Optimizing Nutrition in the Critically Ill Patient

Nutrition and Critical Care
What Do We Know

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Critical Care and Nutrition
- Malnutrition in critical care patients
- Nutrition interventions (enteral and parenteral)
  - Protein and the ICU
  - Lipids and the ICU
- Compounded versus pre-mixed PN
- Supplemental PN

Malnutrition

Evolving Our Legacy
Characteristics of Critical Care Patients

• Heterogeneous population
  – Age range and prior health status
  – Diagnosis and severity of disease
  – Metabolic requirements and catabolic stress status
  – Gastrointestinal function

• Surgical, medical, trauma, transplant, burn, and septic patients with long-term intensive care unit (ICU) stay
  – Inflammatory response with organ function support or failure
  – Worsening oxidative stress, which further promotes inflammation and organ failure


Malnutrition in the ICU

• Approximately 40% of ICU patients are malnourished
  – High catabolic stress leads to increased metabolic needs
  – Malnutrition is associated with poorer outcomes

• Relationship Between Cumulative Energy Deficit and Clinical Outcome

Malnutrition in Critically Ill Patients

• Excess costs for Patients with a likelihood of malnutrition
  – $5,575 per Surgery Patient
  – $2,477 per Medical Patient
  – Elderly represent 12.4% of Population, but 36% of health care costs
  – Those malnourished at admission had hospital charges that were double patients without malnutrition
  – Average LOS was 5.6 days longer than patients without malnutrition

• Excess Cost ($2,477.00)


Variable                      | F   | P value
------------------------------|-----|--------
Length of stay                | 25.18| 0.0001
Complications                 | 15.15| 0.0003
Infections                    | 9.14 | 0.0042
Days on antibiotics           | 17.48| 0.0003
Days of mechanical ventilation| 17.12| 0.0002

Increased Costs for Patients With a Likelihood of Malnutrition
Nutritional Needs of Critical Care Patients

- Carbohydrates: 3 - 5 g/kg/day (minimum 2 g/kg/day)\(^1\)\(^2\)
  - Based on blood glucose concentrations\(^3\)
- Lipids: 1 to 2 g/kg/day\(^4\)
  - Provide a high-density energy source and essential fatty acids (FA)\(^5\)
- Protein: 1.2 to 1.5 g/kg/day\(^6\) (True??)
  - Target non-protein calorie/nitrogen ratio\(^7\) of 70:1 to 100:1
  - Administration of 0.2 to 0.5 g/kg/day of L-glutamine\(^8\)\(^9\)
- Supplemental multivitamins and trace elements\(^10\)


Critical Care and Nutrition

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Negative Energy Balance Has Been Correlated With Complications

- Prospective, observational study of 80 ICU patients
  - Criteria >96 h of mechanical ventilation
  - Indirect calorimetry (IC) used to assess daily energy balance
- Cumulative negative energy balance was 4,787 kcal for ICU stay
  - 21% had a negative caloric balance >10,000 kcal
  - 30% had a negative caloric balance of 4,000-10,000 kcal
- Negative energy balance correlated with complications in the ICU (P<.01)
  - ARDS, sepsis, renal failure, renal replacement therapy

Positive Nutrition Balance Is Associated With Better Outcome

- Proper nutritional support can improve clinical outcomes in critical care patients\(^1\)\(^2\)

Fig. 1. From Bartlett RH, et al. Surgery. 1982;92(4):771-779.


Caloric balance (kcal)

ACCEPT Trial: Improved Survival is Associated with Increased Nutrition

- Cluster randomized trial of 499 patients (1998), in 14 hospitals, intervention (protocol) versus control
- Interventions include evidence-based algorithms to improve nutritional support and its effort on patient outcomes
- Intervention group had significantly lower hospital LOS and trend in reduced mortality


Early Feeding Improves Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early feeding* (n = 374)</th>
<th>Late feeding* (n = 835)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, y</td>
<td>59.3 ± 17.2</td>
<td>61.2 ± 17.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>235/139</td>
<td>525/307</td>
<td>0.2</td>
</tr>
<tr>
<td>Mortality, ICU, n (%)</td>
<td>50 (13.4)</td>
<td>155 (18.6)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Mortality, hospital, n (%)</td>
<td>70 (18.7)</td>
<td>202 (24.2)</td>
<td>(&lt;0.05)</td>
</tr>
<tr>
<td>Mean ICU length of stay ± SD, days</td>
<td>13.8 ± 12.5</td>
<td>13.3 ± 11.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean hospital length of stay ± SD, days</td>
<td>33.4 ± 34.0</td>
<td>32.2 ± 36.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>92 (24.6)</td>
<td>250 (29.9)</td>
<td>0.056</td>
</tr>
<tr>
<td>Acute kidney failure, n (%)</td>
<td>36 (10)</td>
<td>120 (14.4)</td>
<td>(&lt;0.05)</td>
</tr>
<tr>
<td>Mean mechanical ventilation ± SD, days</td>
<td>10.3 ± 10.5</td>
<td>9.9 ± 10.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean NPG energy ± SD, kcal/day</td>
<td>2732 ± 1136</td>
<td>499 ± 456</td>
<td>(&lt;0.05)</td>
</tr>
</tbody>
</table>

*Early feeding: >1500 kcal (besides parenteral glucose) on Days 1-3; late feeding: <1500 kcal (besides parenteral glucose) on Days 1-3.
Effects of Early Enteral Feeding in Critically Ill Patients

- Retrospective analysis of 4049 patients prospectively collected large multi-institutional ICU database requiring mechanical ventilation for >2 days
  - Early feed group: n = 2537 (63%)
  - Late feed group: n = 1512 (37%)
- Early feeding significantly reduces ICU and hospital based mortality
  - Early feed had significantly higher rate of survival (p=0.001)

Enteral Nutrition is Preferred to Parenteral Nutrition

General Beliefs:
- Gut stimulation of immune system
- Protection of gut mucosa
- Avoidance of bacterial translocation
- Reduced associated complications
  - Infections
- Cost

Early Feeding Improves ICU Mortality

- Artificial nutrition (EN and/or PN) should be initiated early in patients with critical illness
  - Early EN versus PN: no difference in effect on mortality
  - Delayed EN versus PN: significant mortality benefit with PN

Meta-analysis of the Effect of EN Versus PN on Mortality

TPN, total parenteral nutrition; EN, enteral nutrition.
*Early EN defined as <24 hours post-ICU admission or injury.
Values shown are the odds ratios with their associated 95% confidence interval.
Figure created using data from Simpson F, Doig GS. Intensive Care Med. 2005;31(1):12-23.
How Important is Protein?

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Retrospective Review of 53 Papers: Total Protein Loss


![Graph of total protein loss in normals and patients](image)

Protein Loss and E/N Ratio


![Graph showing protein loss and E/N ratio](image)
Protein Content of Nutrition and Survival Rate of Sepsis

$\text{Nitrogen Balance}$

*Correlated with Survival

Peck MD et al. 1989 Annals of Surgery

Key Guidelines for Critical Care Patients

- Patients who are not expected to be on a full oral diet within 3 days should receive supplemental nutrition.¹ ²
- Enteral nutrition (EN) is preferred whenever possible.¹ ²
- Initiate PN within 24 to 48 hours if EN is contraindicated or not well tolerated.¹ ²
  - 10% to 20% of ICU patients have very limited tolerance or a contraindication to EN.²
  - Examples: bowel obstruction, short bowel syndrome, abdominal compartment syndrome, mesenteric ischemia.²
- Supplementation with parenteral nutrition (PN) is important if EN alone is insufficient.¹ ³


Algorithm for Selecting a Feeding Route

Adequate nutrition status? 

If status changes 

Yes 

No 

Adequate nutrition status? 

Yes 

No 

Appetite satisfactory and physically able to eat? 

Yes 

No 

Oral diet; supplement as necessary 

If status changes 

Oral diet; maintain nutrition status regularly. Simple PN to maintain hydration if necessary 

Oral diet; maintain nutrition status regularly. Simple PN to maintain hydration if necessary 

Nutritional intake measurements that are not necessary; select feeding route 

Parenteral nutrition 

If status is inadequate, supplement with parenteral nutrition 

If status is inadequate, supplement with parenteral nutrition
Is There a Paradox?

- Nutrition is important in the critically ill patient
- Enteral nutrition is economical and stimulates the gut’s immune system leading to better outcomes
- Parenteral nutrition is associated with many complications and should be reserved to be used as the “last resort.”

Inadequate Delivery of Enteral Nutrition Is Common

- Frequent problems are associated with the delivery and tolerance of EN
- Discrepancies exist between the delivered vs. prescribed EN

<table>
<thead>
<tr>
<th>Study Site</th>
<th># Patients</th>
<th>% Nutritional Goal Met by Enterally Fed Patients</th>
<th>% of Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muncie, IN</td>
<td>50-70%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>50%</td>
<td>50-70%</td>
<td>50%</td>
</tr>
<tr>
<td>Nashville, TN</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Cleveland, OH</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Site</th>
<th>% of Patients Meeting Nutritional Goal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muncie, IN</td>
<td>75%</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>50%</td>
</tr>
<tr>
<td>Nashville, TN</td>
<td>25%</td>
</tr>
<tr>
<td>Cleveland, OH</td>
<td>50%</td>
</tr>
<tr>
<td>Kansas City, KS</td>
<td>25%</td>
</tr>
</tbody>
</table>

GI Intolerance Has Been Associated With Complications in EN Patients

- Prospective, observational study of 153 ICU patients on EN (NG tube)
- 46% patients developed GI intolerance
  - Median intolerance 2 days
  - Nutritional intakes
    - In patients receiving sedation or catecholamines
  - GI intolerance during EN was associated with
    - Nosocomial pneumonia
    - ICU stay
    - ICU mortality
EN Patients Often Receive Fewer Calories Than Prescribed

- Prospective, observational study of 59 ICU patients fed with EN
- EN feed interrupted 27.3% of the time
- Prolonged interruptions: Small-bore feeding tubes (25.6%), ↑ Residual volumes (13.3%), Weaning (11.7%), Other (22.8%)
- EN patients received 50% prescribed caloric needs

Factors Involved in Incomplete Delivery of Prescribed EN

- Start of nutritional support (48.3%)
- Interruptions (37.9%)
- Problems with small-bore feeding tube (25.6%)
- Residual volumes (13.3%)
- Weaning procedures (11.7%)
- Other (22.8%)

Times are expressed as mean (SD)

**Parenteral Nutrition**

**Important Considerations for PN in Critical Care Patients?**

- Patient diversity requires individualized consideration of PN prescription
  - Risk for hyperglycemia
    - Associated with increased risk of death, infectious complications, and increased inflammatory status in stressed and critically ill patients
    - Insulin therapy may be required for maintenance of glycemic control
    - Lipids provide an important alternate energy source
  - Immune system reduction

Benefits of Hyperglycemic Control

- Critically ill patients often develop hyperglycemia, which may lead to infection, polyneuropathy, and other serious complications.
- In a large, prospective, randomized, controlled trial, tight glucose control (≤110 mg/dL) with intensive insulin therapy decreased ICU and hospital mortality versus conventional treatment.

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Important Considerations for PN in Critical Care (cont)

- Biological effects of lipid emulsions (LEs) depend on the composition and quantity of FA:
  - Polyunsaturated FA (PUFA; ω-6 and ω-3) are preferential targets for free radical attack and oxidative damage.
  - High content of ω-6 PUFA may exacerbate the elevated inflammatory status of critically ill patients.
  - ω-6 PUFA may also be immunosuppressive, increasing the risk of infection.
  - Partial substitution with other FA has demonstrated better tolerability and potential clinical benefits in critically ill patients.
    - Medium chain triglycerides
    - ω-9 monounsaturated fatty acids (MUFA)
    - ω-3 PUFA


References:
Why Parenteral Lipids?

- Lipids are a dense (9 kcal/g) source of calories
- Meet caloric intake requirements with limited volume
- Lipids provide essential FA, which are important for recovery from critical illness
- Reduces the need for glucose administration, thereby avoiding potential morbidity and mortality associated with hyperglycemia
- Lipids provide other FA important to immune and other biological functions

FA Classification: Saturation

<table>
<thead>
<tr>
<th>SFA</th>
<th>PUFA</th>
<th>MUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most FA in coconut oil</td>
<td>Primary FA in soybean oil (linoleic acid) and fish oil (EPA and DHA)</td>
<td>Include oleic acid, the primary FA in olive oil</td>
</tr>
<tr>
<td>Increased risk of CV disease, acute adverse effects include endothelial toxicity, atherosclerosis, and inflammation</td>
<td>Include essential FA (linoleic and α-linolenic acid)</td>
<td>Important for cell membrane structure and function</td>
</tr>
<tr>
<td>Should be restricted in the diet</td>
<td>Important for cell membrane structure and function</td>
<td>Should be restricted in the diet</td>
</tr>
</tbody>
</table>

Which Parenteral Lipid for Which Patient?

<table>
<thead>
<tr>
<th>High MUFA LE (Olive Oil)</th>
<th>High PUFA LEs (soybean oil– and fish oil–based LEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal interference with intrinsic immune response</td>
<td>Immunosuppressive</td>
</tr>
<tr>
<td>Does not increase patient inflammatory response</td>
<td>Proinflammatory/antiinflammatory</td>
</tr>
<tr>
<td>Improves resistance to oxidative stress</td>
<td>Preferential targets for lipid peroxidation, leading to oxidative stress</td>
</tr>
<tr>
<td>Best physical stability in total nutrient admixtures</td>
<td>Limited stability in total nutrient admixtures</td>
</tr>
</tbody>
</table>

What Is Oxidative Stress?

- Normally, the production of ROS is balanced by the consumption of these species by anti-oxidants (eg, vitamins E and C, selenium, glutathione)
- Oxidative damage occurs when there is a dysequilibrium between ROS production and antioxidant systems in favor of ROS (pro-oxidants).
  This results in oxidative stress

\[ \text{AOX} \rightarrow \text{ROS} \rightarrow \text{Oxidative stress} \rightarrow \text{Oxidative damage} \]


Parenteral Lipids and Oxidative Stress: Clinical Findings (cont)

TBARS, thiobarbituric acid-reactive substances; MCT, medium-chain triglycerides; LCT, long-chain triglycerides; Lp(a), low-density lipoprotein.

*P < 0.05. **P < 0.001.

Figure was created using data from Demirer S, et al. Poster presented at: the 26th European Society for Clinical Nutrition and Metabolism (ESPEN) Congress; October 10-13, 2006, Istanbul, Turkey.
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Compounded Versus Pre-Mixed PN

Pre-Mixed PN
Commercially mixed and terminally sterilized
Set content (protein, carbohydrates, fats, electrolytes, vitamins and minerals)

Compounded
Each component placed into bag by manual or automated compounding method
No routine sterilization methods

Clinical Outcomes Using Premix Parenteral Nutrition Formulations

- Premier multi-hospital database (n=197); Adults ≥ 18 years
- Multi-chamber bag (MCB); n=4,669
- Compounded bag (COM); n=64,401
- Hospital compounded (HCOM); n=979
- Adjusted for age, diagnosis, PN days, co-morbidities, surgery, ICU stay, severity, hospital
- *p<0.001

Cost per BSI = $18,251
Savings per patient = $857
Clinical Outcomes Using Premix Parenteral Nutrition Formulations

- Premier multi-hospital database (n=197)
- Adults ≥ 18 years
- Multi-chamber bag (MCB); n=2643
- Compounded bag (COM); n=64,401
- Hospital compounded (HCOM); n=979
- *p<0.001

EPICOS: JPEN 2009
(Pontes-Arruda et al)

- PRDBCT, multicenter:
  - n=400, Critically ill, Require PN
  - 28 day follow-up
- Exclusions: < 18 years, survival < 28 days from incurable disease, need for dialysis, GCS < 5, HIV
- OliClinomel, Olive 3CB (n=108)
- Compounding
  - CO (n=41)
  - MCT/LCT (n=54)
- Primary: BSI
- Similar APACHE2

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Supplementary Nutrition

Enteral + Parenteral Nutrition May Improve Patient Outcomes

- Enteral Nutrition
- Parenteral Nutrition

Improved Energy Balance

↓

Improved Patient Outcomes


EN+PN Has Been Associated With Lower Hospital LOS

- RCT with 120 ICU patients
  - 60 EN+PN (Treatment)
  - 60 EN+placebo (Control)
  - No difference in severity of illness
- PN and placebo administered only during 1st 4-7 days
- Goal of 25 total kcal/kg/day
  - Use of commercially prepared PN adjusted to meet goal
- EN+PN met 98% goal vs. 57% for EN
  - Positive energy balance in first 3 days
- No difference in infections, ICU LOS, and mortality
- EN+PN associated with ↓ hospital LOS vs. EN
  - 31.2 vs. 33.7 days; P(H=0.002)

Late Versus Early Supplemental PN
Casaer MP et al NEJM 2011; 365: 506
• New Infections: 22.8 vs 26.2*
• Highest CRP: 191 vs 160 mg/l*
• Mechanical ventilation: 2 vs 2 days (median)*
• Tracheostomy: 5.5 vs 7.0 %
• Renal replacement therapy: 8.6 vs 8.9%
• Hemodynamic support: 82.6 vs 83%
• Bilirubin > 3 mg/dl: 14.5 vs 12.9%
• Hospital stay (median days): 14 vs 18*
• 6 min walk, ADL: similar

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Supplementing EN with PN is Associated with Improved Clinical Outcomes in High Risk Patients

<table>
<thead>
<tr>
<th>TICACOS Trial</th>
<th>Study Group (n = 65)</th>
<th>Control Group (n = 65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean energy delivered/day (kcal/day)</td>
<td>2086 ± 460 1515 ± 756</td>
<td>1480 ± 356 1316 ± 456</td>
<td>0.01 0.09</td>
</tr>
<tr>
<td>from enteral</td>
<td>371 ± 754 1316 ± 456</td>
<td>164 ± 294 0.001</td>
<td></td>
</tr>
<tr>
<td>from parenteral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>21 (32.3%) 31 (47.7)</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>24.6% 26.2%</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Duration ventilation (days, mean)</td>
<td>16.1 ± 14.7 10.5 ± 8.3</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>ICU stay (days, mean)</td>
<td>17.2 ± 14.6 11.7 ± 9.4</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>60-day survival*</td>
<td>57.9 ± 9.9 48.1 ± 7.6%</td>
<td>0.023</td>
<td></td>
</tr>
</tbody>
</table>

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Conclusions: PN in Critical Care
• Malnutrition is common
• Nutrition intervention is an important component of the care of the critically ill patient
• EN versus PN intervention may need another look
• Lipid emulsions are an important part of regimen
• EN+PN approach should be considered
  – When to supplement
  – Be vigilant for underfeeding where EN used as sole nutrition source

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Charleston, SC

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