Nestlé Nutrition Institute

Glucose Management in the ICU: The Evolving Role of Nutrition

Todd W. Rice, MD, MSc
Associate Professor of Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

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Disclosure

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Objectives:

- Explain the evidence demonstrating the amount of optimal calories and protein to administer to critically ill patients.
- Summarize the latest evidence addressing blood glucose control in the ICU.
- Describe harmful effects of hypo- and hyperglycemia in critically ill patients.
- Identify novel nutritional management modalities that have been shown to improve glycemic control and patient outcomes.

Early Nutrition in Critically Ill Patients

Feed Carefully and in Moderation

JAMA, Published online May 20, 2013

Juan B. Ochoa Gautier, MD
Flávia R. Machado, MD, PhD

- Nutrition in Critical Illness has been about providing food
- Has used the same principles as in normal human beings
  - 50% CHO
  - 35% Lipids
  - 15% Protein
- Has failed to demonstrate significant benefits

7. Casaer MP, Hermans G, Wilmer A, Van den Berghe G. Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients (EPaNIC trial): a study protocol and statistical analysis plan for a randomized controlled trial. *Trials*. 2011;12:21.
8. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*. 2013;381(9864):385-393.
9. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med*. 2011;39(5):967-974.
10. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011;37(4):601-609.

However…

- Studies have found that goal nutrition may not result in the best outcomes
- Available data suggest that protein may be more important than non-protein calories
- Levels of serum glucose affect patient outcomes
- Hyperglycemia and hypoglycemia may both worsen outcomes

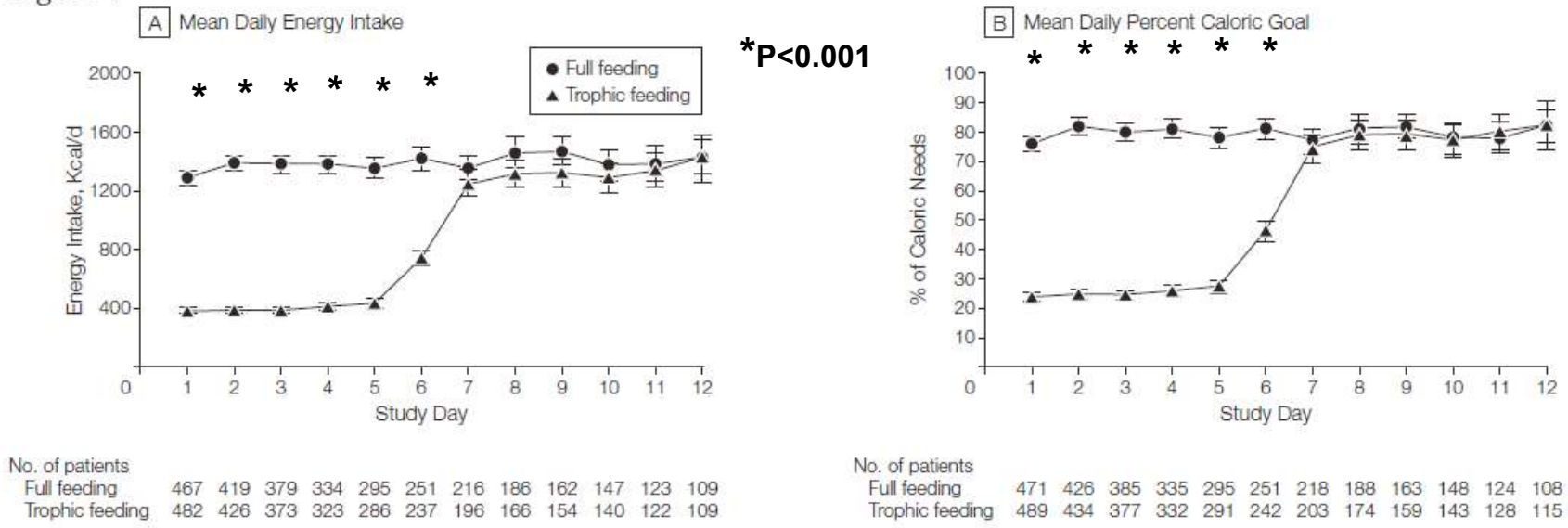
Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury

The EDEN Randomized Trial

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

EDEN: Enteral Feeds Delivered

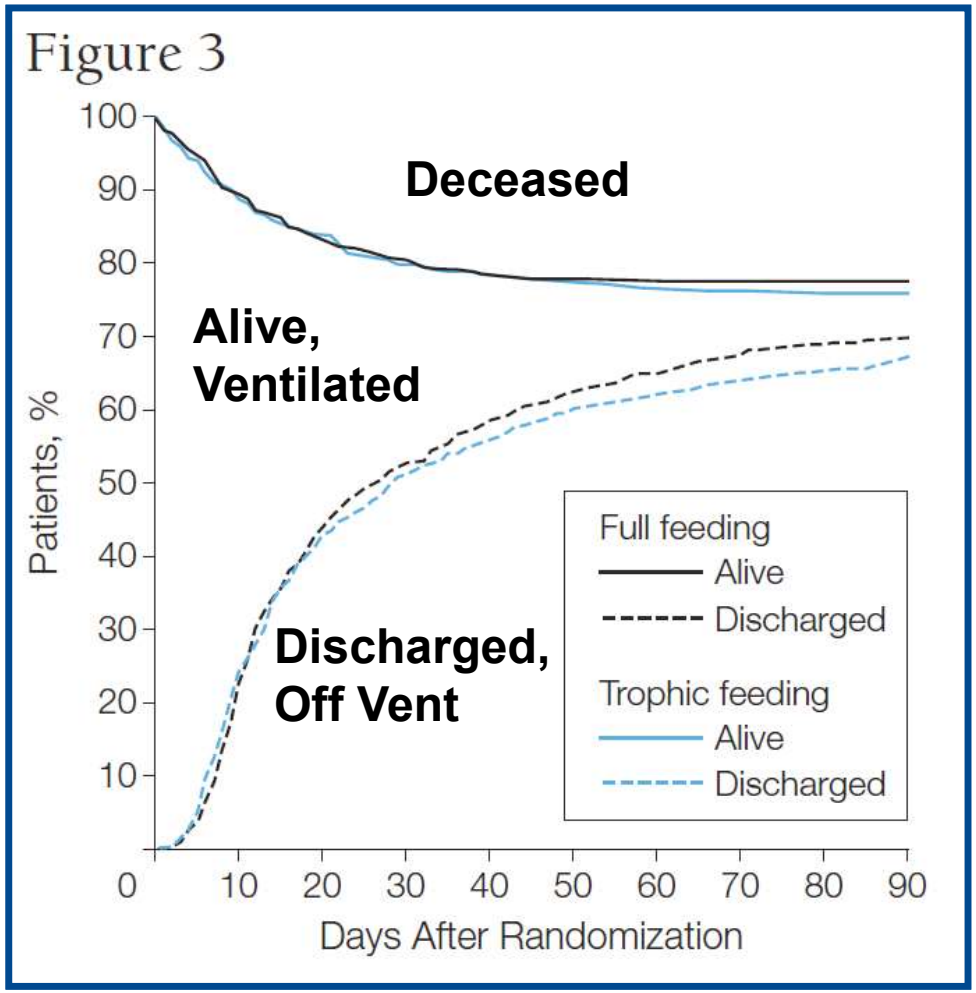
Figure 4



No. of patients												
Full feeding	467	419	379	334	295	251	216	186	162	147	123	109
Trophic feeding	482	426	373	323	286	237	196	166	154	140	122	109

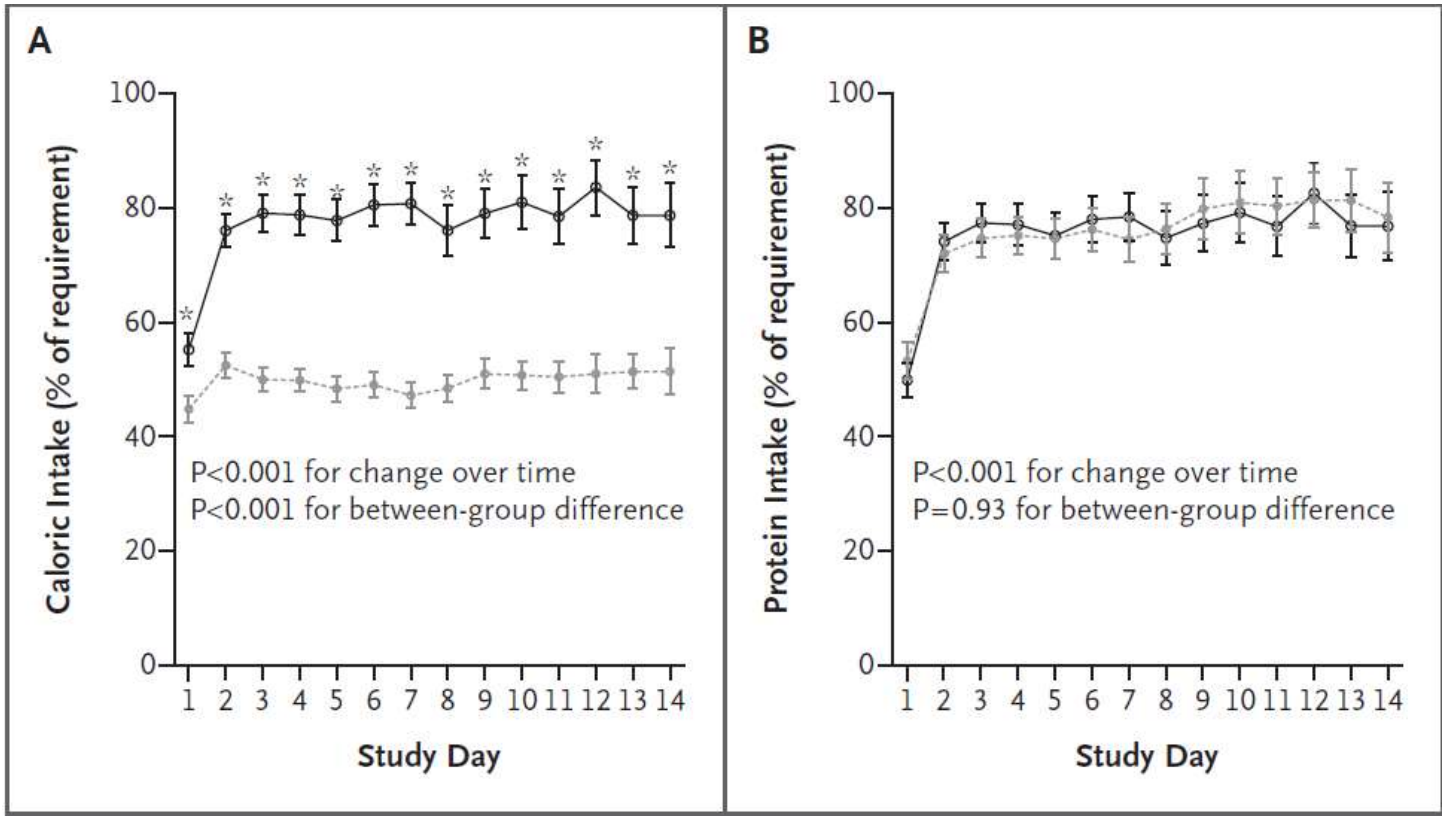
No. of patients												
Full feeding	471	426	385	335	295	251	218	188	163	148	124	108
Trophic feeding	489	434	377	332	291	242	203	174	159	143	128	115

JAMA, February 22/29, 2012-Vol 307, No. 8 795



Rice TW, et al. for NHLBI ARDS Network. *JAMA.* 2012; 307(8):795-803.

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults



Arabi YM, et al. *NEJM.* 2015;372(25):2398-2408.

Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.*

Outcome	Permissive Underfeeding (N = 448)	Standard Feeding (N = 446)	Relative Risk (95% CI)	P Value
Death by 90 days — no./total no. (%)	121/445 (27.2)	127/440 (28.9)	0.94 (0.76–1.16)	0.58
Death in the ICU — no. (%)	72 (16.1)	85 (19.1)	0.84 (0.63–1.12)	0.24
Death by 28 days — no./total no. (%)	93/447 (20.8)	97/444 (21.8)	0.95 (0.74–1.23)	0.7
Death in the hospital — no./total no. (%)	108/447 (24.2)	123/445 (27.6)	0.87 (0.70–1.09)	0.24
Death by 180 days — no./total no. (%)	131/438 (29.9)	140/436 (32.1)	0.93 (0.76–1.14)	0.48
Duration of mechanical ventilation — days				
Median	9	10		0.49†
Interquartile range	5–15	5–16		
Days free from mechanical ventilation				
Median	77	75		0.48†
Interquartile range	0–84	0–84		
ICU length of stay — days				
Median	13	13		0.46†
Interquartile range	8–21	8–20		
ICU-free days				
Median	72	71		0.28†
Interquartile range	0–81	0–79		
Hospital length of stay — days				
Median	28	30		0.24†
Interquartile range	15–54	14–63		
Incident renal-replacement therapy — no./total no. (%)	29/406 (7.1)	45/396 (11.4)	0.63 (0.40–0.98)	0.04

Arabi YM, et al. *NEJM.* 2015;372(25):2398-2408.

Optimal Initial Amount of Enteral Feeding in Critically Ill Patients: Systematic Review and Meta-Analysis

- Meta-analysis of adult ICU patients
- Initial trophic vs full feeding
- 4 RCTs (N=1540 participants total)
- Primary analyses: Mortality

Choi EY, Park DA, Park J. *JPEN.* 2015;39(3):291-300.

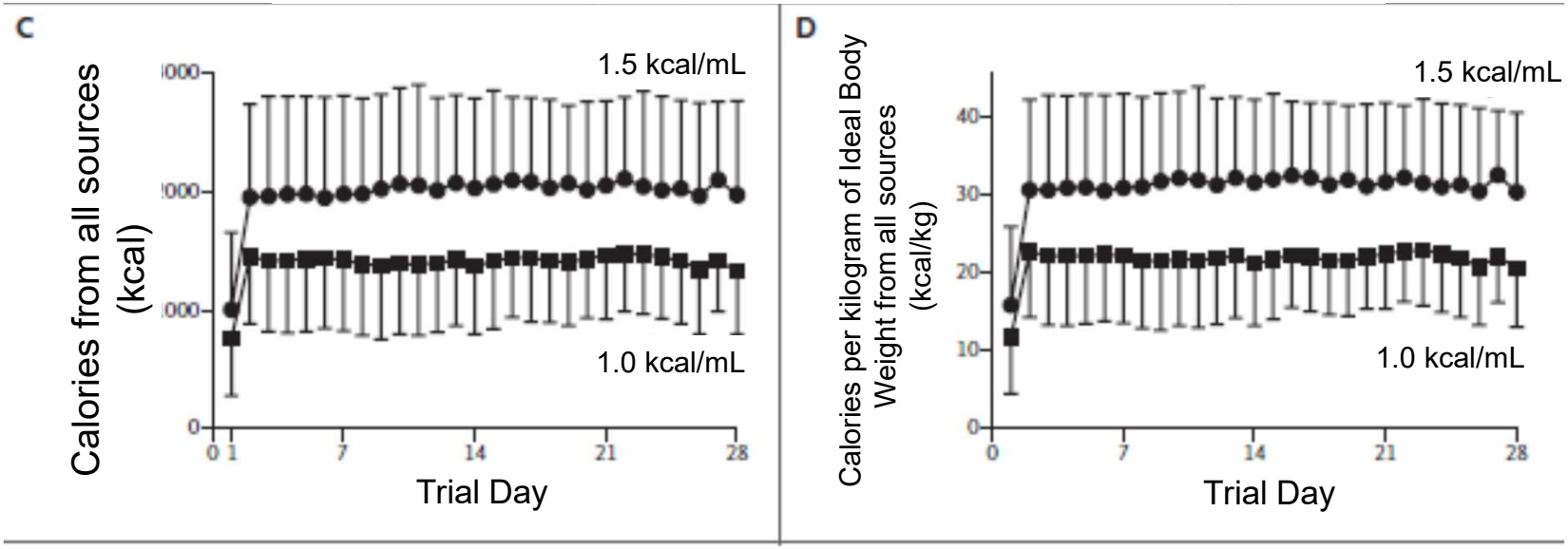
Optimal Initial Amount of Enteral Feeding in Critically Ill Patients: Systematic Review and Meta-Analysis

- No diff in Mortality (OR 0.95; 0.74-1.20; P=0.65)
- Subgroup analysis:
  - Trophic >33% of goal: OR 0.61 (0.39-0.97; P=0.04)
- No difference in Hospital or ICU LOS
- Serious GI Intolerance: 23% trophic vs 31% full (OR 0.66; 0.39-1.12; P=0.12)

Choi EY, Park DA, Park J. *JPEN.* 2015;39(3):291-300.

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators for the ANZICS Clinical Trials Group*



	Trial Day				
	1	7	14	21	28
No. of Patients					
1.5 kcal/mL	1841	871	371	172	82
1.0 kcal/mL	1851	881	350	158	64

TARGET Investigators for ANZICS. *NEJM.* 2018;379(19):1823-34.

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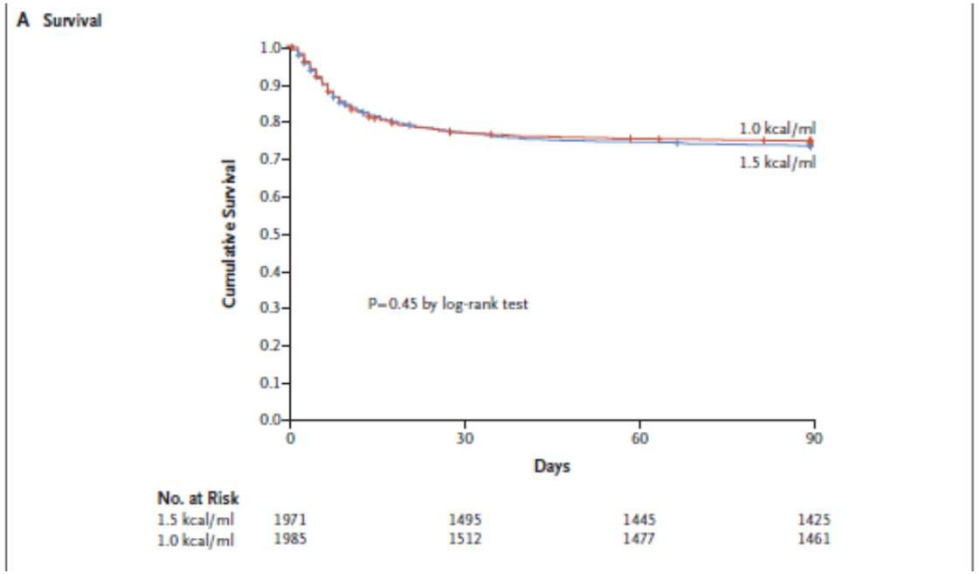
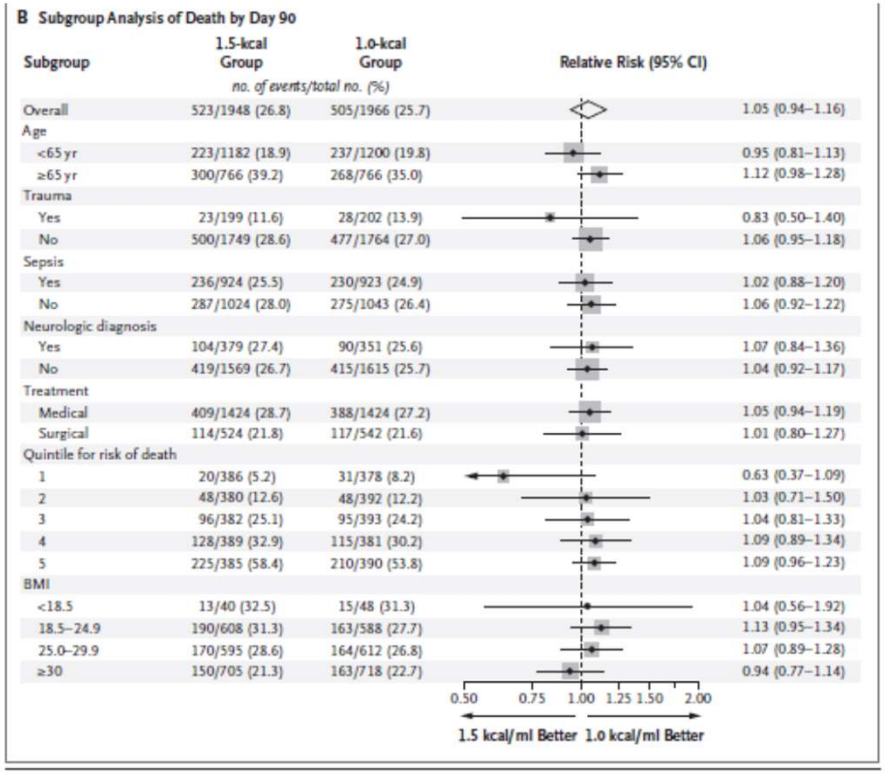




TARGET Investigators for ANZICS. *NEJM.* 2018;379(19):1823-34.

Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study

Oren Zusman, Miriam Theilla, Jonathan Cohen, Ilya Kagan, Itai Bendavid and Pierre Singer

Retrospective Study:
1171 pts in ICU over 13 yrs
all had Indirect Calorimetry

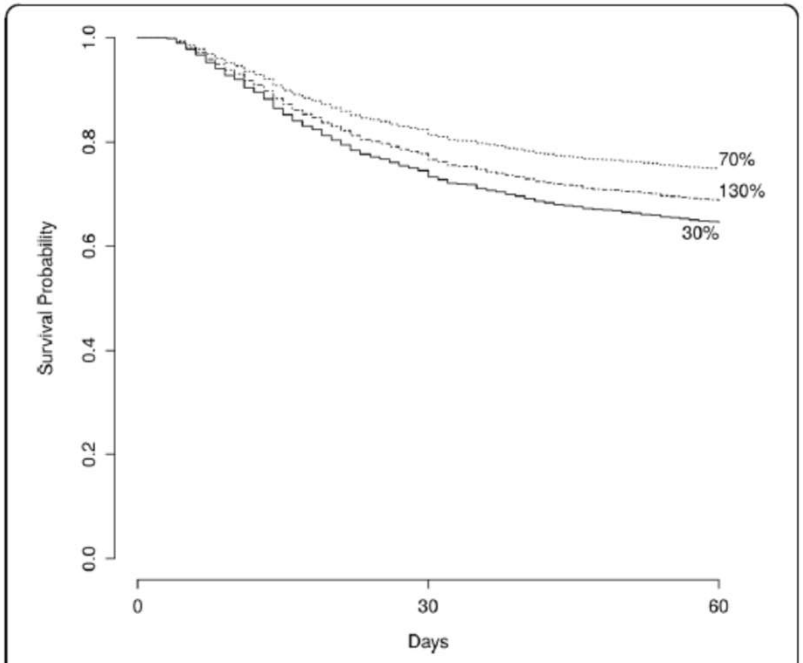


Fig. 3 Association between administered calories/resting energy expenditure (Adcal/REE) percent and 60-day survival. *Labels* correspond to Adcal/REE percent

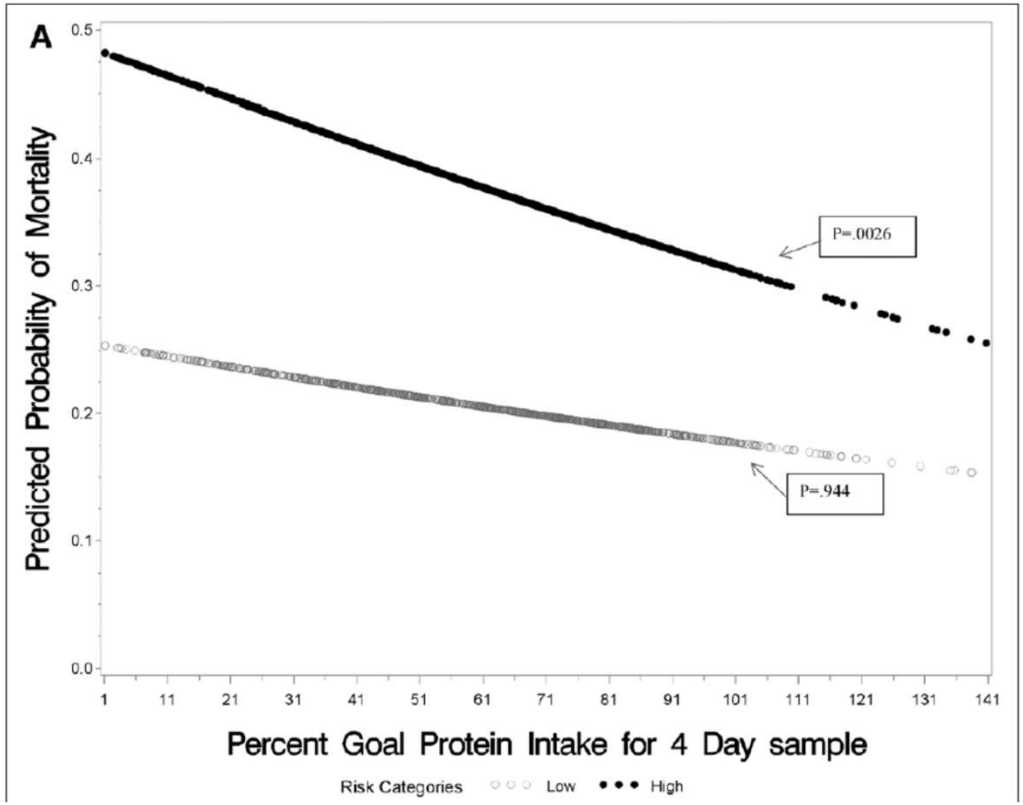
Zusman O, et al. C*rit Care*. 2016;20:367.

However…

- Studies have found that goal nutrition may not result in the best outcomes
- Available data suggest that protein may be more important than non-protein calories
- Levels of serum glucose affect patient outcomes
- Hyperglycemia and hypoglycemia may both worsen outcomes

Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study*

Charlene Compher, PhD, RD, CNSC, FASPEN[1]; Jesse Chittams, MS[1]; Therese Sammarco, MS[1]; Michele Nicolo, MS, RD, CNSC[2]; Daren K. Heyland, MD, MSc, FRCPC[3]



Retrospective Study:
2853 MV pts from 202 ICUs
INS Database

Compher C, et al. *Crit Care Med*. 2017;45:156-63.

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

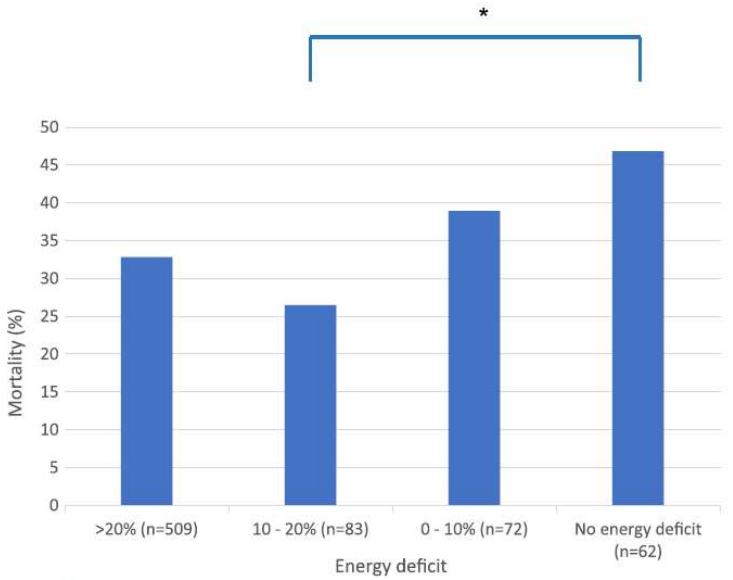


Figure 3 Hospital mortality for cumulative energy deficit over the first 4 days of ICU stay for non-septic patients (n = 726; *P* = 0.053). Reference is the measured resting energy expenditure of the patient. **P* = 0.012.

Protein > 1.2 g/kg/d lower mortality

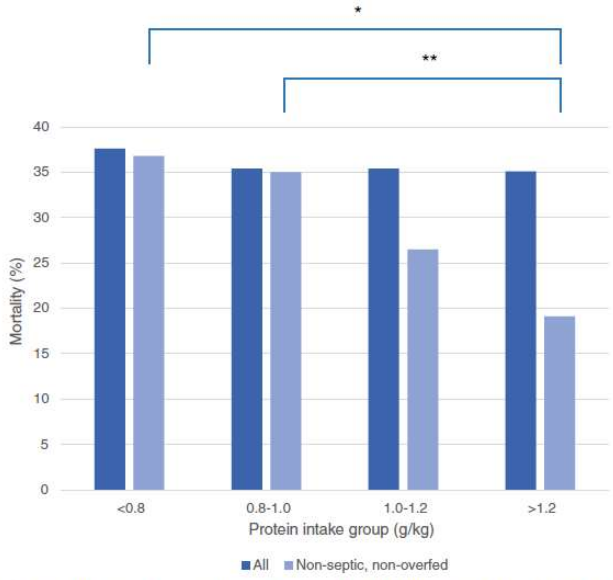


Figure 4 Hospital mortality for all patients per protein intake group and for all non-septic and non-overfed patients per protein intake group. **P* = 0.008; ***P* = 0.047.

Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study

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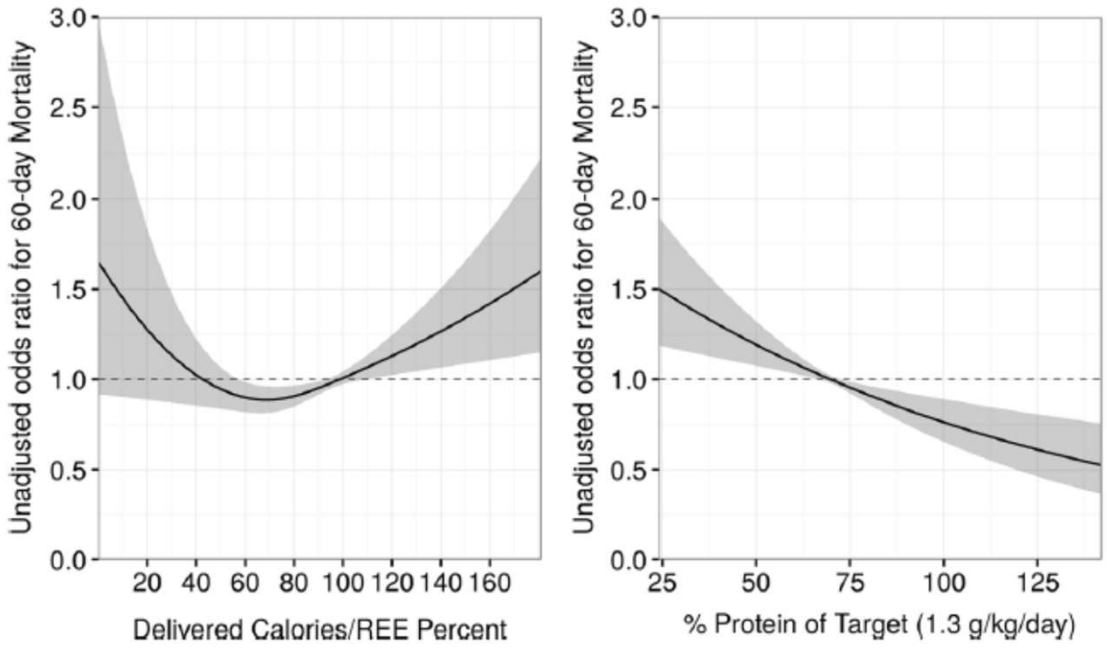

Fig. 2 Association of administered calories/resting energy expenditure (Adcal/REE) percent with 60-day mortality (*left*), and protein intake by daily requirement (1.3 g/kg/d) with 60-day mortality (*right*) by odds ratio. *REE* resting energy expenditure

Zusman O, et al. *Crit Care*. 2016;20:367.

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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 outcomes
- Hypoglycemia is associated with worse outcomes and may be the cause of worse outcomes
- Glucose variability likely plays a role in outcomes also

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

- RCT of 1548 pts from 1 SICU
- Randomized to:
  - Intensive insulin therapy (BS 80-110 mg/dL)
  - Conventional treatment (BS 180-200 mg/dL)
- Treated with insulin infusion
- Primary endpoint: Death during ICU stay

Van den Berghe G, et al. *NEJM.* 2001;345:1359-1367.

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TABLE 2. INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Administration of insulin — no. (%)	307 (39.2)	755 (98.7)	<0.001
Insulin dose — IU/day‡			
Median	33	71	
Interquartile range	17–56	48–100	<0.001
Duration of insulin use — % of ICU stay			
Median	67	100	<0.001
Interquartile range	40–100		
Morning blood glucose — mg/dl§			
All patients	153±33	103±19	<0.001
Patients receiving insulin	173±33	103±18	<0.001

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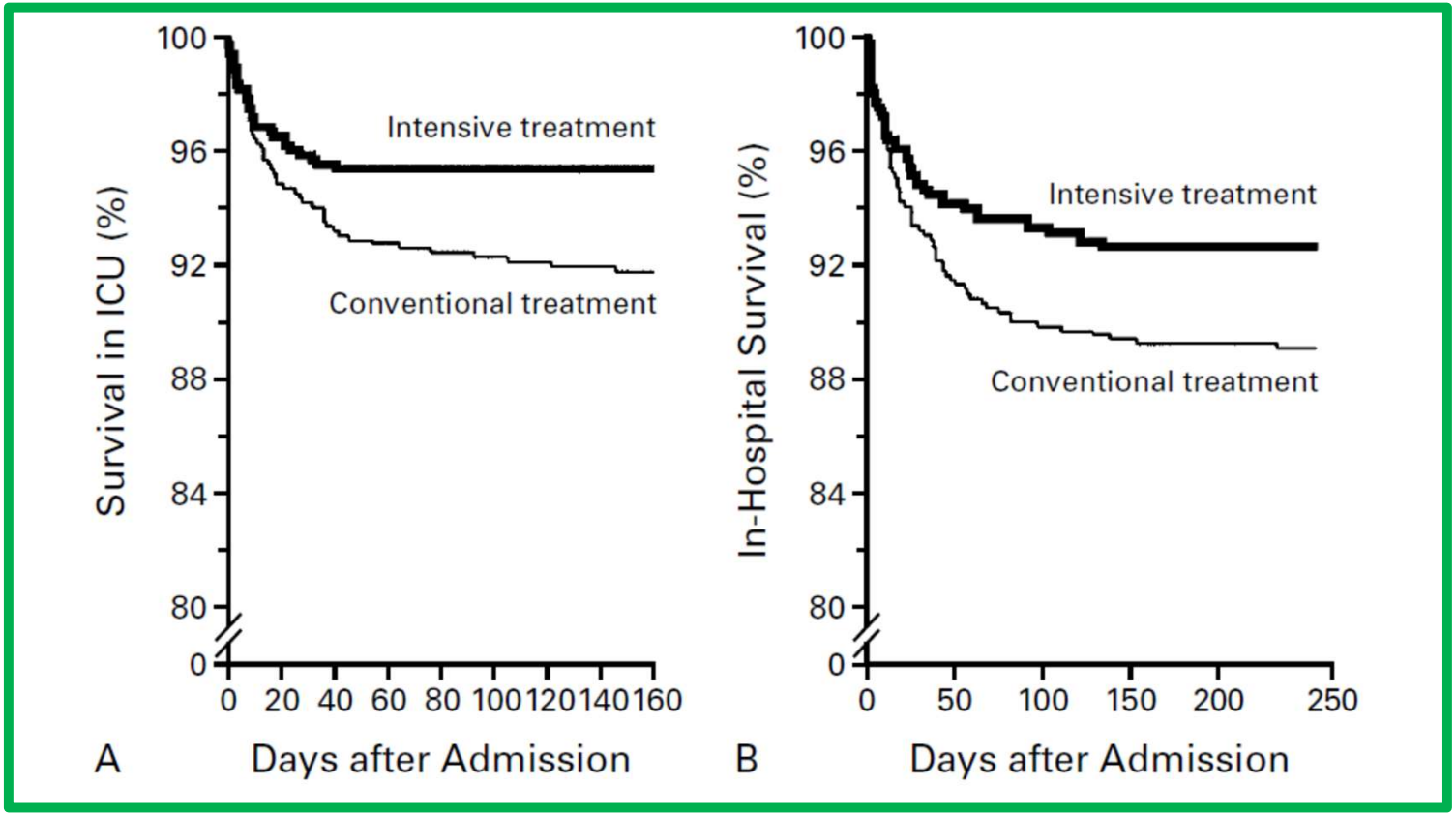
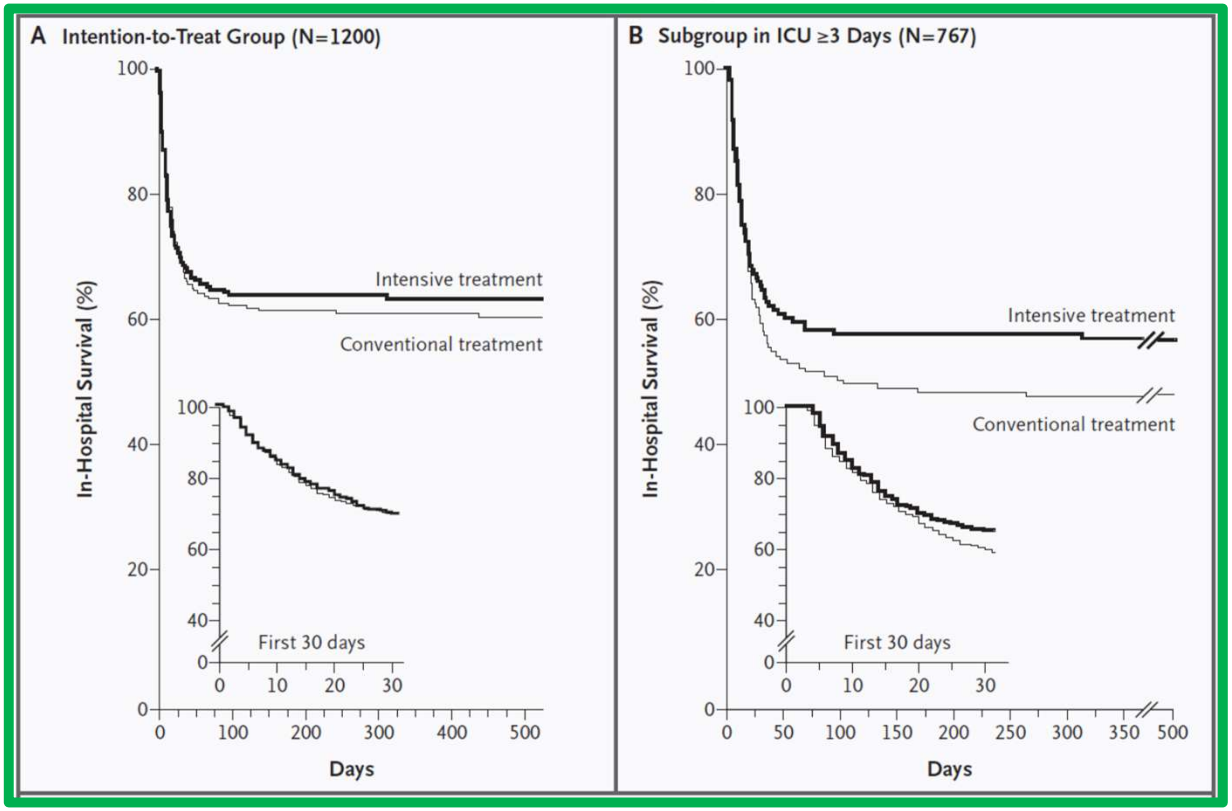


Van den Berghe G, et al. *NEJM.* 2001;345:1359-1367.

Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D., Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.



Van den Berghe G, et al. *NEJM.* 2006;354:449-461.

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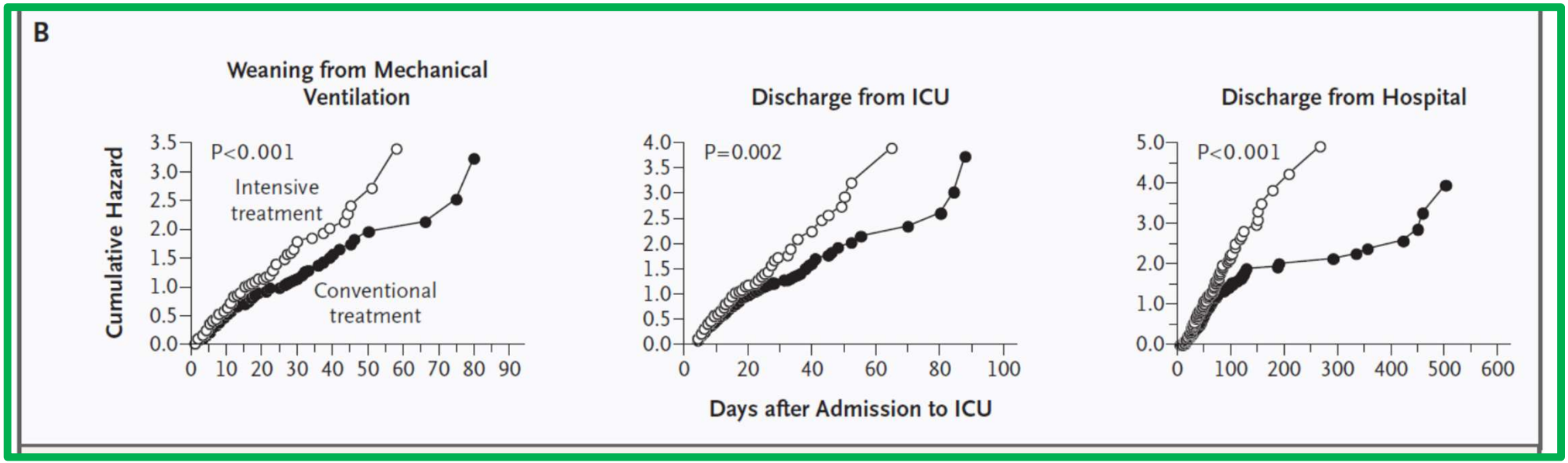

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However…

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- Hyperglycemia and hypoglycemia may both worsen outcomes

Intensive versus Conventional Glucose Control In Critically Ill Patients

The NICE-SUGAR Study Investigators*

- **RCT of 6104 pts from 42 med-surg ICUs**
- **Eligible if ICU LOS expected ≥ 3 days**
- **Randomized to:**
  - **Glucose target: 81-108 mg/dL**
  - **Glucose target: < 180 mg/dL**
- **Primary endpoint: Death by any cause to day 90**

NICE-SUGAR Study Investigators. *NEJM.* 2009;354:449-461.

Intensive versus Conventional Glucose Control In Critically Ill Patients

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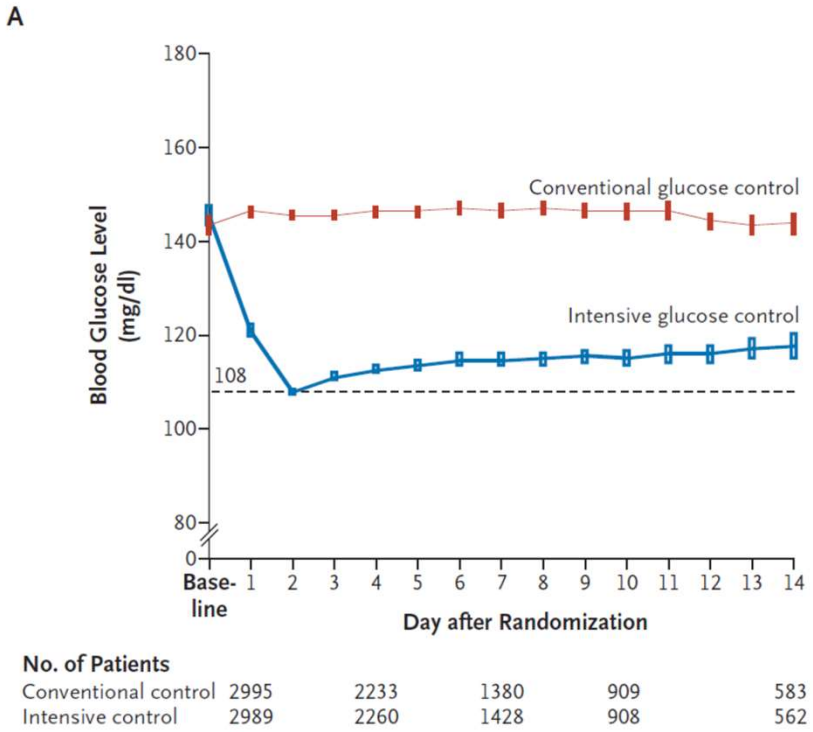
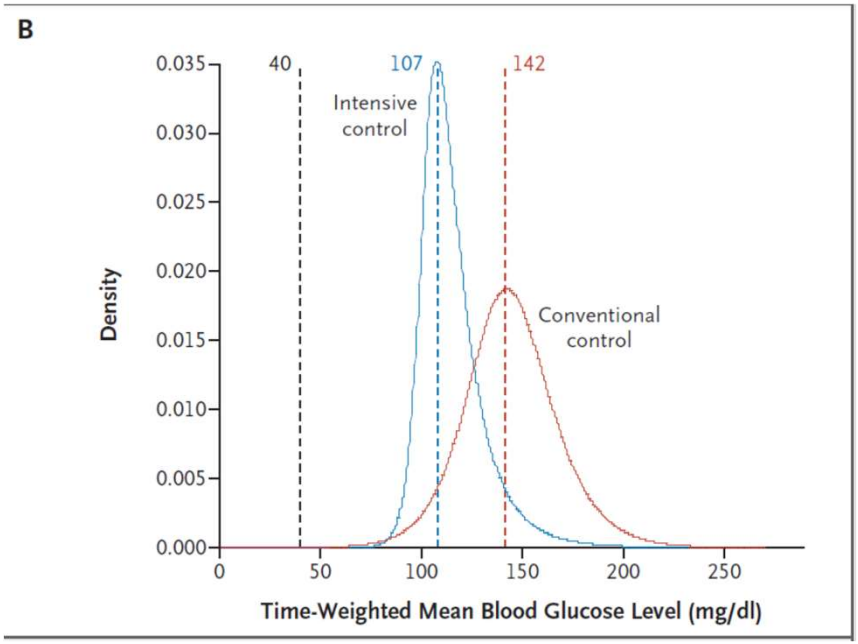




NICE-SUGAR Study Investigators. *NEJM.* 2009;354:449-461.

Table 3. Outcomes and Adverse Events.*

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Days in ICU — median (IQR)	6 (2 to 11)	6 (2 to 11)	0	Log-rank test	0.84
Days in hospital — median (IQR)	17 (8 to 35)	17 (8 to 35)	0	Log-rank test	0.86
Mechanical ventilation — no. of patients/total no. (%)	2894/3014 (96.0)	2872/3014 (95.3)	0.7 (–0.3 to 1.76)	Pearson's test	0.17
Days of mechanical ventilation	6.6±6.6	6.6±6.5	0	Wilcoxon rank-sum test	0.56
Renal-replacement therapy — no. of patients/total no. (%)	465/3014 (15.4)	438/3014 (14.5)	0.9 (–0.9 to 2.7)	Pearson's test	0.34
Days of renal-replacement therapy	0.8±2.6	0.8±2.8	0	Wilcoxon rank-sum test	0.39
No. of new organ failures — no. of patients/total no. (%)‡				Pearson's test	0.11
0	1571/2682 (58.6)	1536/2679 (57.3)			
1	790/2682 (29.5)	837/2679 (31.2)			
2	263/2682 (9.8)	257/2679 (9.6)			
3	44/2682 (1.6)	46/2679 (1.7)			
4	11/2682 (0.4)	2/2679 (0.1)			
5	3/2682 (0.1)	1/2679 (<0.1)			

NICE-SUGAR Study Investigators. *NEJM.* 2009;354:449-461.

Rates of Hypoglycemia

	Moderate Hypoglycemia (41-70 mg/dL)	Severe Hypoglycemia (≤ 40 mg/dL)
Van Den Berghe (Surg) (NEJM 2001)		39/765 **(5.1%)(Rx)** 6 / 783 **(0.8%) (Control)**
Van Den Berghe (Med) (NEJM 2006)		111/595 **(18.7%) (Rx)** 19/605 **(3.1%) (Control)**
NICE-SUGAR NEJM 2009)	2237/3017 **(74.2%) (Rx)** 477/3013 **(15.8%) (Control)**	208/3016 **(6.8%) (Rx)** 15/3014 **(0.5%) (Control)**

Hypoglycemia and Risk of Death In Critically Ill Patients

The NICE-SUGAR Study Investigators*

Table 1. Results of Multivariate Analysis for Factors at Baseline That Were Independent Risk Factors for Subsequent Moderate or Severe Hypoglycemia.*

Variable	Moderate Hypoglycemia		Severe Hypoglycemia	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Treatment group				
Conventional glucose control	1.00		1.00	
Intensive glucose control	24.19 (20.98–27.88)	<0.001	16.39 (9.32–28.81)	<0.001

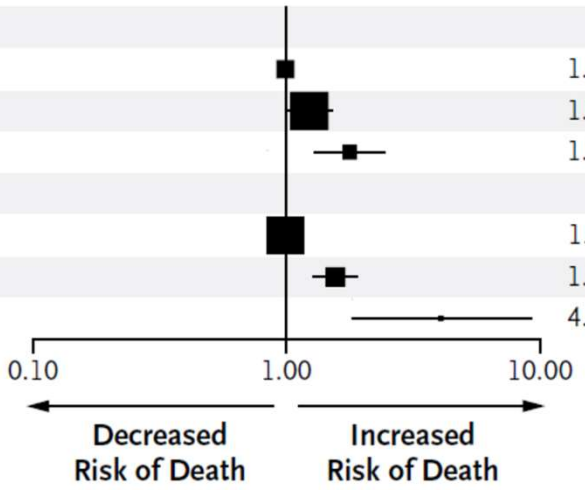
NICE-SUGAR Study Investigators. *NEJM.* 2012;367:1108-1118.

Hypoglycemia and Risk of Death In Critically Ill Patients

The NICE-SUGAR Study Investigators*

A

Subgroup	Deaths	Population	Hazard Ratio (95% CI)	P Value
		no.		
Intensive control				0.22
No hypoglycemia	128	568	1.00	
Moderate hypoglycemia	628	2237	1.24 (1.01–1.52)	
Severe hypoglycemia	72	208	1.79 (1.30–2.46)	
Conventional control				
No hypoglycemia	598	2521	1.00	
Moderate hypoglycemia	146	477	1.57 (1.29–1.91)	
Severe hypoglycemia	7	15	4.12 (1.82–9.32)	



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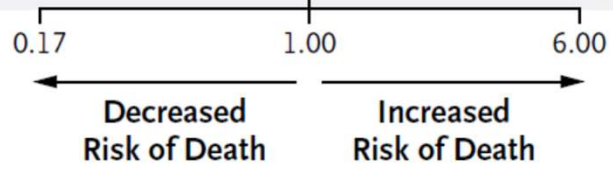
Hypoglycemia and Risk of Death In Critically Ill Patients

The NICE-SUGAR Study Investigators*

A

Subgroup	Deaths	Population	Hazard Ratio (95% CI)	P Value
		no.		
No hypoglycemia	726	3089	1.00	
Moderate hypoglycemia				0.01
1 day	234	878	1.28 (1.09–1.53)	
>1 day	540	1836	1.57 (1.36–1.91)	
Severe hypoglycemia				0.29
1 day	65	186	2.11 (1.61–2.94)	
>1 day	14	37	2.91 (1.71–5.23)	



NICE-SUGAR Study Investigators. *NEJM.* 2012;367:1108-1118.

What if We Could …?

- Maintain better blood glucose control, …
- While reducing the risk for hypoglycemia, …
- All with a nutritional formula?

Mesejo *et al. Critical Care* (2015) 19:390
DOI 10.1186/s13054-015-1108-1

RESEARCH Open Access

Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study

Alfonso Mesejo[1*], Juan Carlos Montejo-González[2*], Clara Vaquerizo-Alonso[3], Gabriela Lobo-Tamer[4], Mercedes Zabarte-Martinez[5], Jose Ignacio Herrero-Meseguer[6], Jose Acosta-Escribano[7], Antonio Blesa-Malpica[8] and Fátima Martinez-Lozano[9]

Table 4 Variables related to glycemic control

	GROUP A (n = 52)	GROUP B (n = 53)	GROUP C (n = 52)	*p* value
Administered insulin (IU/day)	19.1 (13.1)	23.7 (40.1)*a	20.3 (30.1)	<0.05*
Plasma glucose level (mg/dL)	138.6 (39.1)	146.1 (49.9)*a	143.9 (45.9)	<0.01*
Capillary glucose level (mg/dL)	146.1 (45.8)	155.3 (63.6)*a	150.1 (41.9)*b,c	<0.001*a <0.01*b,c
Mean capillary glycemia on ICU day 1 (mg/dL)	147.5 (40.2)	160 (55.5)*d	145.6 (46.6)	<0.01*
Peak glucose level (mg/dL)	181.3 (52)	193.6 (74.6)	191.3 (65.8)	0.68
Number of capillary glycemia measurements	3605	3523	3557	0.57
Number of measurements per patient/day	5.7 (3.4)	5.81 (3.2)	5.46 (2.9)	0.56
Percentage of controls on 80–150 mg/dL	59 %	57.6 %	59.59 %	0.82
Hypoglycemia (50–80 mg/dL)	53 (1.48 %)	127 (3.63 %)*d	44 (1.25 %)	<0.05*
Hypoglycemia (<50 mg/dL)	-	4 (0.11 %)	1 (0.02 %)	0.32
Capillary glucose SD	45.83	63.67*d	41.98	<0.01*

Mesejo A, et al. *Crit Care.* 2015;19:390.

Glycemic Effects of a Low-Carbohydrate Enteral Formula Compared With an Enteral Formula of Standard Composition In Critically Ill Patients: An Open-Label Randomized Controlled Clinical Trial

Table 2. Glycemic Outcomes (n = 101).

Outcome	Low-Carbohydrate Formula (n = 52)	Standard (n = 49)	Mean Difference (95% CI)[b]	*P* Value
Glucose variability[a]				
Mean absolute glucose change (mmol/L/h)	0.8 [0.7–1.2]	0.9 [0.6–1.2]	0.06 (−0.1–0.2)	.510
SD (mmol/L)	1.4 ± 0.7	1.4 ± 0.7	0.05 (−0.2–0.3)	.721
Coefficient of variation (%)	17.7 ± 7.3	16.4 ± 6.9	1.37 (−1.4–4.2)	.334
Glycemic lability index (mmol/L/h)	0.8 ± 1.2	0.6 ± 0.8	0.24 (−0.2–0.6)	.232
CGM glucose (mmol/L)	8.0 ± 1.4	8.3 ± 1.5	−0.38 (−1.0–0.2)	.193
CGM glucose at admission (mmol/L)	8.3 ± 2.4	8.0 ± 2.1	0.3 (−0.6–1.2)	.489
Blood gas glucose (mmol/L)	8.3 ± 1.1	8.7 ± 1.3	−0.31 (−0.8–0.2)	.216
Accu-Chek glucose (mmol/L)	7.8 ± 1.0	8.4 ± 1.1	−0.57 (−1.0 to −0.2)	.007
Time in glucose ranges[a]				
Percentage time				
>15 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0–0.0)	.258
9–15 mmol/L	21.4 [2.9–51.7]	25.0 [3.5–47.4]	−0.31 (−11.6–7.0)	.793
6–9 mmol/L	61.4 [37.4–77.0]	61.9 [45.5–79.5]	−3.68 (−14.3–7.3)	.501
2.2–6 mmol/L	6.6 [1.2–20.1]	3.8 [0.0–13.4]	1.92 (0.0–5.9)	.087
3.9–6 mmol/L	6.5 [1.2–20.1]	3.7 [0.0–13.4]	1.41 (0.0–5.1)	.098
Patients with hypoglycemic event[a]	0 (0.0%)	1 (2.0%)		.485
Patients with hyperglycemic event[a]	2 (3.8%)	7 (14.3%)		.086
Insulin administration				
Day 1, number of patients	41/52 (78.8%)	41/49 (83.7%)		.535
IU	42.0 [8.6–78.5]	42.8 [10.3–73.9]	0.0 (−19.2–14.0)	.798
Day 2, number of patients	29/39 (74.4%)	31/35 (88.6%)		.119
IU	46.8 [0.0–81.7]	68.0 [36.2–102.3]	−27.9 (−48.9–0.0)	.036
Day 3, number of patients	17/27 (63.0%)	23/28 (82.1%)		.110
IU	29.7 [0.0–74.5]	71.0 [23.1–114.6]	−26.0 (−59.1–0.0)	.066
Days 1–3, number of patients	42/52 (80.8%)	42/49 (85.7%)		.507
IU	66.1 [11.0–118.5]	94.4 [14.4–176.9]	−15.0 (−59.6–9.0)	.246

Van Steen SC, et al. JPEN. 2018;42(6):1035-45.

General Poster Session

Safer Glycemic Control Using Fructose-Based Enteral Formula —A Randomized Crossover Clinical Trial

MAGALI KUMBIER, CASSIANO TEIXEIRA, LUCAS HELAL **and** JUSSARA ALMEIDA

Author Affiliations

Diabetes 2018 Jul; 67(Supplement 1): -.
https://doi.org/10.2337/db18-768-P

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Abstract

Background: Glycemic control during nutritional therapy in patients under intensive care has shown a great importance in relation to morbidity and mortality. To avoid glycemic oscillation in patients under enteral nutrition, usually a low-carbohydrate diet is offered, but differing among themselves by carbohydrate type. A question that remains unanswered is whether the presence of fructose interferes with glycemic oscillation or not.

Kumbier M, et al. *Diabetes.* 2018, Jul; 67(Suppl 1):768-P. https://diabetes.diabetesjournals.org/content/67/Supplement_1/768-P

What if We Could Provide…?

- Permissive Underfeeding…
- With less carbohydrate, and…
- Adequate levels of protein (whey protein), …
- And maintain better blood glucose control, …
- While reducing the risk for hypoglycemia, …
- All with a nutritional formula?

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

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

Study Design

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

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

Study Design

- Open-label, Multicenter, RCT
- 7 Academic Medical Centers (North America)
- Plan 280 patients for 160 to complete 5 days Rx
- August 1, 2014 through July 27, 2016

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

Study Design: Patients

- **Inclusion:** Mechanically ventilated critically ill, obese and overweight (BMI 26-45) patients requiring enteral nutrition for ≥ 5 days.

- **Exclusion:** Hepatic failure, trauma admission, major surgery (past 30 days or future 7 days), pregnant, T1DM, Burns, unable to receive EN

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

Intervention

- **Control group**: High protein formula
- **Experimental group**: Very high protein, low carbohydrate formula

	Control Group (Replete®)	Experimental Group (Peptamen® Intense VHP)
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 (29%)
Fat (% energy)	34 g/L (30%)	38 g/L (34%)

Goal: Deliver 1.5 g/kg IBW/day of protein

Outcomes

- **Primary Endpoint**: The rate of glycemic events outside the interval of 6.1 to 8.3 mmol/L (110-150 mg/dL) in the first seven ICU days.
- **Secondary Endpoints:** Serial blood glucose, markers of nutritional status, urine/serum ketones, insulin and dextrose administered, clinical outcomes.

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

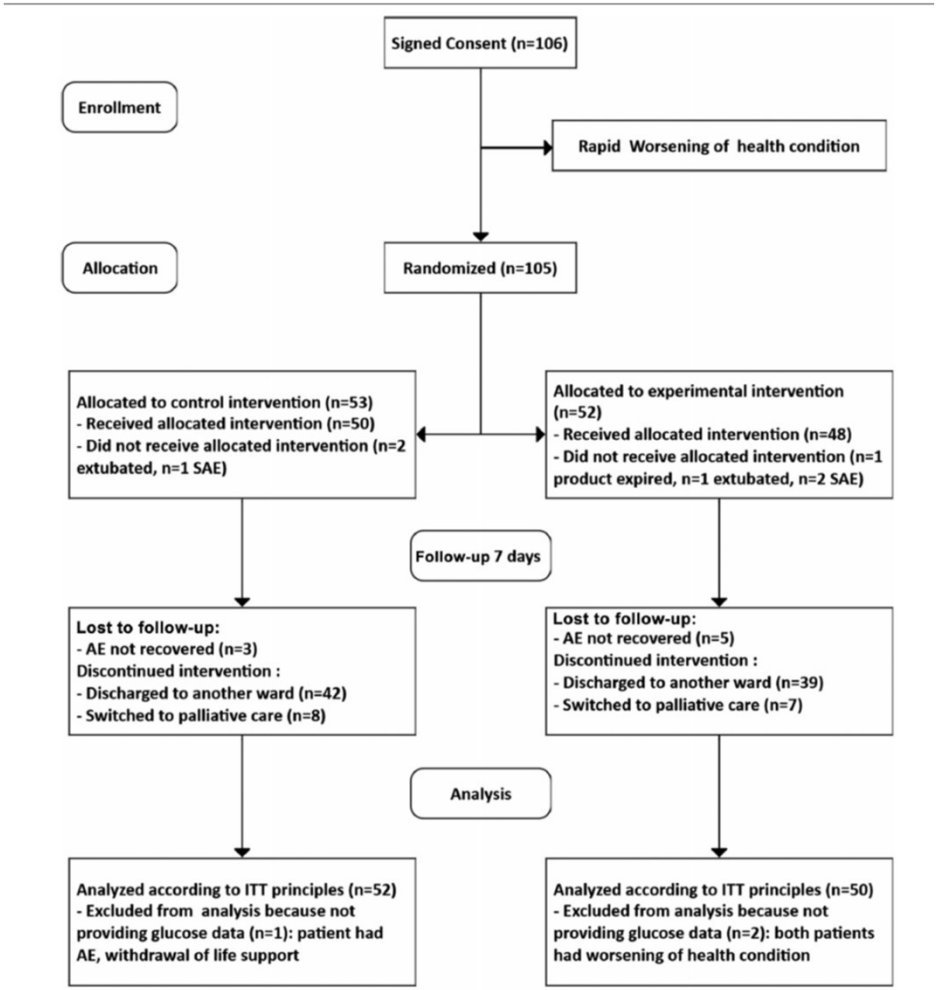
Dietary Management of Blood Glucose in Medical Critically Ill Overweight and Obese Patients: An Open-Label Randomized Trial

DIVINE Study Results

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

Enrollment / ITT Analysis

- 105 pts randomized (53 control, 52 experimental).
- 102 pts w/ glucose measurements included in the ITT analysis (52 control, 50 experimental).



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

Demographics

Table 3. Primary Admission Diagnostics and Baseline Patient Characteristics by Feeding Regimen Group.

Diagnosis		Control n = 53		Experimental n = 52	*P*-Value
Acute respiratory failure, n (%)	18	(34.0)	16	(30.8)	.727
Sepsis, n (%)	14	(26.4)	11	(21.2)	.527
Pneumonia, n (%)	9	(17.0)	9	(17.3)	.965
Neurological, n (%)	6	(11.3)	9	(17.3)	.384
Cardiac, n (%)	4	(7.5)	5	(9.6)	.706
Pulmonary embolism, n (%)	1	(1.9)	1	(1.9)	.989
Kidney injury, n (%)	1	(1.9)	0	(0.0)	NA
Hemorrhagic shock, n (%)	0	(0.0)	1	(1.9)	1.000
Age (years), mean ± SD		63.3 ± 11.9		61.0 ± 14.6	.371
Weight (kg), mean ± SD		94.3 ± 18.7		97.8 ± 18.9	.337
Height (cm), mean ± SD		169.0 ± 12.3		170.9 ± 11.3	.414
BMI (kg/m^2), mean ± SD		33.0 ± 5.8		33.4 ± 4.6	.753
APACHE II score,[a] mean ± SD		25.9 ± 9.2		24.8 ± 8.8	.535
Race: black, %		9.4		17.3	.242
Sex: female, %		54.7		42.3	.205
HgbA1c[b]		6.1 (5.3, 7.1)		6.1 (5.0, 7.4)	.787
DMII, n		16	21	.276	

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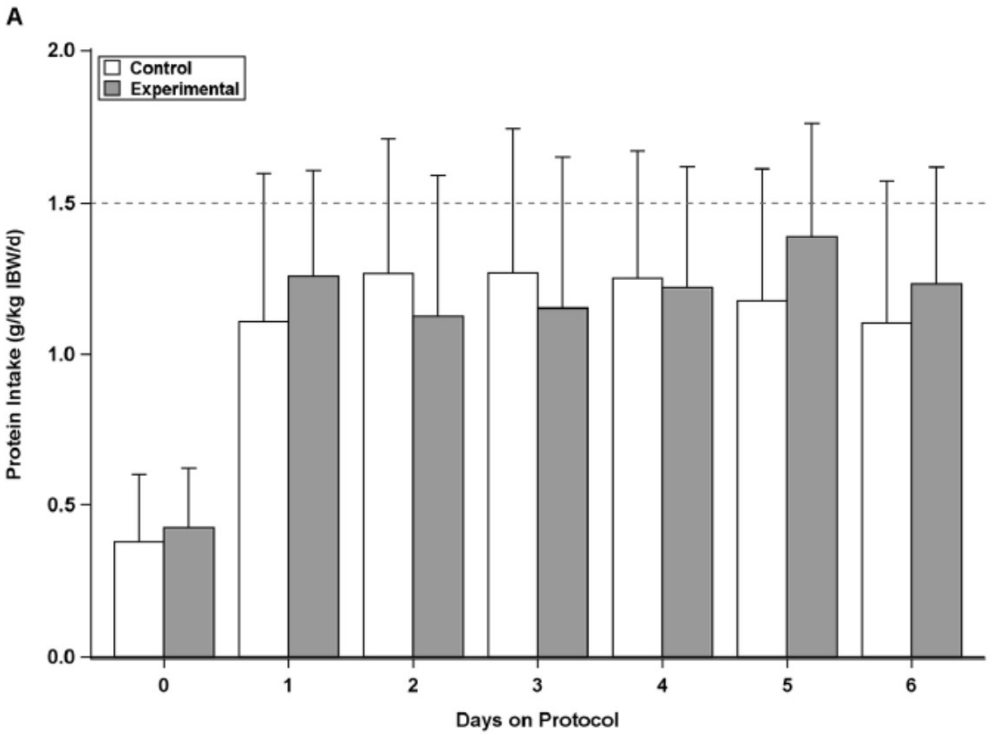
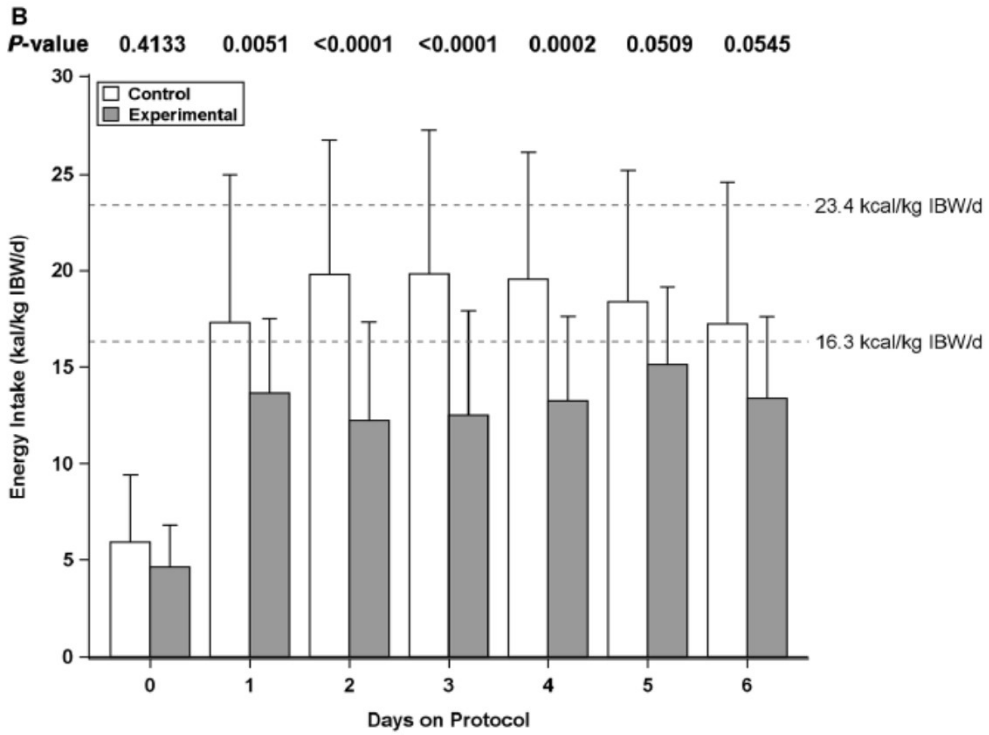
Results: Nutritional Intake

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

Mean Nutritional Intake	Control (N = 51)	Experimental (N = 51)
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

Results: Nutritional Intake





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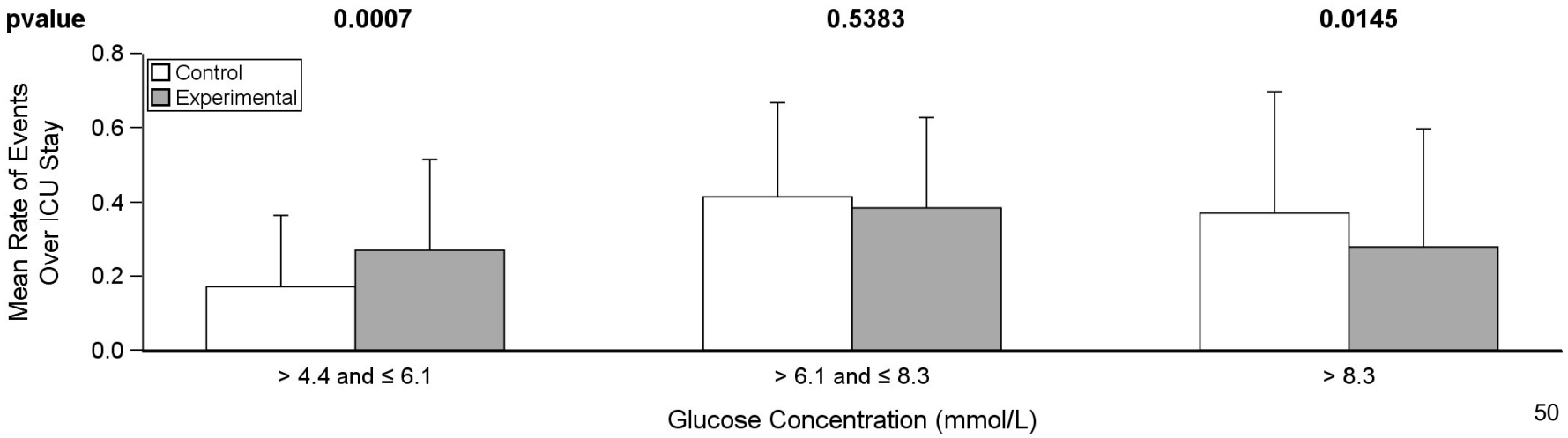
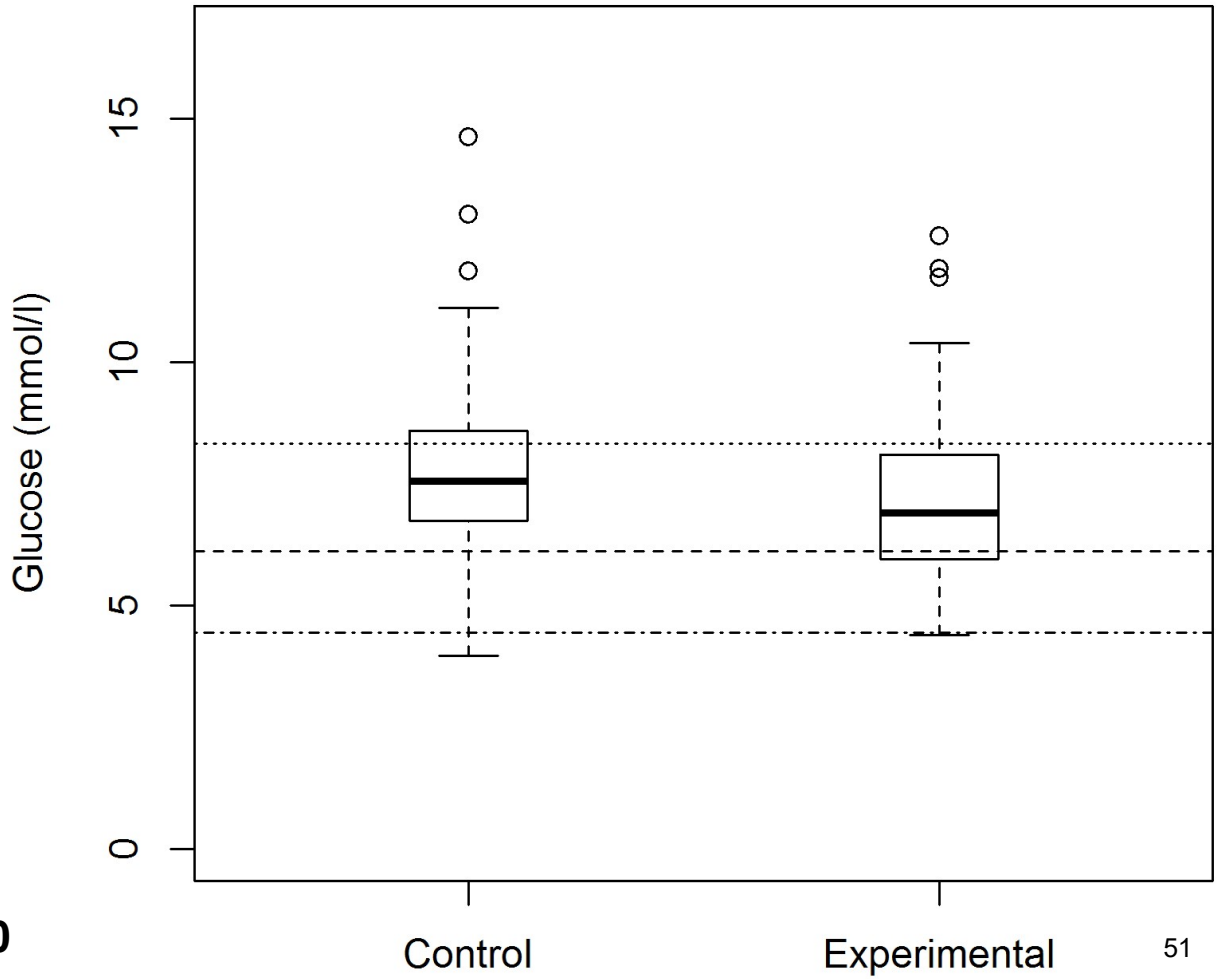
Results: Glucose

- No difference in rate of glycemic events outside the interval of 6.1 to 8.3 mmol/L (110 - 150 meq/dL) (p = 0.5383).
- Significant increase in the mean rate of glycemic events > 4.4 and ≤ 6.1 mmol/L (70 – 110 meq/dL) (+14%, p = 0.0007).
- Significant decrease in values > 8.3 mmol/L (> 150meq/dL) (-13%, p=0.015).



Results: Glucose

- Mean glucose was lower in the experimental group (7.7 ± 0.07 vs 7.0 ± 0.07 mmol/L, p = 0.004).
- No difference in rates of hypo-glycemia (≤ 4.4 mmol/L; <70 meq/dL) (p = 0.23).
- Smaller glycemic dispersion in experimental group (-11%, p = 0.0015).



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

Results: Insulin and Dextrose

- Significant decrease in the frequencies of insulin administration in the experimental group (-11%, p = 0.048).

- No difference in frequencies of rescue dextrose use (p = 0.53).

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Other Results

- **Tolerance and Adverse Events (AEs):**
  - Increased frequency of abdominal distention in the experimental group ($p = 0.022$).
    - Formula related in 1 control and 1 experimental patient, with formula withdrawn from experimental.
  - The number of patients with any AEs were not different ($p = 0.31$).
- **Mortality:**
  - While on protocol 6 (12%) and 2 (4%) deaths in the control and experimental groups, respectively ($p = 0.27$).

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Reason for Better Glucose Control?

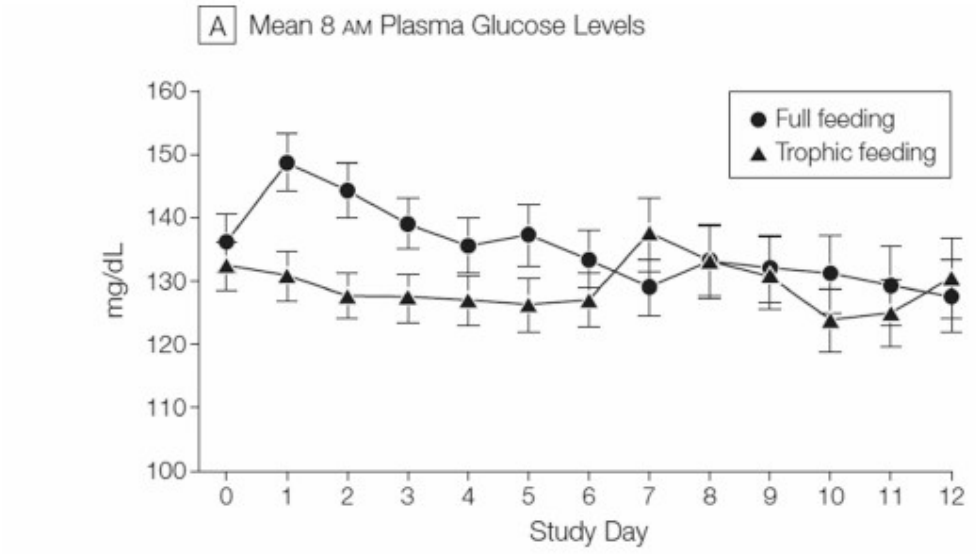
- High protein load improves insulin sensitivity
- Whey protein improves insulin sensitivity
- Lower carbohydrate delivery results in better glucose control
- Lower overall calorie delivery (hypocaloric feeds) results in better glucose control

Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury:

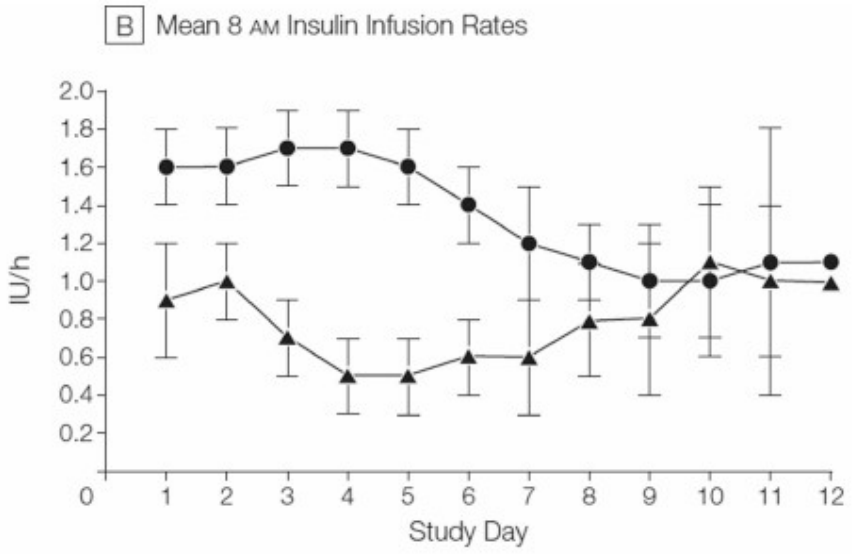
The EDEN Randomized Trial

JAMA. 2012 Feb 22;307(8):795-803

Statistically significant benefit in blood sugar control



No. of patients													
Full feeding	492	486	478	463	436	399	367	337	299	265	243	214	196
Trophic feeding	505	500	483	457	440	399	366	325	295	275	239	220	197



No. of patients													
Full feeding	428	419	413	382	353	326	299	269	236	212	188	175	
Trophic feeding	427	413	395	373	344	318	284	252	228	204	184	166	

Summary of DIVINE

- A very high hydrolyzed whey protein and low carbohydrate formula facilitates blood glucose control in critically ill overweight and obese patients.
- Although the formula did not reduce blood glucose events outside the interval of 6.1 to 8.3 mmol/L, it did lower dispersion of blood glucose as measured by std deviations.
- The experimental formula resulted in a lower incidence of hyperglycemia (> 8.3 mmol/L) (-13%), increased incidence of normoglycemia (4.4-6.1 mmol/L) (+14 %), and decreased insulin use without increased adverse events.

Conclusions

- Nutritional support for critically ill patients needs to be individualized
- Current data suggest that moderate permissive underfeeding, while administering higher levels of protein, may improve outcomes of critically ill patients
- Avoiding hyper- and hypoglycemia likely improves outcomes
- This can be accomplished by specific nutritional formulas
- Further research should be done to see if these formulas improve clinical outcomes

Questions?

Nutrition-related resources and tools are available from the Nestlé Nutrition Institute at
nestlenutrition-institute.org

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