Session Title: Mechanisms of Harm in Feeding Critically Ill Patients

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Presentation Title: Feeding Controversies in Critically Ill Patients

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Presentation Title: The FEDOX Trial: Feeding the Critically Ill During Phases of Altered Redox Status

Disclosures

- “We have no commercial relationships to disclose”

Presentation Overview/Summary

Decisions surrounding the timing and dosing of nutrition support are made for thousands of ICU patients daily and yet remain a topic of controversy. Nutrition support designed to replenish resting energy expenditure (REE) early in critical illness has led to worse clinical outcomes in at least three recent prospective randomized clinical trials. This presentation will use findings from the recent FEDOX Trial to demonstrate 3 potential mechanisms of harm in feeding the critically ill. The first mechanism is the relationship between feeding and oxidative stress. Producing sufficient energy from nutrient substrate requires use of the mitochondrial electron transport chain (ETC). This process is functionally linked to the creation of a tightly regulated series of chemical messengers known as reactive oxygen species (ROS). In health, ROS are kept at low levels by a system of mitochondrial/cellular enzymes and antioxidants, allowing ROS to act as a signal for the redox health of the cell. In inflammatory conditions, however, this system is altered, leading to changes in the physiologic function of the ETC such that its usage produces greater ROS per unit of substrate. This increased ROS is capable of deactivating antioxidant systems, as well as activating further ROS-producing pathways and stimulating localized inflammatory activity. The second mechanism involves the effect of feeding on basic physiologic responses to critical illness and its relationship with oxidative stress. We will discuss the effect of feeding on non-thyroidal illness syndrome and its relationship with oxidative stress. The third mechanism will explore genetic mitochondrial antioxidant enzyme allele status to and its ability to mediate the effect of calorie exposure on oxidative stress.

Learning Objectives

1. Summarize both sides of the argument concerning potential benefits/harms of caloric dosing in critically ill patients
2. Deconstruct the evidence for and against feeding based on the strengths and limitations of the current evidence
3. Summarize the relationship of feeding to oxidative stress and the antioxidant enzyme systems that keep oxidative stress in balance

Key Takeaways/Fast Facts

- The pros and cons of feeding critically ill patients are highly nuanced and warrant further study.
- Feeding the critically ill alter basic physiologic responses to critical illness; the effects of which are unknown.
- A calorie of nutrition support is only useful if it can be safely converted to ATP
Learning Assessment Questions

1. Question 1: The current literature does not support the possibility that feeding may be harmful in critically ill patients.
   A. True  
   B. False

2. Question 2: The nutrition-induced interruption in NTIS has been found to be beneficial.
   A. True  
   B. False

3. Question 3: The effect of feeding on oxidative stress is different between healthy people and the critically ill.
   A. True  
   B. False

4. Question 4: Threshold analyses have found the harmful effect of feeding to begin anywhere between ~16 and ~18 kcals/kg in feeding trial on critically ill patients.
   A. True  
   B. False

5. Question 5: People differ genetically in their ability to process mitochondrial free radical production.
   A. True  
   B. False

Learning Assessment Answers:

1. Answer = False; Rationale: *Three PRCT’s found evidence of harm in patients who met REE.*
2. Answer = False; Rationale: *The benefit or harm of this interruption is unknown. In the FEDOX trial, this interruption was associated with increased oxidative stress.*
3. Answer = True; Rationale: *Profound inflammation causes increased mitochondrial ROS production that inhibits our antioxidant enzyme systems.*
4. Answer = True; Rationale: *Studies whose randomization groups do not straddle this threshold may have a more difficult time capturing this effect.*
5. Answer = True; Rationale: *Certain antioxidant enzyme alleles are more or less efficient at managing oxidative stress and may account for individual differences in the relationship between feeding and outcomes.*

References

Session Title: Mechanisms of Harm in Feeding the Critically Ill Patient

The FEDOX Trial: Feeding the Critically Ill During Phases of Altered Redox Status

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ASPEN 2019 Nutrition Science & Practice Conference

Disclosures

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Relevance

- Thousands of orders for Nutrition Support given for critically ill patients every day.
- Current Clinical Guidelines recommend 25-30 kcals/kg
- Meeting this assumed to be anywhere from benign to beneficial.
- Of the 17 PRCT’s in the last 5 years, only 5 relevant studies met these guidelines in their higher-fed groups. 3, 4, 11-14
  - 2 found feeding beneficial 11,12
  - 3 found feeding harmful 2-4
  - 1 found no difference 14

What does this mean?

We have no idea if our current feeding recommendations in the critically ill are helping or harming.

Potential Mechanisms of Harm in Feeding Critically Ill Patients

- Three potential mechanisms of harm will be explored.
  1. Feeding and Oxidative Stress
  2. Feeding as an interrupter of physiologic responses to critical illness.
  3. Feeding and individual differences in genetic allele status.

Mechanism #1: Feeding and Oxidative Stress

- A calorie is only valuable if it can be turned into ATP
- Converting food into ATP creates backflow of reactive oxygen species in the mitochondria through leaking electrons from the electron transport chain.20
  (Halliwell, 2016)
- In profound inflammation, the electron transport chain is hampered causing it to create more reactive oxygen species in response to the same amount of nutrient substrate.21
  (Exline et al., 2008)
- Leading to further increase in ROS, inhibition of antioxidant enzymes, and death of cell.21,22
  (Bonini et al., 2014)
Mitochondrial ROS Production in Health

The Electron Transport Chain

Energy Substrates

ATP

Nutrition

Substrates

Enzymes

Mitochondrial ROS Production in Critical Illness

The Electron Transport Chain

Energy Substrates

ATP

Nutrition

Substrates

Enzymes

Mitochondrial ROS Production in Critical Illness

The Electron Transport Chain

Energy Substrates

ATP

Nutrition

Substrates

Enzymes

Mitochondrial ROS Production in Critical Illness

The Electron Transport Chain

Energy Substrates

ATP

Nutrition

Substrates

Enzymes
Exogenous Nutrition During Critical Illness

Feeding During Phases of Altered Redox Status (The FEDOX Trial)

**Study Design:** Prospective Randomized Controlled Trial

**Population:** Systemic Inflammatory Response Syndrome (SIRS)

**Intervention:** Patients receive either 100% or 40% of Estimated Caloric Needs

**Duration:** 7 days or until ICU discharge or death (Goal Sample Size = 40)

**Location:** RUMC MICU, NSICU

**Primary Objective**

**Objective 1:** To examine the effects of feeding on oxidative stress

**Hypothesis:** Patients exposed to 100% of energy needs (25-30 kcals/kg) will have increased systemic oxidative stress compared to those receiving 40% of needs (~12 kcals/kg)

**Outcome Variable:** Serum total F₂-isoprostanes

**Eligibility Criteria:**
- Adult patients (>18 years)
- Admitted to RUMC MICU or NSICU
- Who meet criteria for Systemic Inflammatory Response Syndrome (SIRS), and
- Who were mechanically ventilated and able to receive EN
### Results: Demographics

- 485 Patients met preliminary inclusion criteria
  - 448 excluded
- 35 Successfully Recruited
- 34 Received Intervention
- Average Age: $56 \pm 15.57$
  - Predominantly female (57.14%)
  - African American (45.71%)
  - APACHEII = 20.97 $\pm$ 6.98
  - SOFA = 8.83 $\pm$ 4.37
- Baseline Demographics by Group imply randomization was successful

### Results: Exposure Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>100% NRG</th>
<th>40% NRG</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kcals (SD)</td>
<td>948.96(457.67)</td>
<td>1140.5(504.6)</td>
<td>721.5(316.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean Kcals/kg (SD)</td>
<td>13.67(6.24)</td>
<td>16.05(6.04)</td>
<td>10.85(5.39)</td>
<td>0.011</td>
</tr>
<tr>
<td>Mean protein g (SD)</td>
<td>39.10(24.21)</td>
<td>46.62(22.94)</td>
<td>30.18(23.25)</td>
<td>0.021</td>
</tr>
<tr>
<td>Mean protein % Protein (SD)</td>
<td>0.5529(0.2982)</td>
<td>0.6328(0.2711)</td>
<td>0.4581(0.3095)</td>
<td>0.084</td>
</tr>
<tr>
<td>Mean CHO g (SD)</td>
<td>121.79(61.87)</td>
<td>144.8(65.90)</td>
<td>94.45(44.66)</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean Fat g (SD)</td>
<td>31.91(20.21)</td>
<td>39.55(22.14)</td>
<td>22.83(13.25)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

### Results for Specific Aim One: Is Calorie Exposure is Associated with Worse Redox Status?

- Intent to Treat Analysis:
  - No significant differences were found between the two groups for F2-isoprostanes.
  - Heterogeneity in exposure was an issue.
Post Hoc for Specific Aim One: Is Calorie Exposure Associated with Worse Redox Status?

- Two Variables were created to explore calorie exposure in the Post Hoc:
  - **Daily Kcals/Kg**: The total calories per kilogram of dosing weight received over 24 hrs from any source
  - **Recent Kcals/Kg**: The total flow rate of calories from any source into the body per kilogram of dosing weight within two hours of the blood draw

<table>
<thead>
<tr>
<th>Daily Kcals/kg</th>
<th>Recent Kcals/Kg (Hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>&lt;5.81</td>
</tr>
<tr>
<td></td>
<td>&gt;0.25</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>5.81-10.53</td>
</tr>
<tr>
<td></td>
<td>0.25-0.55</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>10.54-16.17</td>
</tr>
<tr>
<td></td>
<td>0.56-1.18</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>&gt;16.17</td>
</tr>
<tr>
<td></td>
<td>&gt;1.18</td>
</tr>
</tbody>
</table>

**Post Hoc Specific Aim 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.9805</td>
<td>0.0539</td>
<td>&lt;0.0001</td>
<td>8.4594</td>
<td>0.7462</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily Kcals/Kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2 vs 1</td>
<td>0.04706</td>
<td>0.0451</td>
<td>0.298</td>
<td>-0.883</td>
<td>0.5440</td>
<td>0.2134</td>
</tr>
<tr>
<td>Quartile 3 vs 1</td>
<td>0.00943</td>
<td>0.0465</td>
<td>0.830</td>
<td>-0.689</td>
<td>0.5493</td>
<td>0.2134</td>
</tr>
<tr>
<td>Quartile 4 vs 1</td>
<td>-0.1189</td>
<td>0.0506</td>
<td>0.021</td>
<td>-1.4815</td>
<td>0.6447</td>
<td>0.0244</td>
</tr>
</tbody>
</table>

**Random Effects Models**

| Intercept          | 0.08723  | 0.0187 | 0.0002  | 14.0325  | 3.8404| 0.0001  |

**Post Hoc Specific Aim 1 Discussion**

To Summarize:

- Amongst 3rd tertile of Daily kcal/kg, having any level of exogenous nutrition flowing is associated with increased oxidative stress.
- This implies the real time metabolism of macronutrients is associated oxidative stress.

If we are able to feed, should we?
**Mechanism #2**

*FeedingInterruptsPhysiologicResponses to Critical Illness*

The Effect of Feeding on Non-Thyroidal Illness Syndrome

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**Consequences of**

- This would be expected to:
  - Down-regulate mitochondrial metabolism
  - Decreasing ETC activity
  - Decreasing ATP productive capacity
  - Retrospective subanalysis have suggested feeding attenuated this process\(^{21}\)

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**Secondary Objective**

**Objective 2:** to explore the relationship between nutrition-induced oxidative stress and Low T3 Syndrome.

**Hypothesis:** The higher fed group will have higher T3 and higher T3:rT3 Ratio and this will be associated with increased nutrition-induced oxidative stress.

**Outcome Variable:** Total T3, reverse T3, T3:rT3 Ratio

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**Results for Specific Aim 2: Feeding Causes Elevations in Total T3**

- **Intent to Treat**
- Adjusted for group differences in baseline T3:rT3 ratio on Study Day 0
- Higher Fed vs Lower Fed:
  - 54% higher ratio on post-intervention day 1 (p=0.001)
- Attenuated over time both linearly (p=0.01) and quadratically (p=0.02)

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**The Role of Thyroid Hormones**

- **Central Regulation:**
  - Critical Illness accompanied by Non-Thyroidal Illness Syndrome, \(^{23}\)
  - Low T3 driven by a flattening of the TSH fluctuation
  - Which is driven by inflammation
- **Peripheral Regulation\(^{24-26}\)**
  - At cellular level, the body controls amount of T3 through deiodinase activity
  - T4 is either activated through conversion to T3 or inactivated through conversion to rT3
  - This process measured by T3:rT3 Ratio

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**Table: Feeding Changes T3:rT3 Ratio**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>p&lt;</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>3.72</td>
<td>0.47</td>
<td>.0001</td>
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<tr>
<td>Group</td>
<td>2.00</td>
<td>0.60</td>
<td>.001</td>
</tr>
<tr>
<td>Study Day</td>
<td>0.17</td>
<td>0.24</td>
<td>.48</td>
</tr>
<tr>
<td>Study Day(^2)</td>
<td>0.01</td>
<td>0.03</td>
<td>.66</td>
</tr>
<tr>
<td>Group*Day</td>
<td>0.83</td>
<td>0.31</td>
<td>.01</td>
</tr>
<tr>
<td>Study Day(^2)</td>
<td>0.09</td>
<td>0.04</td>
<td>.02</td>
</tr>
<tr>
<td>Baseline T3:rT3</td>
<td>0.18</td>
<td>0.09</td>
<td>.04</td>
</tr>
</tbody>
</table>

\(T3:rT3\) Ratio by Feeding Groups Adjusted for Baseline T3:rT3 Ratio

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**Figure: T3:rT3 Ratio by Feeding Groups Adjusted for Baseline T3:rT3 Ratio**

- Low Fed
- High Fed

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\(T3:t3\) Ratio by Feeding Groups Adjusted for Baseline T3:t3 Ratio

---

\(T3:t3\) Ratio by Feeding Groups Adjusted for Baseline T3:t3 Ratio

---
What is driving this?

- If Peripherally Driven:
  - We would expect to see an initial drop in reverse T3 on Study day 1 that rises back up over time.

- If Centrally Driven:
  - We would expect to see a decrease in TSH in the first four days of feeding.

### Centrally Driven: TSH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.02</td>
<td>0.46</td>
<td>0.03</td>
</tr>
<tr>
<td>Group</td>
<td>1.14</td>
<td>0.61</td>
<td>0.07</td>
</tr>
<tr>
<td>Study Day</td>
<td>0.24</td>
<td>0.37</td>
<td>0.52</td>
</tr>
<tr>
<td>Study Day</td>
<td>-0.01</td>
<td>0.069</td>
<td>0.90</td>
</tr>
<tr>
<td>Group</td>
<td>-0.95</td>
<td>0.48</td>
<td>0.05</td>
</tr>
<tr>
<td>Study Day</td>
<td>0.19</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.71</td>
<td>0.09</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**TSH By Feeding Group Adjusted for Baseline TSH**

**T3 and F2-Isoprostanes Stratified by Lower and Higher-Fed Group**

Significant association between T3 and F2-Isoprostanes is driven by the Higher Fed Group (Also Significant).

Relationship in Lower-Fed Group

Highly significant

### T3 and Oxidative Stress: Connecting Specifics Aim 1 and 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.03</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Log T3</td>
<td>-0.1183</td>
<td>0.0452</td>
<td>0.0413</td>
</tr>
<tr>
<td>Study Day</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Log T3 * Study Day</td>
<td>0.18</td>
<td>0.007</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Predicting Log F2-Isoprostanes

We see a similar relationship if we restrict to only those subjects whose EN was within two hours of blood draw. (Highly insignificant)
Effect of T3:rT3 Ratio on Oxidative Stress Overall and by Randomization Group

- Amongst Whole Sample: Every 1-unit increase in T3:rT3 Ratio is associated with 0.01 decrease in F2-Isoprostanes (p=0.04).
- Amongst Patients Whose EN is Off: Every 1-unit increase in T3:rT3 Ratio is associated with 0.05 decrease in F2-Isoprostanes (p=0.04).
- Amongst Patients Whose EN is On: Highly Insignificant. There is no relationship.

Summary of NTIS Findings

- 1. Being in the Higher-fed group caused a temporary interruption in NTIS.
- 2. This interruption corrected itself over time.
- 3. This correction was driven by adjustments in both central (hypothalamic) and peripheral (deiodinase) activity.
- 4. Interruptions in NTIS were associated with increased oxidative stress in the higher but not lower fed group.

Mechanism 3: Feeding and Antioxidant Enzyme Allele Status

- Role of MnSOD and GPx1 Allele Status
  - Different risk alleles exist for our mitochondrial antioxidant enzymes.\textsuperscript{27,28}
  - MnSOD (Alanine or Valine Alleles)
    - Alanine variant more efficiently enters mitochondria
    - Would more efficiently take Superoxide $\rightarrow$ H2O2
  - GPx1 (Leucine or Proline Alleles)
    - Leucine variant not as efficient at neutralizing H2O2 $\rightarrow$ Water

Objective/Hypothesis

Objective 3: to explore if patients who are at least heterozygous for the risk allele of both MnSOD and GpX-1 (double risk allele group) have increased nutrition-induced ROS production compared to all other genotypes.

Hypothesis: Patients in the double risk allele group will be less able to manage H2O2 buildup and will therefore have increased oxidative stress.

Outcome Variable: Enzyme Allele Status

Results for Specific Aim 3: Effect Allele Status of MnSOD and GPx1 on Oxidative Stress

- M1G1\textsuperscript{*}Study Day P=0.003
Results for Specific Aim 3: Feeding and Oxidative Stress by Allele Status

Discussion

• Summary of Findings
  1. Increased calorie exposure is associated a decrease in F2-Isoprostanes but is reversed if active exogenous nutrition is flowing.
  2. Increased calorie exposure causes elevations in T3:rT3 Ratio
  3. T3 is associated with increased F2-Isoprostane production in the higher but not lower fed group
  4. The ability of feeding to increase oxidative stress is modulated by mitochondrial antioxidant enzyme allele status.

The Double Risk Allele Group represented 32.4% of our random sample.

Our findings consistent with and provide a possible explanation for other trials that found harm in feeding.

Funding

• Funded by ASPEN Rhoads Research Foundation
• Received the Daniel H. Teitelbaum Foundational Grant
• IRB Approved by Rush and UIC
Objectives

• Summarize both sides of the argument concerning potential benefits/harms of caloric dosing in critically ill patients
• Deconstruct the evidence for and against feeding based on the strengths and limitations of the current evidence
• Summarize the relationship of feeding to oxidative stress and the antioxidant enzyme systems that keep oxidative stress in balance

Introduction

• Enteral (EN) and parenteral nutrition (PN) considered adjunctive therapies for critical illness
• The delivery of nutrition support is considered essential to:
  • Preserve lean body mass
  • Maintain immune function
  • Avert metabolic complications

Introduction

• The quality of the data should be considered when interpreting the results
• Examine timeline for ICU nutrition studies: pre vs post 2011

ICU Nutrition Timeline

• Prior to 2011, observational studies and small clinical trials observed significant associations between underfeeding (or delayed feeding) and:
  • More infections complications & prolonged LOS
  • Higher mortality
  • Prolonged duration of mechanical ventilation & LOS
  • More infectious complications

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Journal</th>
<th>Results</th>
</tr>
</thead>
</table>

Disclosures

• I have no commercial relationships to disclose
Impression from Pre-2011

- Varied population
- Calorie needs estimated
- Observational and clinical trials examining the influence of nutrition on ICU outcomes have vast differences in:
  - Mode of calorie delivery (EN versus PN)
  - Timing of nutrition support initiation
  - Method to determine calorie requirements
- These variations make study results difficult to interpret

Study group
ICU LOS: 17.2 ± 14.4 days
Vent days: 16.1 ± 14.7 days
Mortality: 25%

Control group
ICU LOS: 11.7 ± 8.4 days
Vent days: 10.5 ± 8.3 days
Mortality: 26%

Casaer M, et al. NEJM. 2011

Likelihood of discharging from the ICU alive progressively decreased as energy delivery increased by 20%.

Prospective Randomized Trial, recruitment started in 2009
- Patients with acute lung injury (ALI) were randomized to:
  - Treatment group: Provision of >75% of estimated energy via EN/PN from intubation to hospital discharge
  - Control group: nutrition care dictated by medical team

Primary outcome:
- Infection

Results of INTACT
- Intervention successfully delivered significantly greater energy to IMNT vs SC from enrollment to hospital discharge
  - Treatment group, n=40
    - 1798 ± 509 calories/day
    - 25.4 calories/kg
    - 85% requirements
  - Control group, n=38
    - 1221 ± 423 calories/day
    - 16.6 calories/kg
    - 55% requirements

Study was terminated early (n=78) due to significantly higher mortality in IMNT group (p=0.017)
- IMNT: 16/40, 40%
- SC: 6/38, 16%

Post-hoc analysis to explore:
- Timing of calorie exposure influenced mortality
- Dosage of calorie exposure influenced mortality

Study subjects were dichotomized as died vs discharged alive

Statistical analysis
- Logistic regression to assess timing of energy delivery on likelihood of death
- Cox proportional hazards to explore the relationship of “early” versus “late” energy exposure on hazards of mortality
- Logistic regression to discern if days 1-7 calorie exposure threshold existed for likelihood of subsequent death
Results of INTACT Post-hoc Analysis

- Timing of calorie exposure:
  - Timing of energy delivery on likelihood of death
    - Average Kcal/kg delivery days 1-3 significantly predicted subsequent death (p=0.03)
  - Relationship of “early” versus “late” energy exposure on hazards of mortality
    - Kcal/kg received during days 1-3 increased hazard of death for days 6+ (HR 1.17, p=0.0004)
    - Kcal/kg received on days 8+ were associated with lower hazard of death (HR 0.95, p=0.04)

- Dosage of calorie exposure:
  - Receiving >18 Kcal/kg during days 1-7 significantly predicted mortality in days 8+ (OR=18.5, p < 0.02).

Retrospective cohort investigation

- Patients who met eligibility criteria for the INTACT trial but did not participate (ENP)
- “natural” cohort group

Data collection

- 24 hours of ALI diagnosis through extubation
- Procedures to demographic variables, calorie delivery, & outcomes exactly as INTACT
- Primary outcome: Mortality

ENP Subjects

Table 1. Relationship Between Likelihood of Death With Calorie Exposure (Expressed as Both Total and Continuous delivery: Delivery/1000 weight days, Relationship in Each Manner).

- ENP Results

ENP Results

Table 2. Relationship Between Rate of Death With Calorie Exposure (Expressed as Both Total and Continuous delivery: Delivery/1000 weight days, Relationship in Each Manner).
Impression from 2011- to present day

- Timing and dose of calorie exposure may influence outcomes:
  - Higher calorie dose
  - Early calorie delivery
  
  Perhaps "early" is surrogate for higher acuity or sickness

Combination of both associated with worse outcomes

Results

Increased calorie delivery & 4 different versions of SOFA:
- Admit SOFA
- Average SOFA: day 1-7
- Highest SOFA
- Absolute SOFA change
  All associated with increased mortality

Conclusion

- Combination of high and early calorie exposure to those with increased severity of illness increased mortality
- Additional research is needed to corroborate these results & provide mechanism
- Current US and Canadian guidelines should consider encourage clinicians to consider severity of illness before initiating nutrition support