<td>4/20</td>
<td>8/26</td>
<td>1.29</td>
</tr>
<tr>
<td>25</td>
<td>0.03 (-0.06, 0.12)</td>
<td>14/105</td>
<td>11/105</td>
<td>6.84</td>
</tr>
<tr>
<td>27</td>
<td>-0.08 (-0.14, -0.01)</td>
<td>3/78</td>
<td>21/181</td>
<td>9.62</td>
</tr>
<tr>
<td>29</td>
<td>0.04 (-0.02, 0.10)</td>
<td>4/71</td>
<td>1/72</td>
<td>10.06</td>
</tr>
<tr>
<td>31</td>
<td>0.00 (-0.07, 0.06)</td>
<td>1/44</td>
<td>1/44</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Overall (I-squared = 38.9%, p = 0.047)**

RD (Risk Difference)

- NOTE: Weights are from random effects analysis
The EFFORT Project

aim#1
Meta-analysis
Current evidence?

aim#2
Therapy algorithm
Consensus

EFFORT
Purpose: To develop an individualized nutritional therapy strategy in a consensus conference based on the meta-analysis (Aim#1) and current recommendations, i.e., from the European and American Society for Enteral and Parenteral Nutrition (ESPEN and ASPEN)
In case of multiple conditions, aim for the highest target.
### Ernährungsziele

<table>
<thead>
<tr>
<th>Kalorienbedarf</th>
<th>Proteinbedarf</th>
<th>Mikronährstoffe</th>
<th>Spezielle Ziele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris Benedict mit adjustiertem Gewicht oder ind. Kalorimetrie</td>
<td>1.2-1.5g/kgKG/Tag (0.8 bei schwerer Niereninsuffizienz ohne Dialyse)</td>
<td>Multivitamin Präparat, andere Mikronährstoffe gemäß Labor</td>
<td>Krankheits-spezifische Anpassungen</td>
</tr>
</tbody>
</table>

---

**Nutritional requirements / goals**

Nutrition Risk Screening (NRS) innerhalb 24-48 Std. nach Spitaleintritt

Wenn NRS ≥ 3 Punkte ⇒ individuelles Assessment des Patienten

Malnutrition vorhanden? Ernährungstherapie gewünscht und sinnvoll?

Wenn Ja ⇒ Festlegung einer Strategie zur Erreichung von individuellen Ernährungszielen
Nutritional requirements/goals

Nutrition Risk Screening (NRS) within 24-48 hours after admission.

If NRS ≥ 3 points → individual assessment of the patient
Malnutrition present? Nutrition therapy desired and sensible?
If yes → specification of a strategy for achieving individual nutrition goals

**Nutritional Goals**

<table>
<thead>
<tr>
<th>Kalorienbedarf</th>
<th>Proteinbedarf</th>
<th>Mikronährstoffe</th>
<th>Spezielle Ziele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris Benedict with adjusted weight or individual calorimetry</td>
<td>1.2-1.5g/kgKG/day (0.8 if severe renal insufficiency without dialysis)</td>
<td>Multivitamin preparation, other micronutrients according to Labor</td>
<td>Disease-specific specific supplementation ¹</td>
</tr>
</tbody>
</table>

**Nutritional Strategy to Achieve Nutritional Goals**

- Stufe 1: oral nutrition + Vitamin and mineral supplements according to 100% RDA (Recommended Daily Allowances)

  - Adjustment to preferences (⁺)
  - Snacking (⁺)
  - Fortification (⁺)
  - Enteral nutrition

- Re-assessment every 24-48 hours: ≥75% of energy and protein needs?

- No and goal achievement not visible
- Escalation stage 2 at earliest 5 days

1. Specific supplementation according to the disease or condition.
Nutritional requirements / goals

Nutrition Risk Screening (NRS) innerhalb 24-48 Std. nach Spitalentritt

wenn NRS ≥ 3 Punkte → individuelles Assessment des Patienten
MISMATCH vorhanden? Ernährungstherapie gewünscht und sinnvoll?
wenn Ja → Festlegung einer Strategie zur Erreichung von individuellen Ernährungszielen

Ernährungsziele

<table>
<thead>
<tr>
<th>Kalorienbedarf</th>
<th>Proteinbedarf</th>
<th>Mikronährstoffe</th>
<th>Spezielle Ziele</th>
</tr>
</thead>
</table>
| Harris Benedict mit adjustiertem Gewicht oder ind. Kalorimetrie | 1.2-1.5g/kgKG/Tag (0.8 bei schwerer Niereninsuffizienz ohne Dialyse) | Multivitamin Präparat, andere Mikronährstoffe gemäss Labor | Krankheits-spezifische Anpassungen

Ernährungsstrategie zum Erreichen der Ernährungsziele

Stufe I: orale Ernährung + Vitamine und Mineralstoffe gemäss 100% RDA (Recommended Daily Allowances)

- Anpassung an Präferenzen
- Zwischenmahlzeiten
- Anreicherung
- Trinknahrungen

Ja

Re-Assessment alle 24-48 Std.: ≥75% des Energie- und Proteinbedarfs?

NEIN und Zielerreichung nicht absehbar
Eskalationsstufe II nach spätestens 5 Tagen

Stufe II: enterale Ernährung orale Ernährung (siehe oben), keine Vitamine per os nötig, wenn enterale Ernährung ≥ 1500kcal

Ja

Re-Assessment alle 24-48 Std.: ≥75% des Energie- und Proteinbedarfs?

NEIN und Zielerreichung nicht absehbar
Eskalationsstufe III spätestens nach weiteren 5 Tagen

Stufe III: Parenterale Ernährung Enterale und/oder orale Ernährung (siehe oben), keine Vitamine wenn enterale Ernährung ≥ 1500kcal

+ je 1 Ampulle Vitalipid, Soluvit und Addamel + stopp Multivitamin

Begleitend minimale orale/enterale Ernährung anstreben (Vermeidung Zottenatrophie)
Nutritional screening of consecutive medical inpatients

Exclusion of patients:
• critical care or post-OP
• long-term nutrition
• terminal condition

Inclusion of patients:
• Nutritional risk score ≥3
• Estimated LOS≥5 days
• Written informed consent

Randomization 1:1

Intervention group
Individualized early nutritional therapy according nutrition guidelines

Control group
Standard nutrition provided by hospital kitchen according to patient appetite

Daily re-assessment of all patients to optimize treatment
Blinded Outcome assessment after 30 and 180 days

Target number: n = 3000
### Main endpoints and statistical considerations

**Outcomes**

<table>
<thead>
<tr>
<th>Functional outcome at 30 days (Barthel) (mean of 80 ±20 points)</th>
<th>Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined treatment failure (~40%)</td>
<td>&gt;95% to detect a 4 point (5%) increase</td>
</tr>
<tr>
<td>- Mortality (~10%)</td>
<td>90% to detect 6% absolute diff</td>
</tr>
<tr>
<td>- ICU admission (~5%)</td>
<td>89% to detect 4% absolute diff</td>
</tr>
<tr>
<td>- Functional decline (-10% Barthel) (~10%)</td>
<td>87% to detect 3% absolute diff</td>
</tr>
<tr>
<td>- Severe complications (~25%)</td>
<td>80% to detect 5% absolute diff</td>
</tr>
<tr>
<td>- Severe complications (~25%)</td>
<td>83% to detect 5% absolute diff</td>
</tr>
</tbody>
</table>

**Other outcomes**

*Short-term nutritional outcomes*
- Handgrip muscle strength, nutritional intake
- Lean body mass, BMI

*Hospital outcomes*
- Length of stay, Hospital–acquired infections

*30-day and 180-day outcomes*
- Quality of life, rehospitalisation

*Safety of intervention*
- GI side effects

*assuming an alpha level of 0.05 total n=3000, lost to follow up 10%*
### Barthel Index of Activities of Daily Living

**Instructions:** Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient’s abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

### The Barthel Index

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bowels</strong></td>
<td>0 = incontinent (or needs to be given enemata) 1 = occasional accident (once/week) 2 = continent</td>
</tr>
<tr>
<td><strong>Transfer</strong></td>
<td>0 = unable – no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td>0 = incontinent, or catheterized and unable to manage 1 = occasional accident (max. once per 24 hours) 2 = continent (for over 7 days)</td>
</tr>
<tr>
<td><strong>Grooming</strong></td>
<td>0 = needs help with personal care 1 = independent for face/hair/teeth/shaving (implements provided)</td>
</tr>
<tr>
<td><strong>Toilet use</strong></td>
<td>0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)</td>
</tr>
<tr>
<td><strong>Feeding</strong></td>
<td>0 = unable 1 = needs help cutting, spreading butter, etc. 2 = independent (food provided within reach)</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td>0 = immobile 1 = wheelchair independent, including corners, etc. 2 = walks with help of one person (verbal or physical) 3 = independent (but may use any aid, e.g., stick)</td>
</tr>
<tr>
<td><strong>Dressing</strong></td>
<td>0 = dependent 1 = needs help, but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)</td>
</tr>
<tr>
<td><strong>Stairs</strong></td>
<td>0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent up and down</td>
</tr>
<tr>
<td><strong>Bathing</strong></td>
<td>0 = dependent 1 = independent (or in shower)</td>
</tr>
</tbody>
</table>

(Collins et al., 1988)

**Total Score:**
Comparative effectiveness research approach

- Comorbidities?
- Infections?
- Quality of life?
- Functional outcome?
- BMI?
- Acute diagnosis?
- Complications?
- Inflammation?
- Hyperglycemia?
- Immune system?
- Stress response?
- Organ dysfunction?
- Acute vs chronic malnutrition?
- Age?
- Gender?
- Effect of nutritional therapy

- Acute vs chronic malnutrition
- Comorbidities
- Infections
- Baseline nutritional risk
- Gender
- BMI
- Age
- Immune system
- Stress response
- Organ dysfunction
- Functional outcome
- Quality of life
- Inflammation
- Hyperglycemia
- Complications
- Acute diagnosis
National and international collaborations

- **Germany**: G Paletta & COCHRANE
- **Denmark**: J Kondrup
- **Belgium**: M Casaer & G Van den Berghe
- **Germany**: G Paletta & COCHRANE
- **KSA**: P Schuetz, B Mueller, EFFORT Team
- **USB**: M Donath, M Christ, U Keller
- **KSLi**: R Meier
- **KSW**: P Ballmer, R Immoberdorf
- **KSM**: C Hoess, V Pavlicek, Team ERB
- **Insel**: Z Stanga, J Donze, Team ERB
- **Univ Basel**: S De Geest & Team
- **Univ Berne**: P Perrig-Chiello & Team
- **CHUV**: F Pralong, P Coti
- **Univ Fribourg**: A Lauber & Team
- **Zofingen**: T Ehmann, B Flückiger
- **LUKS**: Ch Henzen, Team ERB

Countries: Germany, Denmark, Belgium

Institutions and Teams:
- **Univ Basel**: S De Geest & Team
- **KSA**: P Schuetz, B Mueller, EFFORT Team
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- **Zofingen**: T Ehmann, B Flückiger
- **LUKS**: Ch Henzen, Team ERB
Ancillary projects

- Meta-analysis
  - Current evidence?
- Therapy algorithm
  - Consensus
- Randomized trial
  - Harm vs benefit
- Cost benefit analysis
  - Cost vs benefit?
- Mechanistic approach
  - Pathophysiology
- Nurse-sensitive
  - Outcomes?
- Genetics?
- Glucose & Insulin
  - Treatment?
- Psychological factors?
Conclusions

- Clinical nutrition is among the most common interventions,
  *Yet* - there is no evidence-based algorithm for the use in acutely-ill medical inpatients at risk of malnutrition

- In light of recent high-quality evidence from critical care …
  …a reappraisal of how nutrition is used is now required

- The selection, timing, and doses of nutrition should be evaluated
  as carefully as with any other intravenous drug, with the aim of
  maximizing efficacy and minimizing iatrogenic toxicity and costs.

- **EFFORT** will help healthcare professionals and payers worldwide to make
  better-informed decisions regarding nutritional care of frail, elderly and polymorbid individuals with acute illness, who
  represent a large and growing patient population worldwide, and one that accounts for a major share of medical resource consumption.
Methodological / Statistical considerations

Design: RCT vs cluster randomisation
- high number of wards/hospitals
- homogenous patients in each ward

Blinding (placebo) for intervention not possible
- blinded outcome assessment at day 30

Effectiveness vs efficacy trial
- complex intervention, involvement of different players
- pragmatic “real-life” study
- contamination? Non-adherence?

Short period of intervention
- can we improve hard outcomes?
- Recommendation for post-discharge

Nutritional goals vs specific nutritional supplements
- look at differences between hospitals