Critical Care Nutrition

Current Controversies in Critical Care Nutrition

Daren K. Heyland

Professor of Medicine

Queens University, Kingston General Hospital

Kingston, ON Canada

Critical Care Nutrition

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51 different topics

CRITICAL CARE NUTRITION SYSTEMATIC REVIEWS | Click here to read the latest and best summaries of evidence in critical care nutrition

EFFORT

NUTRIC

PEPuP

Español

Critical Care Nutrition at the Clinical Evaluation Research Unit (CERU)

is dedicated to improving nutrition therapies in the critically ill through knowledge *generation*, *synthesis*, and *translation*. We engage in a broad range of research activities and promote a culture of best practices in critical care nutrition. Ultimately, this will result in improved clinical outcomes for critically ill patients and increased efficiencies to our health care systems.

www.criticalcarenutrition.com

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Learning Objectives

- Describe the optimal amount of protein and calories to support positive outcomes in the ICU patient.
- Identify ICU patients that benefit most from nutrition intervention.
- Current role of pharmaconutrients and future research agenda

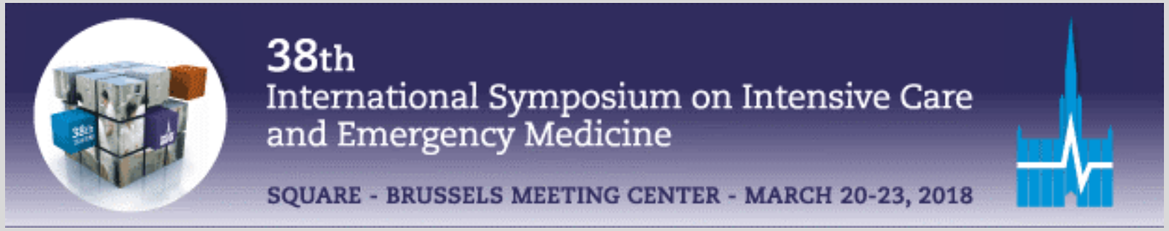
Creating Clarity Out of Confusion!

Large, Negative RCTs

- EPaNIC *NEJM 2011*
- EDEN *JAMA 2012*
- PERMIT *NEJM 2015*
- NEPHROPROTECT *ICM 2015*
- EAT-ICU *ICM 2017*

Feeding: How much is enough?
[Standard presentation]

13:45	Why would fasting be a good idea during acute critical illness? *Greet Van den Berghe*
14:00	Does the ICU patient support permissive underfeeding? *Stephen McClave*
14:15	Refeeding syndrome: is it relevant? *Arthur van Zanten*
14:30	Feeding may not prevent endogenous energy supply *Olav Roovackers*



Slow Starts, Slow Ramp ups

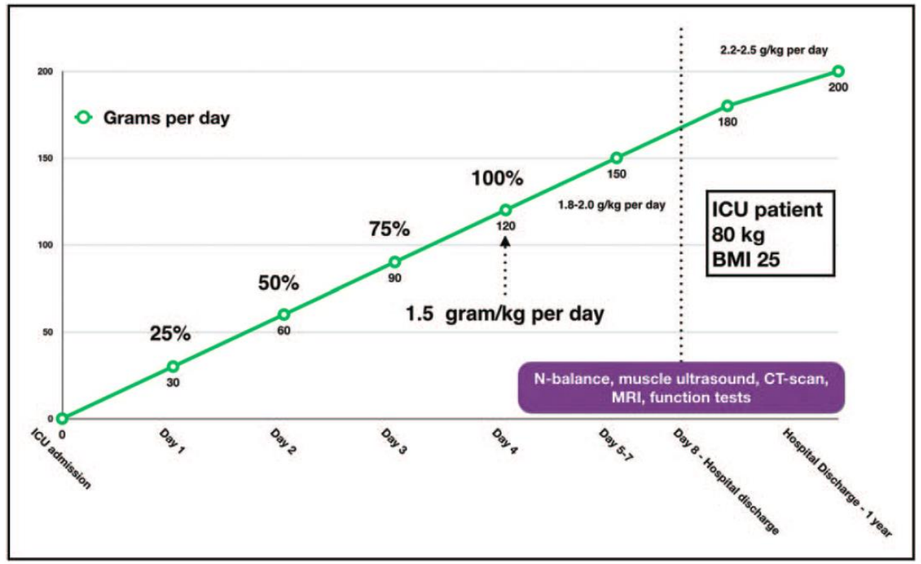


FIGURE 2. Protein targets during critical illness. In this example a weight-based equation (1.5 g/kg/day) is used to commence feeding aiming to reach target on day 4. This patient with an actual body weight of 80 kg has adaily target of 120 g of protein. Monitoring optimal protein intake after day 4 is experimental. Several strategies have been suggested such as N-balance, muscle ultrasound (m. quadriceps), CT-scan or MRI studies to estimate lean body mass, or function tests. None have been proven useful to guide protein targeting. During the post-acute phase of ICU stay higher protein intakes are associated with improved outcomes. CT, computed tomography.

DKH: setting such conservative targets will results in significantly less in the first few days. → Worse outcomes

Koekkoek, Curr Opin Anesthesiol 2018, 31:136–143

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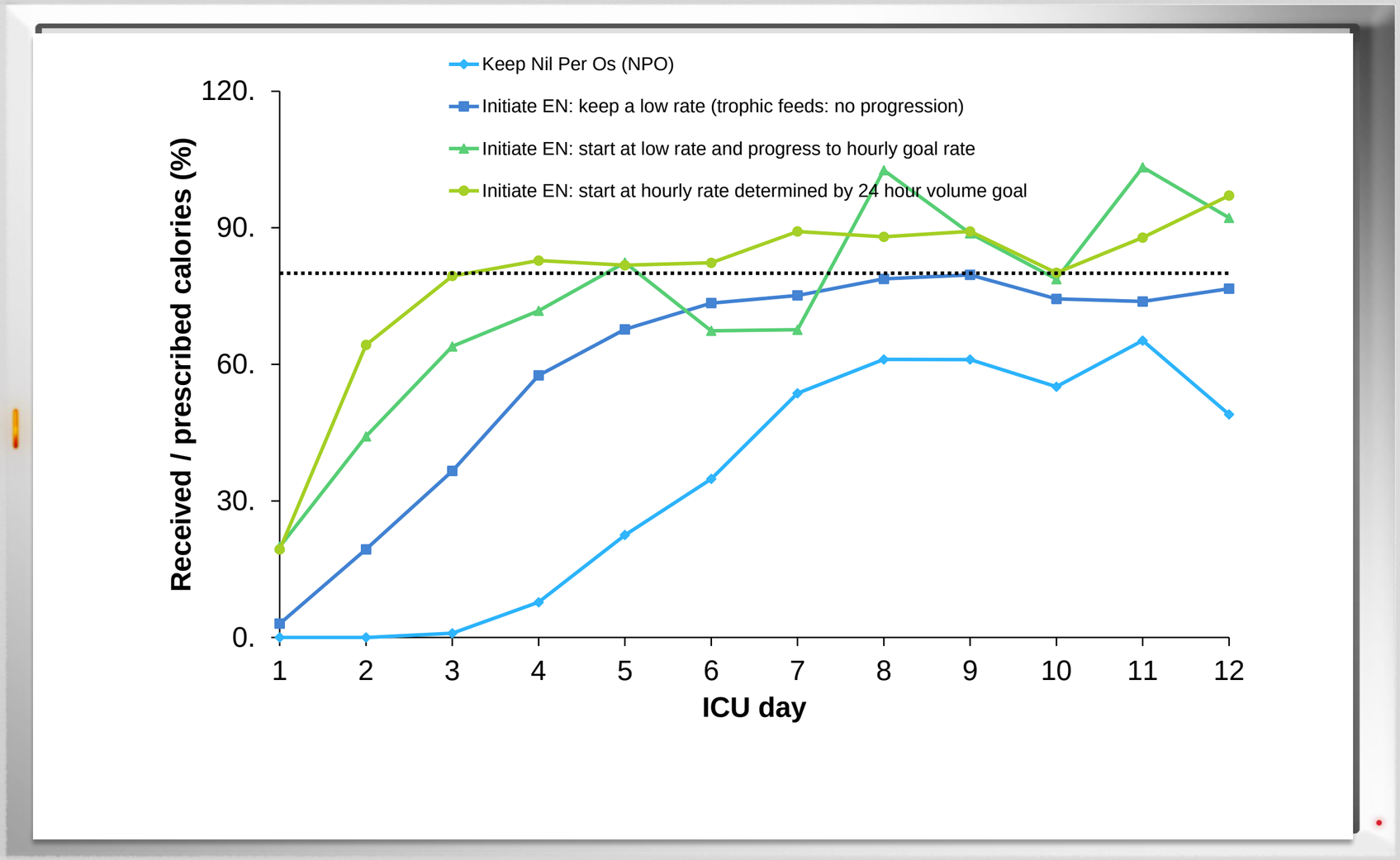
Initial Feeding Strategy Determines Overall Success



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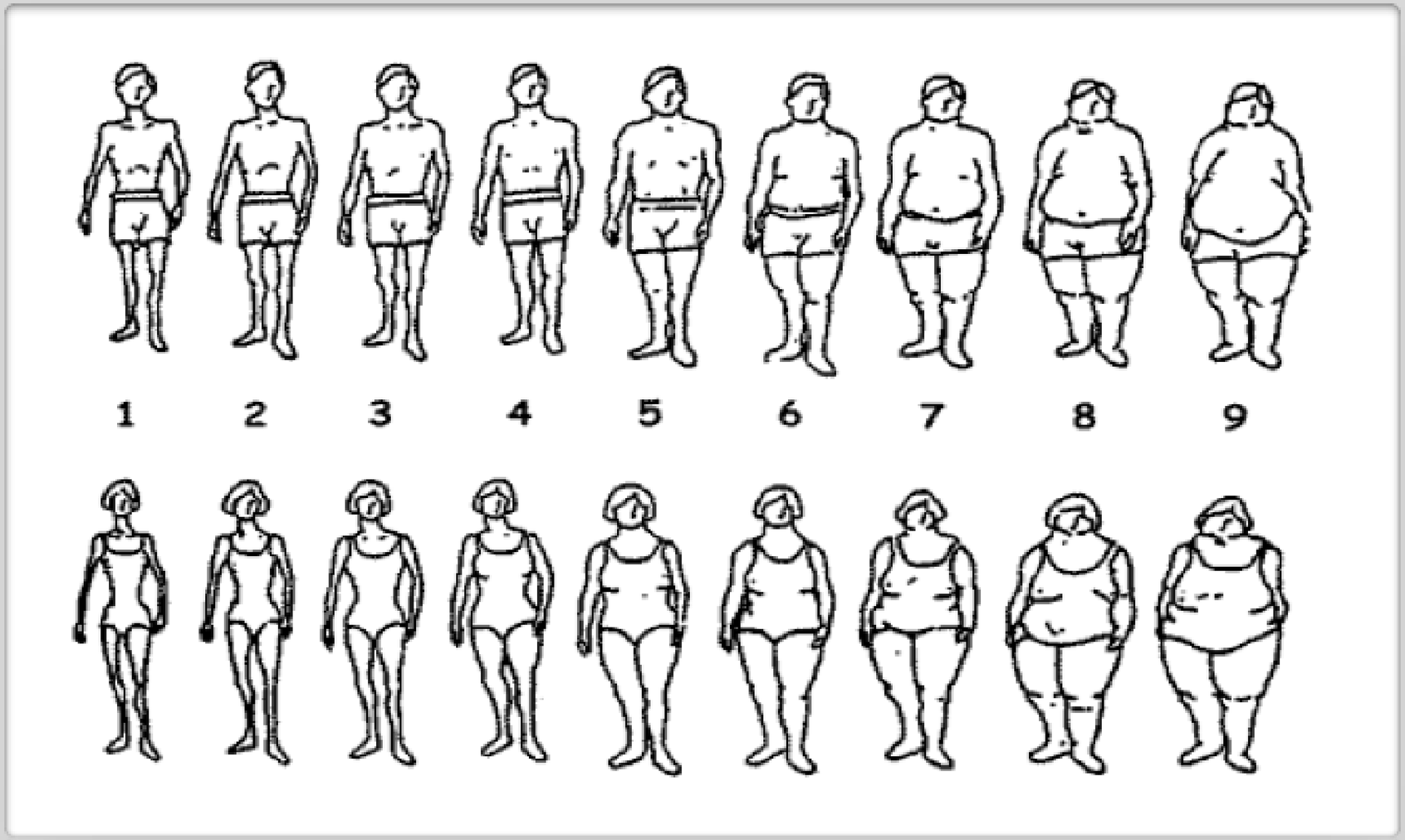
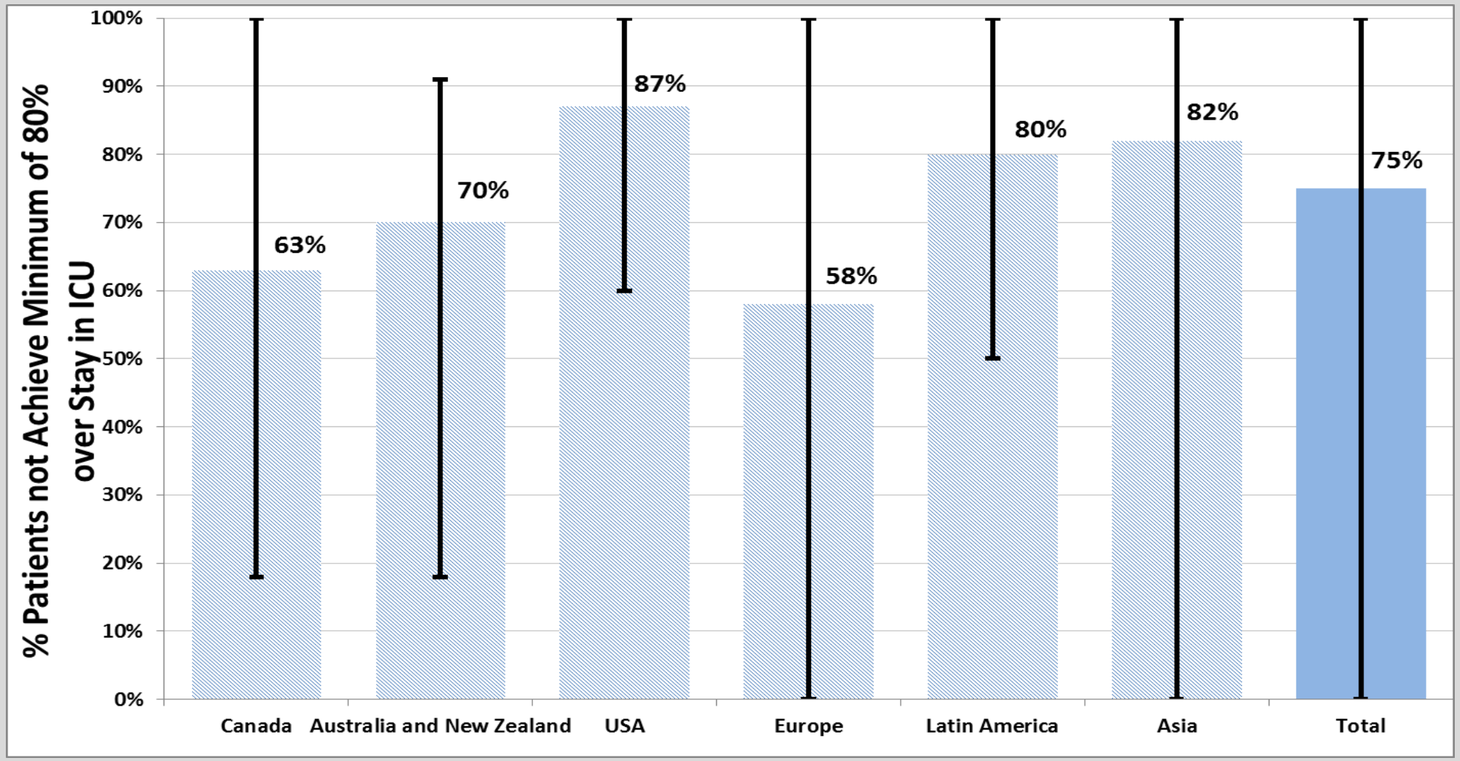
ICU Patients Are Not All Created Equal…
Should We Expect the Impact of Nutrition Therapy to be the Same Across All Patients?



The Prevalence of Iatrogenic Underfeeding in the Nutritionally 'At-Risk' Critically Ill Patient

% high risk patients who failed to meet minimal quality targets (80% overall energy adequacy)



Of all at-risk patients, 14% were ever prescribed volume-based feeds 15% ever received sPN

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Clinical Nutrition 2015

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What do the Guidelines say?

- Canadian CPGs- use of supplemental PN and trophic feeds a function of nutrition risk
- ASPEN/SCCM CPGs- withhold nutrition therapy for patients with low nutrition risk and who cannot maintain volitional intake
- New ESPEN CPGs 2018- no risk stratification

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Implications for Research

4620 patients randomized to early vs. late parenteral nutrition (EPANIC)

- Right patient population?
  - Majority (90%) surgical patients (mostly cardiac-60%)
  - Short stay in ICU (3-4 days)
  - Low mortality (8% ICU, 11% hospital)
  - >70% normal to slightly overweight
- Applicability of the intervention
  - No one gives too much IV glucose in first few days
  - No one practices tight glycemic control
- Not an indictment of PN
  - Clear separation of groups after 2-3 days
  - Early group only received PN on day 3 for 1-2 days on average
  - Late group –only ¼ received any PN

Casaer NEJM 2011

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Implications for Practice

Results of 2014 INS (186 sites worldwide and approx. 4000 patients)

In all comers:

- At a patient level, 16% of patients averaged more than 80% protein adequacy
- At a site level, 6% (11 sites) averaged more than 80% in all patients

In High NUTRIC patients:

- 16% of high NUTRIC Score patients received more than 80% of prescribed amount
- 7% (16 sites) managed to provide more than 80% of prescribed amounts to high-risk patients

Performance in ‘all’ patients same as High NUTRIC patients

Heyland NCP 2017

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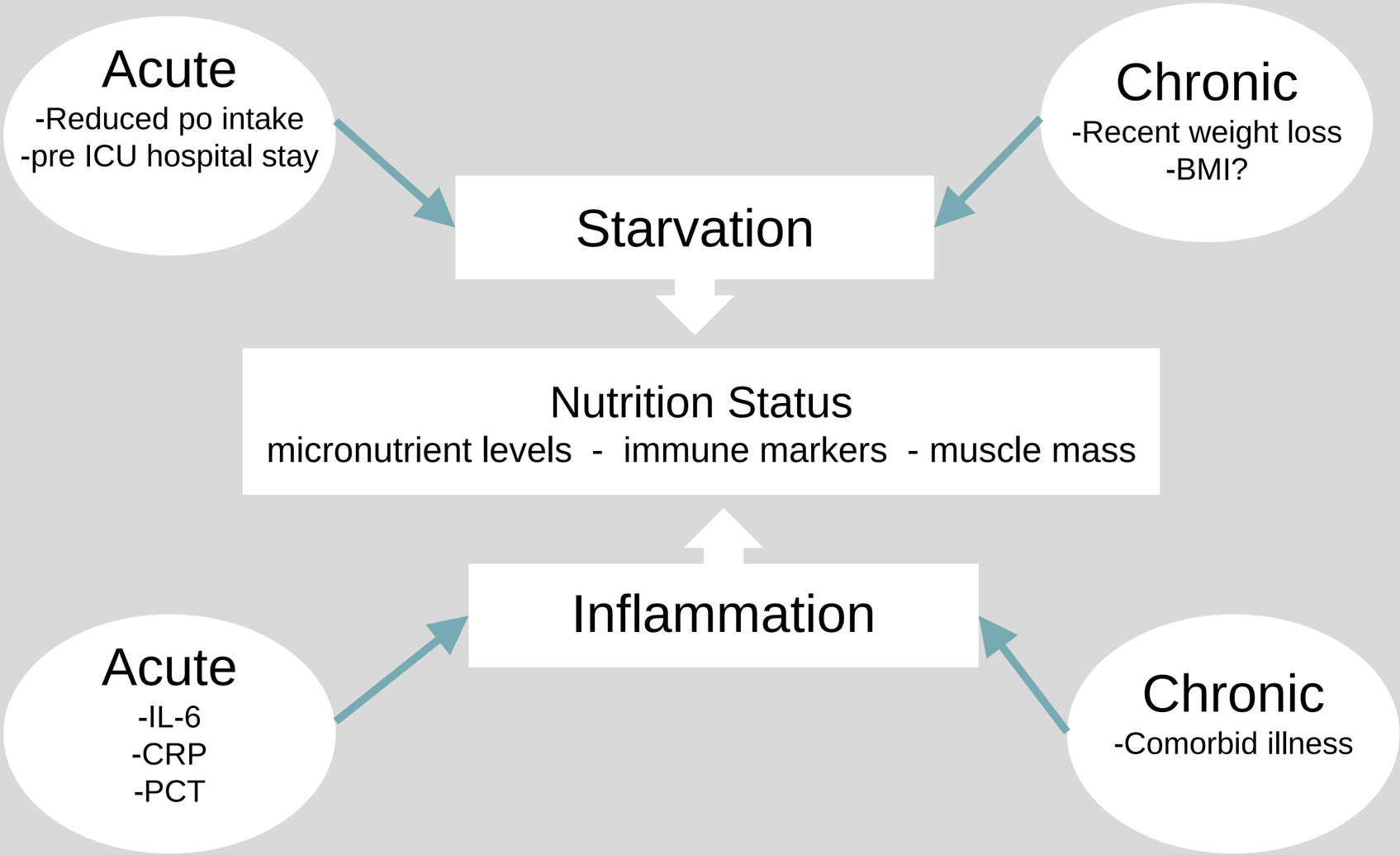
A Conceptual Model for Nutrition Risk Assessment in the Critically Ill



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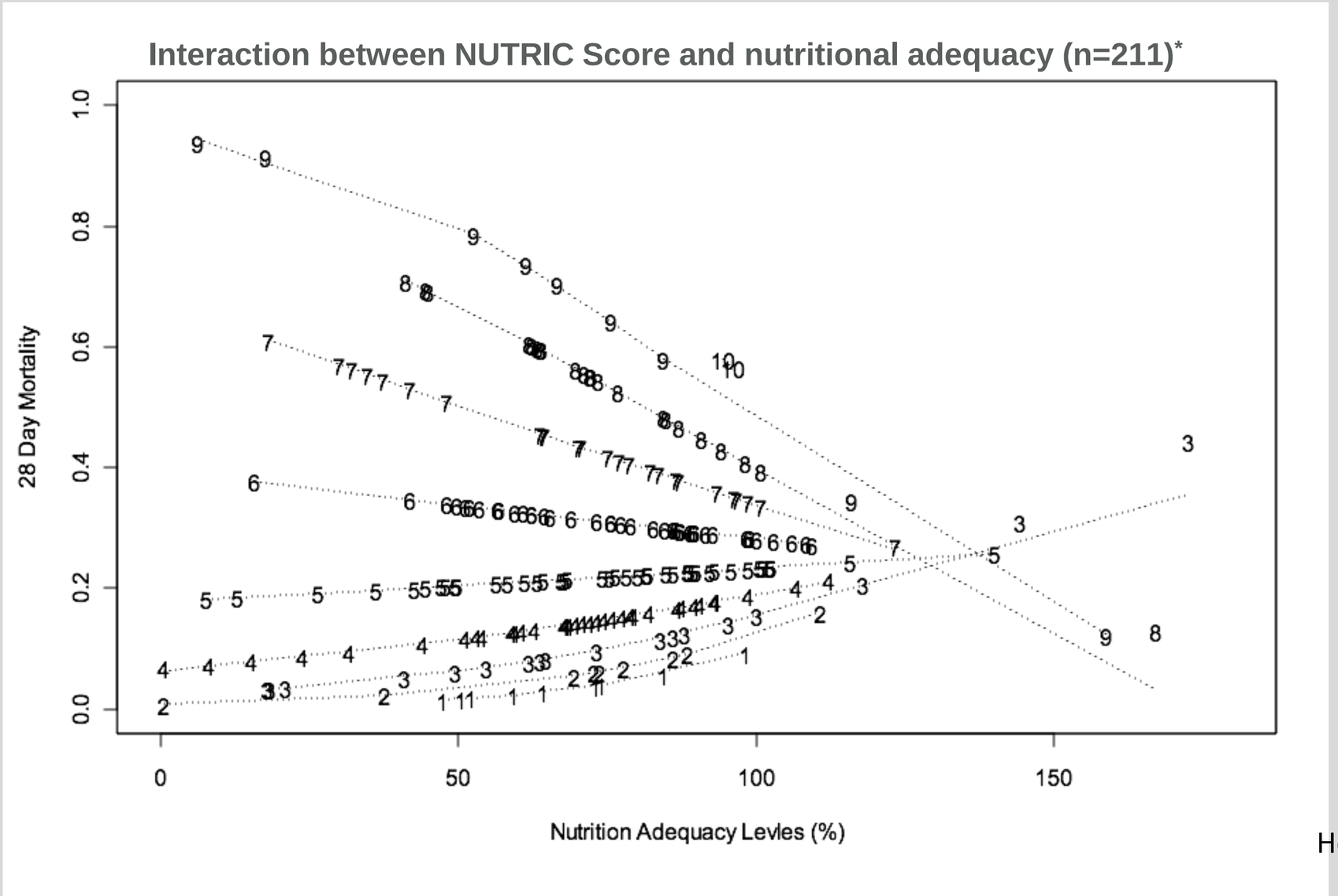
The Development of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)

Variable	Range	Points
Age	<50	0
	50-<75	1
	>=75	2
APACHE II	<15	0
	15-<20	1
	20-28	2
	>=28	3
SOFA	<6	0
	6-<10	1
	>=10	2
# Comorbidities	0-1	0
	2+	1
Days from hospital to ICU admit	0-<1	0
	1+	1
IL6	0-<400	0
	400+	1
AUC	0.783	
Gen R-Squared	0.169	
Gen Max-rescaled R-Squared	0.256	

BMI, CRP, PCT, weight loss, and oral intake were excluded because they were not significantly associated with mortality or their inclusion did not improve the fit of the final model.

The Validation of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)



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Critical Care 2011, 15:R28

The Validation of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)

- Validated in 3 separate databases including the INS Dataset involving over 200 ICU's worldwide [1,2,3]
- Validated without IL-6 levels (modified NUTRIC) [2]
- Independently validated in Dutch, Brazilian, Portuguese, and Asian populations [4,5,6,7]
- Predictive validity superior than MUST (malnutrition assessment)[7]
- Not validated in post hoc analysis of the PERMIT trial [8]

– RCT of different caloric intake (protein more important)

– Underpowered, very wide confidence intervals

- Discriminates patients who benefit the most in post hoc analysis of TOP uP trial

1. Heyland Critical Care 2011, 15:R28
2. Rahman, Clinical Nutrition 2013.
3. Compher, CCM, 2016
4. Rosa Clinical Nutrition ESPEN 2016
5. Mendes J Crit Care 2017
6. Mukhopadhyah Clinical Nutrition 2016
7. De Vries Eur J Clin Nutr 2017
8. Arabi AmJRCCM 2016
9. Wischmeyer Crit Care 2017

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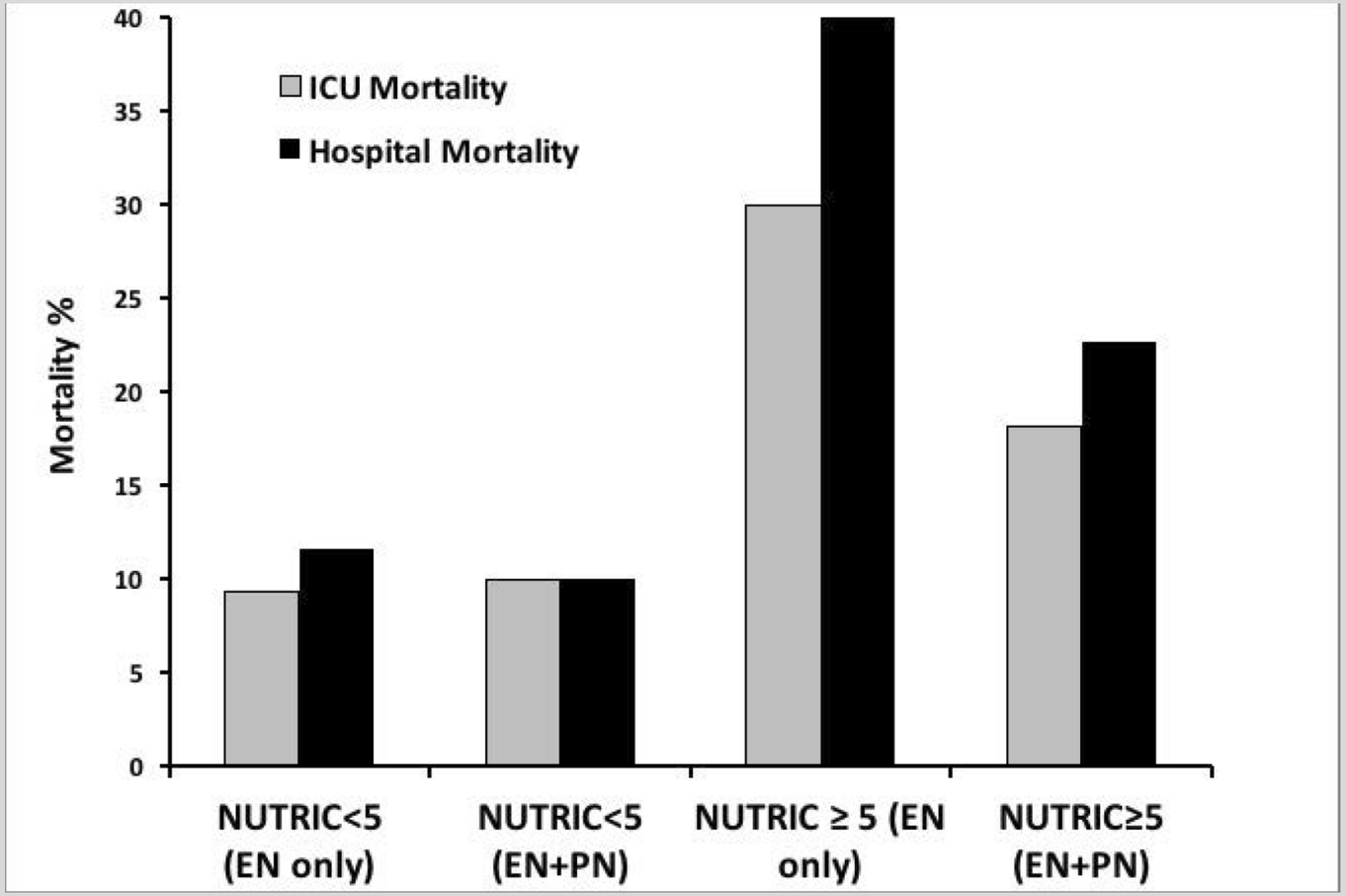
Results of TOP UP Pilot Trial

A RCT of supplemental PN in low and high BMI ICU patients



Post-hoc subgroup analysis

Wischmeyer Crit Care 2017

Review

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Nutrition in Clinical Practice
Volume 34 Number 1
February 2019 96–111

DOI: 10.1002/ncp.10214
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Determination of Nutrition Risk and Status in Critically Ill Patients: What Are Our Considerations?

Zheng-Yii Lee, MSc[1,2]; and Daren K. Heyland, MD, MSc, FRCPC[3]

Abstract

The stress catabolism state predisposes critically ill patients to a high risk of malnutrition. This, coupled with inadequate or delayed nutrition provision, will lead to further deterioration of nutrition status. Preexisting malnutrition and iatrogenic underfeeding are associated with increased risk of adverse complications. Therefore, accurate detection of patients who are malnourished and/or with high nutrition risk is important for timely and optimal nutrition intervention. Various tools have been developed for nutrition screening and assessment for hospitalized patients, but not all are studied or validated in critically ill populations. In this review article, we consider the pathophysiology of malnutrition in critical illness and the currently available literature to develop recommendations for nutrition screening and assessment. We suggest the use of the (modified) Nutrition Risk in the Critically Ill (mNUTRIC) for nutrition risk screening and the subjective global assessment (SGA) together with other criteria relevant to the critically ill patients, such as gastrointestinal function, risk of aspiration, determination of sarcopenia and frailty, and risk of refeeding syndrome for nutrition assessment. Further research is needed to identify suitable nutrition monitoring indicators to determine the response to the provision of nutrition. (*Nutr Clin Pract.* 2019;34:96–111)

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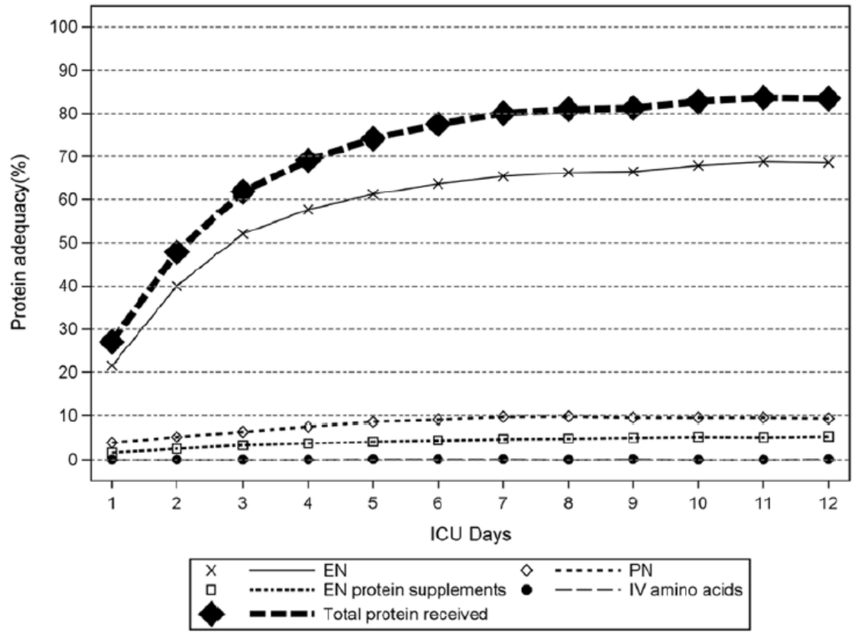
What is current nutrition practice look like today?

Results of 2014 INS

In 2014 INS, on average, patients were prescribed 1.3 grams/kg/day (interquartile range, 1.0-1.5 grams/kg/day, overall range, 0.5-3.8 grams/kg/day).



	ICU Days												
% Protein Adequacy	1	2	3	4	5	6	7	8	9	10	11	12	Overall
EN	21.48	39.99	52.04	57.77	61.28	63.69	65.38	66.29	66.55	67.88	68.88	68.60	45.60
PN	3.95	5.27	6.39	7.53	8.64	9.14	9.72	9.77	9.51	9.55	9.53	9.35	6.35
EN protein supplement	1.64	2.53	3.37	3.74	4.14	4.49	4.79	4.86	5.07	5.27	5.15	5.40	3.24
IV amino acids	0.03	0.02	0.07	0.05	0.08	0.13	0.13	0.06	0.09	0.06	0.07	0.11	0.06
Total protein received	27.11	47.81	61.87	69.09	74.13	77.45	80.02	80.98	81.23	82.76	83.62	83.45	55.25

On average, patients receive 55% of prescription

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Is that sufficient?
Do they need more?

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Hard to Argue that Meeting Caloric Goals is Important!

Large, Negative RCTs

- EPaNIC *NEJM 2011*
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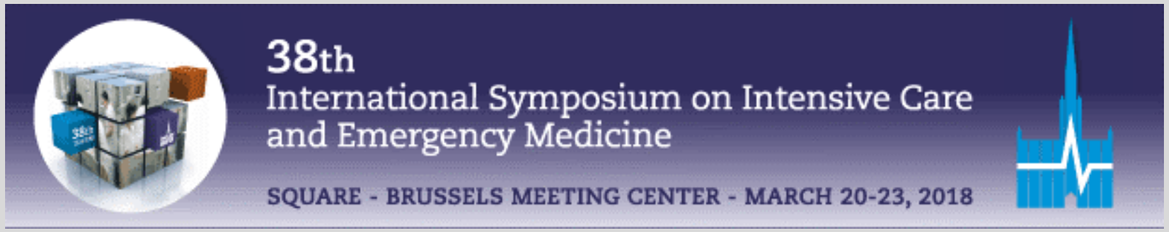

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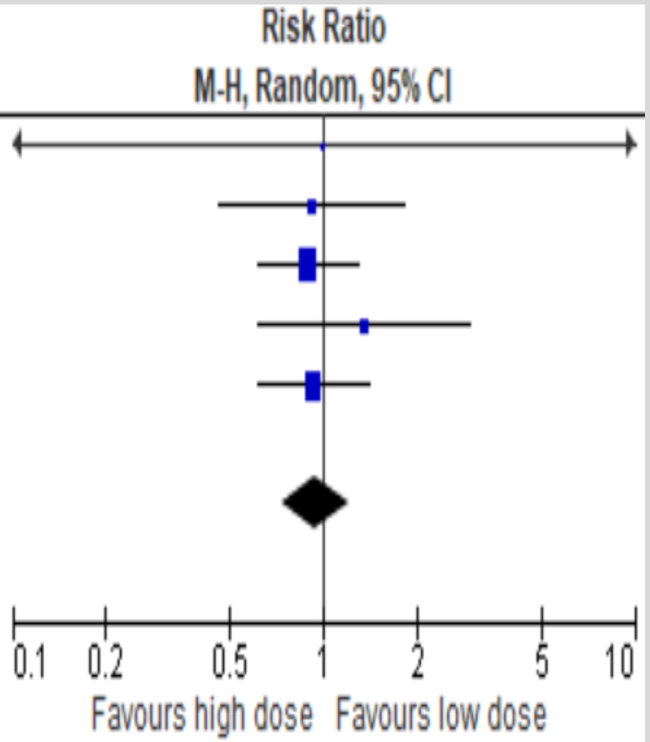
Systematic Review of RCTs of High vs. Low Dose Protein

Study or Subgroup	High Dose Events	High Dose Total	Low Dose Events	Low Dose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	0.9%	1.00 [0.07, 13.87]	1985
Rugeles 2013	11	40	12	40	12.5%	0.92 [0.46, 1.83]	2013
Doig 2015	42	236	47	235	42.3%	0.89 [0.61, 1.29]	2015
Ferrie 2016	12	59	9	60	9.6%	1.36 [0.62, 2.98]	2016
Allingstrup 2017	30	100	32	99	34.8%	0.93 [0.61, 1.40]	2017
Total (95% CI)		**445**		**444**	**100.0%**	**0.94 [0.74, 1.21]**	
Total events	96		101				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.93$, df = 4 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 0.46 (P = 0.65)



Heyland Nutrients 2018

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What is the evidence that exogenously administered amino acids/protein favorably impacts clinical outcomes?

2015 Premier Research Paper

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American Society for Parenteral and Enteral Nutrition

Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study

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

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Volume XX Number X
Month 201X 1–8

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Impact of Protein Intake on 60-day Mortality

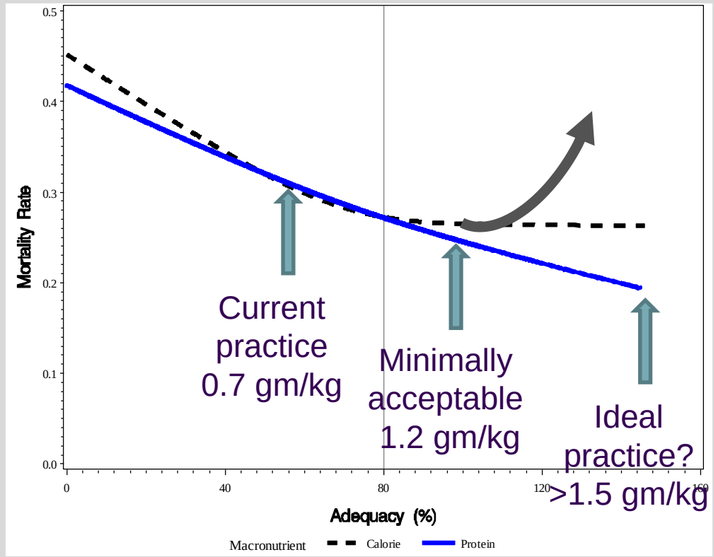
Data from 2828 patients from 2013 International Nutrition Survey

Variable	Patients in ICU ≥ 4 d 60-Day Mortality, Odds Ratio (95% CI)	
	Adjusted[1]	Adjusted[2]
Protein Intake (Delivery ≥ 80% of prescribed vs. < 80%)	0.61 (0.47, 0.818)	0.66 (0.50, 0.88)
Energy Intake (Delivery ≥ 80% vs. < 80% of Prescribed)	0.71 (0.56, 0.89)	0.88 (0.70, 1.11)

[1] Adjusted for BMI, Gender, Admission Type, Age, Evaluable Days, APACHE II Score, SOFA Score
[2] Adjusted for all in model 1 plus for calories and protein

Nicolo JPEN 2015

Rate of Mortality Relative to Adequacy of Protein and Energy Intake Delivered



TIACOS ICM 2011
INTACT JPEN 2014

Heyland JPEN 2015

Post-hoc analysis of EPANIC

Casaer, Wilmer, Hermans, *et al.*: Early Nutrition in the ICU: Less Is More

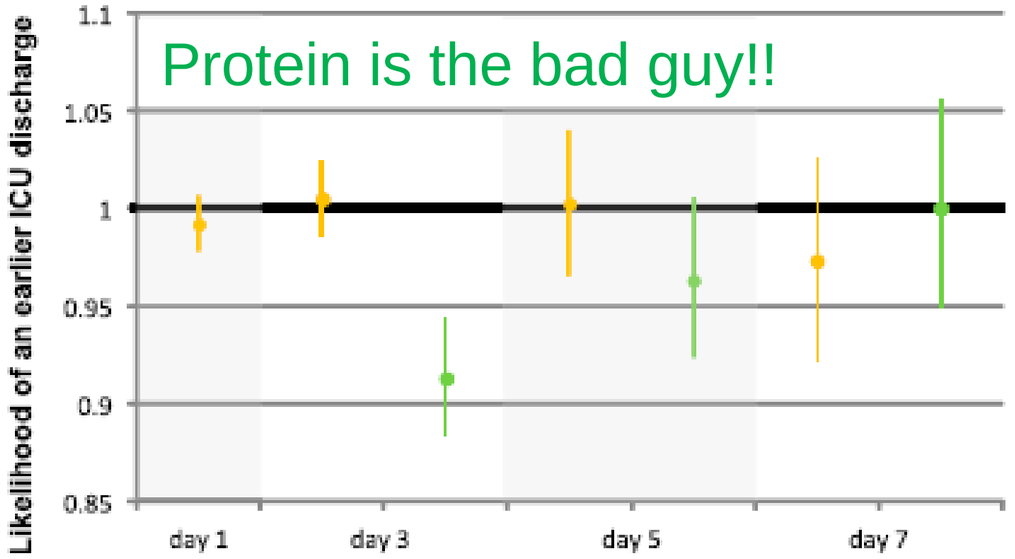


Figure 3. Time to live discharge from the intensive care unit (ICU): Relation to glucose dose as compared with protein dose. Effect size per 10% increments of target per day in cumulative glucose intake (~±28 g/d) (*yellow*) and cumulative protein intake (~±7 g/d) (*green*) in a time-to-alive ICU discharge analysis corrected for severity and type of disease. Normalized glucose target was 276.4 (±70.8) g/day and normalized protein target was 72.3 (±18.5) g/day. This target was derived from the amount of glucose and protein the patient would have received with the standard commercial parenteral (PN) preparation when receiving 100% of his calculated energy target.

Casaer Am J Respir Crit Care Med 2013;187:247–255

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Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis[1,2]

Carol L Braunschweig,[3] Sally Freels,[4] Patricia M Sheean,[5] Sarah J Peterson,[6] Sandra Gomez Perez,[3] Liam McKeever,[3] Omar Lateef,[7] David Gurka,[7] and Giamila Fantuzzi[3]*

- 78 patient with ALI randomized to Intensive Medical therapy (30 kcal/kg/day) or usual care (40-60% of target)
- Stopped early because of excess deaths in intensive group

- Post hoc analysis suggests increased death from early protein!

TABLE 3
Proportional hazards multiple regression models for hazard of death on or after 8 d for INTACT participants[1]

Independent variable	β Hat	SE	*P*	HR (95% CI)
Model 1				
Mean kcal/kg received during days 1–7[2]	0.1575	0.0441	0.0004	1.17 (1.07, 1.28)
Time-dependent mean daily kcal/kg received during days 1–7 and after day 8[2]	−0.0967	0.0471	0.04	0.91 (0.83, 1.0)
Model 2				
Mean daily g protein/kg received during days 1–7[3]	2.18	0.69	0.002	8.87 (2.3, 34.3)
Time-dependent mean daily g protein/kg received during days 1–7 and after day 8[3]	−1.89	1.00	0.06	0.15 (0.02, 1.07)

[1] Models were adjusted for age, sex, and baseline SOFA score, n = 66 (15 deaths). INTACT, Intensive Nutrition in Acute Lung Injury Trial; SOFA, Sequential Organ Failure Assessment.
[2] Mean increase of 1 kcal/kg.
[3] Mean increase of 1 g/kg.

RCTs do not suggest any evidence of harm and observational studies suggest increased protein intake associated with…

- Reduced mortality[1]
- Quicker Time-to-discharge-alive[1]
- Greater preservation of muscle [2,3]
- Reduced infection [4]

- Increased mortality[5]
- Slower time-to-discharge-alive from ICU[6]
- Greater loss of muscle mass and increased weakness[7,8]

1 Nicolo JPEN 2015
2 Ferrie JPEN 2016
3 Fetterplace JPEN 2018
4 Heyland JPEN 2010
5 Braunschweig Am J Clin Nutr 2017
6 Casaer Am J Respir Crit Care Med 2013
7 Puthucheary JAMA 2013
8 Hermans Lancet Respir 2013

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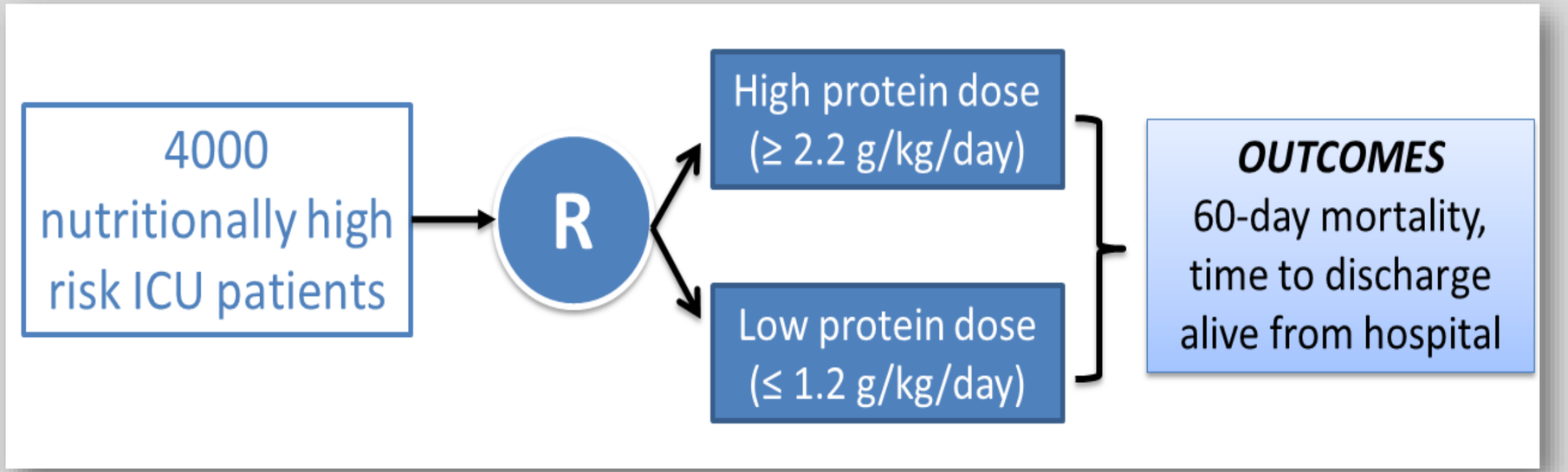
effort study

The Effect of Higher Protein Dosing in Critically Ill Patients: The EFFORT Trial



A multicentre, pragmatic, volunteer-driven, registry-based, randomized, clinical trial.

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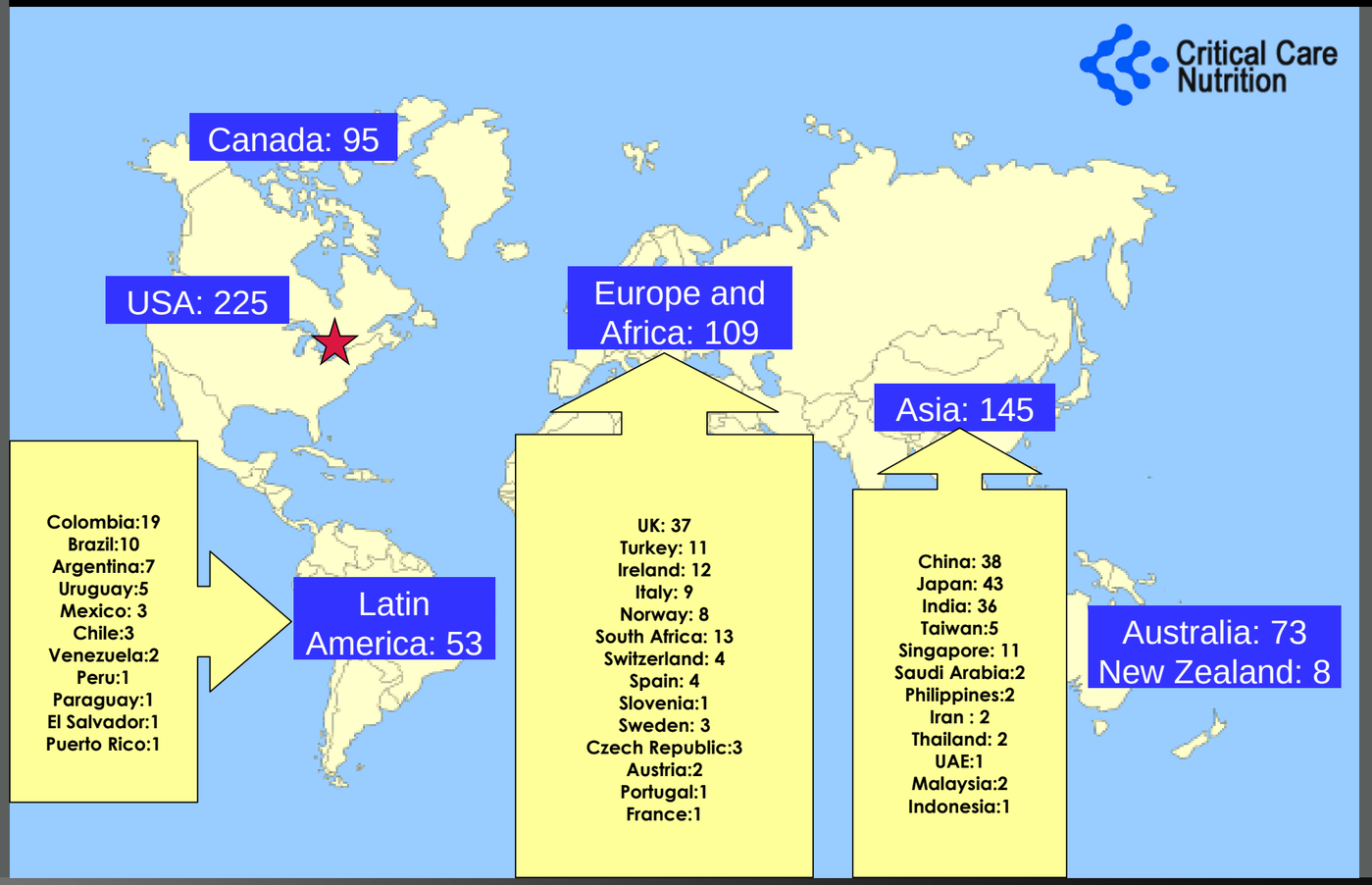
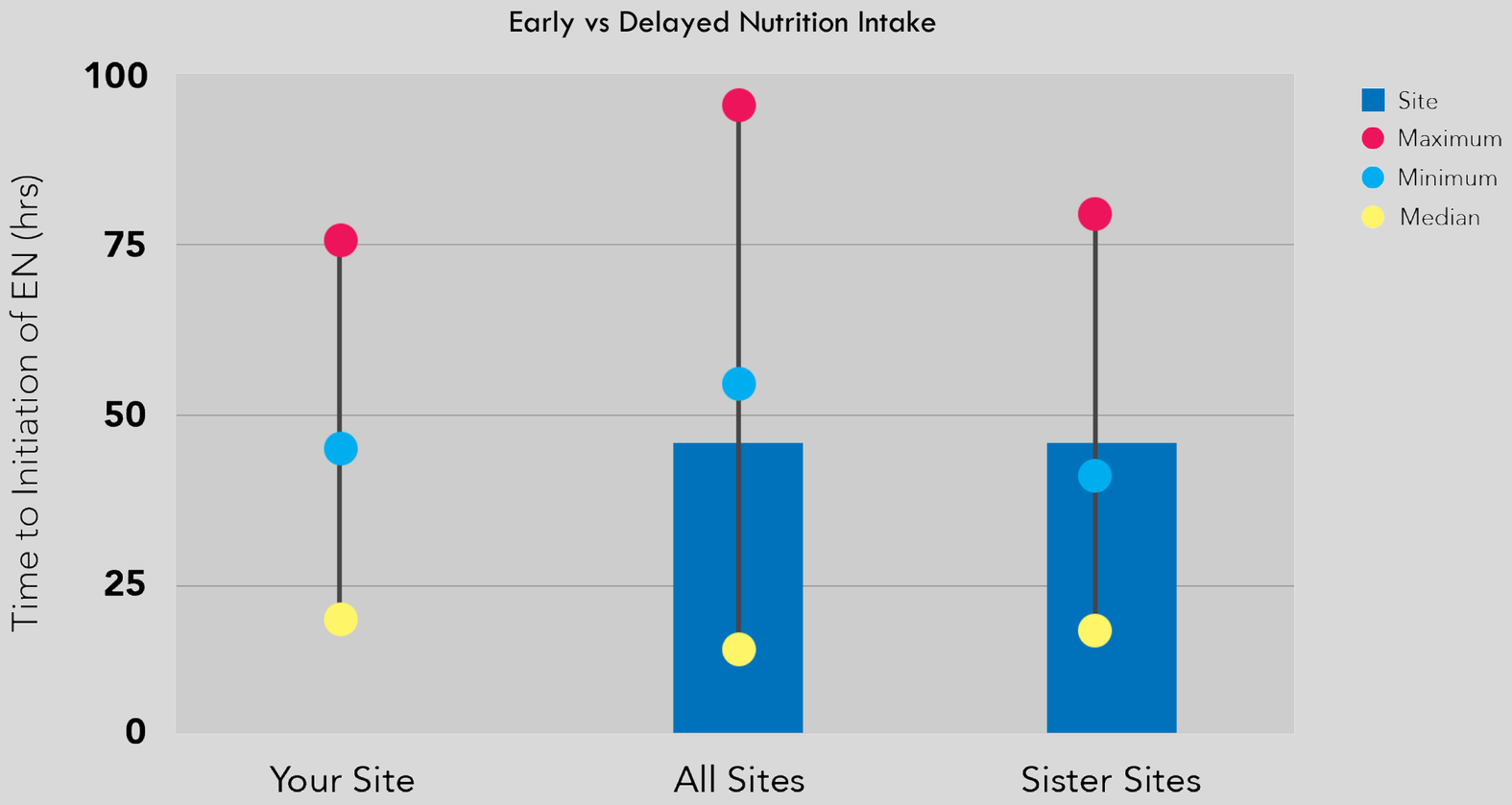
Participation Across the 5 Years of the INS : 708 Distinct ICUs



Value of Bench-marked Site Reports

Recommendations: Based on 8 level 2 studies, we recommend early enteral nutrition (within 24-48 hrs following resuscitation) in critically ill patients.



Study Population

Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
1. >18 years old 2. Nutritionally “high-risk” (meeting one of the below criteria**)** a. Low (≤25) or High BMI (≥35) b. Moderate to severe malnutrition (as defined by local assessments) c. Frailty (Clinical Frailty Scale, 5 or more from proxy) d. Sarcopenia – (SARC-F score of 4 or more from proxy) e. From point of screening, projected duration of mechanical ventilation >4 days) 3**.** Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours	1. >96 continuous hours of mechanical ventilation before screening	Intervention is likely most effective when delivered early
	2. Expected death or withdrawal of life-sustaining treatments within 7 days from screening	Patients unlikely to receive benefit
	3. Pregnant	Unknown effects on fetus
	4. The responsible clinician feels that the patient either needs low or high protein	Uncertainty doesn’t exist; patient safety issues
	5. Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group.	Site will be unable to reach high protein dose prescription.

How do I achieve the high protein intake?

- High protein containing EN solutions
- EN protein supplements
- PN
- Parenteral amino acids
- Or combinations of the above!

PEP uP Protocol

The PEP uP Protocol!

The Efficacy of Enhanced **P**rotein-**E**nergy **P**rovision via the Enteral Ro**u**te in Critically Ill **P**atients:

- Different feeding options based on hemodynamic stability and suitability for high volume intragastric feeds.
- In select patients, we start the EN immediately at goal rate, not at 25 mL/hr.
- We 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 very high protein solution; semi elemental solution then progress to polymeric
- Motility agents and protein supplements are started immediately, rather than started when there is a problem
- Tolerate higher GRV threshold (300 mL or more)

A Major Paradigm Shift in How we Feed Enterally

Heyland Crit Care 2010

see www.criticalcarenutrition.com for more information on PEP uP tools

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Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol in Critically Ill Patients: Results of a Cluster Randomized Trial

Daren K. Heyland, MD, MSc[1,2,3]; Lauren Murch, MSc[1]; Naomi Cahill, RD, PhD[1,2]; Michele McCall, RD, MSc[4]; John Muscedere, MD[1,3]; Henry T. Stelfox, MD, PhD[5,6,7]; Tricia Bray, RN, MN[8]; Teddie Tanguay, RN, NP, MN[9]; Xuran Jiang, MSc[1]; Andrew G. Day, MSc[1]

- Resulted in a significant improvement in nutrition delivery (12-14% increase with no overfeeding)
- No change in clinical outcomes (not powered to do so)
- Observed a 4% reduction in mortality from baseline in PEP uP group

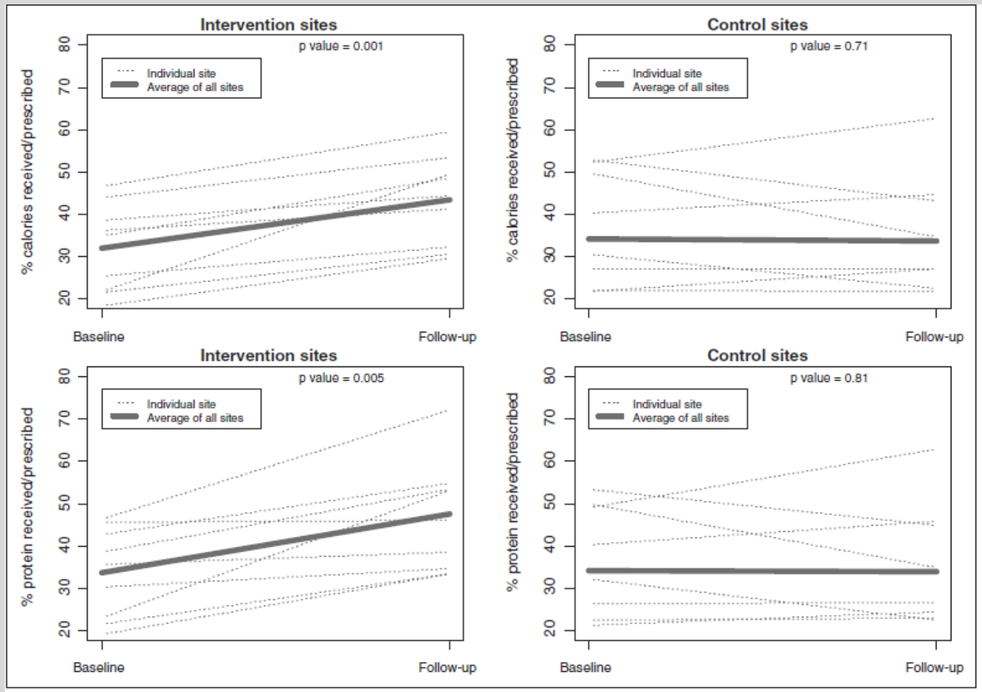


Figure 2. Changes in protein and energy adequacy in control and intervention sites. This figure shows the pre- and postdata collection overall and by site connected by lines. *Thick line* shows average improvement in protein and caloric adequacy in intervention and control sites. *Dashed lines* reflect changes at individual sites.

TABLE 4. Clinical Outcomes Between Groups and Across Time (All Patients – *n* = 1,059)

Variable	Intervention		Control		*p*[a]
	Baseline	Follow-Up	Baseline	Follow-Up	
n	270	252	270	267	
ICU mortality (%)	47 (17.4)	35 (13.9)	49 (18.1)	42 (15.7)	0.57
Died within 60 d of ICU admission (%)	70 (25.9)	68 (27.0)	65 (24.1)	63 (23.6)	0.53
Length of stay among 60-d survivors					
Days on mechanical ventilation	3.7 (1.6, 9.1)	4.3 (1.3, 9.9)	3.1 (1.4, 8.4)	3.0 (1.4, 7.3)	0.57
Days in ICU	6.1 (3.4, 11.4)	7.2 (3.4, 11.1)	6.4 (3.3, 12.6)	5.7 (2.8, 11.8)	0.35
Days in hospital	14.2 (8.1, 29.8)	13.5 (8.1, 28.4)	16.7 (7.5, 27.7)	13.8 (7.1, 26.6)	0.73

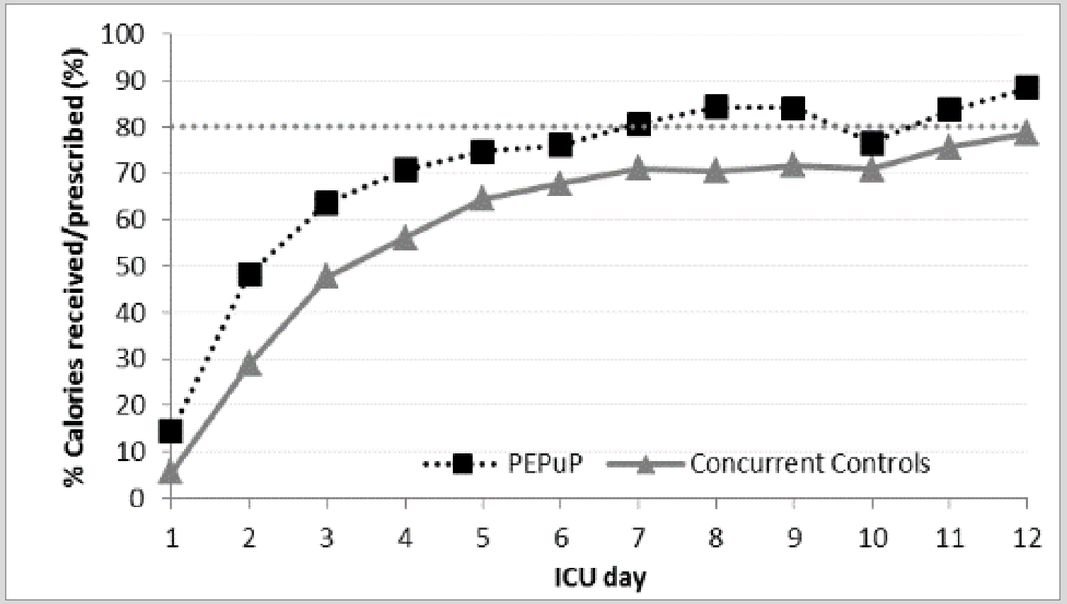
[a]*p* values test against the null hypothesis that the mean within ICU change is the same in both arms.

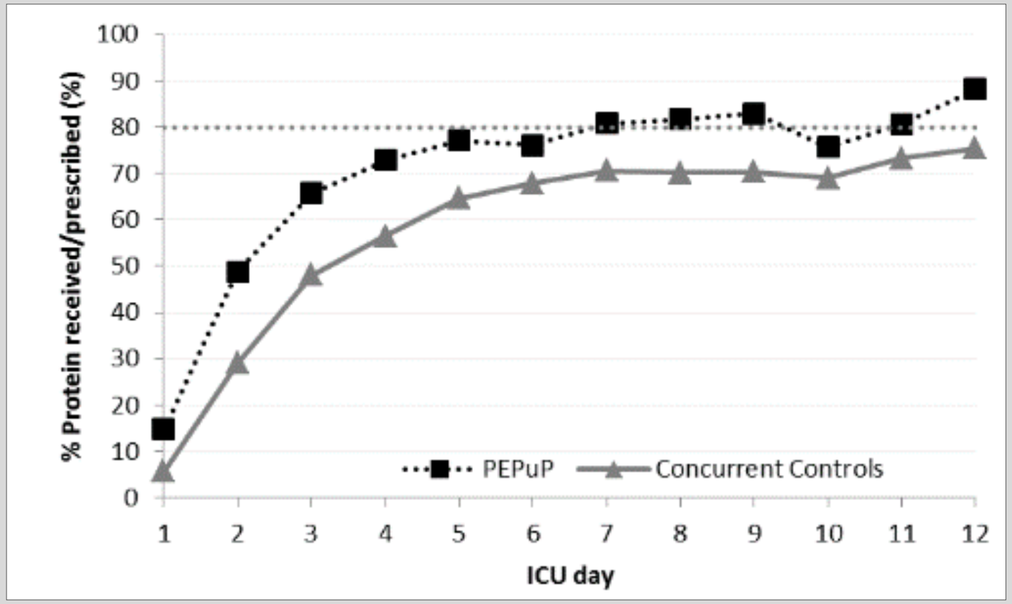
Heyland CCM 2013

Critical Care Nutrition

Results of the Canadian PEP uP Collaborative

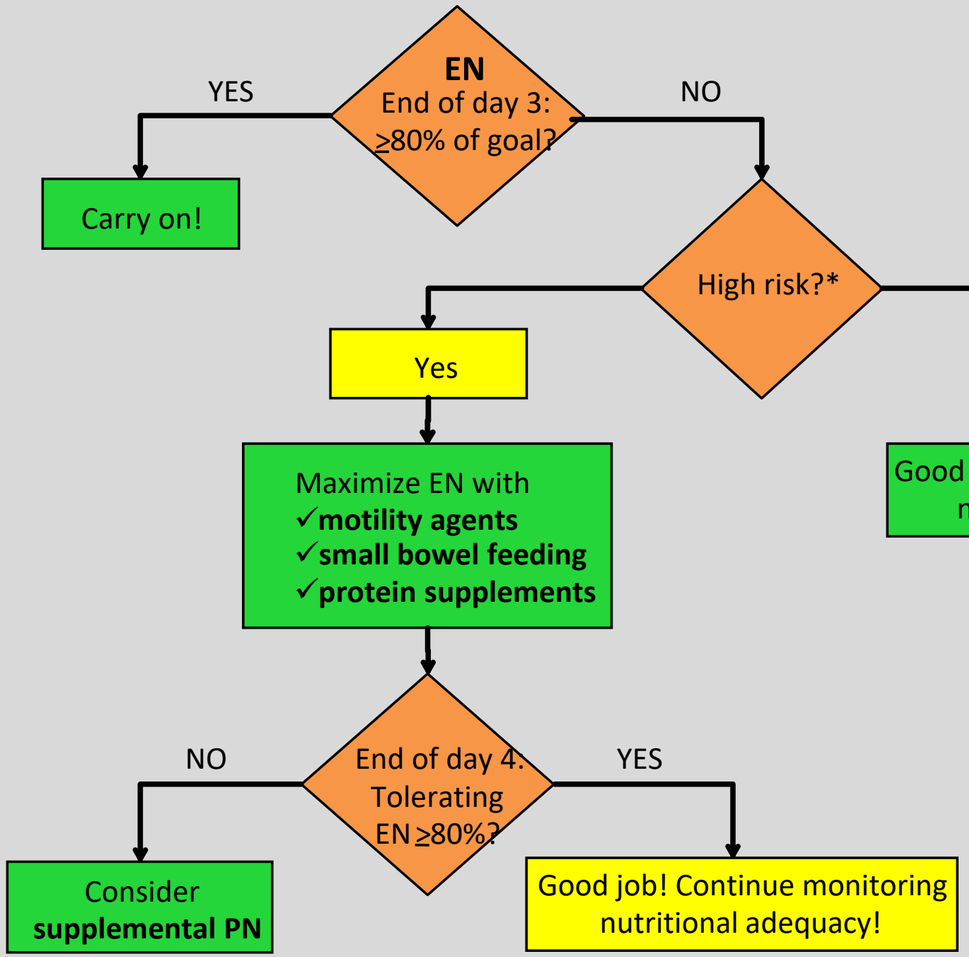
Results of 2013 International Nutrition Survey (INS)





Heyland JPEN 2014

Start PEP uP Protocol in all patients within 24-48 hrs of admission



* Nutric Score > 5 or
  - mod-severe malnourished
  - Frail and/or sarcopenia?
- ICU LOS > 96 hrs

For more information on the EFFORT Trial (or EFFORT-X)

See www.criticalcarenutrition.com

Or contact:

Daren Heyland
Dkh2@queensu.ca
Or
Zheng Yii Lee
zheng_yii@hotmail.com

Critical Care Nutrition

aspen
American Society for Parenteral and Enteral Nutrition

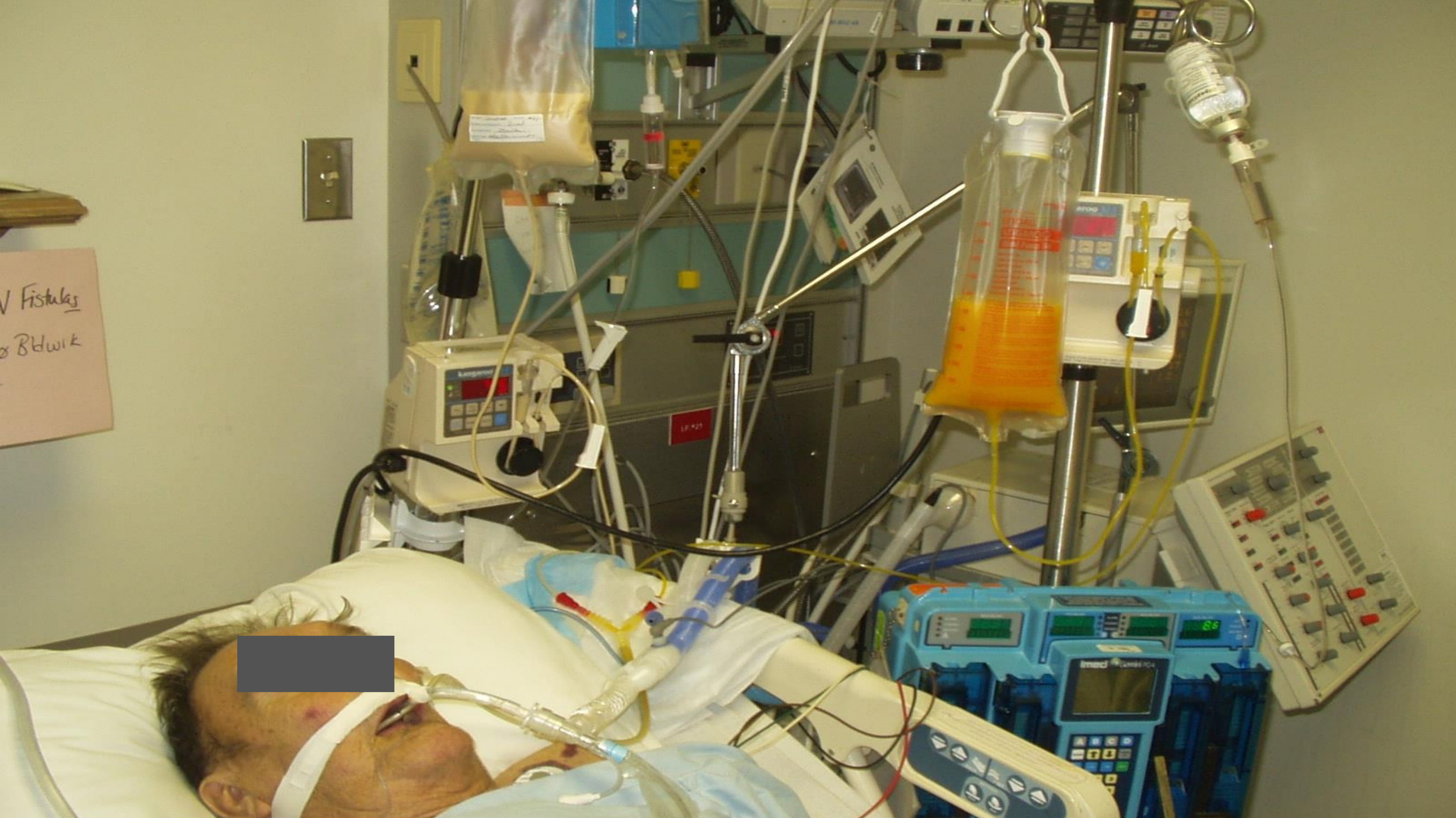
effort study

Pharmaconutrition

Nutrition therapy that modulates the underlying disease process and impacts outcome

Adjunctive
Supportive
Care

Proactive
Primary
Therapy


V Fistulas
Bldwik

Critical Care Nutrition

Pharmaconutrition: End of an Era?

Critical Care Nutrition

“We do not recommend…”

- Arginine-containing diets
- IV/EN glutamine supplementation
- IV/PN selenium, alone or in combination with other antioxidants
- IV/PN combined vitamins and trace elements
- Fish oils

Critical Care Nutrition

Large-scale Trials Have Failed to Demonstrate Any Positive Treatment Effect

REDOXS, Metaplus, SIGNET	Glutamine and Antioxidants
SISPCT	IV Selenium
Omega	Fish Oils
Meta-analysis of large scale RCTs	Arginine

Critical Care Nutrition

Where do we go from here?

Critical Care Nutrition

Glutamine:
A conditionally essential amino acid?

Glutamine levels drop:
- following extreme physical exercice
- after major surgery
- during critical illness

Low glutamine levels are associated with:
- immune dysfunction
- higer mortality in critically ill patients

Novak F, Heyland DK, A Avenell et al., Crit Care Med 2002
Oudemans-van Straaten HM, Bosman RJ, Treskes Met al., Intensive Car Med 2001

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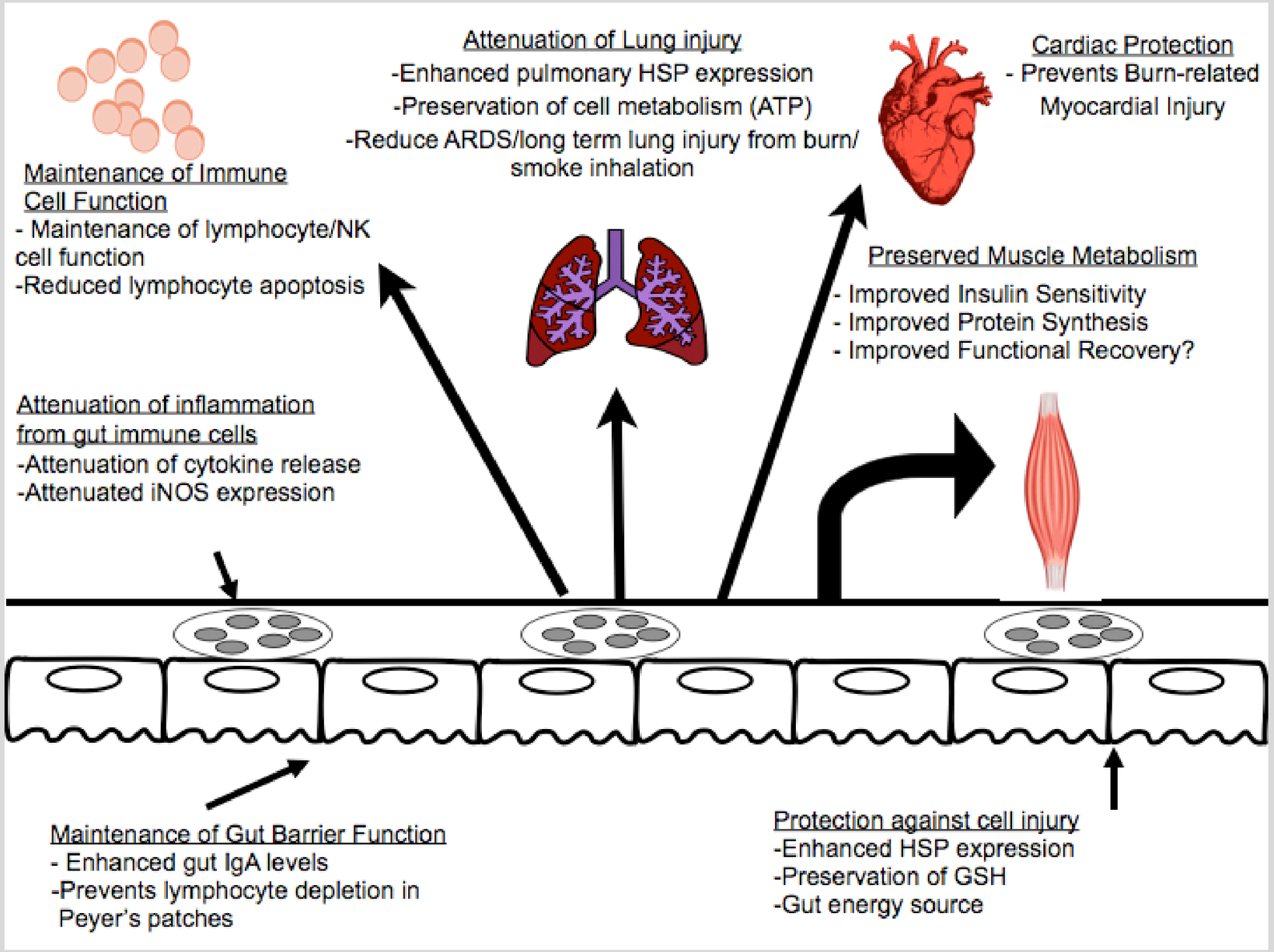
Putative Mechanisms of Glutamine Supplementation



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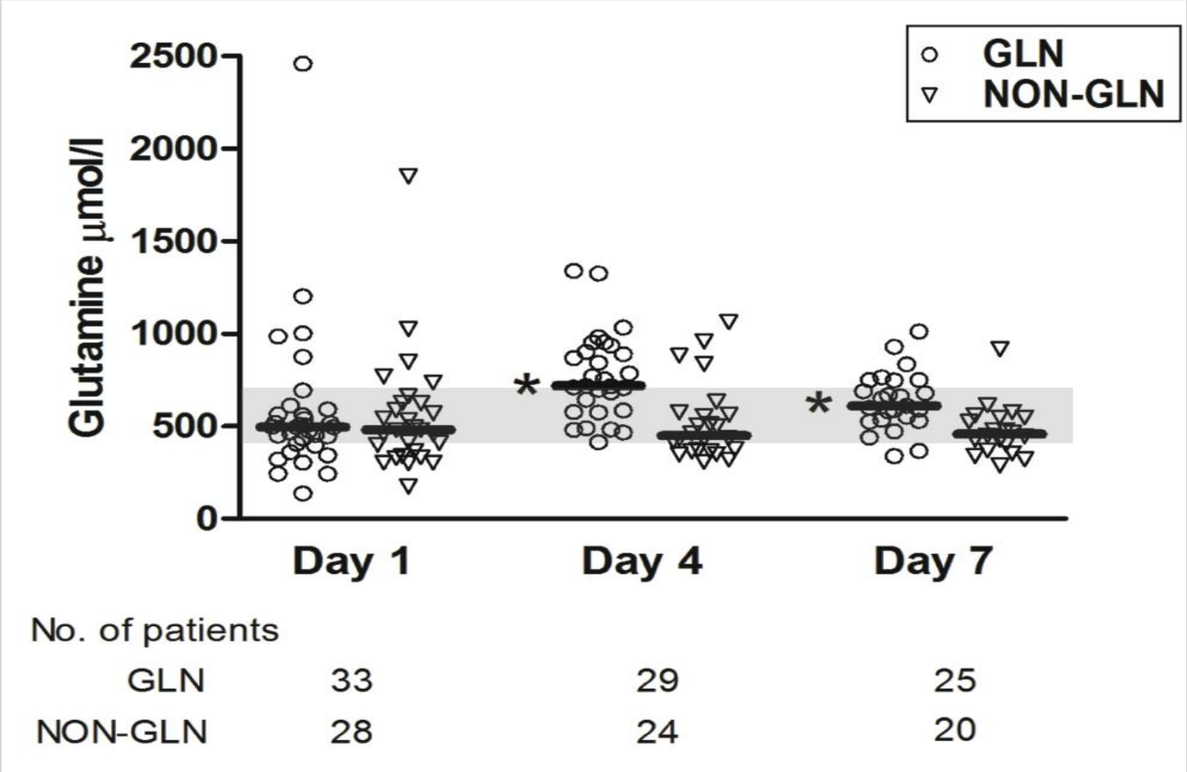
- Randomized >1200 critically ill patients with multi-organ failure
- High dose of combined EN/IV doses
- Demonstrated increased mortality overall
- Subgroup analysis suggested this was in renal failure patients

Heyland N Engl J Med 2013;368:1489-97.

Critical Care Nutrition

Plasma Levels of Glutamine in Subset of Patients from REDOXS Study

P <0.001



Heyland N Engl J Med 2013;368:1489-97.

Glutamine and glutathione at ICU admission in relation to outcome

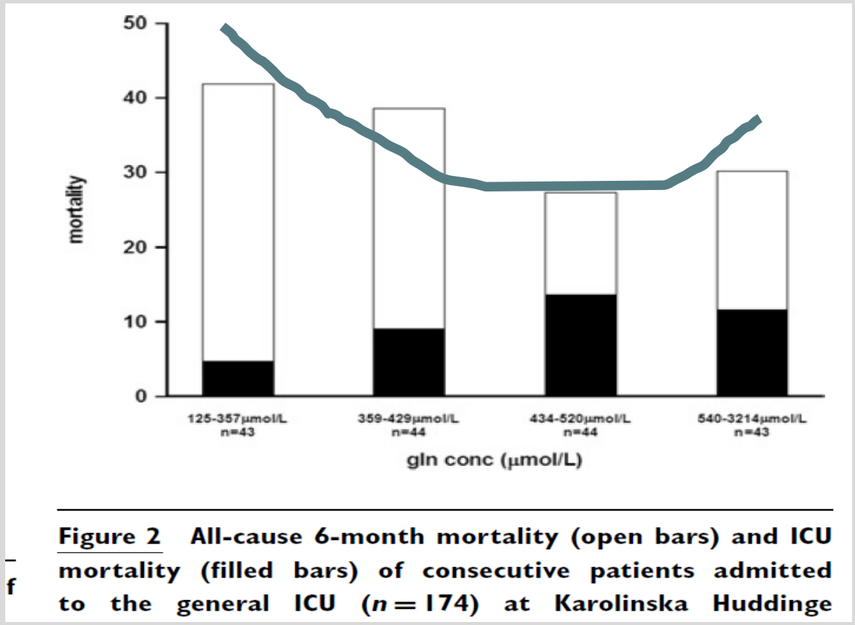


Figure 2 All-cause 6-month mortality (open bars) and ICU mortality (filled bars) of consecutive patients admitted to the general ICU ($n = 174$) at Karolinska Huddinge

(b) Stepwise multiple logistic regression analysis

	OR (CI)	*P*
Intercept	0.002 (0.0002–0.016)	
APACHE (per patient)	1.14 (1.07–1.22)	<0.001
Gln <400 or >930	2.95 (1.38–6.32)	0.005
Age (per year)	1.04 (1.01–1.07)	0.006
rGSH/tGSH >0.65	2.35 (1.02–5.41)	<0.001

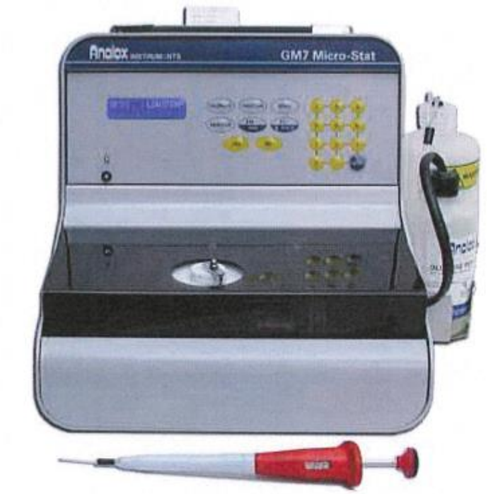
Rodas Clinical Science (2012) 122, 591–597

Critical Care Nutrition

Future Trials Require Bedside Testing?

GM7 Micro-Stat

Rapid Multi-Assay Analyser



A Research Analyser with a Unique Assay Menu Including:

- Acetoacetate
- Alcohol
- Ammonia
- Cholesterol
- Creatinine
- Glucose
- Glutamine
- Glycerol
- Lactate
- 3-Hydroxybutyrate
- Pyruvate
- Triglycerides
- Urate
- Urea

Major Application Areas:

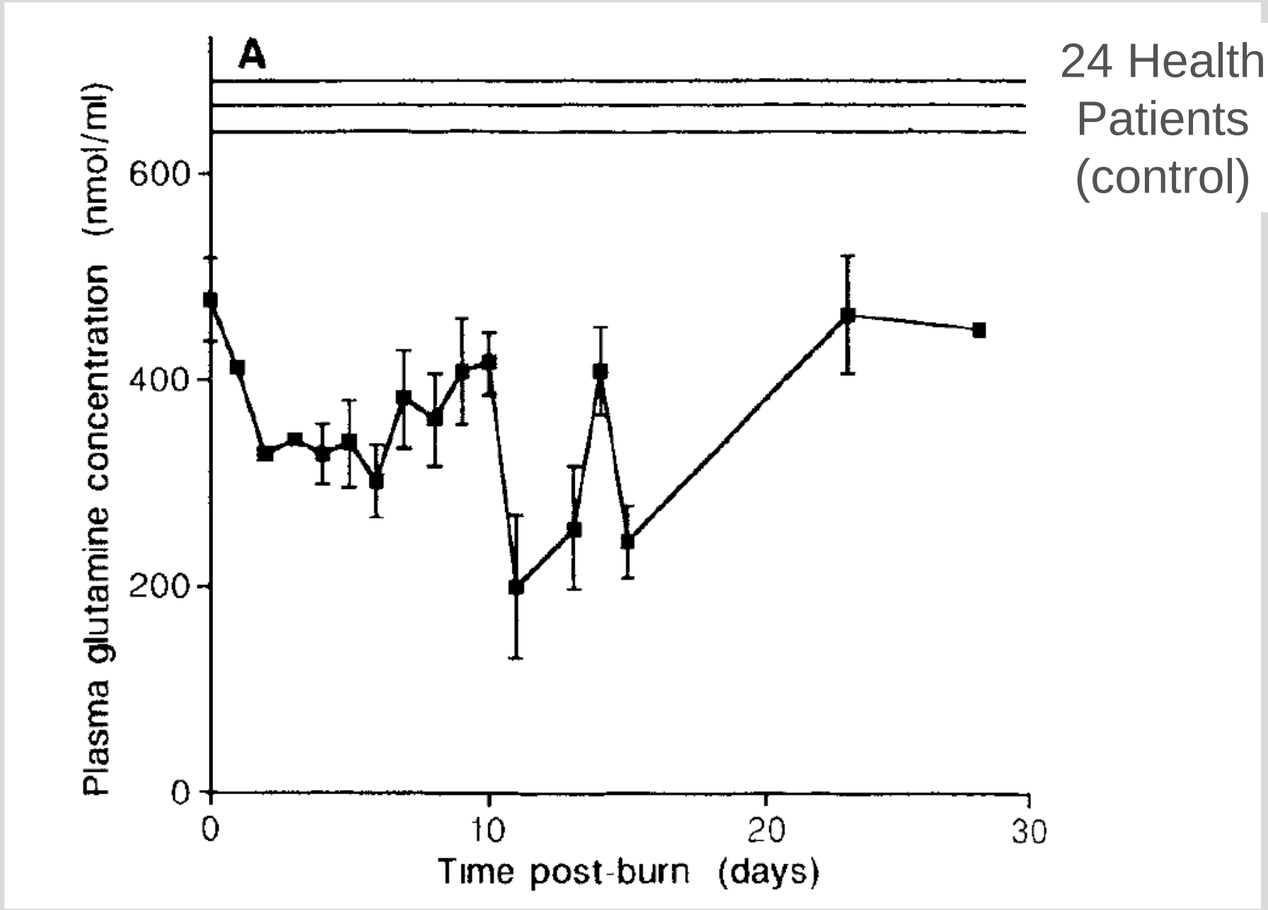
- Diabetes Research Studies
- Clinical Research
- Metabolic studies
- Biochemical Research
- Sports Medicine

Main Features:

- Extended range of analytes for diabetes research studies
- Small Sample size typically 3-25µl
- One low-cost electrode membrane for all analytes
- Printed results in 20-25 Seconds
- Data output facility

Critical Care Nutrition

Plasma Glutamine Levels in Burn-injured Patients



24 Health Patients (control)

Parry-Billings Lancet 1990

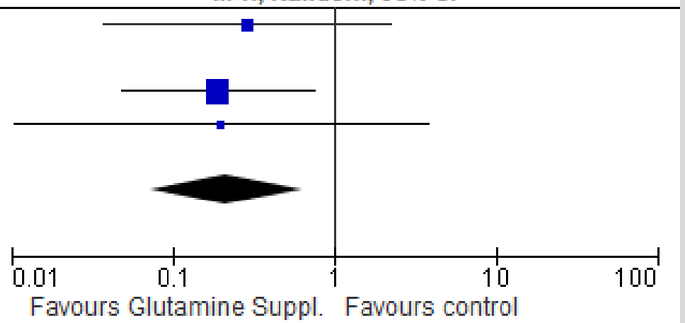
The existing data in burn-injured patients is positive…

Effect on Mortality (n=4)

Study or Subgroup	Glutamine Supplementation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Wischmeyer 2001	1	12	4	14	27.0%	0.29 [0.04, 2.27]	2001
Zhou 2003	0	20	0	20		Not estimable	2003
Garrel 2003	2	21	12	24	59.9%	0.19 [0.05, 0.76]	2003
Pattenshetti 2009	0	15	2	15	13.0%	0.20 [0.01, 3.85]	2009
Total (95% CI)		**68**		**73**	**100.0%**	**0.22 [0.07, 0.62]**	
Total events	3		18				

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 2.82 (P = 0.005)

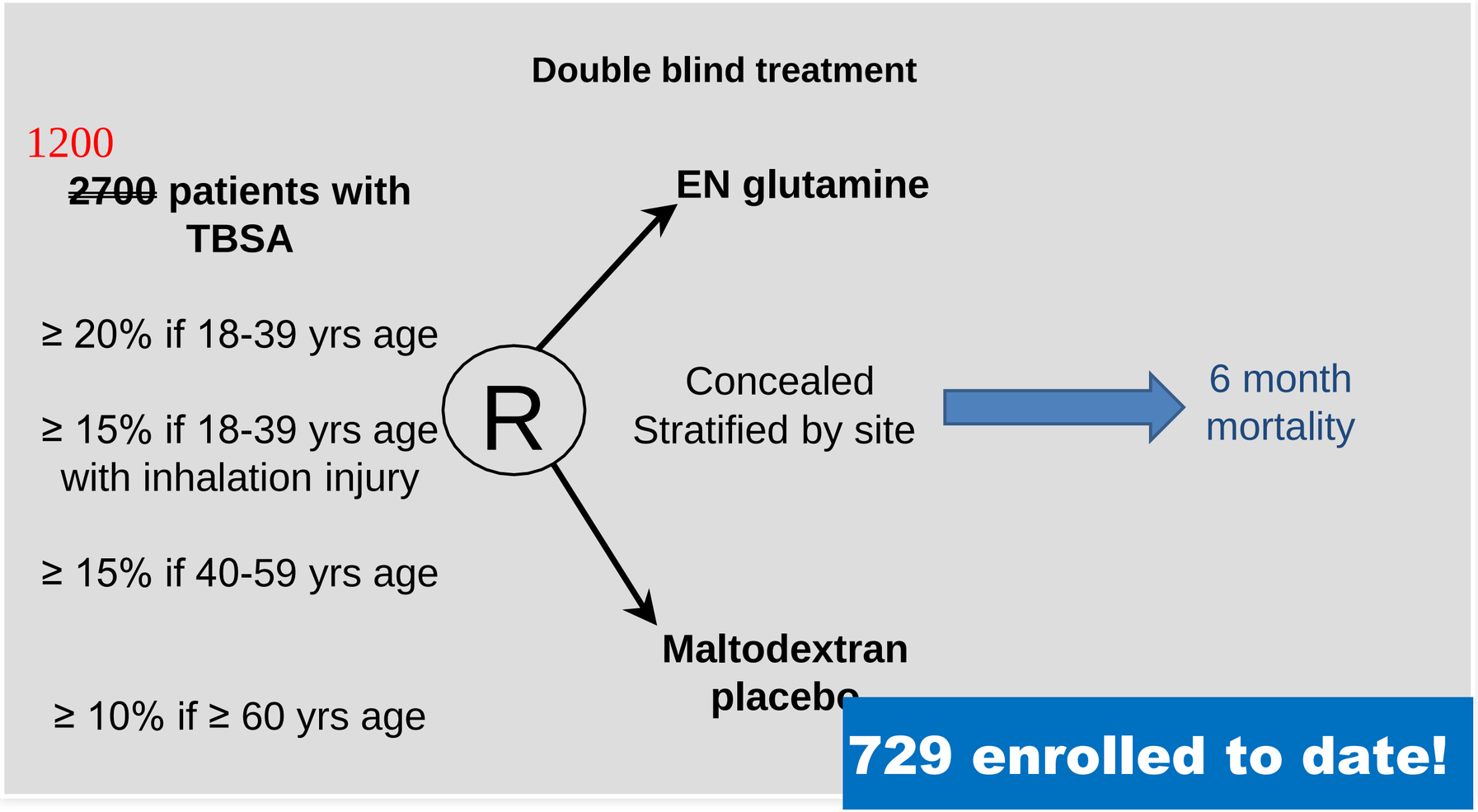


RR, 0.22, 95% CI 0.07, 0.62, p = 0.005

…But the existing data set is small and from single centered studies (unreliable estimate). Therefore, we need a larger, multicenter trial!

THE RE-*ENERGIZE* STUDY

A RandomizEd Trial of ENtERal Glutamine to MinimIZE Thermal Injury:



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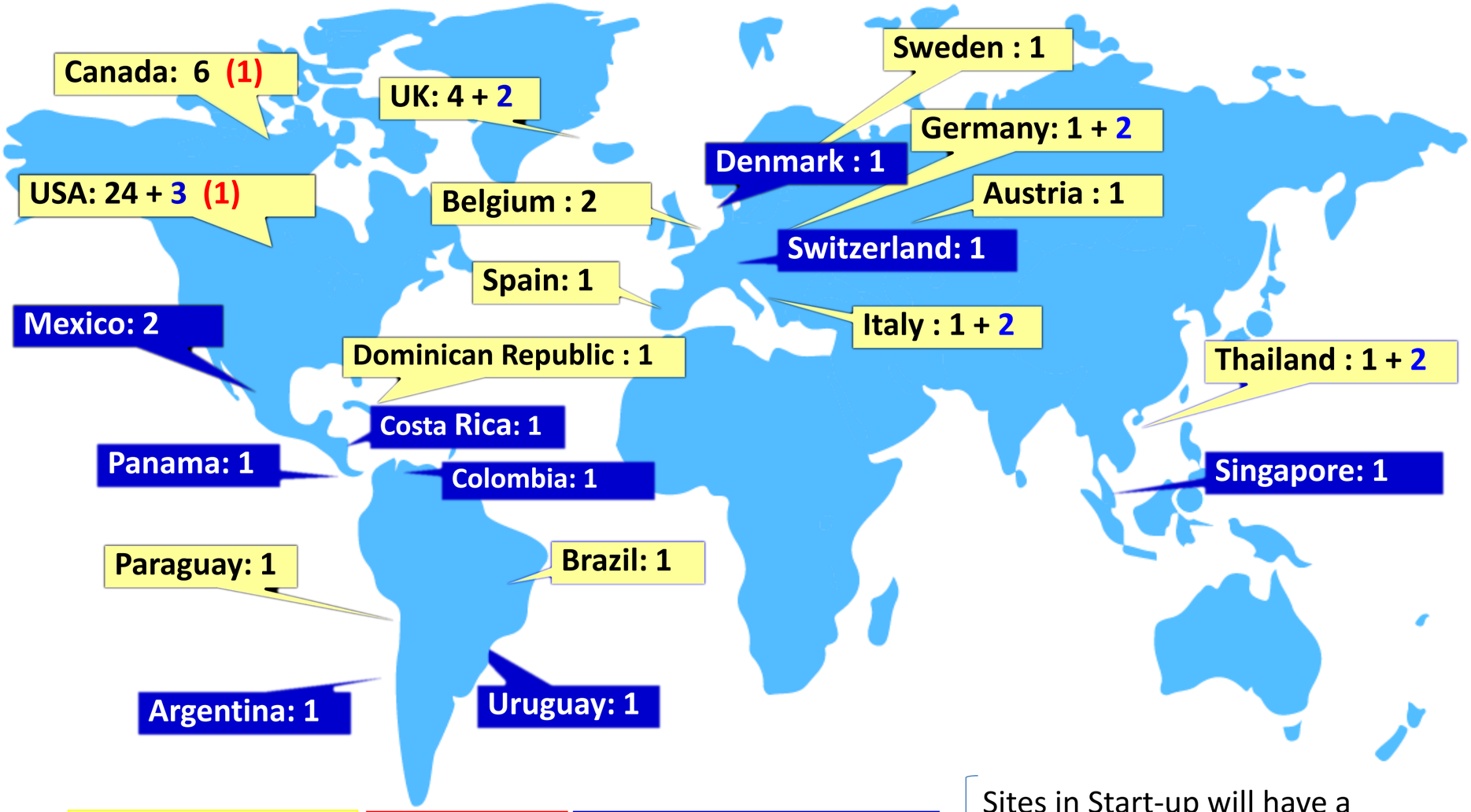
THE RE-ENERGIZE STUDY

Total: 66 Sites Worldwide



Active Sites: 45 | **Closed: 2** | **Sites in Start-up: 21**

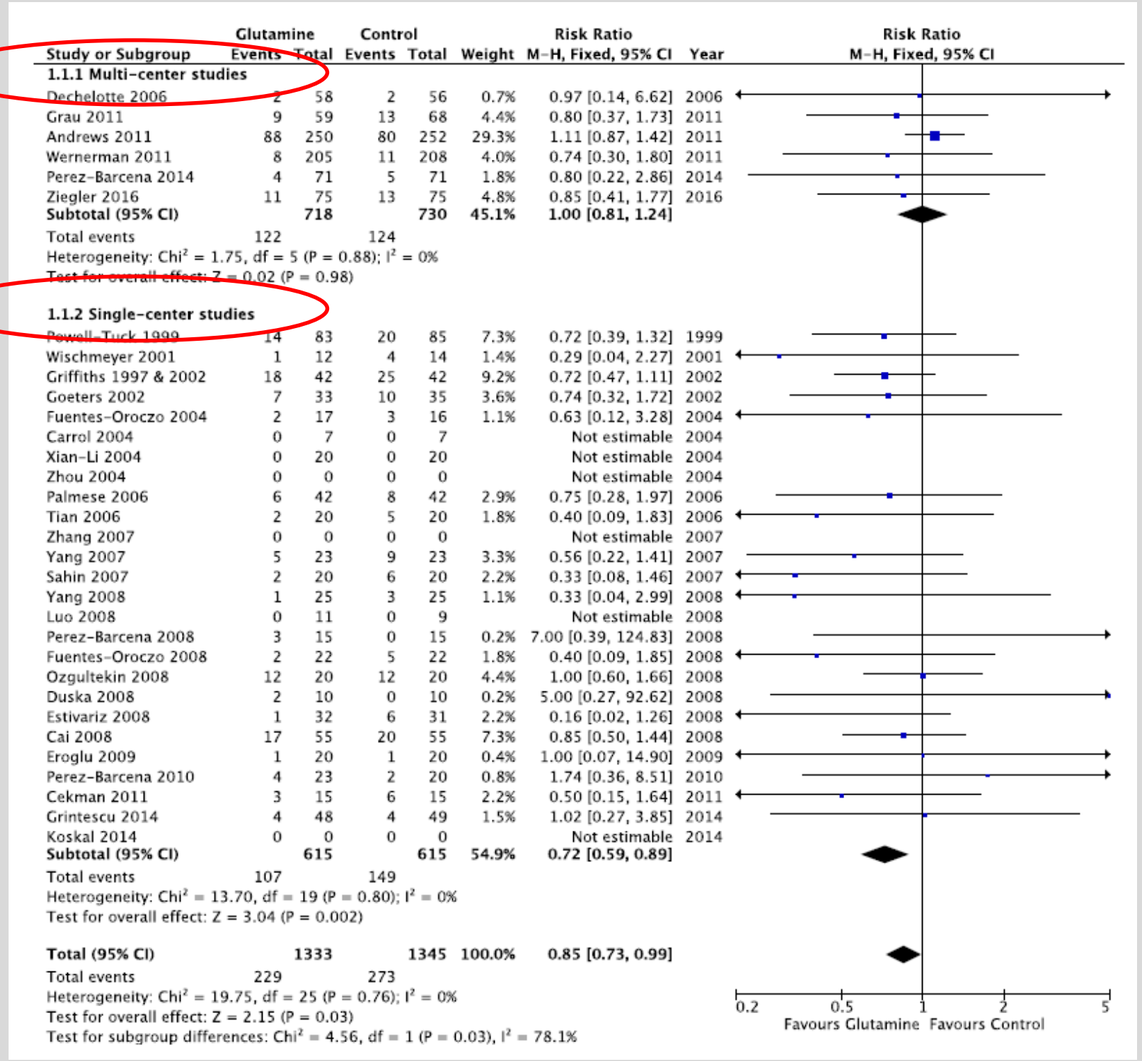
Sites in Start-up will have a deadline of 31 March 2019 for activation

Critical Care Nutrition

Updated Meta-analysis of IV Glutamine

Influence of the number of study sites involved in the trial

Hospital Mortality



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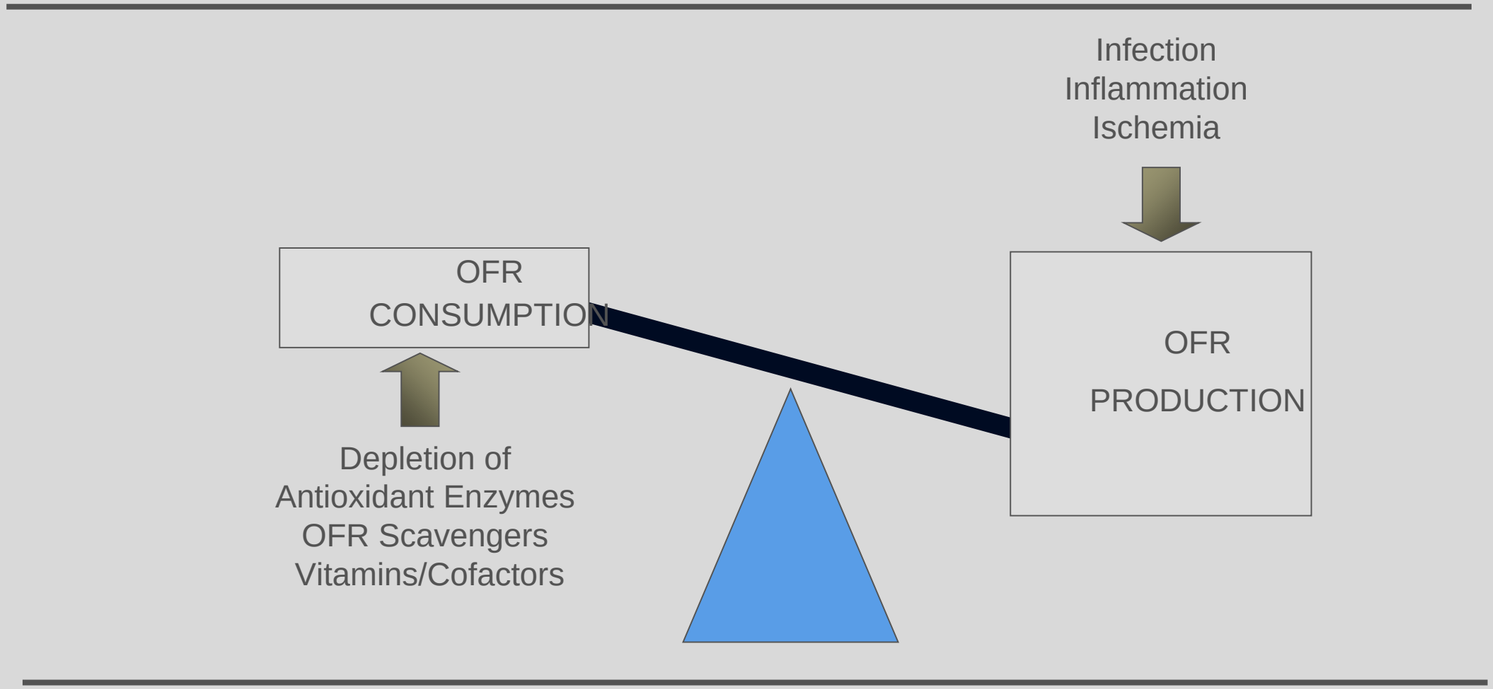
Rationale for Antioxidants

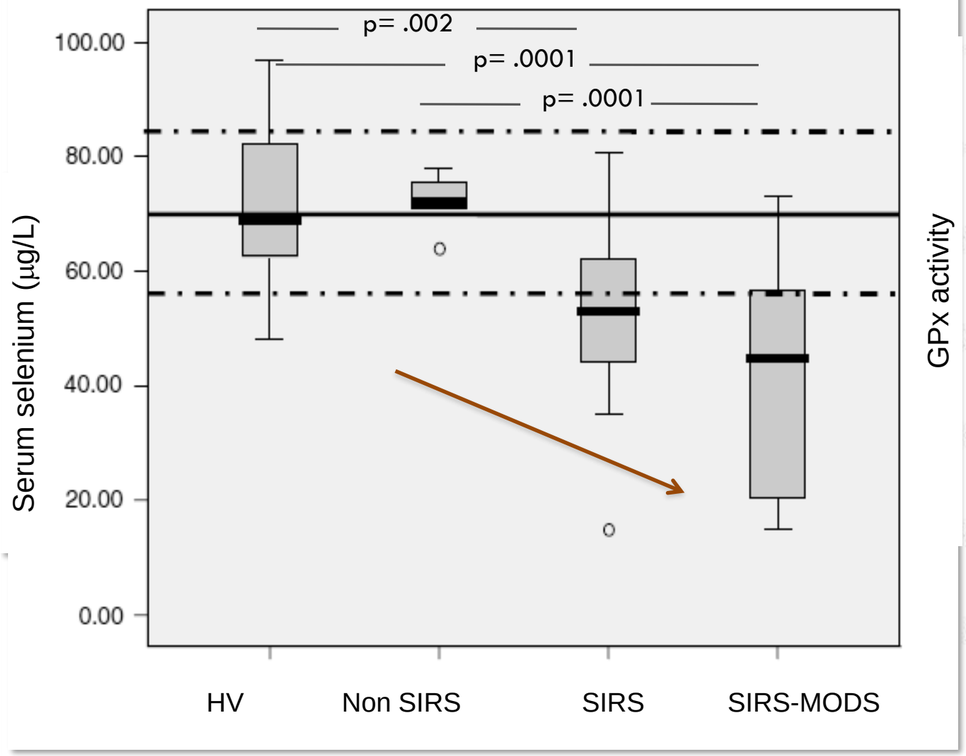


OFR production > OFR consumption = OXIDATIVE STRESS → Impaired
- organ function
- immune function
- mucosal barrier function

→ Complications and Death

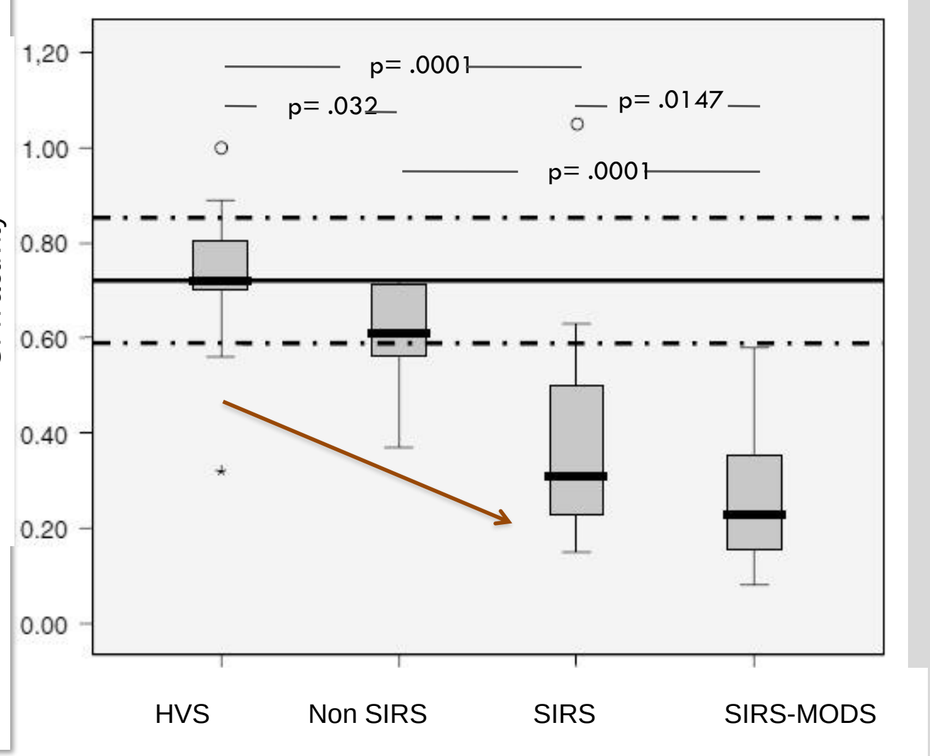
Selenium in Critical Illness

Circulating serum levels



HV=healthy volunteers

Glutathionperoxidase (GPx) activity

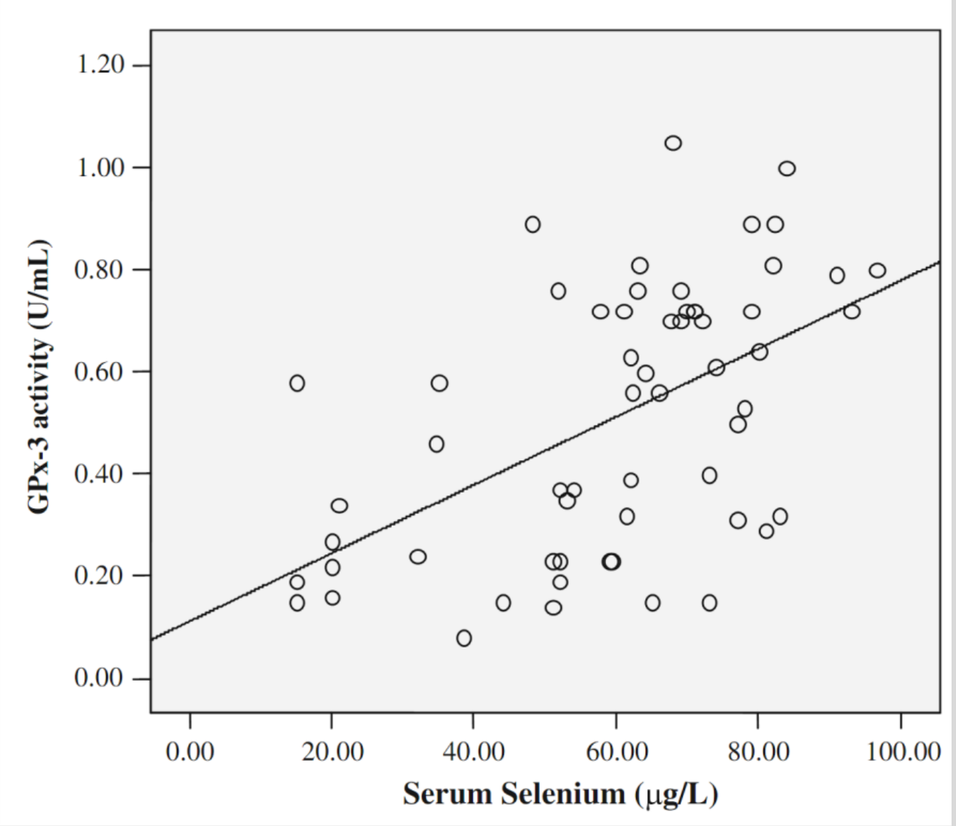


Manzanares W, *et al*. Intensive Care Med 2009; 32:882-889.

Critical Care Nutrition

Selenium in Critical Illness

Correlation of selenium levels and GPx activity

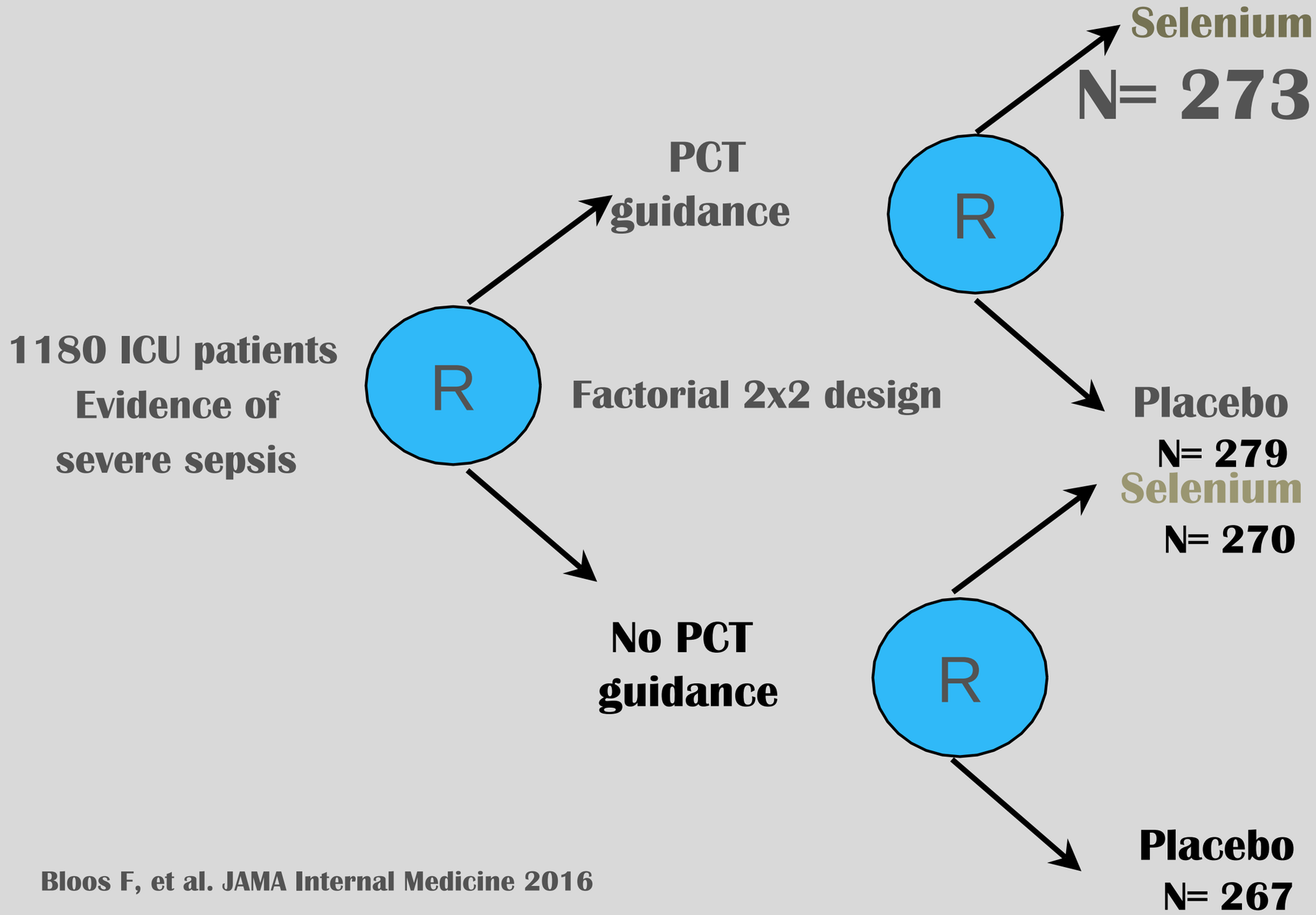


Low plasma selenium levels result in suboptimal AOX-enzyme activities!

Manzanares W. et al.
Intensive Care Med (2009) 35:882–889

Critical Care Nutrition

The SISPCT study



Bloos F, et al. JAMA Internal Medicine 2016

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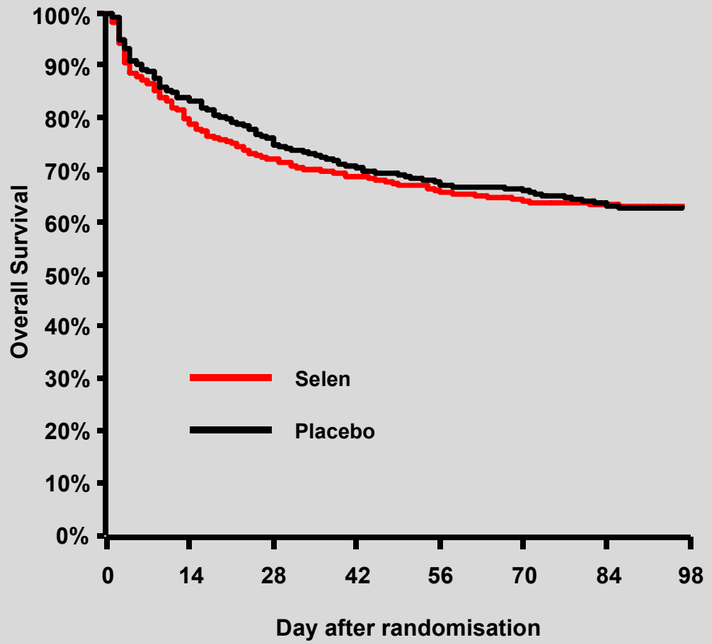
Survival Curves: Placebo versus Selenium

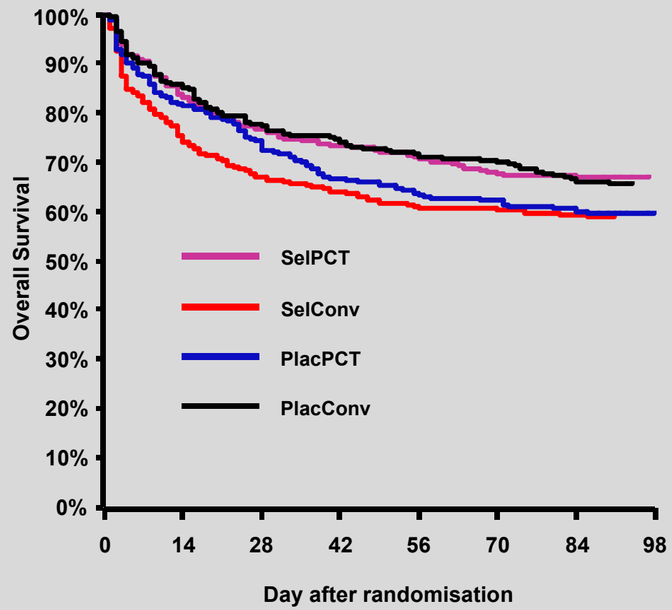
2A



Patients at risk

Placebo	546	453	408	370	354	347	333	1
Selen	543	428	386	353	338	329	324	1

2C



Patients at risk

PlacConv	267	226	203	192	184	181	171	0
PlacPCT	279	227	205	178	170	166	162	1
SelConv	270	201	178	163	154	153	150	0
SelPCT	273	227	208	190	184	176	174	0

Bloos F, et al. JAMA Internal Medicine 2016.

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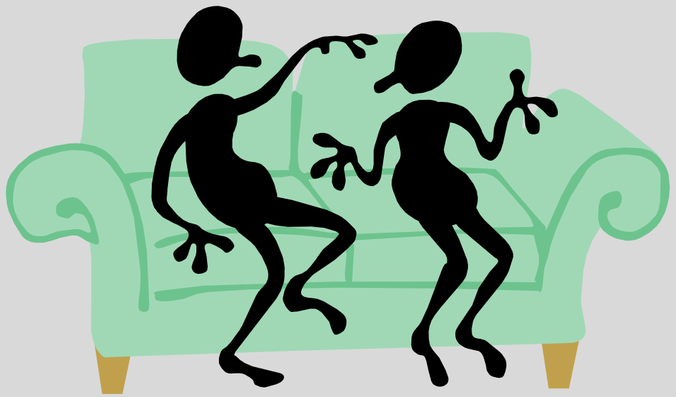
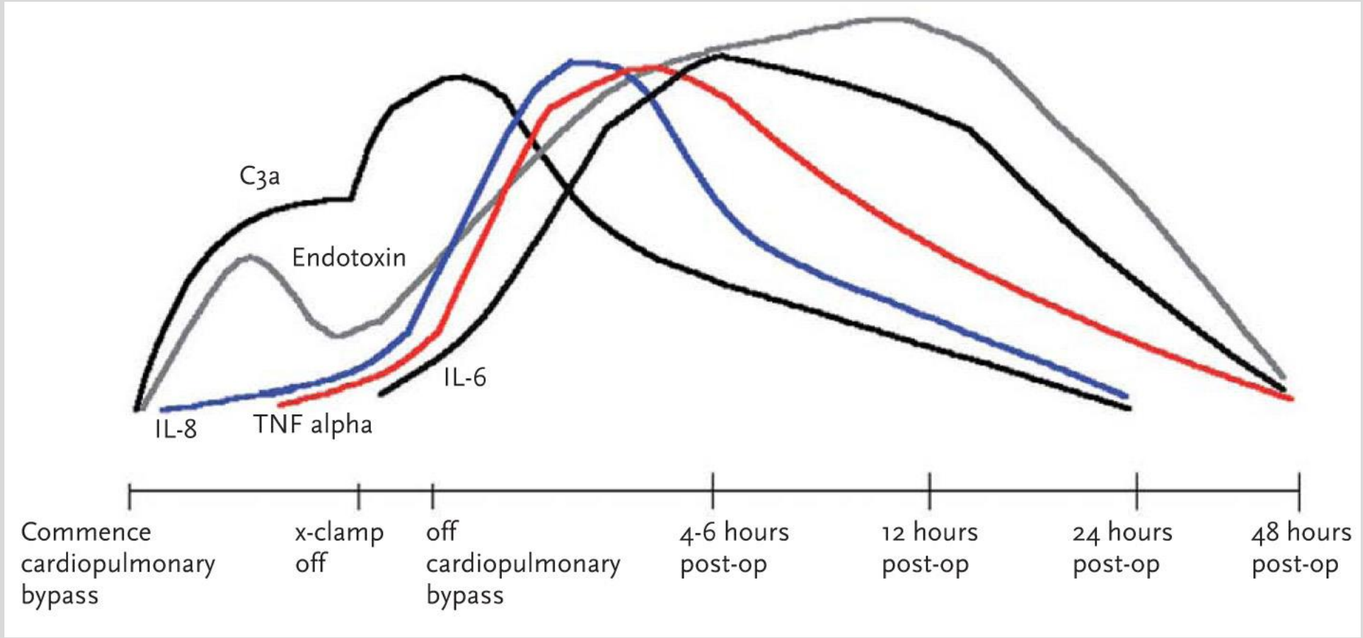
Is sepsis too heterogeneous of a disease to manifest a positive treatment effect?



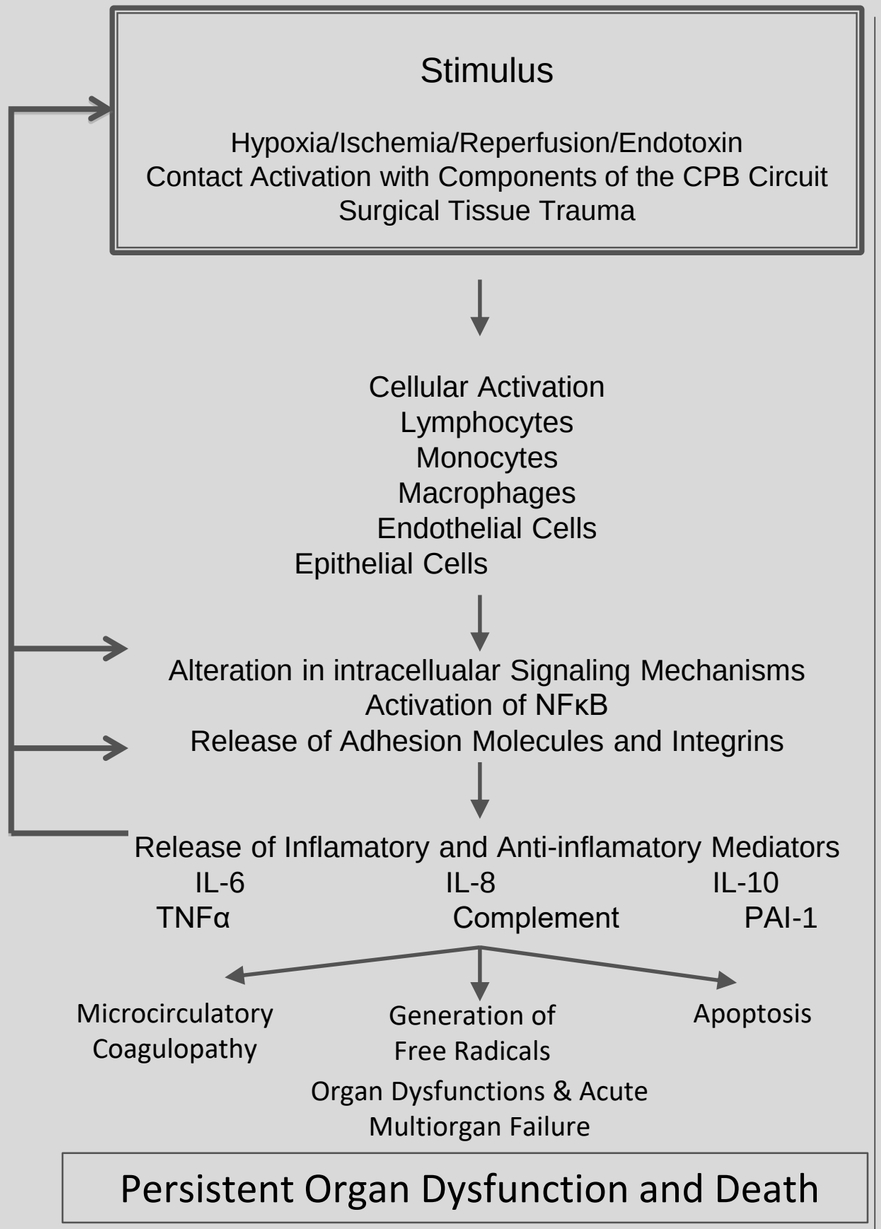
Critical Care Nutrition

Why Cardiac Surgery as a Model for a Trial of Pharmaconutrition?



- Scheduled insult
- Mortality & Morbidity relatively common
- Morbidity often involves multiple organs = systemic process
- Large body of evidence implicating excessive systemic inflammation

The Systemic Inflammatory Response In Cardiac Surgery



Treatment Approaches

Block or reduce stimulus
E.g., Coated Circuits, SDD, Pulsatile Perfusion, Leukofiltration, Cardioplegia, Oxygenator Off-pump Surgery, Cardiotomy Suction, Limitations to transfusion, Cell Washing

Block Cellular Activation
E.g., Agents directed at blocking Adhesion Molecules or Integrins, Open Lung Mechanical Ventilation

SELENIUM

Block Signaling Mechanisms
E.g., Insulin, Pentoxyfylline, Glucocorticoids, Serine Protease Inhibitors, Statins, Phosphodiesterase Inhibitors, Eritoran

Antimediator Therapies
E.g., Anti-Complement Strategies, Monoclonal Antibodies, Receptor Blocking Agents

Block or Reduce Free Radical Production
E.g., NAC, Methylene Blue

Use of Life-Sustaining Treatments

Critical Care Nutrition

Applied nutritional investigation

Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite

Christian Stoppe M.D. [a,b,*], Jan Spillner M.D. [c], Rolf Rossaint M.D. [a], Mark Coburn M.D. [a], Gereon Schälte M.D. [a], Anika Wildenhues M.D. [a], Gernot Marx M.D. [d], Steffen Rex M.D. [a,e]

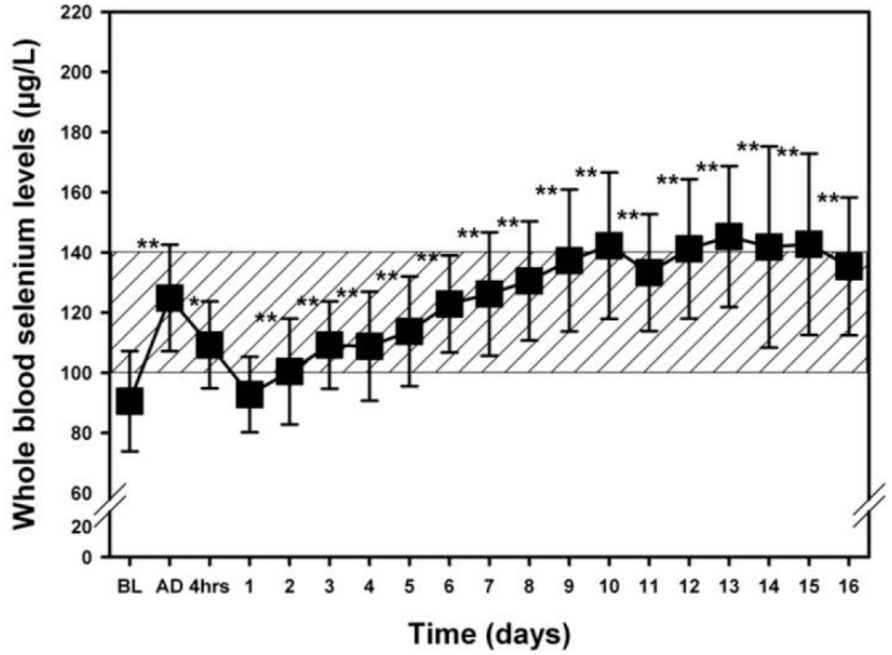


Fig. 2. Perioperative time course of whole blood concentrations of selenium. The shaded area indicates the reference range for whole blood selenium concentration in Germany. Selenium concentrations of the sole patient remaining from the 17th to 22nd day in the intensive care unit are not depicted, but values were within the reference range. AD, admission to the ICU; BL, baseline before induction of anesthesia; 4 hrs: 4 h after admission to ICU. $^{*}P < 0.05$ (0.01) versus baseline. $^{**}P < 0.05$ (0.01) versus baseline.

- Open label, observational
- 104 CPB patients
- ICU LOS 3.3 ± 4.5 d
- 2000 µg Na_2SeO_3 IV bolus, then 1000 µg Na_2SeO_3 per ICU day
- 42 patients matched (EuroSCORE / Surgical Procedure) to historical control

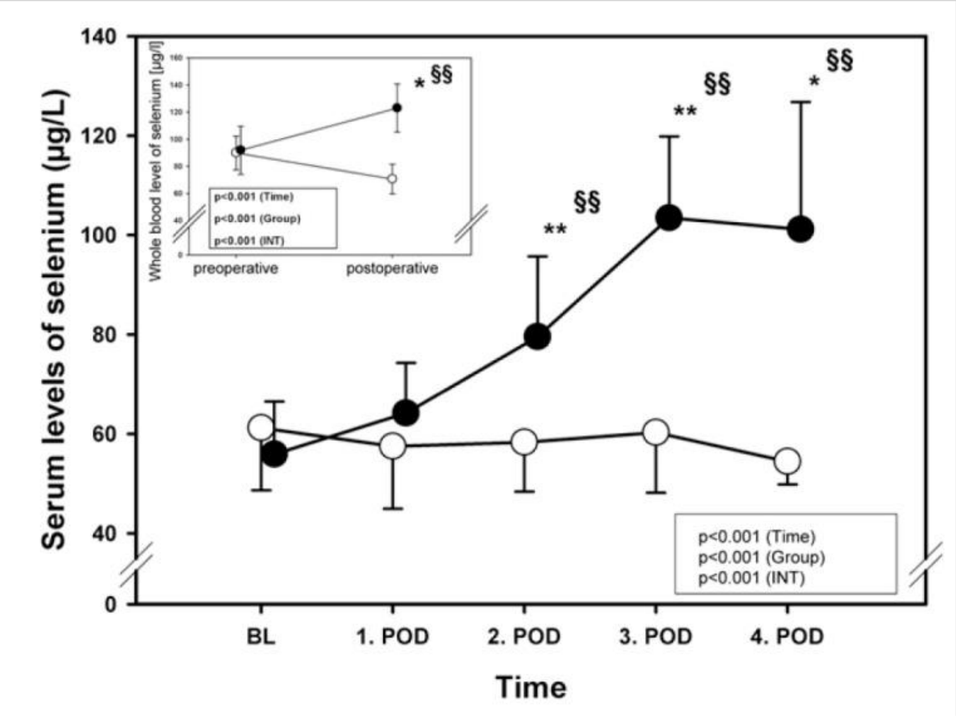
Nutrition 29 (2013) : 158-165

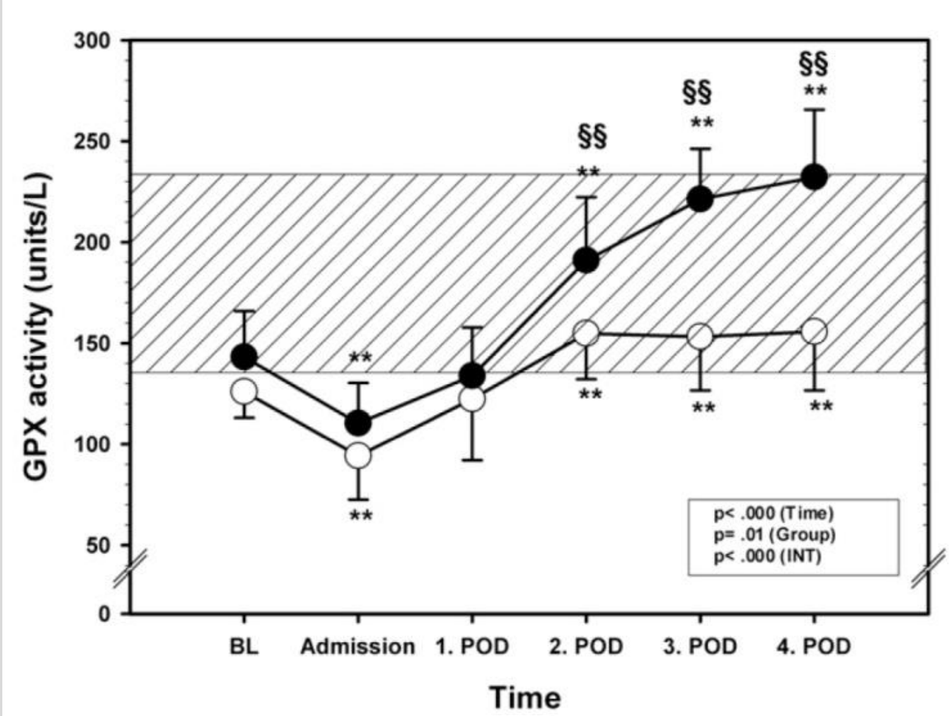
Critical Care Nutrition

Applied nutritional investigation

Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite

Christian Stoppe M.D. [a,b,*], Jan Spillner M.D. [c], Rolf Rossaint M.D. [a], Mark Coburn M.D. [a], Gereon Schälte M.D. [a], Anika Wildenhues M.D. [a], Gernot Marx M.D. [d], Steffen Rex M.D. [a,e]



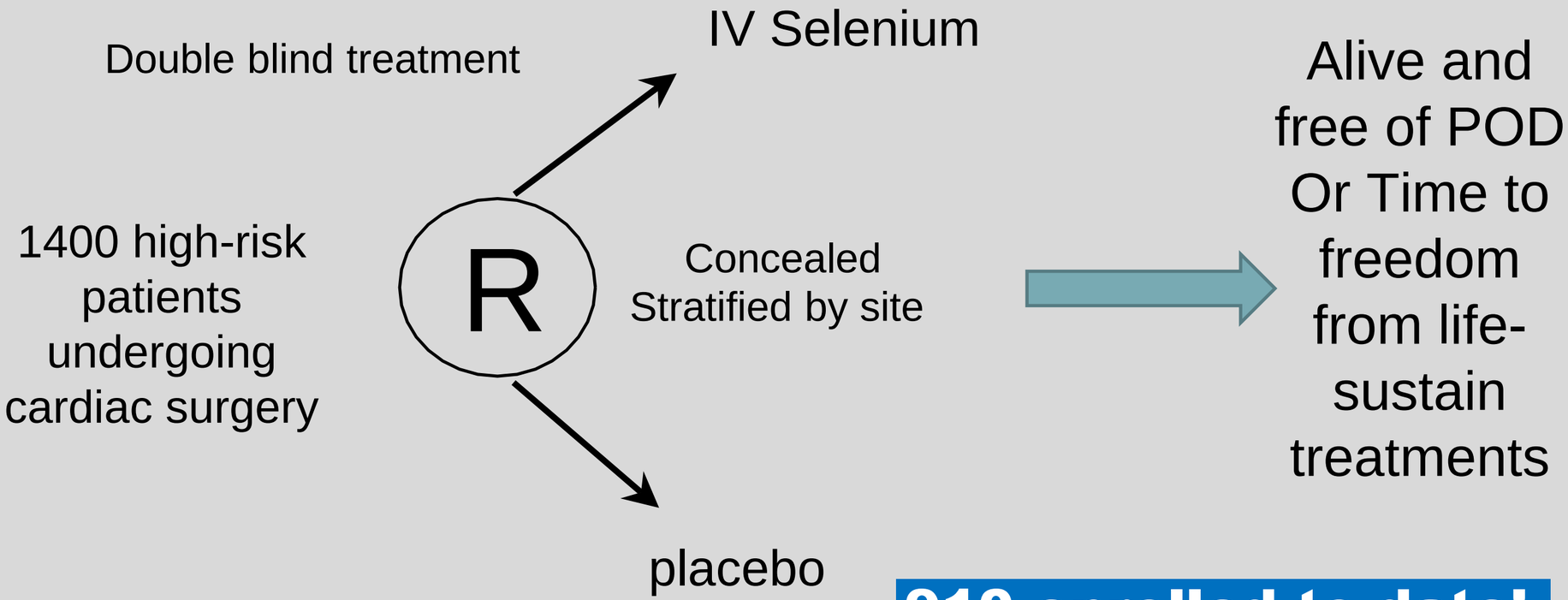


Nutrition 29 (2013) : 158-165

Critical Care Nutrition

SodiUm SeleniTe Adminstration IN Cardiac Surgery (SUSTAIN CSX®-trial)

SUSTAIN



910 enrolled to date!

Critical Care Nutrition

High Dose Vitamin C Supplementation?

- Vitamin C
  - potent antioxidant
  - support endothelium reducing permeability and microvascular dysfunction
  - multiple effects on immunity
  - Co-factor in synthesis of catecholamines
  - Promotes wound healing

Critical Care Nutrition

Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Single Center Study

- Cocktail of Hydrocortisone 50 mg q 6h x 7 days, IV Ascorbic Acid 1.5 grams q 6h, and Thiamine 200 mg q 12h x 4 days

TABLE 2] Outcome and Treatment Variables

Variable	Treated (n = 47)	Control (n = 47)
Hospital mortality, No. (%)	4 (8.5)	19 (40.4)[a]
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4 [a]
RRT for AKI, No. (%)	3 of 31 (10%)	11 of 30 (33%)[b]
ΔSOFA, 72 h	4.8 ± 2.4	0.9 ± 2.7[a]
Procalcitonin clearance, median % and IQR, 72 h	86.4 (80.1-90.8)	33.9 (−62.4 to 64.3)[a]

AKI = acute kidney injury; LOS = length of stay; RRT = renal replacement therapy; ΔSOFA = change in Sepsis-Related Organ Failure Assessment score. See Table 1 legend for expansion of other abbreviations.
[a] $P < .001$.
[b] $P = .02$.

Marik Chest 2017

Critical Care Nutrition

Journal of Research in Pharmacy Practice

Original Article

Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock

Mohadeseh Hosseini Zabet[1], Mostafa Mohammadi[2], Masoud Ramezani[2], Hossein Khalili[1]

- Single-center RCT of 28 patients
- Treated patients received 25 mg/kg intravenous ascorbic acid every 6 h for 72 h.

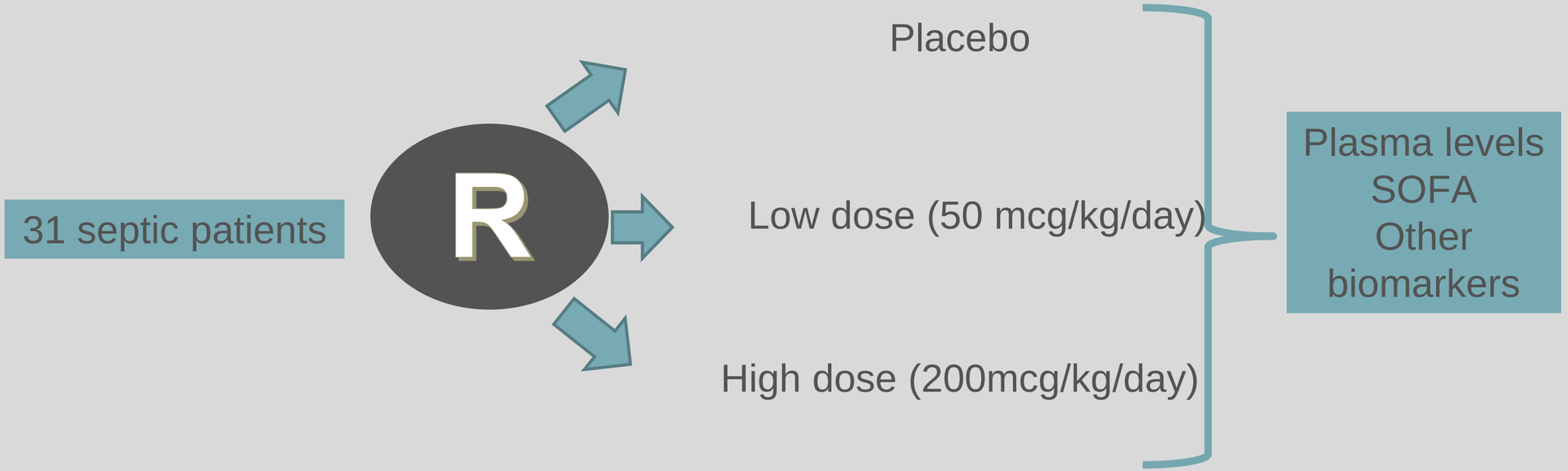
Table 4: Primary and secondary outcomes of the study in ascorbic and placebo groups

Characteristics	Ascorbic acid group (*n*=14)	Control group (*n*=14)	*P*
Mean dose of norepinephrine (mcg/min) during the study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
Length of ICU stay (days)	21.45±10.23	20.57±13.04	0.85
28-day mortality	2 (14.28)	9 (64.28)	0.009

Data presented as mean±SD or *n* (%). SD=Standard deviation, ICU=Intensive Care Unit

Zabet J Res Pharm Pract 2016;5:94-100.

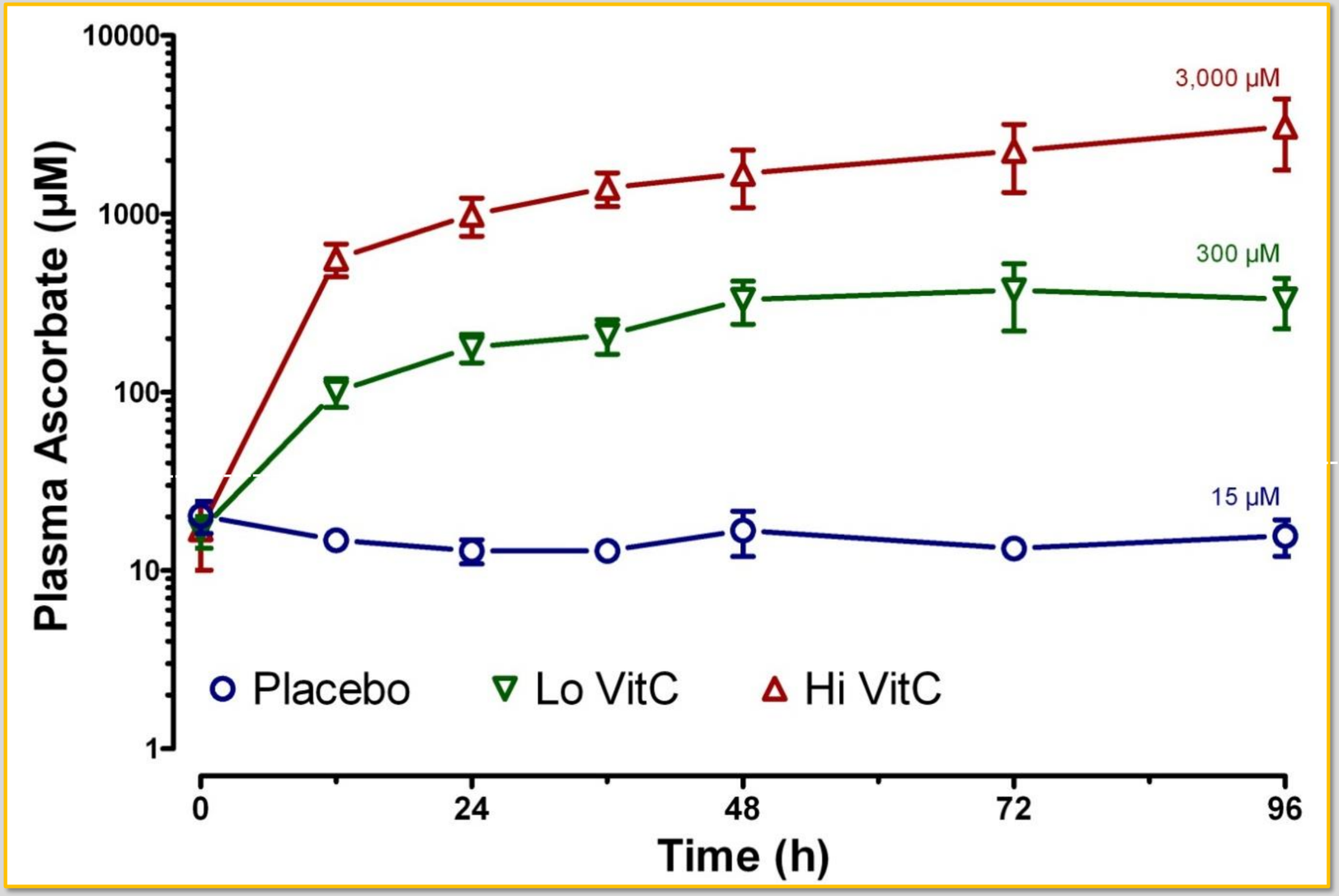
Phase I Vit C dosing study in Sepsis



Fowler et al. J Translational Medicine 2014;12:32

Critical Care Nutrition

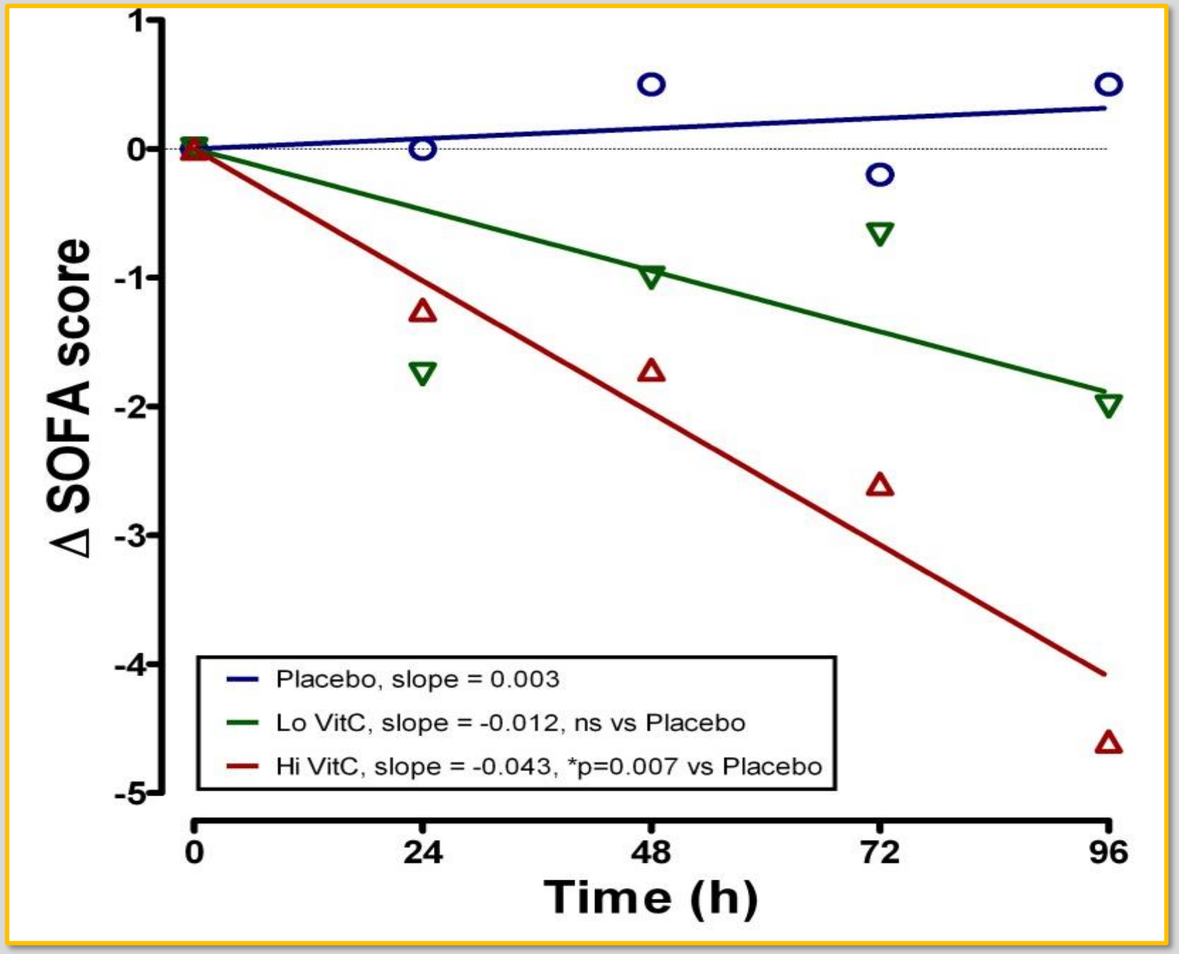
Plasma Vitamin C Levels



Fowler et al. J Translational Medicine 2014;12:32

Critical Care Nutrition

EFFECT on Organ Failure and other Mechanistic Endpoints



+ Reduced CRP and PCT (markers of inflammation)
+ Reduced Thrombomodulin (marker of vascular injury)

Await results of Phase II trial!

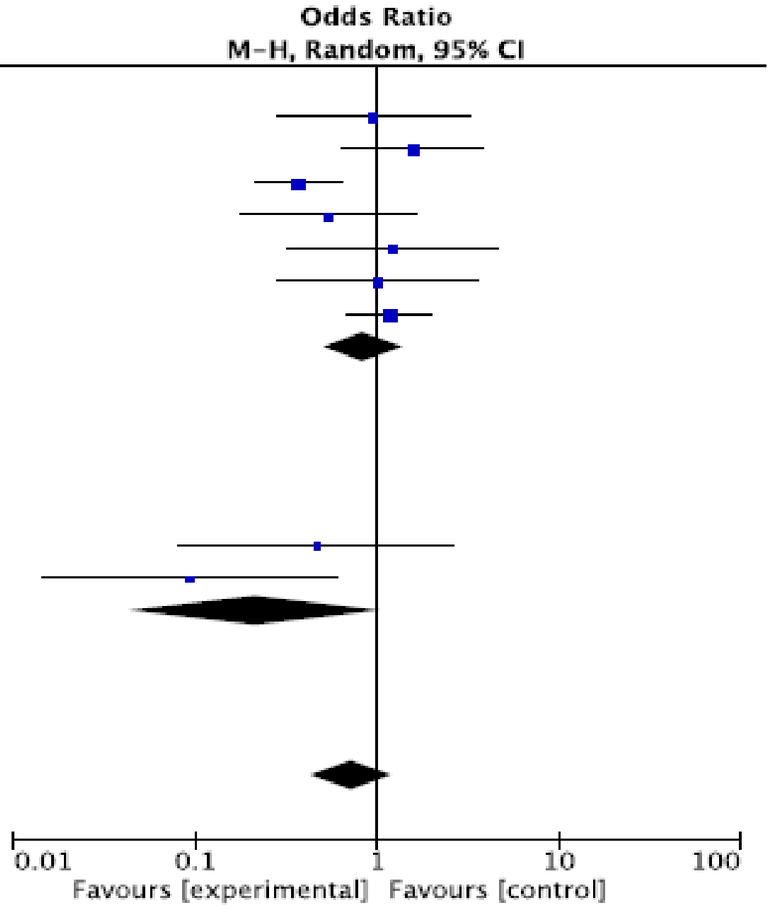
Fowler et al. J Translational Medicine 2014;12:32

Critical Care Nutrition

Test Monotherapy, Not Combination therapy?

Systematic review of Vit C supplementation

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 Combined therapy						
Beale 2008	7	27	7	26	9.8%	0.95 [0.28, 3.22]
Berger 2008	14	102	9	98	13.4%	1.57 [0.65, 3.82]
Crimi 2004	49	112	76	112	17.9%	0.37 [0.21, 0.64]
Nathens 2002	5	301	9	294	10.9%	0.53 [0.18, 1.62]
Preiser 2000	8	20	6	17	8.8%	1.22 [0.32, 4.66]
Schneider 2011	6	29	6	29	9.3%	1.00 [0.28, 3.56]
van Zanten 2014	38	152	33	149	18.1%	1.17 [0.69, 2.00]
Subtotal (95% CI)		**743**		**725**	**88.2%**	**0.84 [0.51, 1.38]**
Total events	127		146			
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 13.05$, df = 6 (P = 0.04); $I^2 = 54\%$						
Test for overall effect: Z = 0.68 (P = 0.49)						
3.1.2 Monotherapy						
Fowler 2014	7	16	5	8	6.2%	0.47 [0.08, 2.66]
Zabet 2016	2	14	9	14	5.6%	0.09 [0.01, 0.59]
Subtotal (95% CI)		**30**		**22**	**11.8%**	**0.21 [0.04, 1.05]**
Total events	9		14			
Heterogeneity: $Tau^2 = 0.47$; $Chi^2 = 1.56$, df = 1 (P = 0.21); $I^2 = 36\%$						
Test for overall effect: Z = 1.90 (P = 0.06)						
Total (95% CI)		**773**		**747**	**100.0%**	**0.72 [0.43, 1.20]**
Total events	136		160			
Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 18.27$, df = 8 (P = 0.02); $I^2 = 56\%$						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: $Chi^2 = 2.60$, df = 1 (P = 0.11), $I^2 = 61.5\%$						



Langlois JPEN 2019 (in press)

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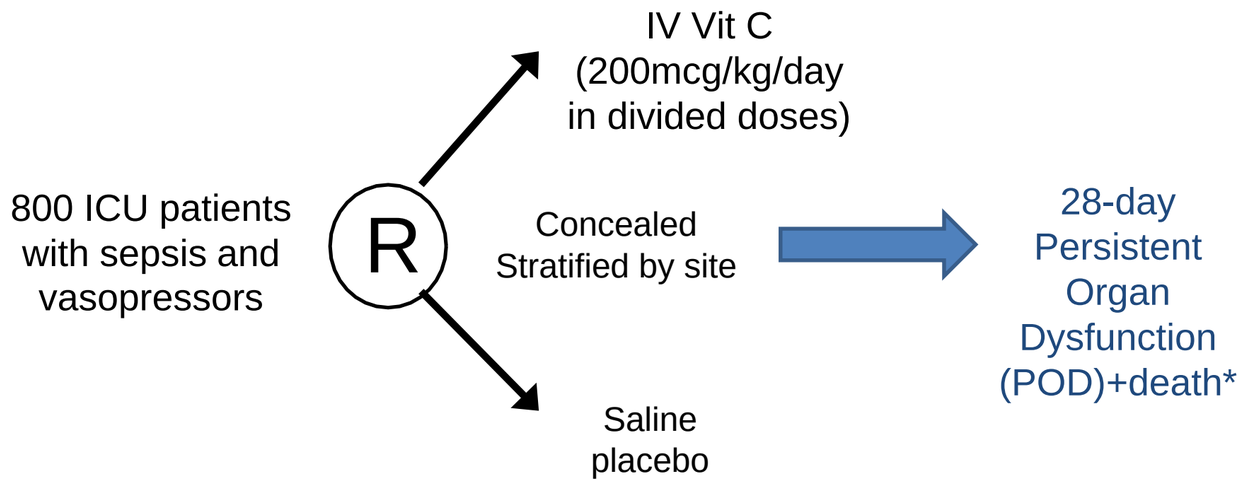
LOVIT

The **L**essening **O**rgan Injury/Dysfunction with **VIT**amin C (LOVIT) Trial

Double blind treatment



*Heyland Crit Care 2011

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Biggest Controversy of Them ALL

Do you see yourself as a Doctor that looks after patients ONLY

Or

As someone that examines and contributes to improving the system that we have created to care for these vulnerable patients?

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Critical Care Nutrition at the Clinical Evaluation Research Unit (CERU)

is dedicated to improving nutrition therapies in the critically ill through knowledge *generation*, *synthesis*, and *translation*. We engage in a broad range of research activities and promote a culture of best practices in critical care nutrition. Ultimately, this will result in improved clinical outcomes for critically ill patients and increased efficiencies to our health care systems.

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Summary

- Evidence base informing clinical nutrition practices is weak with conflicting signals
- Probably nutritionally high-risk patients will benefit the most from macronutrients;
- Protein more important that calories
- Pharmaconutrition still alive as a concept
- More research needed to define optimal dose of protein/calories and value of various micronutrients
- We need your help! See yourself as part of the solution!

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QUESTIONS?