USE OF PEPTIDE BASED FORMULATIONS FOR OPTIMIZING ENTERAL NUTRITION DELIVERY, GI TOLERANCE, AND METABOLIC MANAGEMENT

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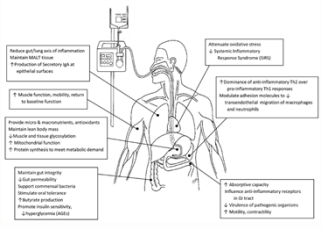
Objectives

- Explain the mechanism of action with peptides as part of a specialized enteral nutrition regimen.
- Identify the role of peptides in the compromised GI patient receiving tube feeding.
- Describe recent evidence with peptide-based diets including outcomes regarding the metabolic management of adult tube-fed patients.

José M Saavedra, MD - Disclosures

- Former Chief Medical Officer
  Nestlé Nutrition, Vevey Switzerland
- Chairman of the Board, Nestlé Nutrition Institute



Delivery of enteral nutrition is critical and paramount to the successful medical management of compromised and vulnerable populations

McClave et al, Crit Care Med 2014; 42:2600–2610)

Enteral nutrition is by far the preferred route for nutrient delivery, but challenges must be overcome…

Factors affecting GI function

- Poor GI perfusion / oxygenation
- Poor gastric and enteral digestive and enzymatic function
- Changes in gut pH
- Altered microbiota (antibiotics, stasis)
- Altered Motility
- **No enteral nutrient provision (mucosal malnutrition)**

Physiologic consequences

Dysmotility

Maldigestion & Malabsorption

Loss of mucosal barrier and immune function

Clinical consequences

- Undernutrition
- Metabolic disturbances
- Infection, toxemia
- Morbidity & Mortality
- **GI intolerance**
  reflux, vomiting, abdominal distension, diarrhea

Enteral nutrition is by far the preferred route for nutrient delivery, but challenges must be overcome, and a vicious iatrogenic cycle can be created

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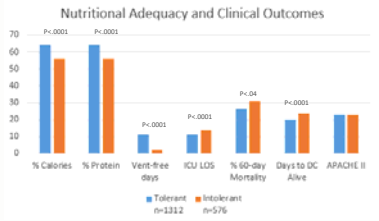
GI intolerance, a consequence of GI dysfunction, particularly malabsorption, is **-very-** common in the critical care - and chronic care settings.

- 36% of enterally fed patients can develop diarrhea during the ICU stay (1)
- 60% reported to develop delayed gastric emptying &
- 27% reported to develop intra- abdominal hypertension in the ICU(2)
- >40% of patients develop symptoms of GI intolerance in the first week of stay and are associated with negative outcomes (3).

1 Ferrie S,East V, *AustCritCare*. 2007;20(1):7–13.
2 Reintam A et al, *Crit Care*. 2008;12(4):R90.
3 Reintam A et al, *Intensive Care Med*. 2013;39(5):899–909.

Frequency and consequences of GI intolerance in the ICU

International retrospective observational cohort in 167 ICUs, 1,888 ICU patients



Incidence of GI intolerance was 30.5%

GI Intolerance was associated with:

Lower nutrition adequacy vs the tolerant (56% vs 64%, $P < .0001$),

Fewer VFDs (2.5 vs 11.2, $P < .0001$),

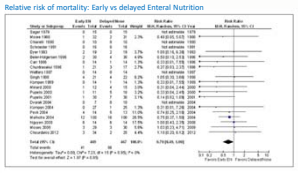
Increased ICU stay (14.4 vs 11.3 days, $P < .0001$),

Increased mortality (30.8% vs 26.2, $P = .04$).

Gungabissoon U et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. *JPEN J Parenter Enteral Nutr*. 2015;39(4):441–448.

SCCM & ASPEN Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

Relative risk of mortality: Early vs delayed Enteral Nutrition



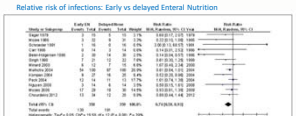
Early EN can reduce mortality by 30%
RR 0.70, 95% CI 0.49, 1.00
Pooled Analysis - 21 Randomized Control Studies

- ***B1. We recommend that nutrition support therapy in the form of early EN be initiated within 24–48 hours in the critically ill patient who is unable to maintain volitional intake.***

McClave S, et al. JPEN 2016;40:159-211.

SCCM & ASPEN Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

Relative risk of infections: Early vs delayed Enteral Nutrition



Early EN can reduce infections by 26%
RR 0.74, 95% CI 0.58, 0.93
Pooled Analysis - 13 Randomized Control Studies

- ***B2. We suggest the use of EN over PN in critically ill patients who require nutrition support therapy.***

McClave S, et al. JPEN 2016;40:159-211.

Providing Early EN to the critically ill is not a question of "if"
but of "how", "what", "how much"

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but of "how", "what", "how much"

SCCM & ASPEN Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

- ***D3a. We recommend that enteral feeding protocols be designed and implemented to increase the overall percentage of goal calories provided.***
- ***D3b. Based on expert consensus, we suggest that use of a volume-based feeding protocol or a top-down multistrategy protocol be considered.***

Develop and implement a feeding plan…

Example: The PEPuP Protocol - Efficacy of Enhanced Protein-Energy Provision via the Enteral Route in Critically Ill Patients:

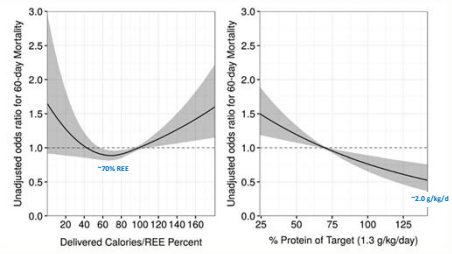
A Multicenter QI Collaborative

- Protocolized feeding plan with options based on hemodynamic stability and suitability for high volume intragastric feeds.
- Initiate feeding Day 1 at 25mL/hr on and convert to volume based feeding on Day 2 (or use 10mL/hr for trophic feeding).
- Target a 24-hour volume of EN rather than an hourly rate and provide the nurse with the latitude to increase the hourly rate to make up the 24 hour volume.
- Start with a semi-elemental solution, progress to polymeric as tolerated.
- Tolerate higher GRV threshold (300 mL or more).
- Motility agents and protein supplements started immediately, rather than started when there is a problem.

Heyland D, et al. *JPEN* 2015;39:698-706.

Providing Early EN to the critically ill is not a question of "if"
but of "how", "what", "how much"

What : Delivery of adequate energy and protein are critical in improving clinical outcomes, including improved morbidity and mortality

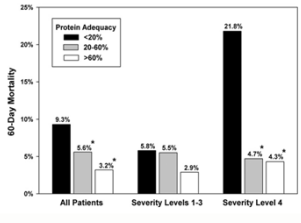


Aiming for energy and protein delivery that increases the chances for successful outcomes

Zusman et al. Critical Care 2016, 20:367

Association of administered calories/resting energy expenditure (Adcal/REE) percent with 60-day mortality (left), and protein intake by daily requirement (1.3 g/kg/d) with 60-day mortality (right) by odds ratio. REE resting energy expenditure

Focus on Protein: Delivery of adequate protein is critical in improving clinical outcomes, including improved morbidity and mortality in critically ill pediatric patients



Higher protein – without 'overshooting' on calories' significantly decreases mortality.

Relation between enteral protein adequacy and 60-d mortal- ity in relation to the severity of illness at admission in mechanically venti- lated children (n = 1245). Adequacy equals the delivered amount as a percentage of prescribed goal. *Significantly lower mortality than in ref-erence category of ,20%, P , 0.01 (Fisher's exact test). The interaction between the severity of illness and protein intake adequacy was significant, P = 0.014 (Wald's test = 8.62 on 2 df).

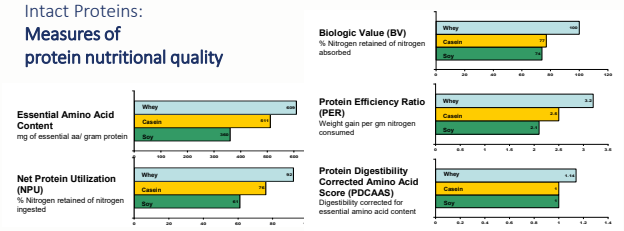
Mehta N et al. Am J Clin Nutr 2015;102:199–206.

Choosing a protein source for EN

- Proteins: Casein, Whey, Soy
- Hydrolyzed proteins: Range of large, midsize and small peptides
- Crystalline amino acids

Choosing a protein source for EN

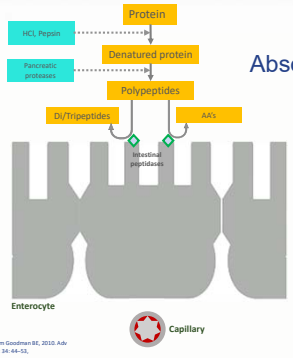
Intact Proteins:
Measures of protein nutritional quality



Physiologic Effects of Whey Protein

Nutritional and Gastrointestinal	Immune and Metabolic
26% BCAA and abundant in leucine for enhanced muscle protein synthesis[1,5]	**Prebiotic:** Selectively supports growth of Bifidobacteria [2,5]
Abundant in cysteine: Increases glutathione synthesis to protect against free radicals [2,5]	**Antimicrobial**: Binds C. Diff and inhibits cholera toxin [2]
Antioxidant capacity: Suppresses oxidative stress [2]	**Immunoglobulins**: Modulate immune function [2,5]
Enhanced Gastric Emptying [4,5]	**Insulinotrophic:** Increases maximal plasma insulin concentration >28% [3,5]

1. Ha E, Zemel B. J Nutr Biochem 2003;14:251-258. 2. Yalcin A. Curr Pharm Design 2006;12:1637-1643. 3. Power O, et al. Amino Acids 2009;37:333-339. 4. Fried MD et al. J Pediatr 1992;120:569-572. 5. Gupta C, Prakash D. Beverages 2017;3,31:doi:10.3390/beverages3030031.

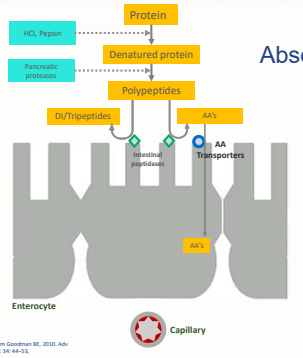


Absorption of dietary protein

Dietary protein digestion requires a functional gastric, pancreatic and intestinal pH and enzymatic set of processes, coupled with adequate motility- *all of which can be compromised in acutely ill patients.*

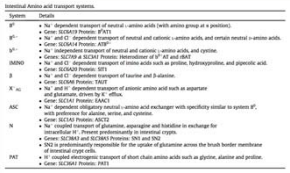
Peptides are primarily hydrolyzed to di-tripeptides and amino acids by intestinal peptidases

Adapted from Goodman BE, 2010. Adv Physiol Educ 34: 44-53.



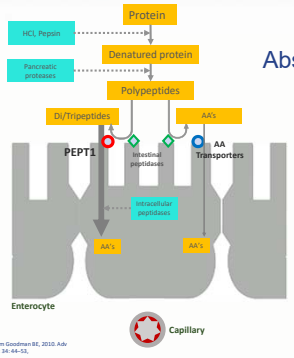
Absorption of dietary protein

Amino acids enter the enterocytes via numerous transporters which vary in solute specificity, Na, Cl, H-, or K dependency, and may represent electroneutral or electrogenic transport processes.



Kiela PR et al. Best Practice & Research Clinical Gastroenterology 30 (2016) 145e159

Adapted from Goodman BE, 2010. Adv Physiol Educ 34: 44-53.



Absorption of dietary protein

… however, the bulk of amino acids (~80%) enter the enterocytes as di- and tripeptides, via the PEPT1 (or SLC15) transport system.

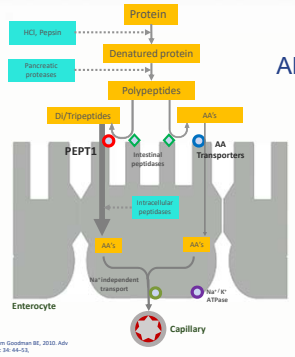
Amino acids infused into human intestine in peptide form are more readily absorbed than if infused into the intestinal lumen as free amino acids

This provides a highly effective and safety redundancy mechanism for the absorption of many amino acids.

Adibi SA et al. J Clin Invest 1975; 56: 1355-1363.

Adapted from Goodman BE, 2010. Adv Physiol Educ 34: 44-53.

Absorption of dietary protein

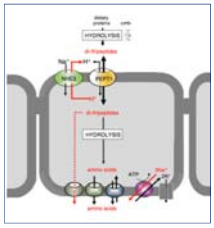


Intracellular peptidases hydrolyze peptides to amino acids.

Ultimately, amino acids are transferred across the basolateral membrane to circulation by Na independent transport systems. Some di or tripeptides may also be transported directly into circulation.

Adapted from Goodman BE, 2010. Adv Physiol Educ 34: 44–53,

Di- and Tripeptide Absorption

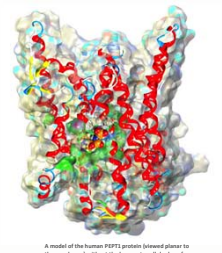


Adapted from Daniel H, Zietek T, Exp Physiol 100.12 (2015) pp 1441–1450

- **PEPT1 acts as a cotransporter of di-and tripeptides with hydrogen ions**
- **It is strictly dependent on the transmembrane proton gradient** generated by the sodium–proton exchanger NHE3 in the apical membrane, which maintains an electro- chemical proton gradient that allows the uptake of di- and tripeptides against a concentration gradient
- **The Na+ ion is then moved out of the cell by a Na+ion/K+ion ATPase pump on the basolateral membrane (3 Na+ are transported out and 2 K+ion are into the cell, normalizing the electro chemical gradient.**

Freeman HJ World J Gastrointest Pharmacol Ther 2015; 6(2): 22-27.

The PEPT1 Protein Transporter



A model of the human PEPT1 protein (viewed planar to the membrane) without the large extracellular loop for which no conformational information is available

- An 'archaic' transport mechanism, developed very early in evolution, cloned from many species.
- Estimated to be about 708 amino acids
- Mainly expressed in proximal small intestine.
- Very effective high capacity non-specific transporter
- Effective in the uptake of most of the potential 400 di- and 8,000 tripeptide sequences
- Expression increased by high protein diets, as well as fasting and starvation, and persists with intestinal disease, even with severe mucosal damage.
- Colonic expression described in patients with short bowel and IBD
- Transports non nutrient "peptide mimetic" therapeutic agents e.g. antibiotics like cephalosporins and penicillins, some antiviral agents (acyclovir, ganciclovir) and ACE inhibitors.

Daniel H, Zietek T, Exp Physiol 100.12 (2015) pp 1441–1450.

Utilization of whey protein hydrolyzed into peptides in protein synthesis (humans)

HIGHLIGHTED TOPIC | *Regulation of Protein Metabolism in Exercise and Recovery*

Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men

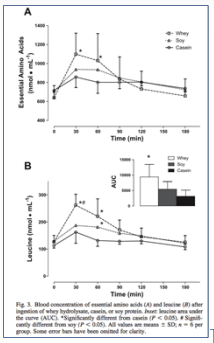
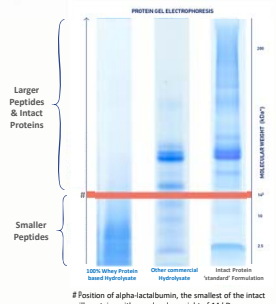


Fig. 3. Blood concentration of essential amino acids (A) and leucine (B) after ingestion of whey hydrolysate, casein, or soy protein. *Incr leucine area under the curve (AUC). *Significantly different from casein ($P < 0.05$). #Significantly different from soy ($P < 0.05$). All values are means ± SD; $n = 8$ per group. Some error bars have been omitted for clarity.

Peptide profiles in enteral nutrition formulations



Position of alpha-lactalbumin, the smallest of the intact milk proteins with a molecular weight of 14 kDa.

Enteral formulations, including enzymatically produced hydrolysates vary significantly in their profiles and distribution of peptides.

Nestlé Data on file

Switching to peptide based formula – improved enteral feeding tolerance in adults in long term care

Switching to a 100% whey peptide-based formula improved feeding tolerance in at least half of adults in a complex long term care facility.

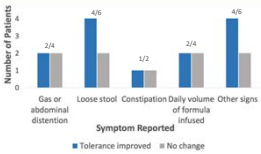
- Small retrospective study in tube fed adults
- Living in a complex continuing care facility.
- 329 records screened, 10 patients met criteria
- EN providing ≥ 90% of estimated daily calorie and protein needs
- Received intact protein formula at least 3 days prior to switch, remained on peptide-based formula ≥ 2 weeks after switch

Switched from an intact protein formula to a 100% whey hydrolysate, peptide-based formula due to reported feeding intolerance

FINDINGS

- **Signs of intolerance improved in at least half of the subjects**
- **4/8 subjects had a reduction or discontinuation in medications prescribed for intolerance after the switch.**

Improvement in Sx of GI Intolerance following switch to Hydrolyzed Whey Protein EN



Hopkins B et al. Presented at the Canadian Nutrition Society Annual Conference, May 3, 2019 in Niagara Falls, ON. Sponsored by Nestlé Health Science

Switching to peptide based - improved Enteral Feeding Tolerance in children with developmental delay

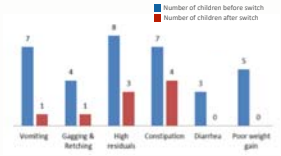
Switching to a 100% whey, peptide-based formula improved symptoms of feeding intolerance in a majority of these developmentally delayed children.

- Small retrospective chart review in 13 children (8.4 ± 4.6 years) with developmental delay.
- All had primary dx of developmental delay
- 77% of subjects were fed by G-tube. 85% had a Nissen fundoplication
- Subjects switched from an intact protein formula to a 100% whey hydrolysate, peptide-based formula due to reported feeding intolerance

FINDINGS

- **92% experienced improved feeding tolerance, 75% improved within 1 week after formula switch.**

Tolerance Parameters Changes



Minor G et al Global Pediatric Health, 2016, Vol. 3: 1–6.

Nestlé Nutrition Institute

Switch to peptide based formulation leads to enteral feeding tolerance improvement in home EN patients.

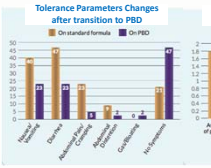
Switching to a peptide-based formulation diets (PBD) improved symptoms of feeding intolerance in a majority of home enteral nutrition patients, and decreased use of health resources

- Retrospective chart review of patients on home enteral nutrition (May 2017 to Jan 2018)
- Most common indication for hydrolyzed EN was fat malabsorption (29%) followed by pancreatic insufficiency (24%) and post-operative chyle leak (20%).

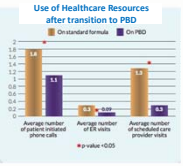
FINDINGS

- **The overall number of GI sx of intolerance were significantly reduced.**
- **Significant reduction in**
  - **Patient-initiated calls to HCP (p=.0051**
  - **ER (p=.0273**
  - **Scheduled care provider visits <0.0001)**
- **91% of peptide based diets were 100% hydrolyzed whey based products**

Tolerance Parameters Changes after transition to PBD



Use of Healthcare Resources after transition to PBD



Adapted Kuchkuntla AR, et al. Abstract at ASPEN 2019, Phoenix, AZ.
Study funded by Nestlé Health Science.

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Peptide-based formulation associated with improved albumin, prealbumin and TLC in postoperative ICU patients.

- Retrospective study comparing post-operative patients placed on intact protein and a protein hydrolysate (peptide based) milk protein formulation (both 16% protein)
- Serum albumin < 3.0 g/dL were enrolled
- Fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days.
- 72 adult ICU patients enrolled (hydrolysate/ intact protein: 40/32)

FINDINGS

- **Serum albumin (postop D 10), prealbumin (postop day 5 & 10), and TLC were significantly higher in the hydrolyzed peptide based formulation**
- **The average maximum gastric residual during their ICU stays was also significantly lower in the hydrolyzed formula group.**
- **No difference found in incidence of diarrhea or infections**
- **Dipeptide- and tripeptide-based enteral formulas were nutritionally efficacious and better tolerated than whole protein formulas.**

Liu MY et al. World J Gastrointest Surg. 2016 Oct 27; 8(10): 700–705.

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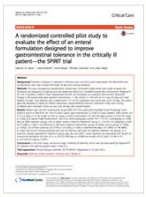


Peptide-based high protein formula allowed for 30% greater delivery of protein in ICU patients. No differences found in occurrence of diarrhea.

- Prospective, double-blind, randomized, controlled single-center pilot study
- Assessed incidence and frequency of diarrhea with whey protein based peptide formula vs. intact protein formula
- The caloric goal was adjusted to needs by indirect calorimetry. Gastrointestinal function, nutritional intake, and nursing workload were recorded. Follow-up was until 28 days after randomization.
- N=90 (Intervention/Control: 46 / 44), ICU stay ≥5 d, tube fed ≥3 days, initiated within 72 h of ICU admission
- **FINDINGS**
- **Higher protein delivered in intervention group 1.13 (0.78–1.31) vs 0.80 (0.70–0.94) g/kg/day; p < 0.001).**
- **No difference in incidence of diarrhea*.**
- **No difference in energy delivery and time to delivery.**
- **Occurrence of diarrhea was associated with**
  - **Length of mechanical ventilation**
  - **Length of ICU stay (11.0 (8.9–13.1) vs. 5.0 (3.8–6.2) days; p = 0.001).**

* N° of 'stool events' was low in both groups. Study used frequency based criteria for diarrhea although the majority of patients who developed loose stools were fitted with 'stool collectors' that did not allow for adequate stool frequency assessment.

Jakob SM et al. Crit Care. 2017 Jun 10;21(1):140.

Nestlé Nutrition Institute

Peptide-based formulation led to improved overall tolerance (any gastrointestinal adverse event) in adult ICU patients.

Prospective randomized trial
Critically ill medical & surgical patients were randomized to protein hydrolysate, peptide based (25% protein) or intact (18%) protein formulation
49 patients, 25/24: intervention/control

FINDINGS

- **In protein hydrolysate, peptide based formula group there were significantly fewer days with adverse events (any)- undesired gastrointestinal events**
- **No difference in other clinical outcomes, including differences in individual GI sx of intolerance**
- Enteral nutrient delivery not reported

Seres DS et al. Clin Nutr.2017;36(3):706-709.

Early EN with Semi-elemental Provides Cost Savings Compared to Polymeric Diets

- GI intolerance is associated with frequent feeding interruptions/reduction in EN delivery
- GI intolerance **is an independent risk factor** for prolonged ICU stay & death

Cost estimation of GI Intolerance:

Assuming an occurrence GI intolerance of 31 of 100patiebts, and a median ICU stay of 14.4 days versus 11.3 days due to GI intolerance *

For 100 patients	100% Tolerant	31% Intolerant	Difference
ICU LOS Days	1130.0	1226.1	+ 96.1 days
Total ICU Costs	$5,326,820	$5,779,835	**+$453,015**

Estimation using Cost Consequence Modeling:

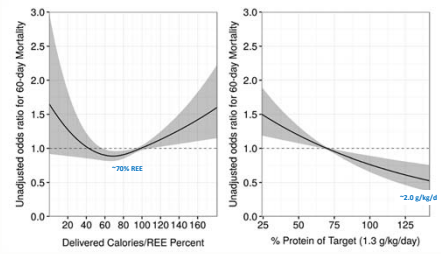
The use of peptide based instead of intact protein formulas can result in cost savings -through the reduction in length of ICU stay- if only >7% of GI intolerance cases are avoided**.

*Gungabissoon et al. JPEN 2015;39:441-448. **Curry A, et al. ClinicoEconomics and Outcomes Res 2018;10:293-300.

Nestlé Nutrition Institute

Providing Early EN to the critically ill is not a question of "if"
but of "how", "what", "how much".

Delivering energy and protein to fit the needs of the critically ill



Moderated energy delivery &
High protein level
- high quality protein,
- readily digestible & absorbable

Improves GI, immune and metabolic functions, decreasing morbidity and mortality

Zusman et al. Critical Care 2016, 20:367.

Conclusions

Adequately planned and implemented
early enteral nutrition can improve outcomes.

- Early enteral delivery of adequate energy, maximizing effective protein delivery increases chances for better outcomes
- Higher protein formulations allow the right 'balance' of energy and protein to fit the needs of critically ill.
- Whey hydrolysates with predominance of small peptides can deliver high quality protein, facilitate absorption, and decrease chances for intolerance, particularly in the critically ill.

Adequately planned and implemented
early enteral nutrition can save money.

Nestlé Nutrition Institute

Use of Peptide-based Formulations For Optimizing Enteral Nutrition Delivery, GI Tolerance, and Metabolic Management

Juan B. Ochoa Gautier, MD, FACS, FCCM
Associate Critical Care Medicine – Geisinger Health System (1/28/2019)
Director Surgical Intensive Care Unit
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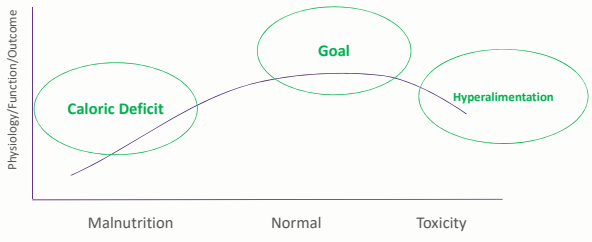
Juan B. Ochoa, MD - Disclosures

- Former employee of Nestlé Health Care Nutrition, North America
  - Member of the Board of Directors
- Nestlé Health Science
  - Chief Medical Officer for North America until July 2018
- Consultant
  - Medaware Systems - https://www.medawaresystems.com/
- NIH Funding - Principal source of revenue through the years
  - I am an author in some of these publications
- This presentation is for sole educational purposes.
- I have tried, to the best of my ability to review the available scientific (peer-reviewed) literature and prepare an objective, balanced presentation.

Nutrition Paradigm in Critical Care – Optimal Caloric Intake



Conventional vs. Hypocaloric Nutrition- Outcomes

Title of Trial	First Author	Year Of Pub	Source	Outcomes
Effect of a Calorically dense…	Bryk	2005	JPEN	**Retrospective - Hypocaloric benefit**
EPANIC	Casaer	2011	NEJM	**Harm with Meeting caloric goals**
Trophic vs full energy	Rice	2011	Crit Care Med	**No Benefit of meeting caloric goals**
Optimisation of Energy Provision…	Heidegger	2013	Lancet	**Benefit of rescue in patients failing EN**
TICACOS	Singer	2011	Int. Care Med	**Trend towards lower mortality**
Early Parenteral Nutrition	Doig	2013	JAMA	**No Benefit of meeting caloric goals**
Permissive Underfeeding	Arabi	2015	NEJM	**No Benefit of meeting caloric goals**
High Protein, Hypocaloric	Rugeles	2016	J of Crit Care	**No Benefit of meeting caloric goals**
Early Goal Directed Nutrition	Allingstrup	2017	Int. Care Med	**No Benefit of meeting caloric goals**

Early-goal directed nutrition versus standard of care…

Allingstrup, M. et. Al. **Intensive care Medicine, 2017 22 September**

- Personal Component Score PCS score at 6 months - No difference (mean difference 0.0, 95% CI −5.9 to 5.8, *p* = 0.99)
- No difference in mortality, rates of organ failures, serious adverse reactions or infections in the ICU, length of ICU or hospital stay, or days alive without life support at 90 days.

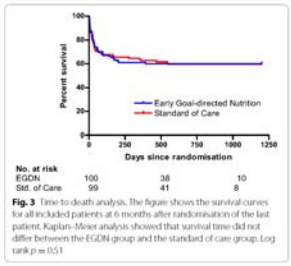


Fig. 3 Time to death analysis. The figure shows the survival curves for all included patients at 6 months after randomisation of the last patient. Kaplan–Meier analysis showed that survival time did not differ between the EGDN group and the standard of care group. Log rank p = 0.51

Conventional vs. Hypocaloric Nutrition - Glycemia

Title of Trial	First Author	Outcomes	Effect Glycemia Meeting Caloric Goals
Effect of a Calorically dense…	Bryk	Retrospective - Hypocaloric benefit	**Increase**
EPANIC	Casaer	Harm with Meeting caloric goals	**Increase**
Trophic vs full energy	Rice	No Benefit of meeting caloric goals	**Increase**
Optimisation of Energy Provision…	Heidegger	Benefit of rescue in patients failing EN	**?**
TICACOS	Singer	Trend towards lower mortality	**?**
Early Parenteral Nutrition	Doig	No Benefit of meeting caloric goals	**?**
Permissive Underfeeding	Arabi	No Benefit of meeting caloric goals	**Increase**
High Protein, Hypocaloric	Rugeles	No Benefit of meeting caloric goals	**Increase**
Early Goal Directed Nutrition	Allingstrup	No Benefit of meeting caloric goals	**Increase**

Systematic Scoping Review on Clinical Burden of Hyperglycemia in ICU Patients[3]

Studies show hyperglycemia in the ICU can lead to poor patient outcomes:

- Higher levels of blood glucose are associated with higher risk of mortality
- Hyperglycemia is an independent risk factor for infections
- Blood glucose is an independent predictor of length of stay in the ICU and hospital
- Hyperglycemia in hospitalized patients is significantly associated with increased disease severity and use of healthcare resources

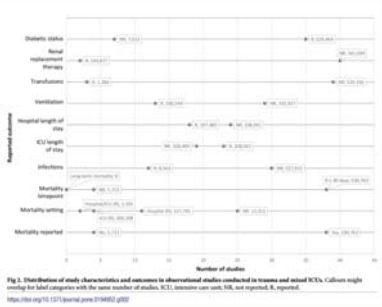
So What?

Hyperglycemia is present in up to 86% of adults and 64% of children in the ICU[1,2]

1. Farrokhi et al Best Pract Res Clin Endocrinol Metab. 2011 October ; 25(5): 813–824.
2. Van den Burgh et al. N Engl J Med 2001;345:1359-67.
3. Olariu E, et al. PLoS ONE 2018;13(4):e0194952.

Conventional Nutrition (1st week) –side effects (hyperglycemia)

PLoS ONE 13(4): e0194952



Elena Olariu[1], Nicholas Pooley[1], Aurelie Danel[2], Montserrat Miret[3], Jean-Charles Preiser[3]*

1 PrMiR Ltd, London, United Kingdom, 2 Nestle´ Health Science, Vevey, Switzerland, 3 Department of Intensive Care, Erasme University Hospital, Universite´ Libre de Bruxelles, Brussels, Belgium

- > 40 Studies
- Stress hyperglycemia
- Different Clinical endpoints

- Hyperglycemia is an independent predictor of poor clinical outcome

Glucose in Critically Ill Patients

- Hyperglycemia is common in critically ill patients
- Critical illness worsens insulin sensitivity / resistance
- Hyperglycemia is associated with the severity of critical illness
- Hyperglycemia may be the cause of worse outcome

Time of New Nutrition Paradigms in Critical Care?

Allow a Caloric Deficit?

Permissive Underfeeding

-Does not achieve any nutritional goals
- ↓ Calories – OK
- Low Protein
- Does not meet micronutrient needs

-Permits gastrointestinal trophism

-Facilitates a starvation response
- Physiologic (autophagy)
- Compensatory response

-For how long?

What about Protein?

Hypocaloric Nutrition

-Achieves some nutritional goals
- ↓ Calories – OK
- Normal to high Protein
- Meets micronutrient needs

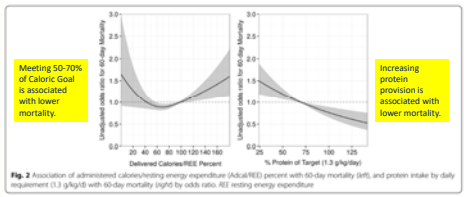
-Permits gastrointestinal trophism

-Facilitates a caloric starvation response
- Physiologic
  - Mobilize lipid stores
  - Maintains anabolism
- May interfere with autophagy

-For how long?
- Buying time while mobilizing lipid stores

Dickerson RN et al. JPEN 2013;37:342-351. Patel JJ et al. JPEN 2017; https://doi.org/10.1177/0148607117721908

Resting Energy Expenditure, Calorie and Protein Consumption in Critically Ill Patients: A Retrospective Cohort Study



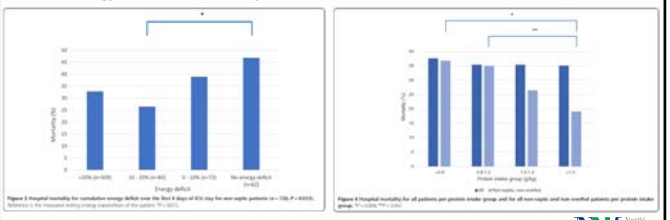
Zusman et al. Critical Care (2016) 20:367

High Protein Intake is Associated with Low Mortality and Energy Overfeeding with High Mortality

Weijs et al. Critical Care 2014 – 843 ICU patients -

10-20% Energy deficit decreases mortality

Protein > 1.2 g/kg/d lower mortality



What are the Right Tools to facilitate the delivery of optimal calories and higher protein to the critically ill patient?

What are the possible Metabolic Benefits?

What is the Evidence?

Dietary Management of Blood Glucose in Medical Critically Ill Overweight and Obese Patients: An Open-Label Randomized Trial*

The DIVINE study:
DIetary management of glucose VarIability iN thE ICU

*Nestlé-initiated & funded study

Rice TW et al. JPEN 2019;43(4):471-480.

The DIVINE Study

Objective: To determine whether blood glucose control could be facilitated by using an enteral nutrition formula containing low carbohydrates, medium chain triglycerides, and very high levels of hydrolyzed whey protein ensuring optimal protein delivery

Design:
-Prospective, Open-label, Multicenter, RCT
-7 Academic Medical Centers (North America)
-August 1, 2014 through July 27, 2016
-Mechanically ventilated critically ill adults, obese and overweight (BMI 26-45) subjects requiring enteral nutrition for at least 5 days.

Rice TW et al. JPEN 2019;43(4):471-480.

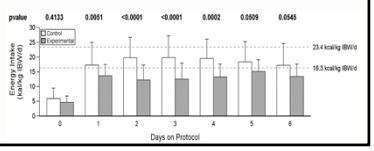
Divine Study Results: Nutrition Intake

Mean Nutrition Intake:

- Both groups received similar amounts of protein (p = 0.83).
- Experimental group received less calories (p < 0.0001).
- Experimental group received less carbohydrate (p < 0.0001).

Mean Nutritional Intake*	Control	Experimental
Energy (kcal/kg IBW/day)	18.2 ± 6.0	12.5 ± 3.7
Protein (g/kg IBW/day)	1.2 ± 0.4	1.1 ± 0.3
Carbohydrate (g/kg IBW/day)	2.0 ± 0.7	0.9 ± 0.3
Fat (g/kg IBW/day)	0.6 ± 0.2	0.5 ± 0.1
Caloric Density (kcal/mL)	1.0	1.0
Protein (% energy)	64 g/L (25%)	92 g/L (37%)
Carbohydrate (% energy)	112 g/L (45%)	76 g/L (30%)
Fat (% energy)	34 g/L (30%)	38 g/L (33%)

* Based on average over days 1-5.

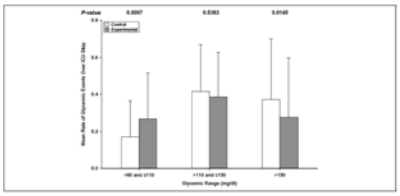


Rice TW et al. JPEN 2019;43(4):471-480.

Divine Study Results:

- **102 patients ITT Analysis**
- **Decrease of 10.8% in average blood glucose (126 mg/dL [114, 143] vs. 138 mg/dL [125, 158]; (p = 0.004)**
- Decrease in mean rate of glucose > 150 mg/dL (p=0.015)
- Increase in events with normal blood glucose 80-110 mg/dL (p=0.0007)
- No significant difference in glycemic events ≤ 80 mg/dL
- **10.9% decrease (p=0.048) in number of times insulin administered**
- Increase in serum Alkaline Phosphatase in the control group (p<0.05)
- Increase in serum Carbon Dioxide in the control group (<0.05)

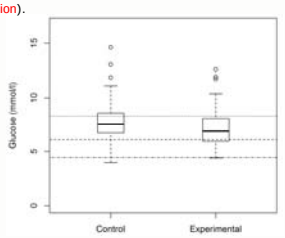
Mean Rate of Glycemic Events



Rice TW et al. JPEN 2019;43(4):471-480.

Divine Study Results

- Geometric mean glucose concentration was significantly lower in the experimental group (7.7 ± 0.07 vs 7.0 ± 0.07 mmol/L, p = 0.004).
- Significantly smaller glycemic dispersion in the experimental group (-11%, p = 0.0015) (standard deviation).



Rice TW et al. JPEN 2019;43(4):471-480.

Dispersion – Finfer et al. Crit Care 2013, 17:229.

Divine Study Conclusions - A very high protein with Enzymatically Hydrolyzed 100% Whey and Low Carbohydrate Formula

Is associated with:

- Lower dispersion of blood glucose as measured by standard deviations
- Lower incidence of hyperglycemia (> 8.3 mmol/L) (-13%), increased incidence of normoglycemia (4.4-6.1 mmol/L) (+14 %)
- Decreased insulin use
- Hypoglycemic events were not increased

Is not associated with:

- A reduction of blood glucose events outside the interval of 6.1 to 8.3 mmol/L

These are important metabolic differences that may have clinical significance

Rice TW et al. JPEN 2019;43(4):471-480.

Reason for Better Glucose Control?

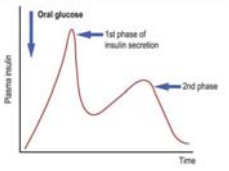
- High protein load improves insulin sensitivity
- Whey protein improves insulin sensitivity
- Lower carbohydrate delivery results in better glucose control
- Lower overall calorie delivery (hypocaloric feeds) results in better glucose control
- MCT may be insulinotropic

BACKGROUND DATA-Stages of Insulin Release

There is an initial rapid phase of insulin secretion, followed by a less intense but more sustained release.

Two Phase Approach

- **Phase I: Glucose Mediated Insulin Release (Nutrient stimulated)**
  Glucose triggers insulin release from beta cells in pancreas
- **Phase II: GLP-1 and GIP Mediated Insulin Release (Non-Nutrient stimulated)**
  - *GLP-1 inhibits* α-cell secretion (glucagon-glycogen-glucose release)
  - *GLP-1 inhibits β-cell secretion (insulin from pancreas)*



https://doctorlib.info/medical/biochemistry/23.html

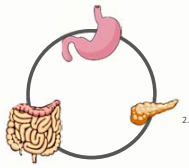
Hare K, et al. Diabetes 2010;59:1765-1770.
Seino Y et al. J Diab Invest 2010;1:8-23.

Mechanisms of Action: Incretin Hormone Secretion

- *Incretin hormones are any of several GI hormones that bring about the release of insulin*
- *GLP-1 Glucagon Like Peptide 1 – incretin hormone released by lower intestine and colon that moderates gut motility*
- *GIP Gastric Inhibitory Peptide – incretin hormone secreted by upper small intestines*
- *DPP-IV Dipeptidyl Peptidase IV – Multi-acting enzyme which inactivates GLP-1 and GIP*
- *Glucagon – Hormone secreted by the pancreas to increase blood glucose through glycogen or muscle breakdown*

4. Whey protein *hydrolysates* inhibit DPP-IV; DPP-IV breaks down incretin hormones.

3. GLP-1 secreted throughout intestinal tract with most coming from distal ileum/colon; augments insulin secretion as well as increases insulin sensitivity in muscle and fat tissue; GLP-1 suppresses glucagon secretion.



1. Whey protein is high in BCAA, empties the stomach quickly and stimulates incretin hormone release of GLP-1 and GIP.

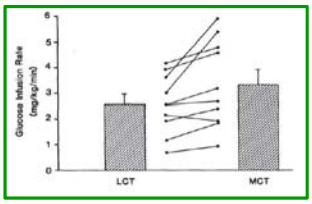
2. GIP stimulates insulin release from pancreas. Whey *hydrolysates* stimulate greater GIP release than intact whey protein.

Tolholst, et al. J Physiol 2009;587.1:27-32.

Insulinotropic Effects of MCT

Amount of glucose needed to maintain euglycemia during insulin infusion increased after MCT given:

- Accelerated beta oxidation
- Increased fatty acid from MCT inhibits need for glucose oxidation, uptake and storage

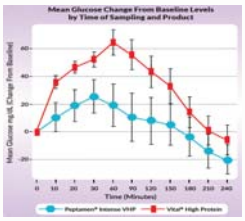


Eckel R,et al. Diabetes 1992;41:641-47.

Very High Protein, Low Carbohydrate, 100% Whey Based Enteral Formula is Associated with Lower Blood Glucose Response

Study Results

- Peptamen® Intense VHP provides better postprandial blood glucose (BG) compared to Vital® High Protein.
  - **Significant increase** in BG levels within 10 minutes with Vital High Protein (p<0.005)
  - **Significant difference** in BG between groups up to 150 minutes after EN infusion
  - **Maximum increase** in blood sugar was lowest for the Peptamen® Intense VHP group
  - **Faster return to baseline** BG levels with Peptamen Intense VHP
  - **Clinical trend** toward lower endogenous insulin production over time, as measured by serum insulin (p>0.1)



Vital® is a registered trademark of Abbott Laboratories.

*Huhmann MB, Yamamoto S, Neutel JM, Cohen SS, & *Ochoa JB; Nutrition and Diabetes 2018;8:45.
*Employed by Nestlé Health Science.

So, What about Protein?

Narrowing the Protein Deficit Gap in Critically Ill Patients Using a Very High Protein Enteral Formula

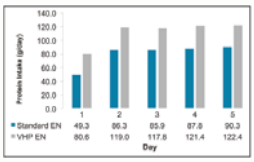
Methods:

- Retrospective, med/surg pts
- ≥ 5 days EN week-1 ICU
- Record daily pro/energy/tolerance

Results:

- 20 subjects standard EN
- 20 subjects Peptamen® Intense VHP
- Protein ***prescribed*** was significantly higher in VHP group (p=0.003)
- Protein ***delivered*** was significantly higher in the VHP group (p=0.0002)
- Average protein of 1.45 g/kg/day delivered to VHP group vs 1.1 g/kg/day in standard EN group No difference in EN tolerance, feeding interruptions or propofol use

Daily Protein Intake from EN (g/day)



Conclusion: EN feeding with a VHP formula in ICU patients resulted in higher protein intakes without increasing energy intake in the first five days of exclusive EN.

ApSimon M, Johnston C, Winder B, *Hopkins B. Abstract of Distinction ASPEN 2019, Phoenix AZ

*Nestle Employee
Funded by Nestlé Health Science

Should Hypocaloric Hyperproteic Nutrition become the Standard of Care in Critically Ill Patients?

Objective

Determine demographics of today's ICU and describe most appropriate EN delivery

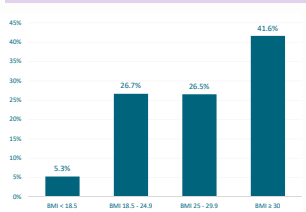
Design

- Retrospective analysis of 2,000 ICU patient encounters
- 1,899 patients/12,321 days

Results

- 62.2 years old / 55.2% male
- Hosp LOS 13.6 days / ICU LOS 6.9 days
- Days on mechanical ventilation 4
- 30-day readmission 19.3%
- **70% overweight or obese**

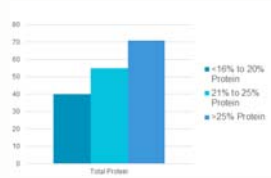
BMI by Percentage of Population



Hussein R, Berger A, *Ochoa-Gautier J. Abstract at ISIECM 2019, Brussels, Belgium and ASPEN 2019, Phoenix, AZ
Study funded by Nestlé Health Science. * Nestlé employee

Results

Protein Intake by Formula Type



Effect of Protein Intake on Mortality

Conclusion

- Significant improvement in mortality is seen with increased protein delivery
- Higher protein and less CHO seem to generate best outcomes for critically ill patients
- Patients on VHPLC formula received significantly more protein than when other ENF were used. p<0.0001

Hussein R, Berger A, Ochoa-Gautier J. Abstract at ISIECM 2019, Brussels, Belgium and ASPEN 2019, Phoenix, AZ

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QUESTIONS?

Visit the Nestlé Nutrition Institute for resources and tools

nestlenutrition-institute.org

Visit MyCE to access CE programs for dietitians and nurses

MyCEducation.com