“QUE RETENIR DE L'ACTUALITÉ en Nutrition artificielle en réanimation en 2023”

Jean Reignier
Service de Médecine Intensive-Réanimation
CHU de Nantes

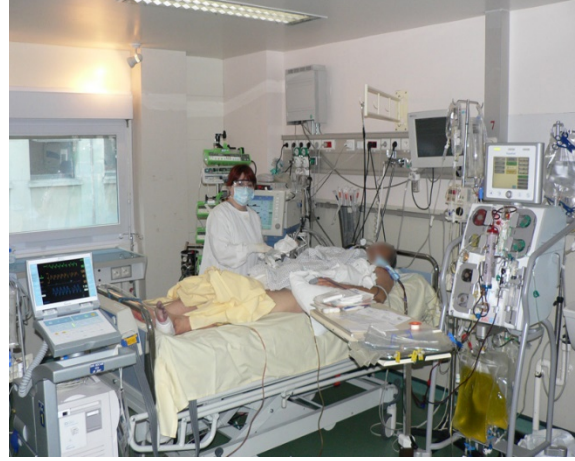
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

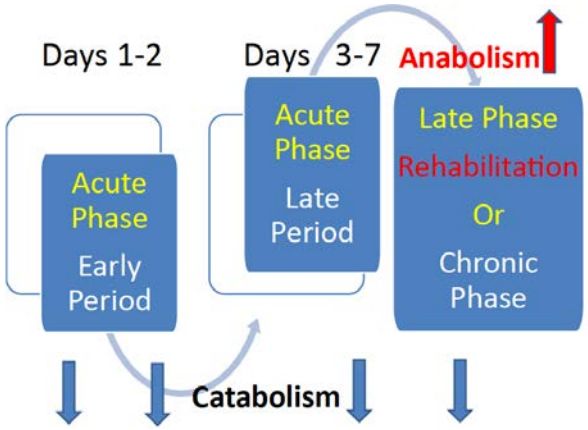
MÉDECINE INTENSIVE RÉANIMATION CHU NANTES

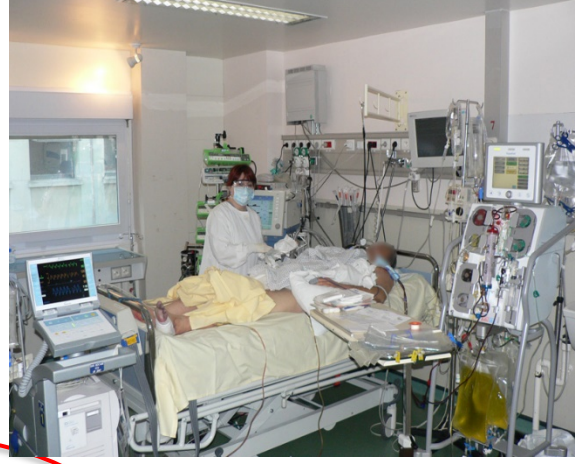
AER ACTUALITÉS EN RÉANIMATION

Liens d’intérêts

- Aucun




Days 1-2
Days 3-7
Anabolism
Acute Phase
Early Period
Acute Phase
Late Period
Late Phase
Rehabilitation
Or
Chronic Phase
Catabolism



Age

Pathologie chronique

Dénutrition chronique

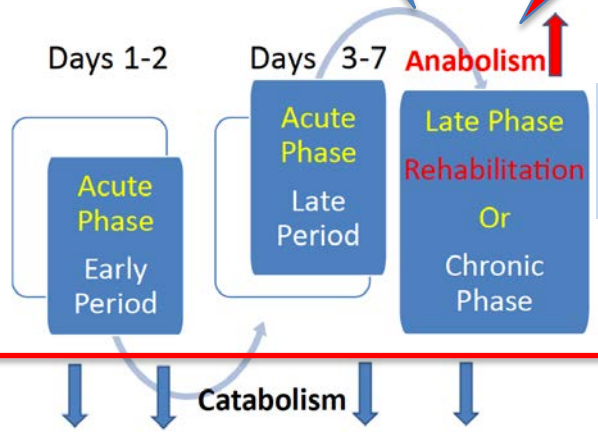
Rechutes

Gestion difficile du support nutritionnel

Reprise difficile de l'alimentation orale

Etat nutritionnel avant la réanimation

Dénutrition récente



Durée de VM

Durée de séjour

Etat nutritionnel à la sortie de réanimation

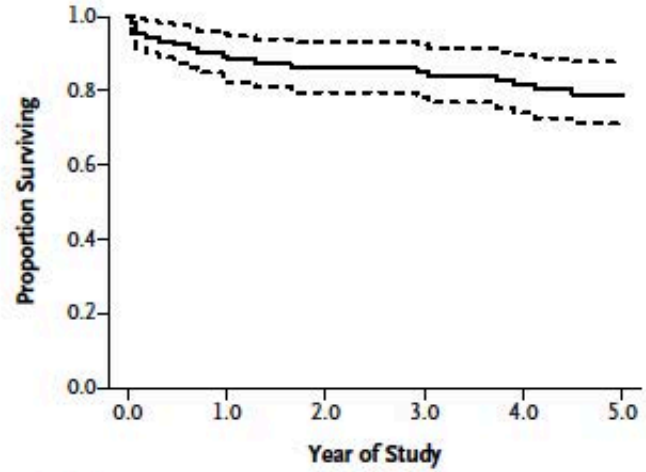
Etat fonctionnel à la sortie de réanimation

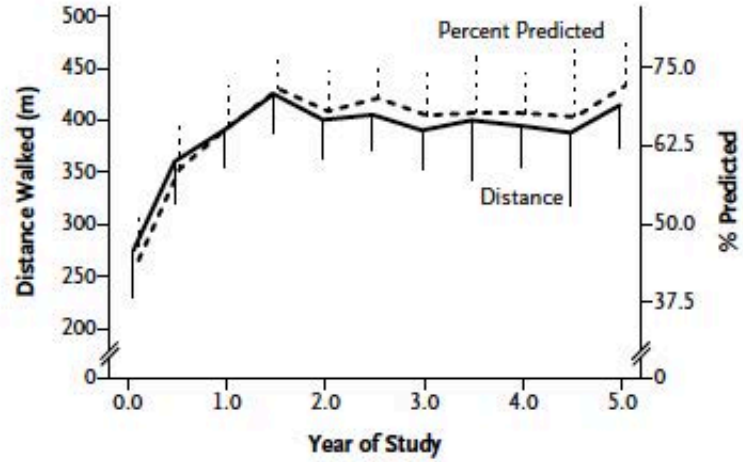
Etat fonctionnel à distance de la réanimation

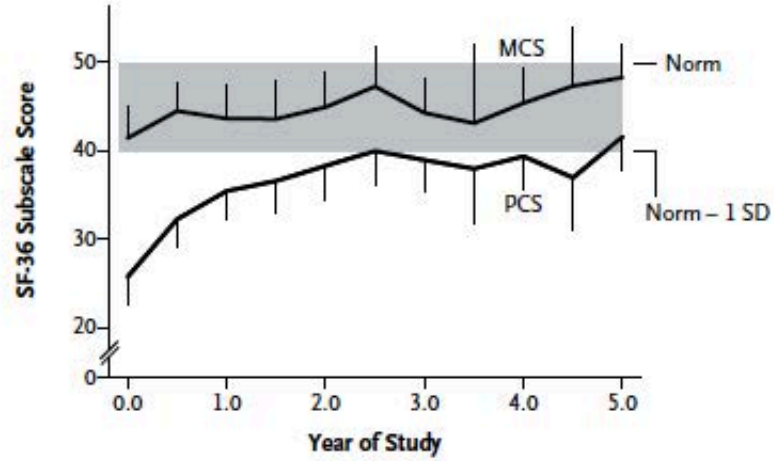
SDRA

Marche

Qualité de vie



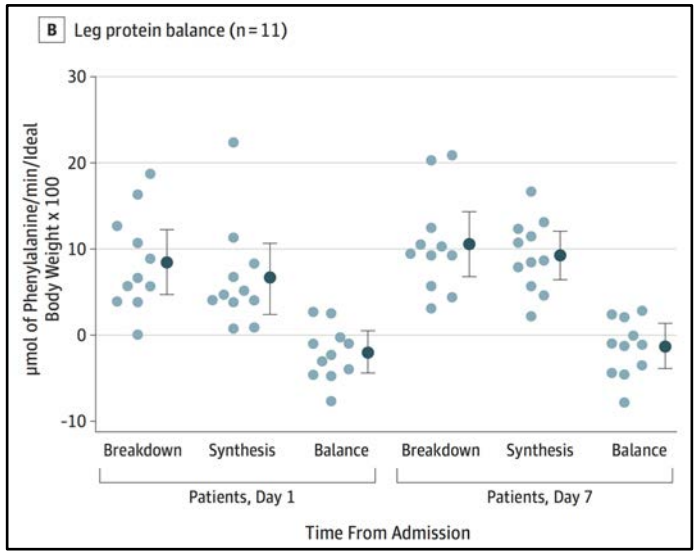




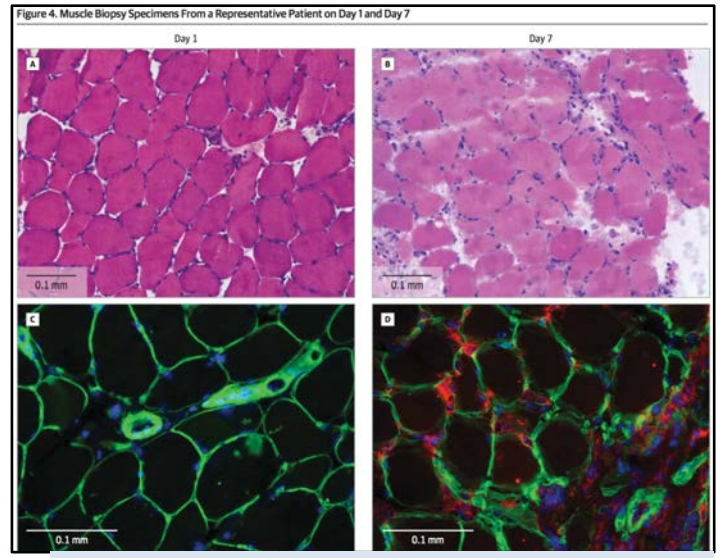
Herridge, NEJM 2011

Acute Skeletal Muscle Wasting in Critical Illness

Puthucheary, JAMA 2013



Balance protéique négative…



Destruction musculaire précoce

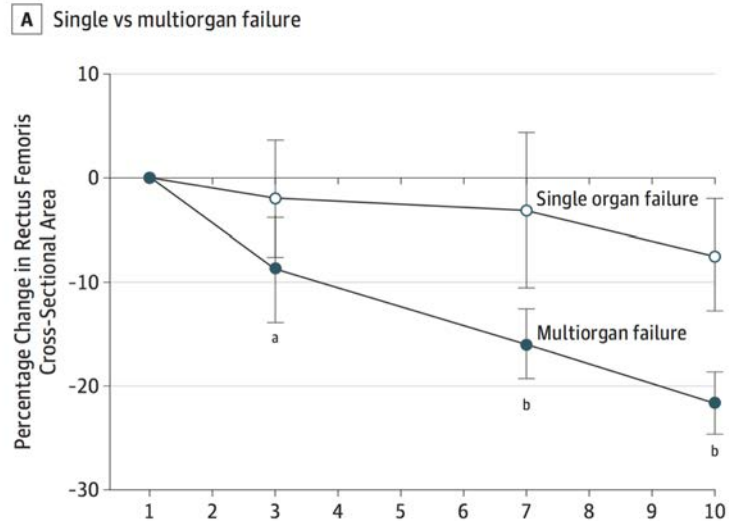
Faiblesse musculaire acquise en réanimation

=

- Sevrage retardé de la VM
- Durées de séjour accrues
- Surmortalité à court terme et à un an proportionnelle à l'atteinte initiale

Hermans, Am J Respir Crit Care Med 2014

Figure 5. Measurements of Muscle Wasting During Critical Illness by Organ Failure



Objectifs de la réanimation concernant le patient

- **Sauver la vie**
- **Favoriser la récupération fonctionnelle la plus rapide possible et préserver la qualité de vie**

Are we creating survivors. . .or victims in critical care? Delivering targeted nutrition to improve outcomes

Paul E. Wischmeyer

Recommandations conférence d'experts

Recommandations des experts de la Société de Réanimation de Langue Française

Nutrition entérale en réanimation

Experts recommendations of the Société de Réanimation de Langue Française

Enteral nutrition in critical care

M. Thuong *, S. Leteurtre

Service de réanimation polyvalente, hôpital Delafontaine, 2, rue du Docteur-Delafontaine, 93205 Saint-Denis, France

Reçu et accepté le 24 avril 2003

L'apport énergétique quotidien usuel est de 25 à 35 kcal/kg (calories totales, apport protéique inclus), chez l'adulte. (…) [*A.fort*].

• En période aiguë, l'objectif quantitatif à atteindre et à ne pas dépasser est la couverture de 100 % de la dépense énergétique, soit estimée, soit mesurée ou calculée [*A.faible*].

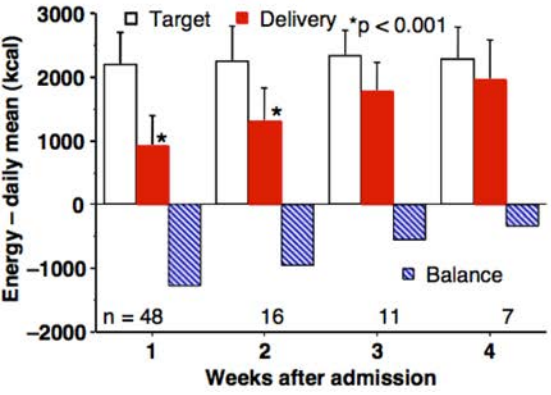
• Chez l'adulte, quel que soit l'état d'hypercatabolisme, il est rare d'avoir à dépasser, en phase aiguë, un apport énergétique supérieur à 35 kcal/kg/j. Des niveaux supérieurs à 35 kcal kg–1 j–1 peuvent être requis en phase de récupération (ou « post-agressive ») [*A.fort*].

Déficit calorique = risque accru de complications

Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients

Stéphane Villet[a], René L. Chiolero[b], Marc D. Bollmann[b], Jean-Pierre Revelly[b], Marie-Christine Cayeux RN[b], Jacques Delarue[c], Mette M. Berger[b,*]

Clinical Nutrition (2005) 24, 502–509



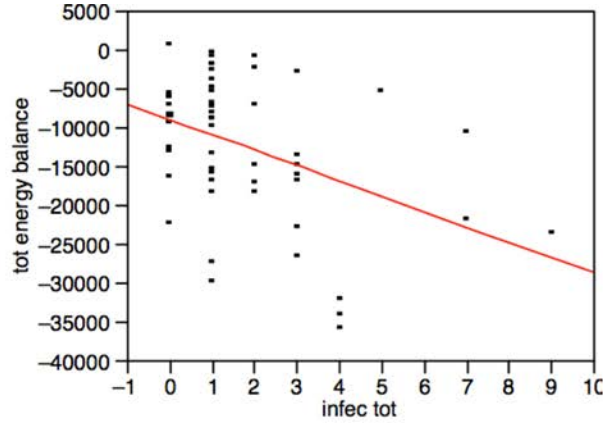


Table 4 Relationship between complications and cumulated energy deficit by regression analysis.

Variables	*F*	*P*
Length of stay	25.18	0.0001
Complications	15.15	0.0003
Infections	9.14	0.0042
Days on antibiotics	17.48	0.0003
Start of nutrition	17.17	0.0002
Days of mechanical ventilation	17.12	0.0002

Elke et al. Critical Care 2014, 18:R29
http://ccforum.com/content/18/1/R29

CRITICAL CARE

RESEARCH Open Access

Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database

Gunnar Elke[1], Miao Wang[2], Norbert Weiler[1], Andrew G Day[2] and Daren K Heyland[2*]

2270 patients ventilés
Voie entérale exclusive (début <48h après admission)
Sepsis
Apports prescrits : 1758 kcal/j (24 kcal/kg/j)
Apports reçus : 1057 kcal/j (14.5 kcal/kg/j) (61%)
Mortalité J60: 31%

Table 3 Relationship between enteral nutrition and 60-day mortality

	Unadjusted			Adjusted		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
A: Total study population (n = 2,270)						
Energy intake						
Per 1,000 kcal	0.51	(0.41-0.64)	<0.001	0.61	(0.48-0.77)	<0.001
Protein intake						
Per 30 gram	0.70	(0.61-0.80)	<0.001	0.76	(0.65-0.87)	<0.001
B: Sensitivity analysis (n = 1,560)						
Energy intake						
Per 1,000 kcal	0.56	(0.44-0.71)	<0.001	0.61	(0.48-0.79)	<0.001
Protein intake						
Per 30 gram	0.72	(0.62-0.83)	<0.001	0.75	(0.64-0.87)	<0.001

Odds of 60-day mortality per increase of 1,000 kilocalories (top) and 30 gram of protein (bottom) received per day both unadjusted and adjusting for nutrition days, BMI, age, and APACHE II score. Panel A shows data in the total study population and Panel B the data for the patients included in the sensitivity analysis who received enteral nutrition at least 7 days in the ICU and who were alive and evaluable for subsequent outcome. CI, confidence interval; kcal, kilocalories.

Europe 2006

ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Intensive care ☆

K.G. Kreymann[a,*], M.M. Berger[b], N.E.P. Deutz[c], M. Hiesmayr[d], P. Jolliet[e], G. Kazandjiev[f], G. Nitenberg[g], G. van den Berghe[h], J. Wernerman[i], DGEM: ☆☆ C. Ebner, W. Hartl, C. Heymann, C. Spies

8. Under what conditions should PN be added to EN?

In patients who tolerate EN and can be fed approximately to the target values no additional **PN should be given** (A).

In patients who cannot be fed sufficient enterally the deficit should be supplemented parenterally (C). In patients intolerant to EN, careful parenteral nutrition may be proposed at a level equal to but not exceeding the nutritional needs of the patient (C). Overfeeding should be avoided.

USA 2009

Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary*

Robert G. Martindale, MD, PhD; Stephen A. McClave, MD; Vincent W. Vanek, MD; Mary McCarthy, RN, PhD; Pamela Roberts, MD; Beth Taylor, RD; Juan B. Ochoa, MD; Lena Napolitano, MD; Gail Cresci, RD; American College of Critical Care Medicine; and the A.S.P.E.N. Board of Directors

8. When to Use PN

If early EN is not feasible or available over the first 7 days following admission to the ICU, **no nutrition support therapy (standard therapy) should be provided** (Grade C). In the patient who was previously healthy before critical illness with no evidence of protein calorie malnutrition, use of PN should be reserved and initiated only after the first 7 days of hospitalization (when EN is not available) (Grade E).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Adults

Michael P. Casaer, M.D., Dieter Mesotten, M.D., Ph.D., Greet Hermans, M.D., Ph.D., Pieter J. Wouters, R.N., M.Sc., Miet Schetz, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Sophie Van Cromphaut, M.D., Ph.D., Catherine Ingels, M.D., Philippe Meersseman, M.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D., Yves Debaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D., Aime Van Assche, M.D., Simon Vanderheyden, B.Sc., Alexander Wilmer, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.*

N Engl J Med 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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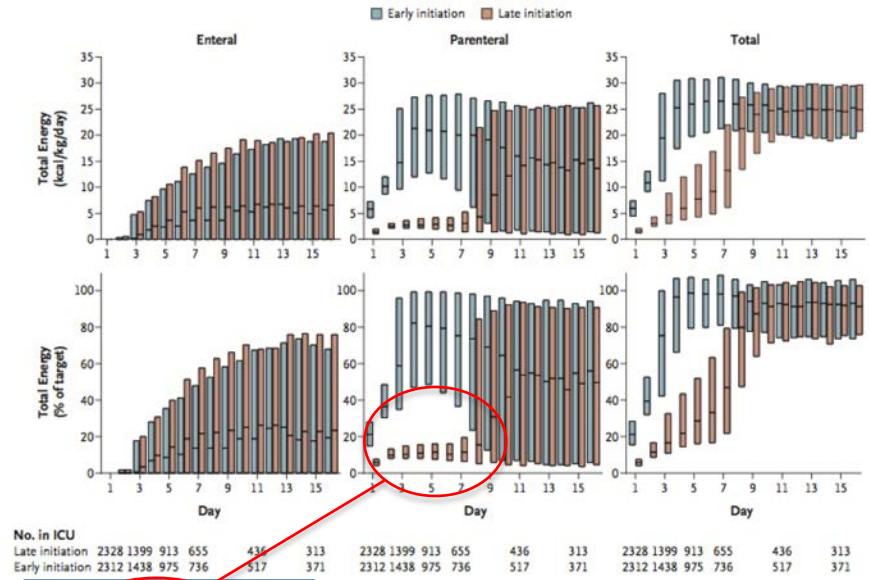
N Engl J Med 2011

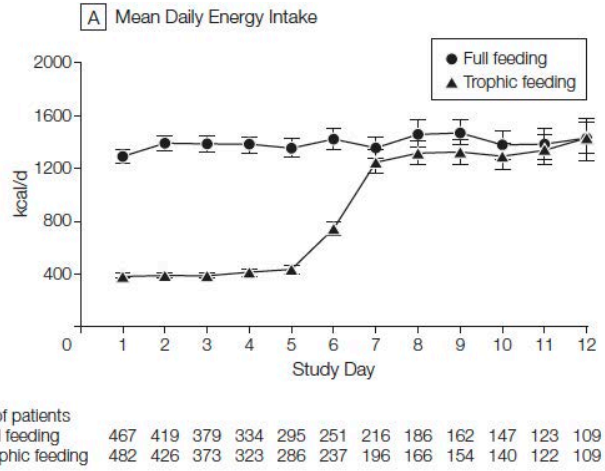


Primary outcome	Late PN	Early PN	
Duration of stay in ICU§			
Median (interquartile range) — days	3 (2–7)	4 (2–9)	0.02
Duration >3 days — no. (%)	1117 (48.0)	1185 (51.3)	0.02
Hazard ratio (95% CI) for time to discharge alive from ICU	1.06 (1.00–1.13)		0.04
Secondary outcome			
New infection — no. (%)			
Any	531 (22.8)	605 (26.2)	0.008
Airway or lung	381 (16.4)	447 (19.3)	0.009
Bloodstream	142 (6.1)	174 (7.5)	0.05
Wound	64 (2.7)	98 (4.2)	0.006
Urinary tract	60 (2.6)	72 (3.1)	0.28

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

The EDEN Randomized Trial

Rice, JAMA 2012



400 kcal/j = 1400 kcal/j pendant les 6 1ers jours

Outcome	Trophic Feeding (n = 508)	Full Feeding (n = 492)	*P* Value
Ventilator-free days, No. (95% CI)	14.9 (13.9-15.8)	15.0 (14.1-15.9)	.89
Failure-free days, No. (95% CI)			
Cardiovascular	19.1 (18.2-20.0)	18.9 (18.1-19.8)	.75
Renal	20.0 (19.0-20/9)	19.4 (18.4-20.5)	.43
Hepatic	22.0 (21.2-22.9)	22.6 (21.8-23.5)	.37
Coagulation	22.3 (21.4-23.1)	23.1 (22.3-23.9)	.16
ICU-free days, No. (95% CI)	14.4 (13.5-15.3)	14.7 (13.8-15.6)	.67
60-d mortality, No. (%) [95% CI]	118 (23.2) [19.6-26.9]	109 (22.2) [18.5-25.8]	.77
Development of infections, No. (%) [95% CI]			
VAP	37 (7.3) [5.0-9.5]	33 (6.7) [4.5-8.9]	.72
Clostridium difficile colitis	15 (3.0) [1.5-4.4]	13 (2.6) [1.2-4.1]	.77
Bacteremia, No. (%)	59 (11.6) [8.8-14.4]	46 (9.3) [6.8-11.9]	.24

Physical and Cognitive Performance of Patients with Acute Lung Injury 1 Year after Initial Trophic versus Full Enteral Feeding

EDEN Trial Follow-up

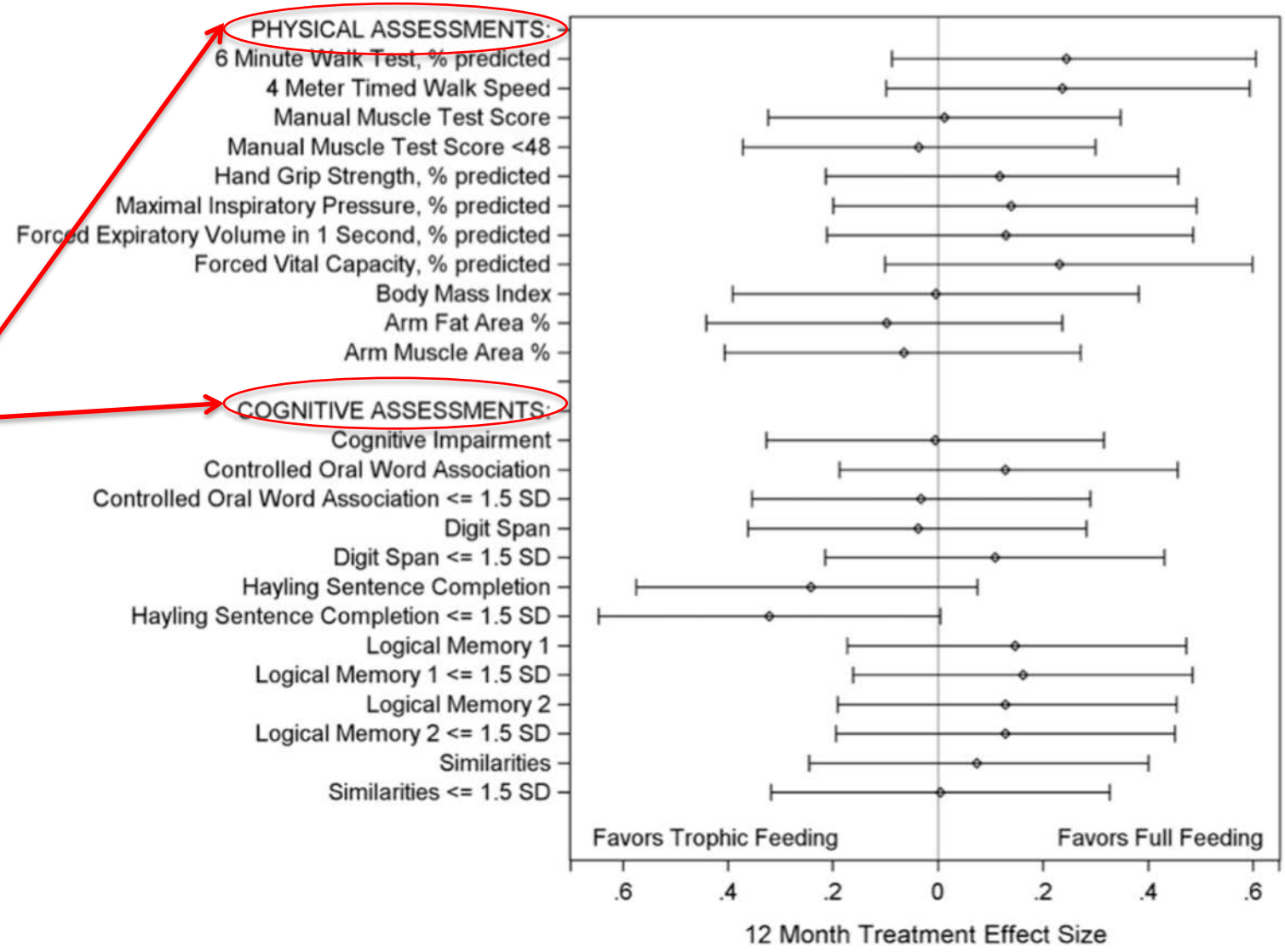
Needham, Am J Respir Crit Care Med 2013

Un an après:

400 kcal/j

=

1400 kcal/j



The NEW ENGLAND JOURNAL of MEDICINE

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

Arabi, N Engl J Med 2015

- 894 patients
- Mechanical ventilation: 97%
- Vasoactive drug: 55%

Underfeeding: 40-60% of caloric requirements

Standard: 70-100%

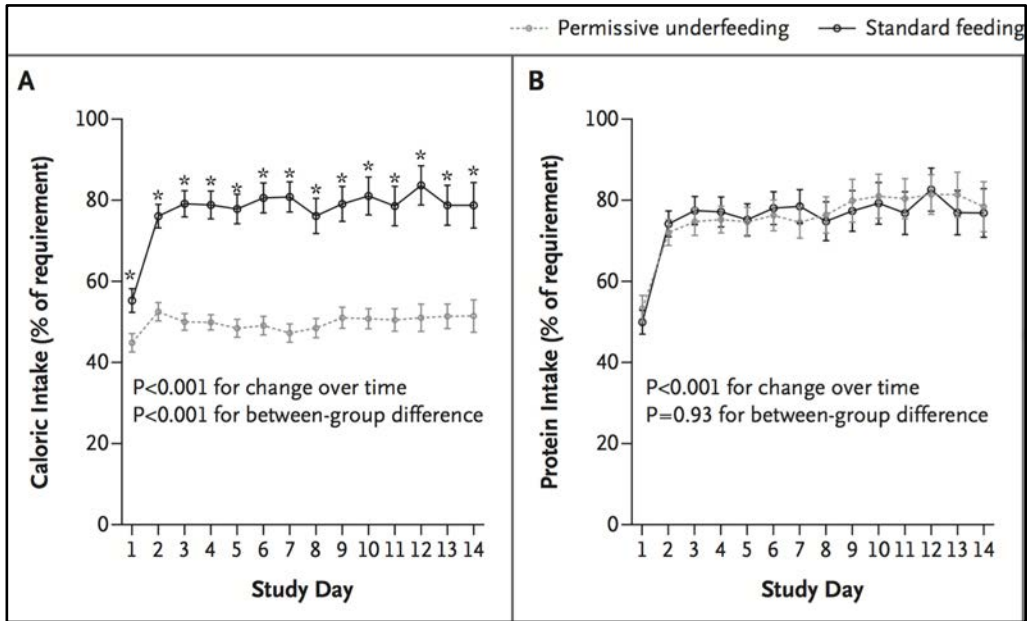
Underfeeding: 835 kcal/d (46% of caloric requirements)

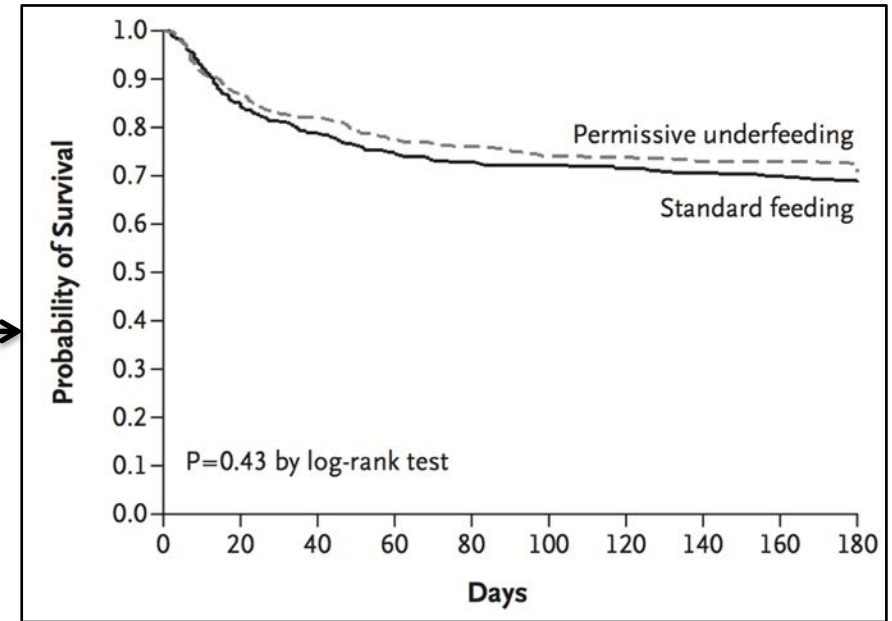
Standard: 1826 kcal/d (71%)

Day-90 mortaliry

Underfeeding: 27.2%

Standard: 28.9%

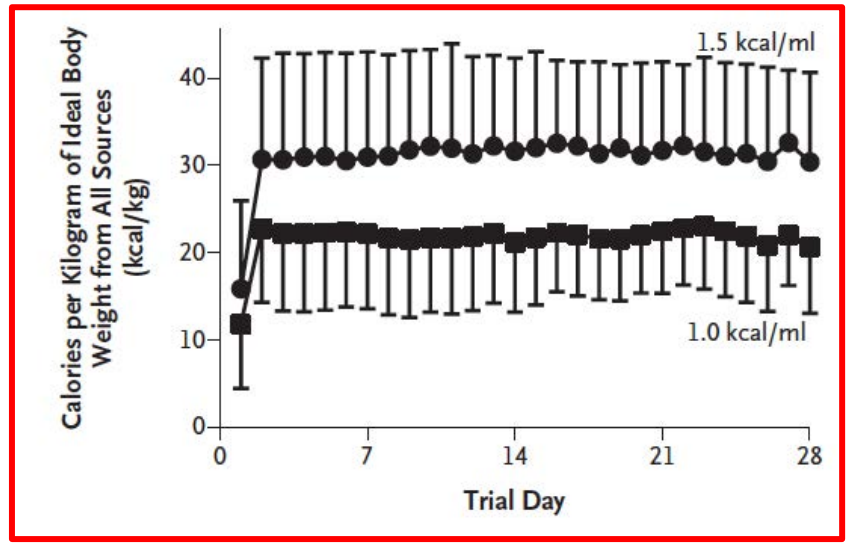




ORIGINAL ARTICLE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*



3957 patients ventilés 24 vs 36 kcal/kg/j

Apports caloriques 1863 +/- 478 kcal/j vs1262 +/- 313 kcal/j
Protéines:1.09 +/- 0.22 g/kg/j vs 1.08 +/- 0.23 g/kg/j

Aucun impact sur:

- **Survie à J90 (CJP)**
- **Défaillances vitales**
- **Infections**
- **Durée de séjour**

ORIGINAL ARTICLE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

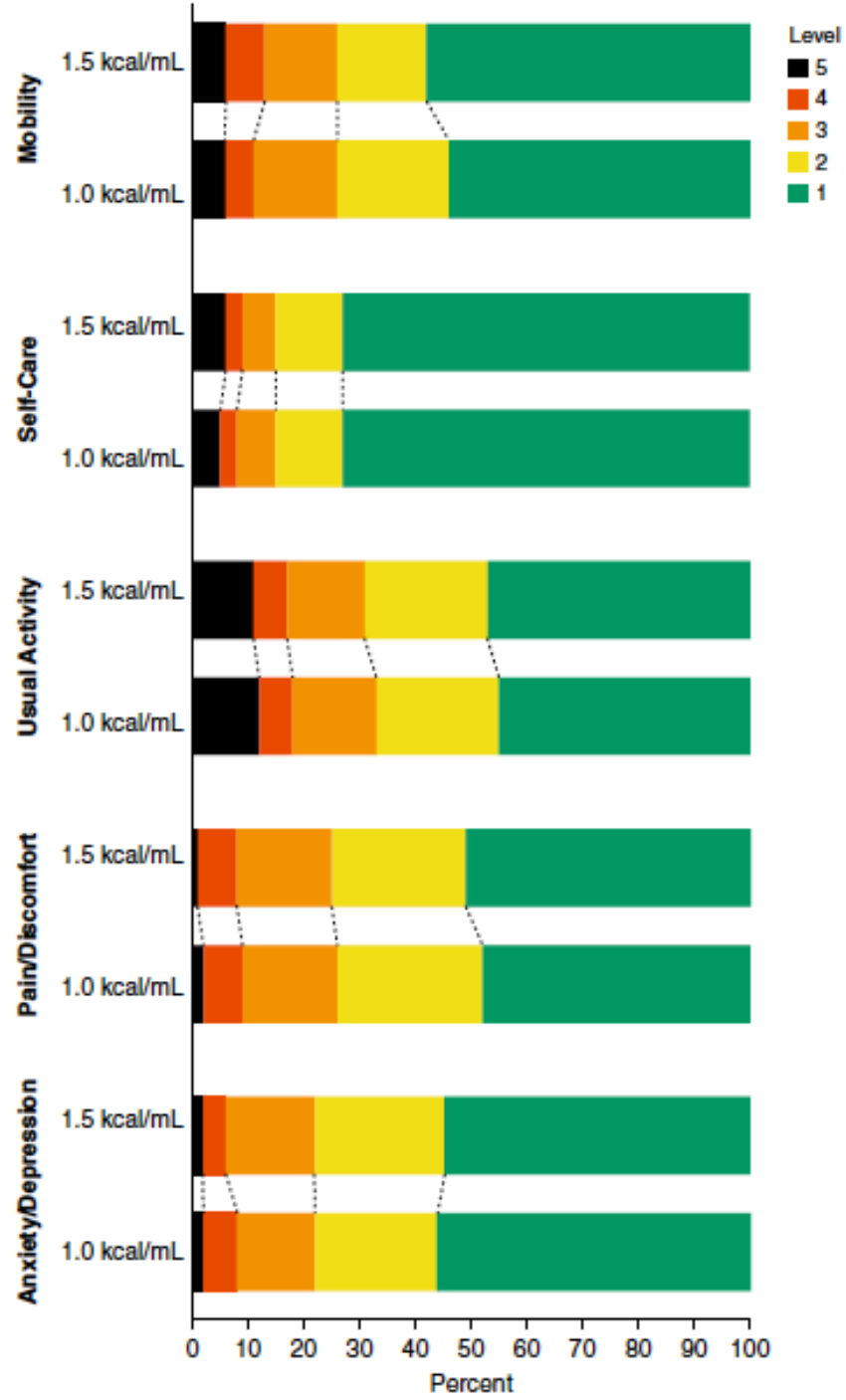
3957 patients
1 vs 1,5 kcal/kg/j

Outcomes Six Months after Delivering 100% or 70% of Enteral Calorie Requirements during Critical Illness (TARGET)

A Randomized Controlled Trial

Adam M. Deane[1], Lorraine Little[2], Rinaldo Bellomo[3], Marianne J. Chapman[4], Andrew R. Davies[2], Suzie Ferrie[5], Michael Horowitz[6], Sally Hurford[7], Kylie Lange[6], Edward Litton[8], Diane Mackle[7], Stephanie O'Connor[4], Jane Parker[2], Sandra L. Peake[4], Jeffrey J. Presneill[1], Emma J. Ridley[2], Vanessa Singh[2], Frank van Haren[9], Patricia Williams[4], Paul Young[7], and Theodore J. Iwashyna[10]; on behalf of the TARGET Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Aucun impact sur qualité de vie à 6 mois

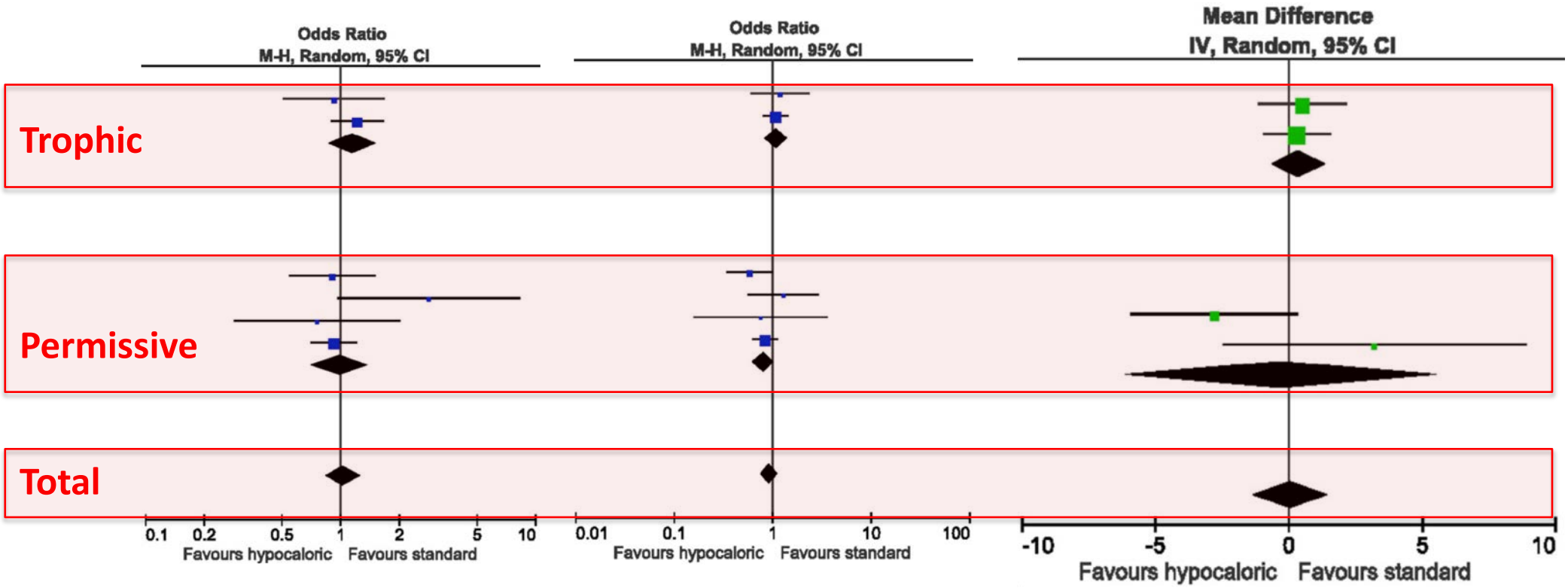


Intensive Care Med (2016) 42:316–323
DOI 10.1007/s00134-015-4131-4

SYSTEMATIC REVIEW

Paul E. Marik
Michael H. Hooper

Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis



Hospital acquired infections **Hospital mortality** **Hospital LOS**

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

Beth E. Taylor, RD, DCN;[1] Stephen A. McClave, MD;[2] Robert G. Martindale, MD, PhD;[3] Malissa M. Warren, RD;[4] Debbie R. Johnson, RN, MS;[5] Carol Braunschweig, RD, PhD;[6] Mary S. McCarthy, RN, PhD;[7] Evangelia Davanos, PharmD;[8] Todd W. Rice, MD, MSc;[9] Gail A. Cresci, RD, PhD;[10] Jane M. Gervasio, PharmD;[11] Gordon S. Sacks, PharmD;[12] Pamela R. Roberts, MD;[13] Charlene Compher, RD, PhD;[14] and the Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition

Crit Care Med 2016

25-30 Kcal/kg/j (Proteins: 1,2-2g/kg/j)

Efforts to provide > 80% of estimated or calculated goal energy and protein within 48–72 hours should be made in order to achieve the clinical benefit of EN over the first week of hospitalization.

ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a, *], Annika Reintam Blaser [b, c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

Clin Nutrition 2018

Definition

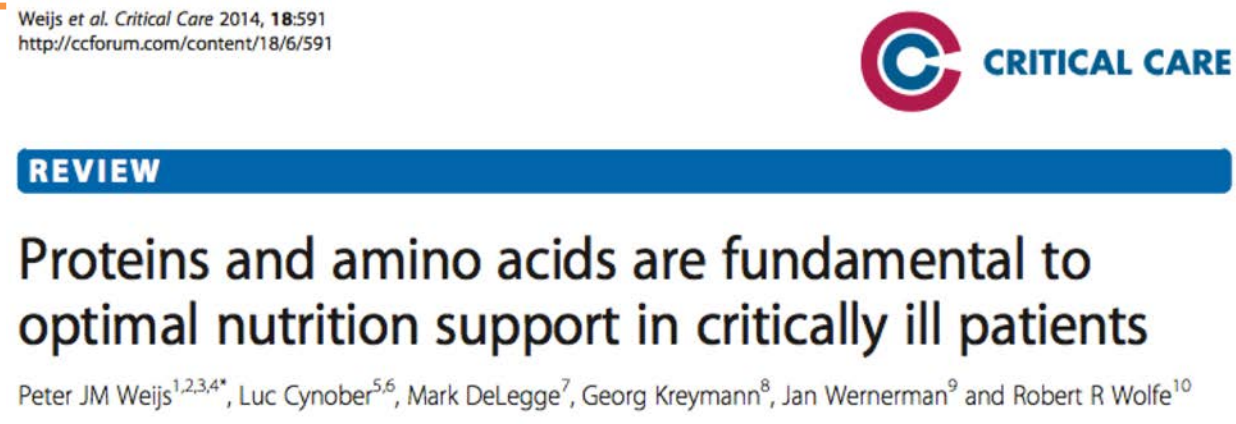
Hypocaloric or underfeeding is an energy administration below 70% of the defined target.

Recommendation 19

If predictive equations are used to estimate the energy need, hypocaloric nutrition (below 70% estimated needs) should be preferred over isocaloric nutrition for the first week of ICU stay. (Grade of recommendation B)

Apports protéiques

- **Les besoins en énergie et en protéines** peuvent ne pas évoluer de manière parallèle et **doivent être considérés séparément.**
- Chez le patient de réanimation**, les protéines semblent être le macronutriment le plus important** pour la restauration musculaire, la cicatrisation des plaies et le soutien de la fonction immunitaire.


Weijs *et al. Critical Care* 2014, **18**:591
http://ccforum.com/content/18/6/591

CRITICAL CARE

REVIEW

Proteins and amino acids are fundamental to optimal nutrition support in critically ill patients

Peter JM Weijs[1,2,3,4*], Luc Cynober[5,6], Mark DeLegge[7], Georg Kreymann[8], Jan Wernerman[9] and Robert R Wolfe[10]

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Acute Skeletal Muscle Wasting in Critical Illness

Puthucheary JAMA 2013

« Unexpectedly, higher protein delivery in the first week was associated with greater muscle wasting ».

Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial

Hermans Lancet Respir Med 2013

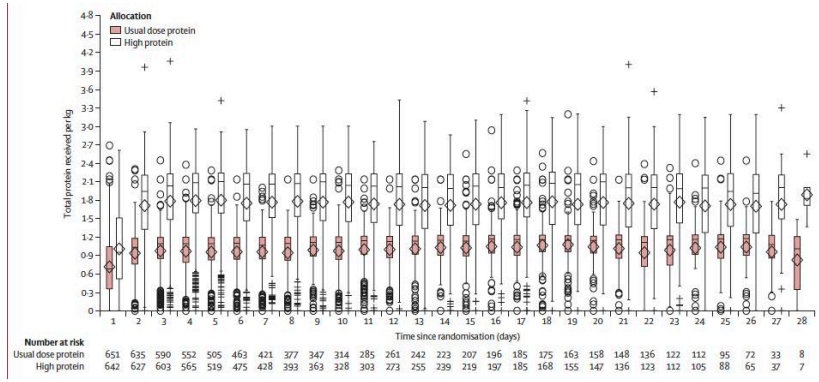
Le délai de récupération de l'atteinte musculaire est significativement plus long si l'on compense le déficit d'apports en macronutriments avant J7.

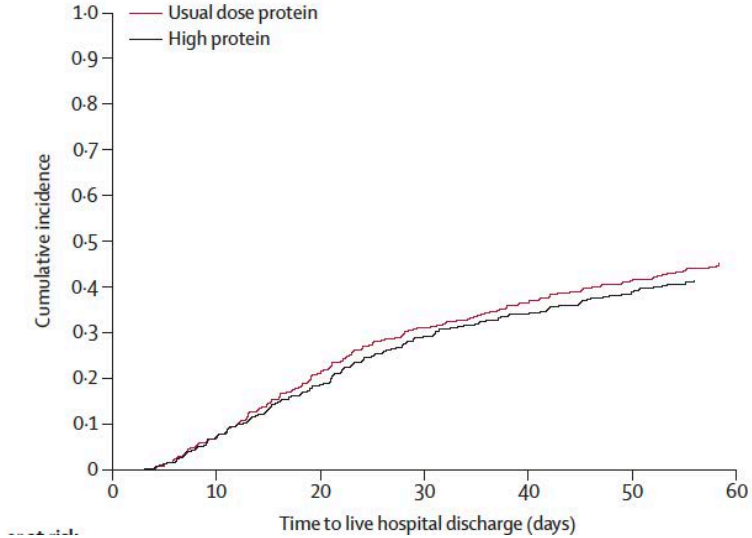
The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C González, Kevin O'Reilly, Racquel Regala, Courtney Wedemire, Miguel Ibarra-Estrada, Christian Stoppe, Luis Ortiz-Reyes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

Lancet, 2023

- Proteines:
  - Prescribed: 2·2 vs 1·2 g/kg per day
  - Received: 1·6 vs 0·9 g/kg per day
- Calories received: 14·7 *vs* 13·2 kcal/kg per day





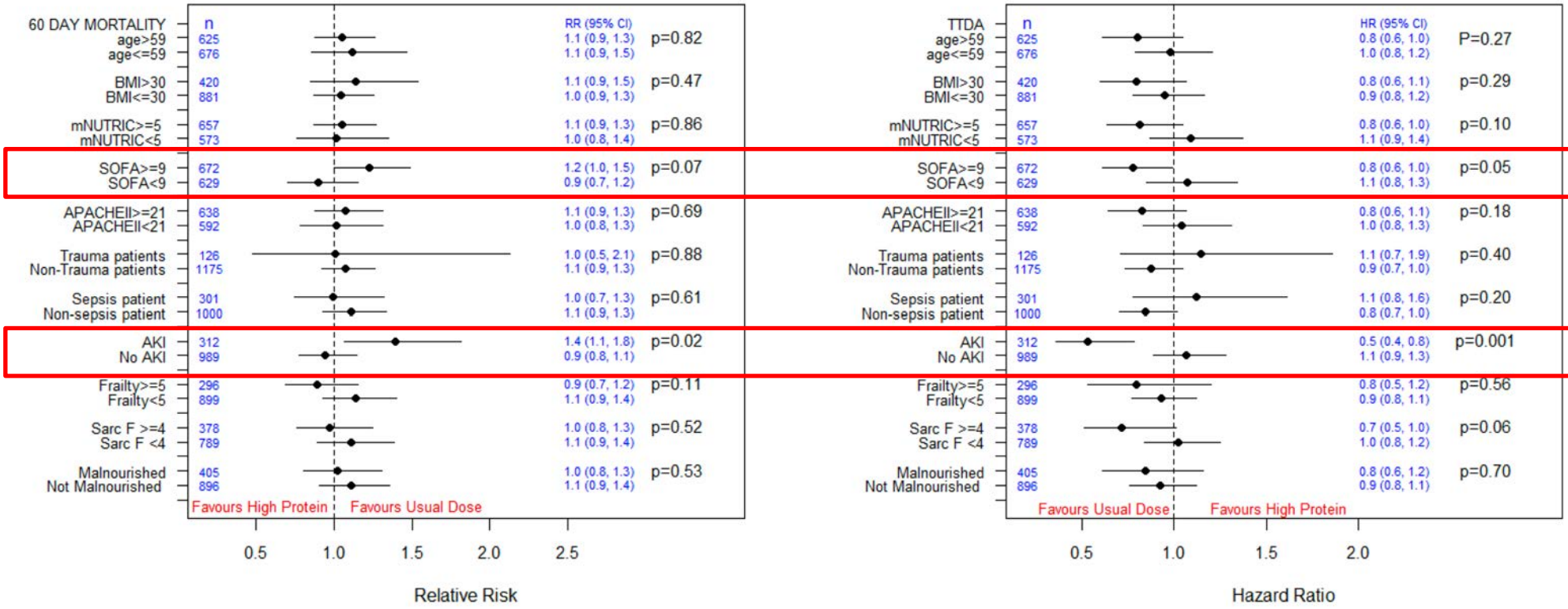
Time-to-discharge-alive (primary outcome)
HR 0·91, 95% CI 0·77–1·07; p=0·27.

No difference:
- Mortality (34.6 vs 32.1%)
- Duration of MV
- Length of stay

The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C González, Kevin O'Reilly, Racquel Regala, Courtney Wedemire, Miguel Ibarra-Estrada, Christian Stoppe, Luis Ortiz-Reyes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

Lancet, 2023



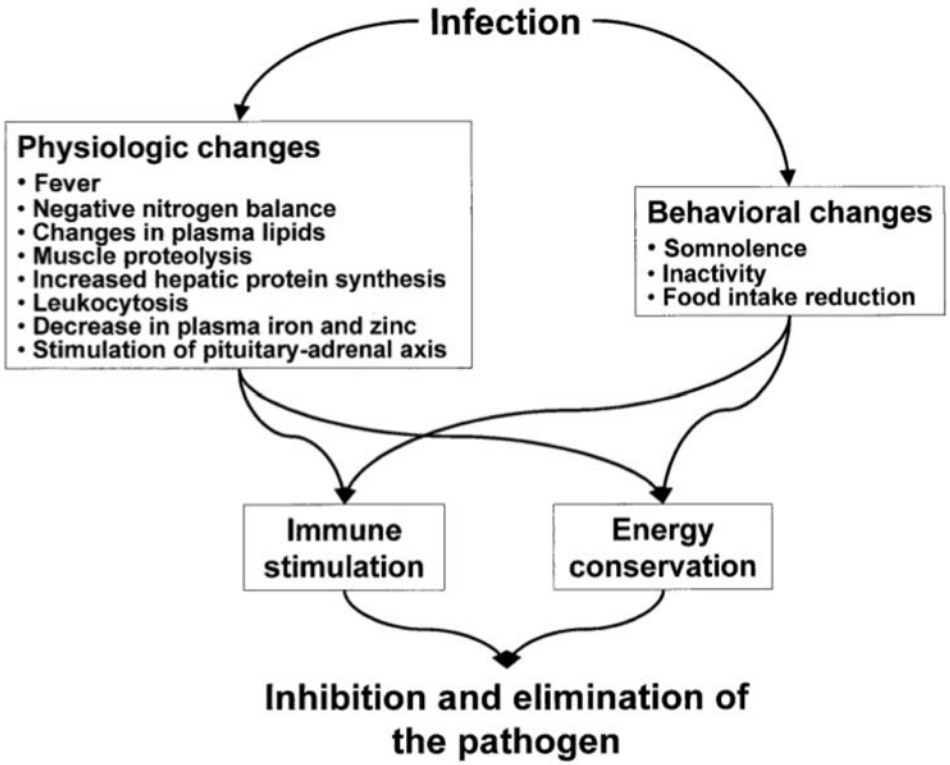
La supplémentation protéique aggrave les patients les plus graves et ceux ptrésentant une insufsisance rénale aigue

Anorexia of Infection: Current Prospects

Wolfgang Langhans, DVM

From the Institute of Animal Sciences, Swiss Federal Institute of Technology, Zurich, Switzerland

Nutrition 2000



Anorexia during infection= part of the "acute phase response":

- behavioral changes
  → the need to search for food
  → **saving energy**
- Decreased availability of food-derived micronutrients
  → **Reduced the growth of pathogenic microorganisms**.
- **limiting the potentially detrimental metabolic effects** of the acute phase response.

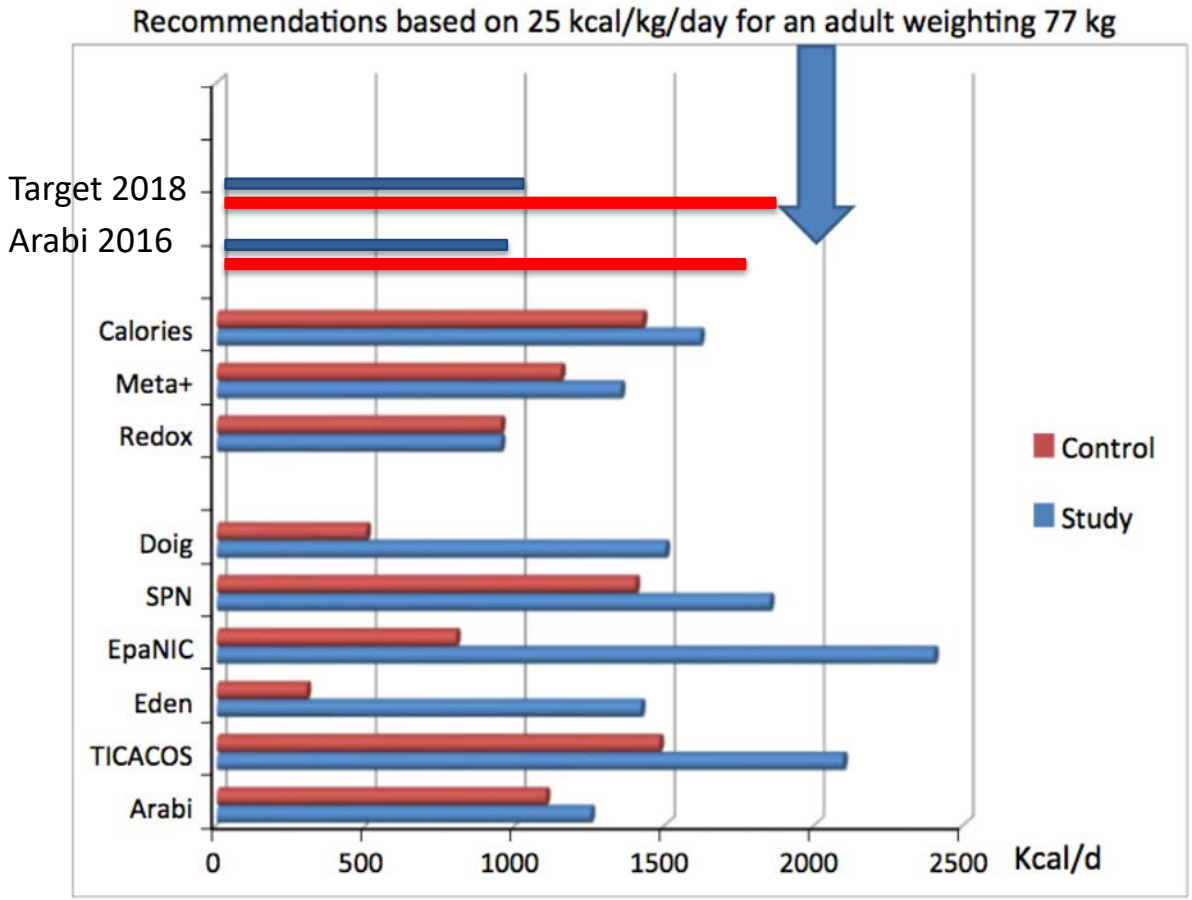
Problem = long lasting anorexia
→ delays recovery

Intensive Care Med (2015) 41:154–156
DOI 10.1007/s00134-014-3537-8

EDITORIAL

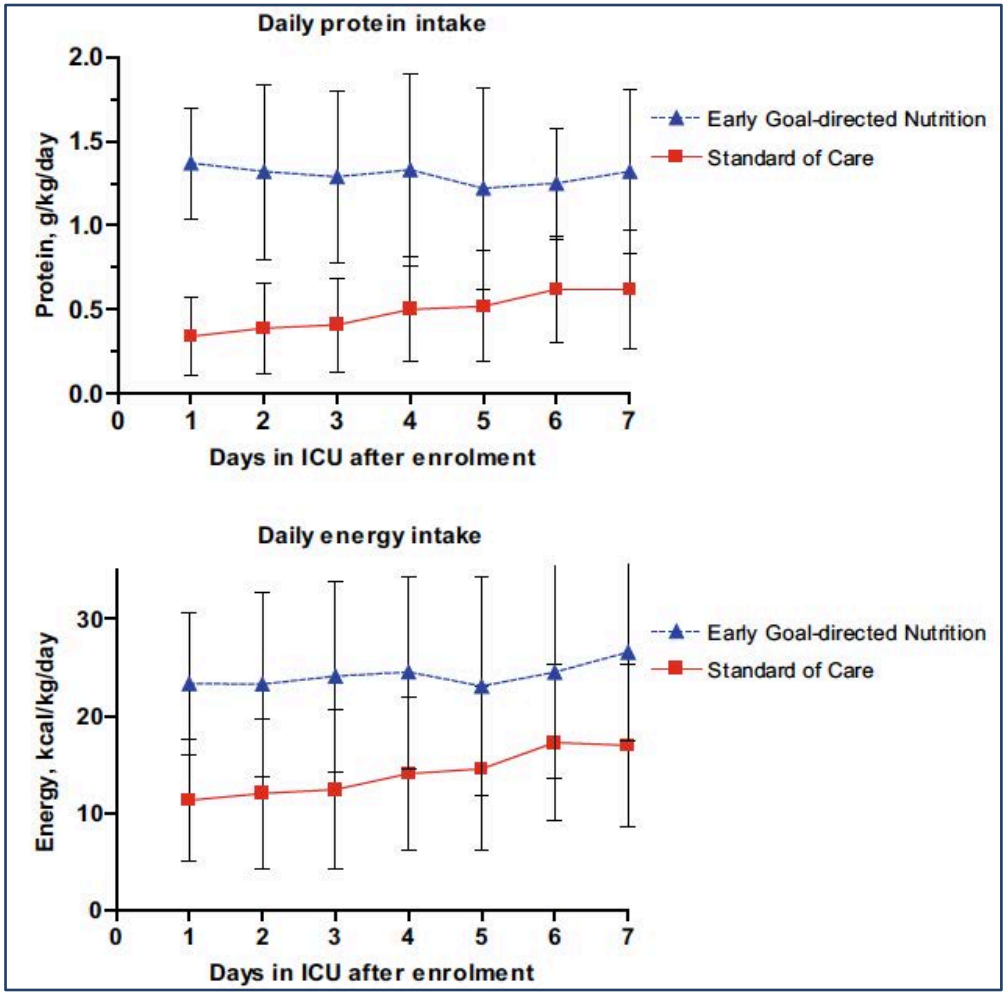
Pierre Singer
Jonathan Cohen

Nutrition in the ICU: proof of the pudding is in the tasting



Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial

Allingstrup Intensive Care Med 2017



- Standard: 25kcal/kg/j (NE)
- Intervention: calorimétrie indirecte et urée urinaire(/24h) (au moins 1,5g/kg/j)

199 patients traités par MV> 72 heures

→Aucun impact sur:

- **Qualité de vie (PCS score à 6 mois)**

- **Mortalité**
- **Infections**
- **Durée de séjour**
- **Nouvelle défaillance vitale**
- **Traitement de suppléance (EER, amine)**

How much « less » calories and proteins is more for the critically ill?

Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3)

Jean Reignier, Gaetan Plantefeve, Jean-Paul Mira, Laurent Argaud, Pierre Asfar, Nadia Aissaoui, Julio Badie, Nicolae-Vlad Botoc, Laurent Brisard, Hoang-Nam Bui, Delphine Chatellier, Louis Chauvelot, Alain Combes, Christophe Cracco, Michael Darmon, Vincent Das, Matthieu Debarre, Agathe Delbove, Jérôme Devaquet, Louis-Marie Dumont, Olivier Gontier, Samuel Groyer, Laurent Guérin, Bertrand Guidet, Yannick Hourmant, Samir Jaber, Fabien Lambiotte, Christophe Leroy, Philippe Letocart, Benjamin Madeux, Julien Maizel, Olivier Martinet, Frédéric Martino, Virginie Maxime, Emmanuelle Mercier, Mai-Anh Nay, Saad Nseir, Johanna Oziel, Walter Picard, Gael Piton, Jean-Pierre Quenot, Florian Reizine, Anne Renault, Jack Richecoeur, Jean-Philippe Rigaud, Francis Schneider, Daniel Silva, Michel Sirodot, Bertrand Souweine, Fabienne Tamion, Nicolas Terzi, Didier Thévenin, Guillaume Thiery, Nathalie Thieulot-Rolin, Jean-Francois Timsit, Francois Tinturier, Patrice Tirot, Thierry Vanderlinden, Isabelle Vinatier, Christophe Vinsonneau, Sebastian Voicu, Jean-Baptiste Lascarrou, Amélie Le Gouge, for the NUTRIREA-3 Trial Investigators and the Clinical Research in Intensive Care and Sepsis (CRICS-TRIGGERSEP) Group

THE LANCET
Respiratory Medicine

61 participating ICUs in France

Supported by a grant of the French Ministry of Health

61 centres participants

Gaetan Plantefeve; Jean-Pierre Quenot; Djillali Annane; Laurent Argaud; Pierre Asfar; Nadia Aissaoui-Balanant; Julio Badie; Nicolae-Vlad Botoc; Laurent Brisard; Hoang-Nam Bui; Delphine Chatellier; Louis Chauvelot; Alain Combes; Michael Darmon; Vincent Das; Matthieu Debarre,; Agathe Delbove; Jérôme Devaquet; Louis-Marie Dumont; Olivier Gontier; Samuel Groyer; Laurent Guérin; Bertrand Guidet; Yannick Hourmant; Samir Jaber; Fabien Lambiotte; Christophe Leroy; Philippe Letocart; Benjamin Madeux; Julien Maizel; Olivier Martinet; Frédéric Martino; Emmanuelle Mercier; Jean-Paul Mira; Mai-Anh Nay; Saad Nseir; Johanna Oziel; Walter Picard; Gael Piton; Florian Reizine; Anne Renault; Jack Richecoeur; Jean-Philippe Rigaud; Francis Schneider; David Schnell; Daniel Silva; Michel Sirodot; Bertrand Souweine; Fabienne Tamion; Nicolas Terzi; Didier Thévenin; Guillaume Thiery; Nathalie Thieulot-Rolin; Jean-Francois Timsit; Francois Tinturier; Patrice Tirot; Thierry Vanderlinden; Isabelle Vinatier; Christophe Vinsonneau; Sebastian Voicu

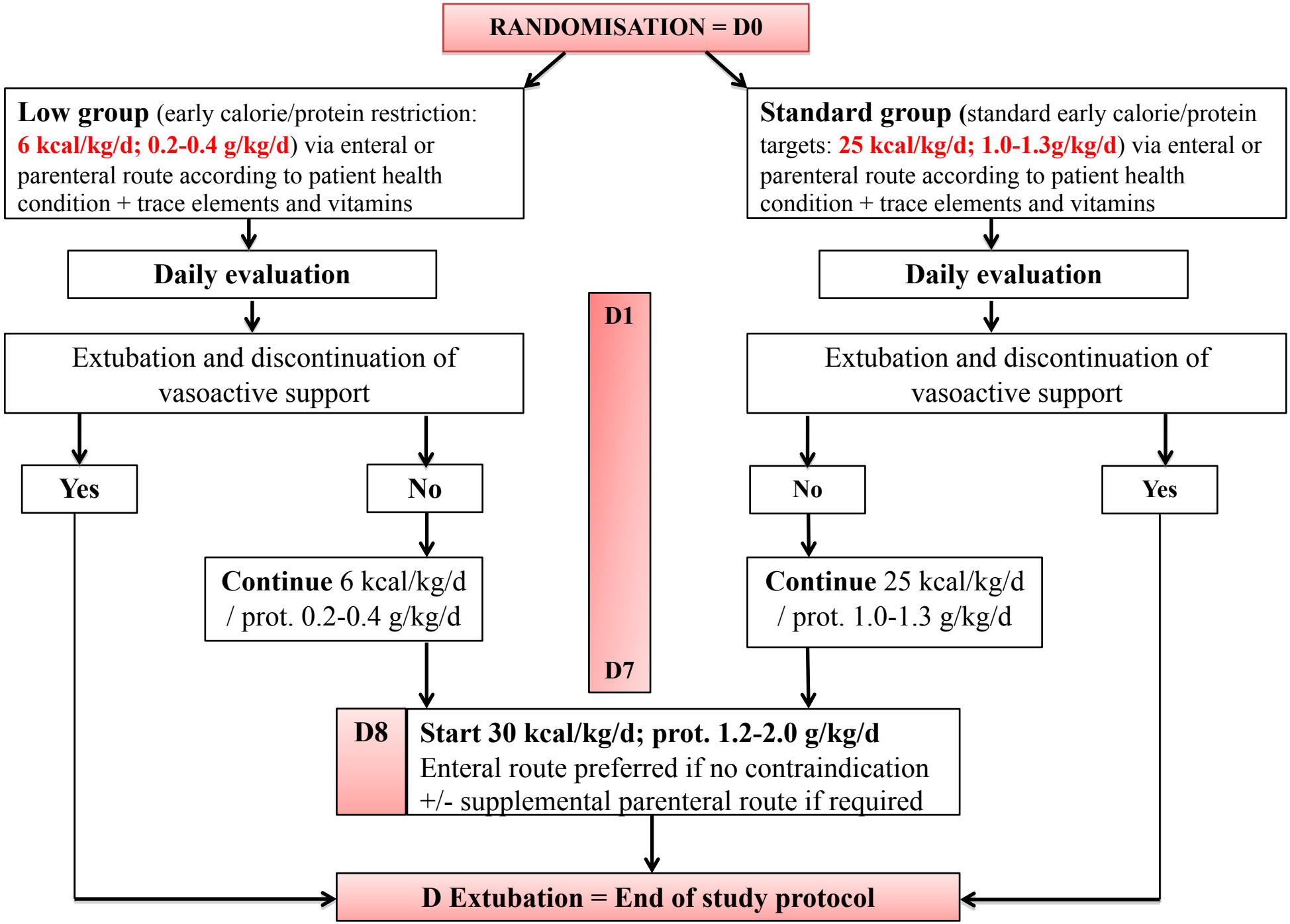
Patients

–Invasive **mechanical ventilation started in the ICU within the past 24 h**, or started before ICU admission with ICU admission within the past 24 h, for an expected duration of at least 48 hours after inclusion

–Treatment with a **vasoactive agent for shock** (adrenaline, dobutamine, or noradrenaline)

–**Nutritional support expected to be started within 24 h after intubation** or within 24 h after ICU admission when mechanical ventilation was started before ICU admission

–Age older than 18 years


RANDOMISATION = D0
Low group (early calorie/protein restriction: 6 kcal/kg/d; 0.2-0.4 g/kg/d) via enteral or parenteral route according to patient health condition + trace elements and vitamins
Standard group (standard early calorie/protein targets: 25 kcal/kg/d; 1.0-1.3g/kg/d) via enteral or parenteral route according to patient health condition + trace elements and vitamins
Daily evaluation
Daily evaluation
D1
D7
Extubation and discontinuation of vasoactive support
Extubation and discontinuation of vasoactive support
Yes
No
No
Yes
Continue 6 kcal/kg/d / prot. 0.2-0.4 g/kg/d
Continue 25 kcal/kg/d / prot. 1.0-1.3 g/kg/d
D8
Start 30 kcal/kg/d; prot. 1.2-2.0 g/kg/d
Enteral route preferred if no contraindication
+/- supplemental parenteral route if required
D Extubation = End of study protocol

Primary end-points

Two alternative primary end-points will be evaluated:

- **All-cause mortality by day 90 (D90)**.
- **Time to discharge alive from the ICU.**

Predefined criteria

The trial will be considered positive if significant between-group differences are found for one or both alternative primary endpoints.

Time to discharge alive from the ICU.

- The time of ICU discharge to a regular ward may be affected by the availability of beds on regular wards, which may induce bias.
- A patient will be considered ready for ICU discharge by the bedside physicians as soon as all predefined clinical conditions for ICU discharge are fulfilled regardless of ward-bed availability:

  ❑*No longer in need for, or at risk of, invasive mechanical ventilation*

  AND

  ❑*No longer in need for, or at risk of, vasoactive support*

  AND

  ❑*No agitation or altered consciousness requiring close monitoring and management*

  AND

  ❑*No severe acute metabolic or hematologic disorder requiring close monitoring and management*

- Checked daily in all patients weaned from invasive MV and vasoactive drugs.
- A similar strategy regarding this endpoint used previously in studies on nutrition in the ICU.

Casaer MP, Hermans G, Wilmer A, Van den Berghe G, (2011) 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 12: 21

Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Casaer MP, Garcia Guerra G, Hanot J, Joffe A, Tibboel D, Joosten K, Van den Berghe G, (2016) Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 374: 1111-1122

Calcul d’effectif

- Assuming a 43% day-90 mortality rate in the Standard group and a 5% absolute decrease in day-90 mortality (to 38%) in the Low group, with the alpha risk set at 4.9% (as two interim analyses are planned) and the beta risk at 20%, 1522 patients are needed in each group, i.e., a theoretical total of **3044 patients**.
- This sample size will provide 94% power to detect a 1.5-day difference in time to ICU discharge alive between the two groups (mean, 14.5 days in the control group versus 13.0 days in the experimental group).

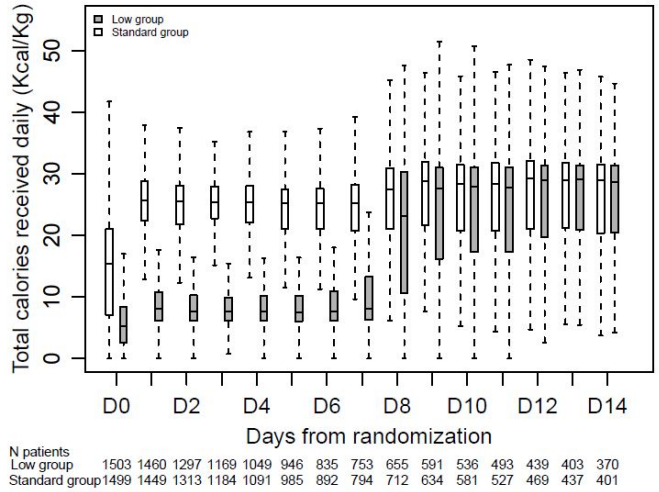
Caractéristiques démographiques

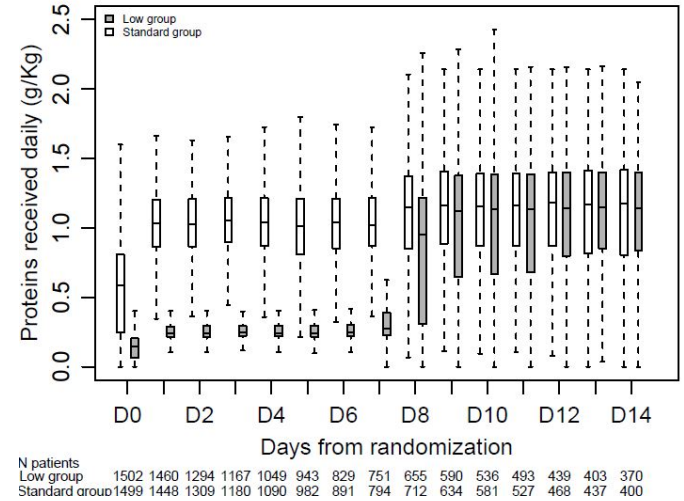
	Low group (n=1521)	Standard group (n=1515)
Age (y)	66 ± 13	66 ± 13
Males, n (%)	1010 (66.4)	1026 (67.7)
Weight (kg)	76.5 [65.0 ; 89.5]	77.0 [65.3 ; 90.0]
BMI (kg/m²)	26.7 [23.0 ; 31.1]	27.0 [23.0 ; 31.5]
Preexisting malnutrition, n (%)		
No malnutrition	1362 (90.0)	1379 (91.2)
Moderate	64 (4.2)	62 (4.1)
Severe	87 (5.8)	71 (4.7)
SAPS II	60 [48 ; 74]	61 [48 ; 74]
SOFA at baseline	10 [8 ; 13]	10 [8 ; 13]
Medical diagnosis at admission, n (%)	1253 (82.8)	1258 (83.1)
Cause of shock		
Cardiac	254 (16.8)	283 (18.7)
Sepsis	889 (58.7)	874 (57.7)
Non septic SIRS	84 (5.5)	94 (6.2)
Other	288 (19)	263 (17.4)

	Hypo group (n=1521)	Standard group (n=1515)
Ongoing treatments, n (%)		
Prone position	90 (6.0)	93 (6.1)
Sedative agents	1368 (90.5)	1351 (89.3)
NMB agents	483 (32.0)	497 (32.8)
Insulin	593 (39.2)	664 (43.9)
Antiulcer medication	656 (43.4)	686 (45.3)
Prokinetic agents *	39 (2.6)	52 (3.4)
Anti-infectious treatment	1298 (85.8)	1290 (85.3)
Renal replacement therapy	161 (10.6)	183 (12.1)
Vasopressor support	1481 (97.9)	1486 (98.2)
Norepinephrine alone	1274 (84.3)	1259 (83.2)
Epinephrine alone	9 (0.6)	14 (0.9)
Dobutamine alone	13 (0.9)	12 (0.8)
At least two drugs	185 (12.2)	201 (13.3)
Norepinephrine dose, µg/kg/min*	0.50 [0.25 ; 0.99]	0.50 [0.25 ; 1.00]
FiO2 *	50.0 [40.0 ; 80.0]	60.0 [40.0 ; 90.0]
PEP (cmH2O) *	7.0 [5.0 ; 10.0]	7.0 [5.0 ; 10.0]

Adhésion au protocole de l'étude

Calories





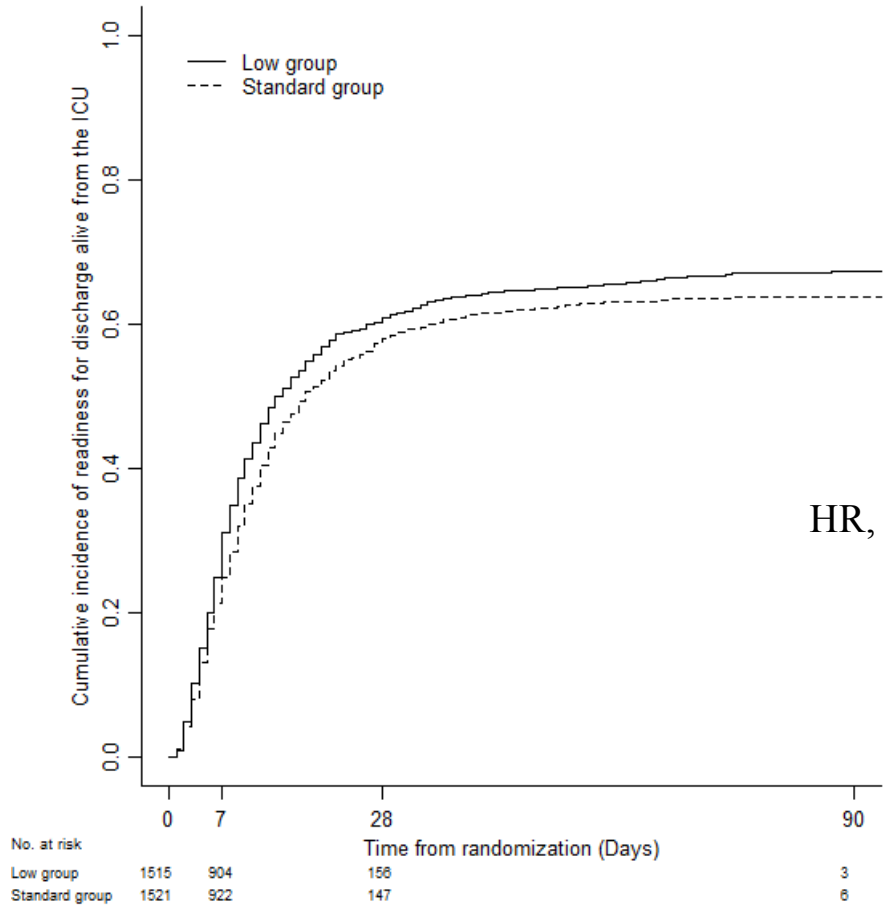
Proteins

	Low group (n=1521)	**Standard group (n=1515)**
Daily total calories goal (Kcal/kg/d)	5.7 [5.0 ; 6.4]	22.7 [19.4 ; 24.7]
Daily total protein goal (g/kg/d)	0.2 [0.2 ; 0.3]	1.0 [0.8 ; 1.2]
Daily calorie intake (Kcal/kg/24 h) *	7.4 [5.8 ; 9.5]	22.0 [17.5 ; 24.9]
Daily protein intake (g/kg/d)	0.2 [0.2 ; 0.3]	0.9 [0.7 ; 1.0]

Primary outcomes

	Hypo group (n=1521)	**Standard group (n=1515)**	Absolute difference (95% CI)	Hazard Ratio (95% CI)	p value
Day-90 mortality (%)	628/1521 (**41.3**)	648/1515 (**42.8**)	-1.5 [-5.0; 2.0]		**0·41**
Time to readiness for ICU discharge (d)	**8·0** [5·0 ; 14·0]	**9·0** [5·0 ; 17·0]		1·12 [1.02; 1·22]	**0.015**

Time to readiness for ICU discharge

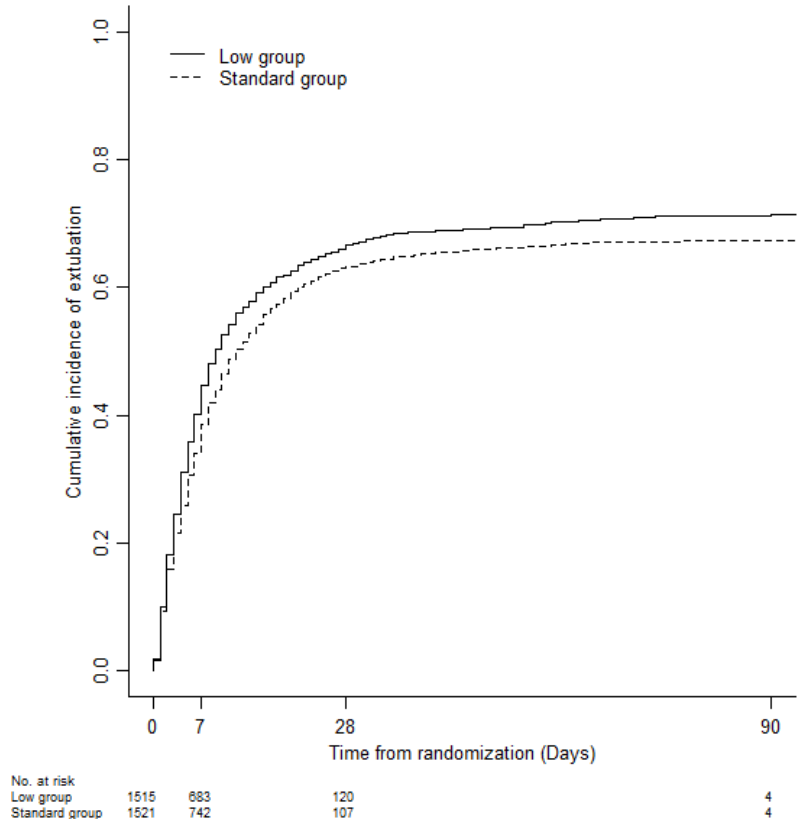


HR, 1.12; 95%CI, 1.02 to 1.22; *P*=0.015

Secondary outcomes

	Hypo group (n=1521)	**Standard group (n=1515)**	Hazard Ratio (95% CI)	p value
ICU length of stay, d [IQR]	9 [5; 15]	10 [6; 17]	1.11 [1.02 ; 1.21]	0.02
Acute-care hospital length of stay, d [IQR]	21 [12; 38]	22 [14; 39]	1.06 [0.97 ; 1.17]	0.19

Weaning from mechanical ventilation



HR, 0.12 (95% CI, 1.03 to 1.22; *P*=0.007)

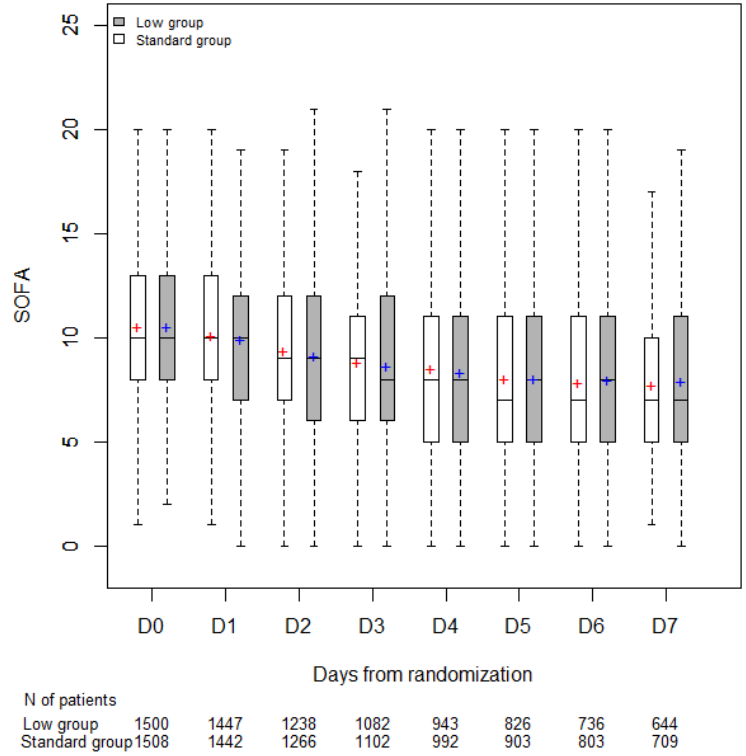
Outcome during the intervention period (Day 0-7)

	Hypo group (n=1521)	**Standard group (n=1515)**	Hazard Ratio (95% CI)	p value
Highest blood glucose level, mmol/L, [IQR]	11.6 [9.6 ; 14.5]	13.7 [11.2 ; 17.1]		<0.0001
Patients receiving insulin (%)	63.1	77.7	0·74 [0·70 ; 0·80]	<0.001
Patients with hypoglycaemia <2.3 (%)	6.0	4.9	1.24 [0.91 ; 1.69]	0·17

Outcome during the intervention period (Day 0-7)

	Hypo group (n=1521)	**Standard group (n=1515)**	Hazard Ratio (95% CI)	p value
Maximum blood lactate level, g/l [IQR]	2.8 [1.8 ; 5.2]	3.0 [2.0 ; 5.6]		0.0025
Patients with normalisation of the blood lactate level (%)	86.5	84.1	1.09 [1.02 ; 1.16]	0·01

Evolution of SOFA score during the intervention period (Day 0-7)



-0.08 [-0.13 ; -0.02]

p= 0.0077

Secondary outcomes : infections

	Hypo group (n=1521)	**Standard group (n=1515)**	Hazard Ratio (95% CI)	p value
ICU-acquired infection (%)	**15.3**	**17.5**	**0·85 [0·71; 1·01]**	**0·06**
Ventilator-associated pneumonia (%)	11.2	10.9	0·98 [0·79; 1·21]	0·82
Bacteraemia (%)	4	5·5	0·73 [0·53; 1·01]	0·06
CVC-related infection (%)	1.5	1.9	0.81 [0·48; 1·37]	0·44
Urinary tract infection (%)	0.72	0.77	1·2 [0·54; 2·67]	0·66
Soft-tissue infection (N patients)	7	5		
Other infection (%)	1.7	2.4	0.78 [0·48; 1·28]	0·33

Secondary outcomes : gastrointestinal and liver complications

	Hypo group (n=1521)	**Standard group (n=1515)**	Hazard Ratio (95% CI)	p value
Vomiting (%)	20.2	25.5	0.77 [0·67; 0.89]	0.0005
Diarrhoea (%)	28.9	33.3	0.83 [0.73; 0.94]	0·004
Constipation (%)	27.8	28.7	0.97 [0.86; 1.10]	0·64
Bowel ischaemia (%)	0.9	1.8	0.50 [0.26;0.95]	0·03
Acute colonic pseudo-obstruction (N patients)	8	2		
Liver dysfunction (%)	53.2	58.2	0.90 [0.83; 0.98]	0.018

Conclusion

Nutrition hypocalorique et hypoprotidique à la phase aigue

→ Pas d'effet sur la mortalité mais récupération plus rapide
→ Et moins de complications digestives
→ Vigilance chez les patients graves et les dialysés (EFFORT)

Après la phase aigue?

1. Les apports sont très souvent insuffisants, en particulier juste avant et après le sevrage de la VM, ou chez les patients très patients ayant une anorexie persistante ou des troubles de la déglutition.
2. Il n'y a aucune étude permettant de préciser un niveau cible et les moyens d'y parvenir
3. Il ne semble pas nécessaire d'augmenter les apports au-delà de 25-30 kcal/kg/j et 1-1.5 g/kg/j de protéines

La nutrition seule ne peut tout…

"Impact of a rehabilitation program including nutrition and mobilization in critically ill patients: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-4)"

Impact d'un programme de réhabilitation précoce, personnalisée et prolongée associant nutrition et mobilisation chez le patient de réanimation: un essai multicentrique, randomisé et contrôlé (NUTRIREA-4).

PHRCN 2023 Début des inclusions Mai 2024

Merci