Masterclass Critical Care Nutrition 2019

How to time parenteral nutrition during critical illness?

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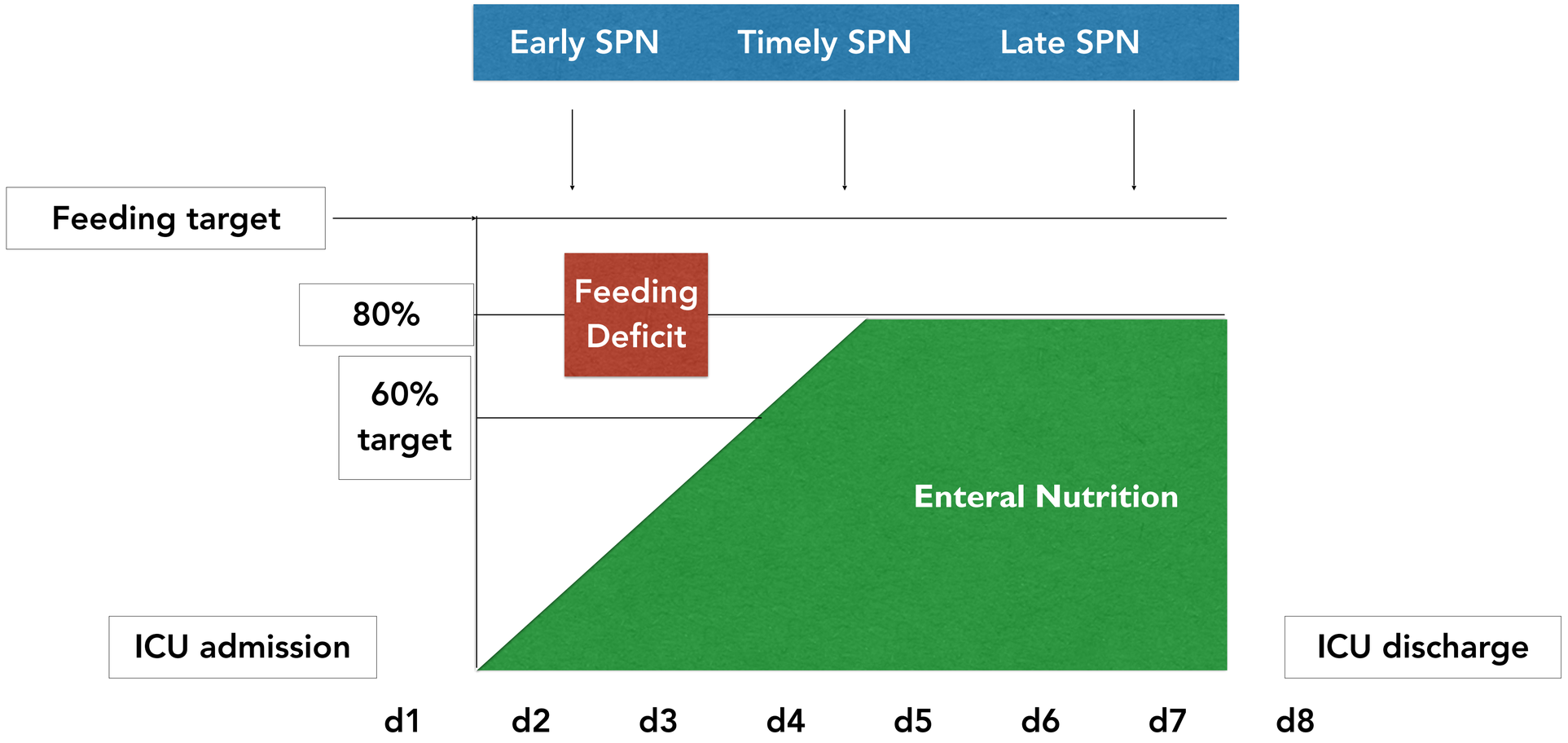
Enteral Nutrition and SPN



Divergent recommendations in guidelines

ESPEN

SCCM / ASPEN

All patients who are not expected to be on normal nutrition within 3d should receive PN within 24 to 48 h if EN is contraindicated or if they cannot tolerate EN

Singer P et al.
Clin Nutr. 2009; 28(4): 387-400.

In patients with low or high nutrition risk, use of SPN be considered after 7-10d if unable to meet >60% of energy and protein requirements by EN alone. Initiating SPN prior to 7-10d does not improve outcomes and may be detrimental

McClave SA et al.
JPEN J Parenter Enteral Nutr. 2009;33(3):277-316.

Should we use TPN to enhance energy delivery?

The NEW ENGLAND JOURNAL of MEDICINE

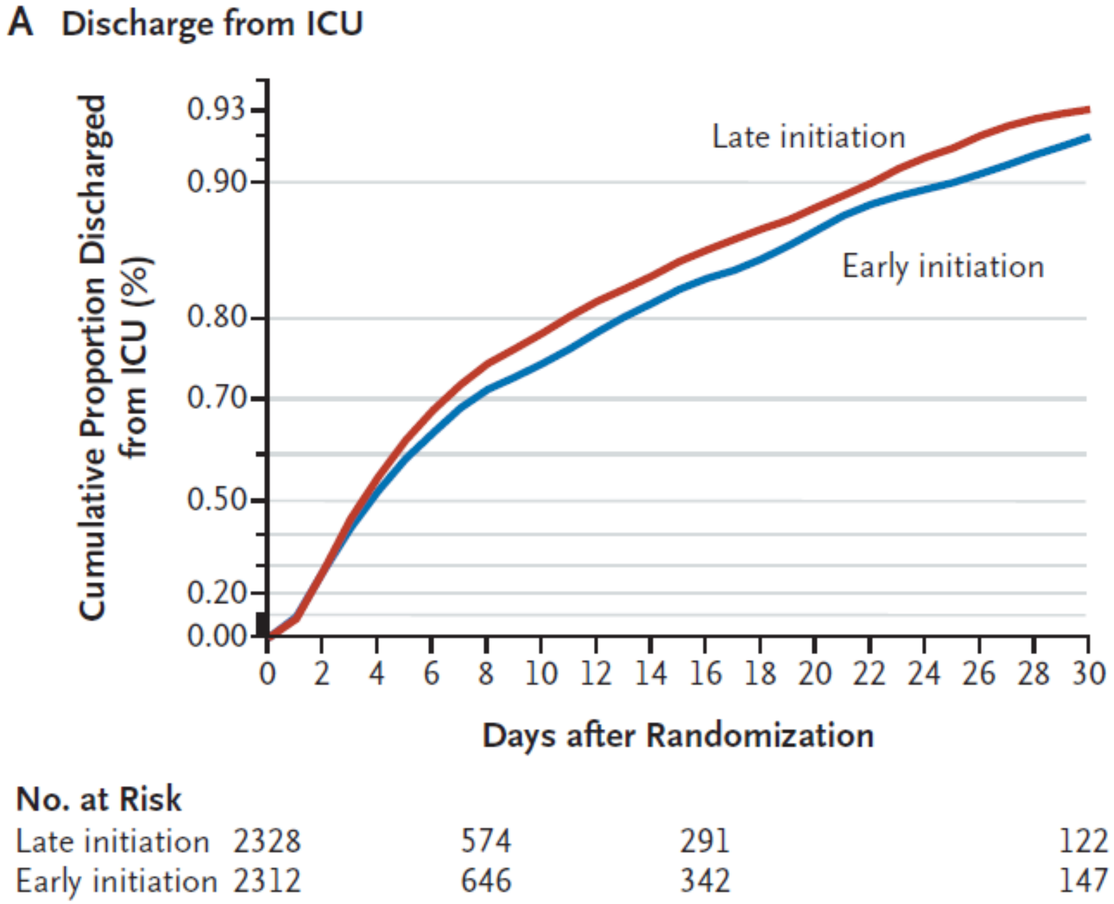
ORIGINAL ARTICLE

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.*

Casaer M et al. N Engl J Med 2011; 365: 506-517

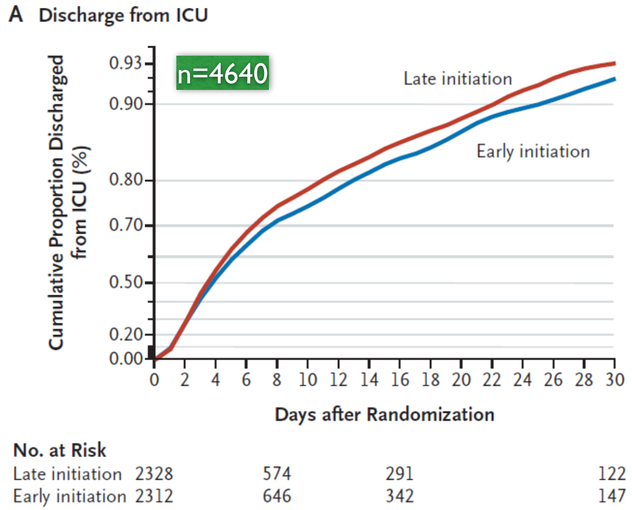
EPaNIC trial: primary end point



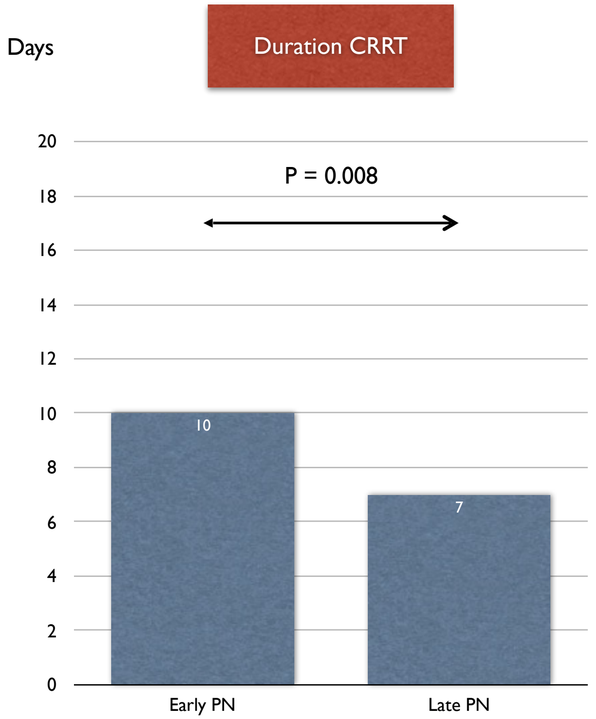
Hazard ratio (95% CI) for time to discharge alive from ICU 1.06 (1.00–1.13)

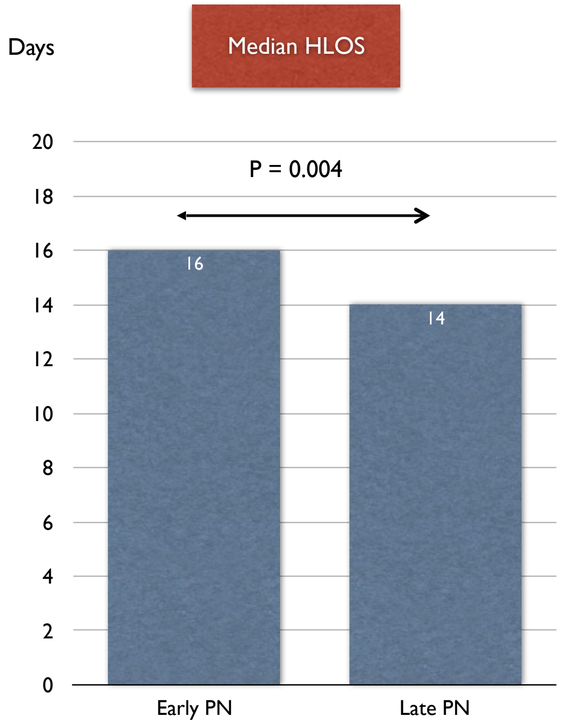
Casaer M et al. N Engl J Med 2011; 365: 506-517

EPaNIC trial: primary end point

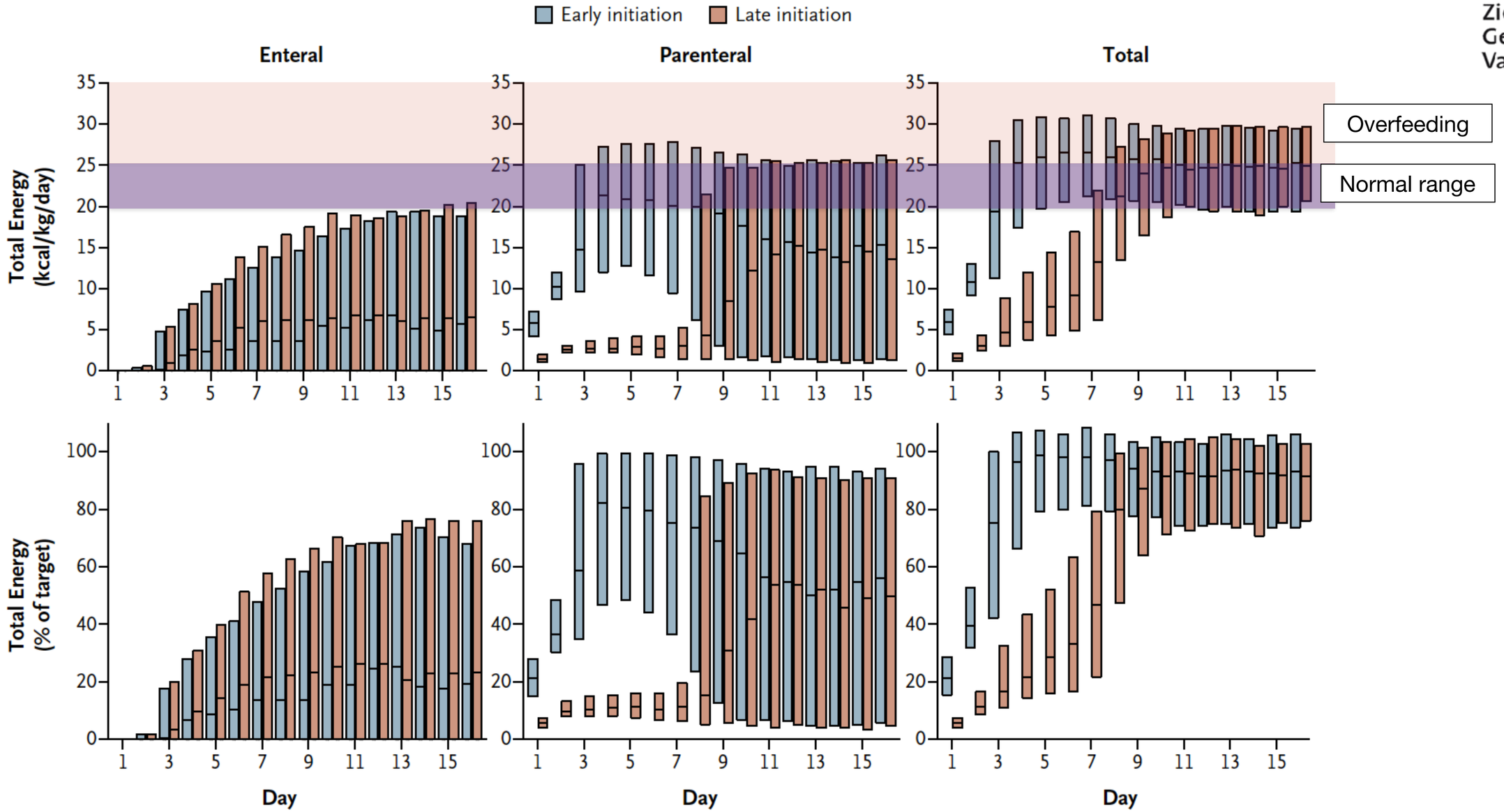


Hazard ratio (95% CI) for time to discharge alive from ICU 1.06 (1.00–1.13)





Casaer M et al. N Engl J Med 2011; 365: 506-517



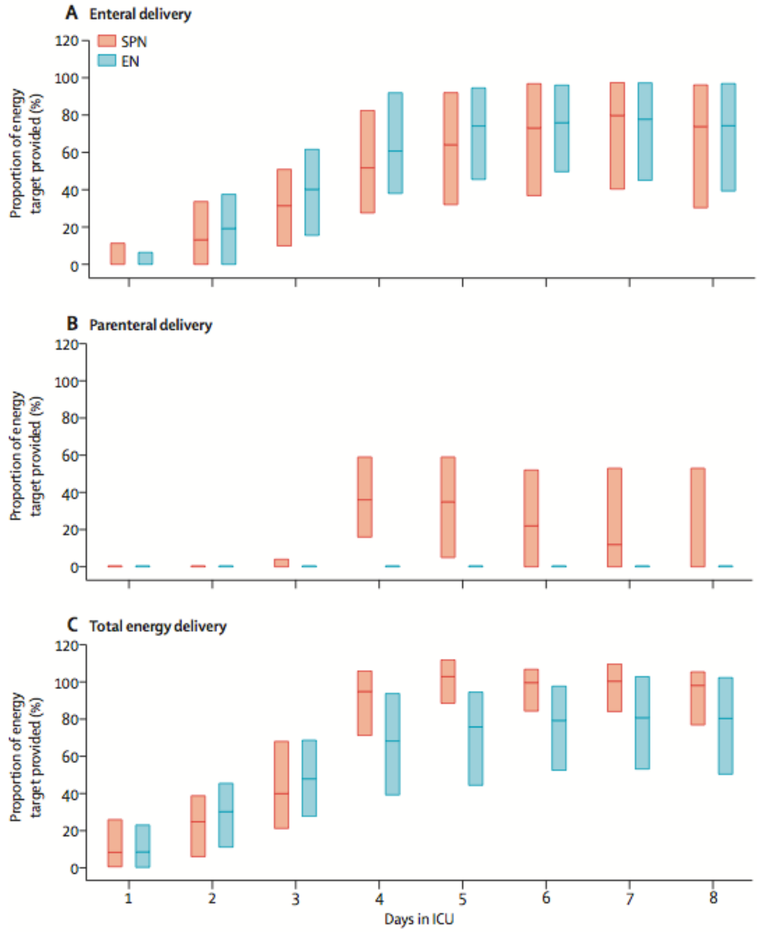
No. in ICU

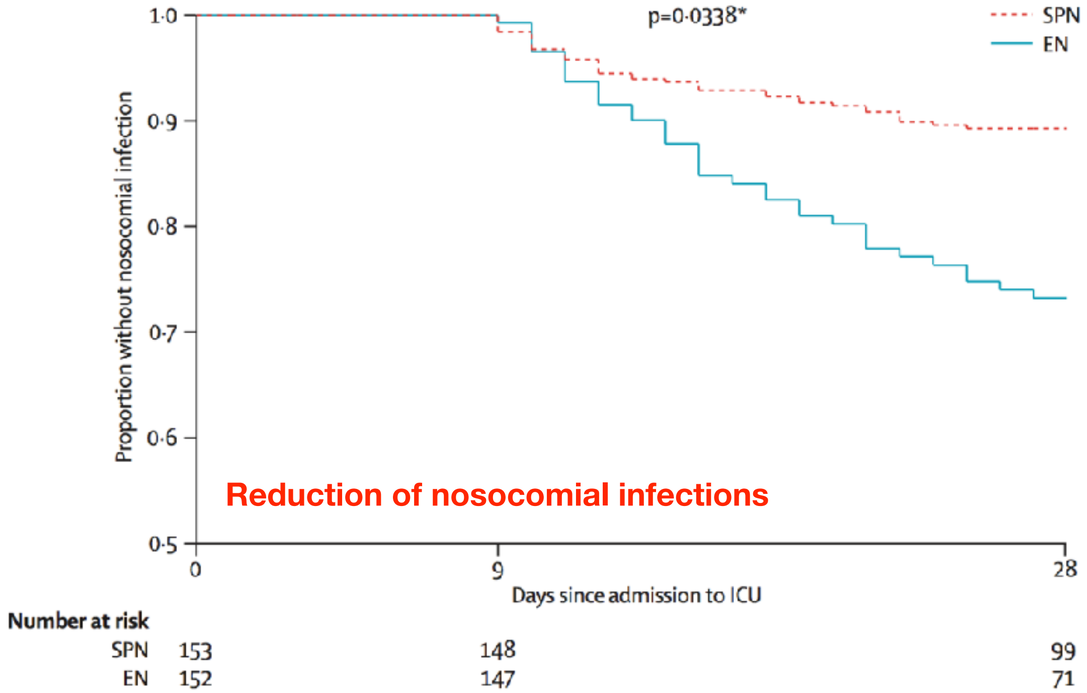
Late initiation	2328	1399	913	655	436	313	2328	1399	913	655	436	313	2328	1399	913	655	436	313
Early initiation	2312	1438	975	736	517	371	2312	1438	975	736	517	371	2312	1438	975	736	517	371

Casaer M et al. N Engl J Med 2011; 365: 506-517

Supplemental Parenteral Nutrition (SPN) Trial

153 patients SPN (unable to tolerate 60% EN target on day 3) and 152 EN





Reduction of nosocomial infections

En delivery day 4-8: 28 kcal/kg*day in SPN group (103% of target), compared with 20 kcal/kg* in EN group (77%)

Heidegger CP. Lancet 2013; 381: 385–93

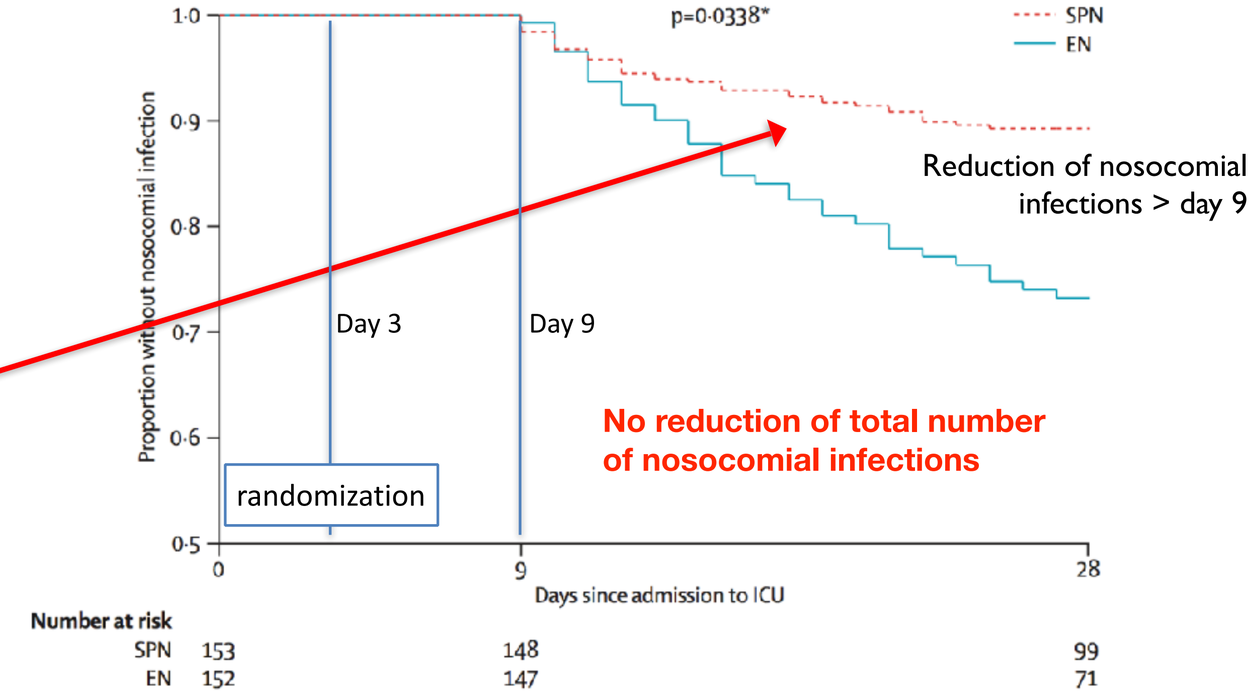
Supplemental Parenteral Nutrition (SPN) Trial

153 patients SPN (unable to tolerate 60% EN target on day 3) and 152 EN

	Enteral nutrition	Supplemental parenteral nutrition
Day 4–8	18%	23%
Day 9–28	21%	15%
Day 4–28	39%	37%*

Data are % of patients. Data obtained from reference 1. *Difference not statistically significant.

Table: Rate of hospital acquired pneumonia



Reduction of nosocomial infections > day 9

No reduction of total number of nosocomial infections

More early infections

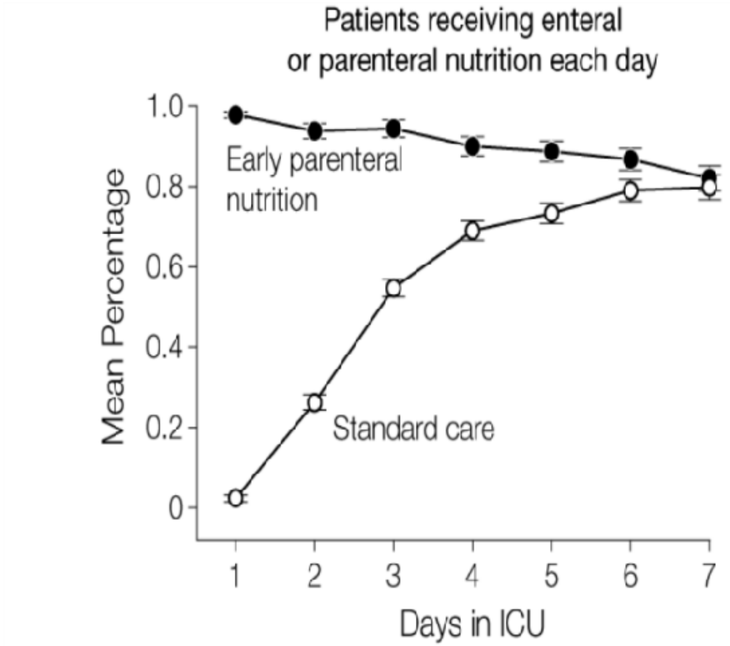
En delivery day 4-8: 28 kcal/kg*day in SPN group (103% of target), compared with 20 kcal/kg* in EN group (77%)

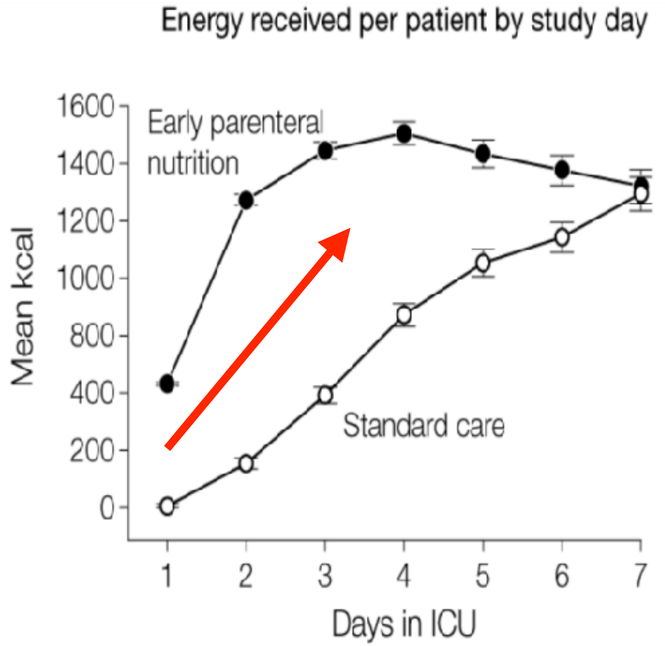
Heidegger CP. Lancet 2013; 381: 385–93

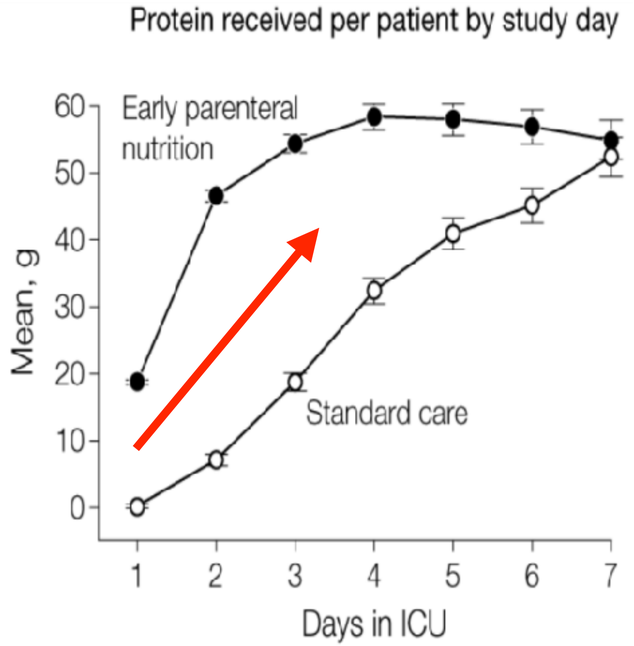
Early PN in critically ill patients with short-term relative contraindications to EEN: a randomized controlled trial

slow build-up in both groups

slow build-up in both groups







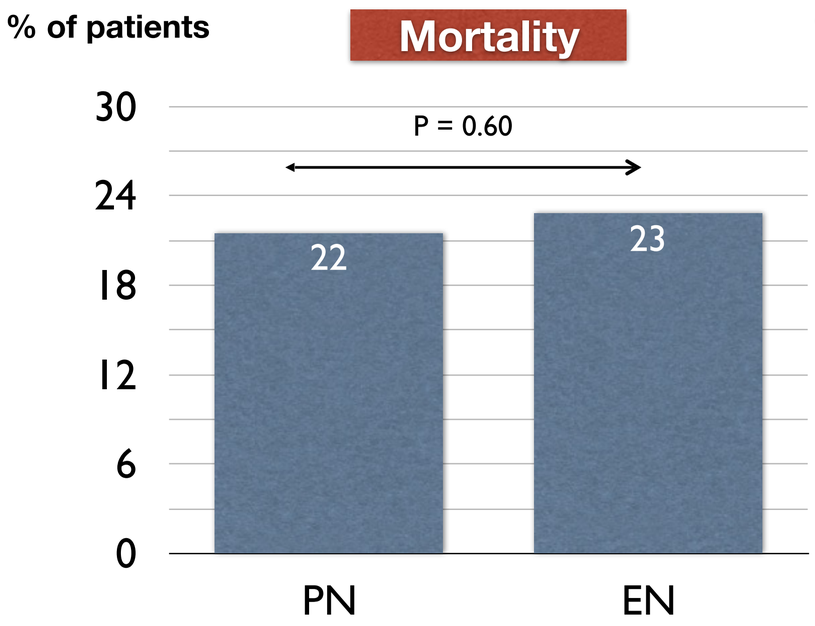
No. of patients							
Early parenteral nutrition	681	676	611	518	435	376	313
Standard care	682	675	599	480	410	353	301

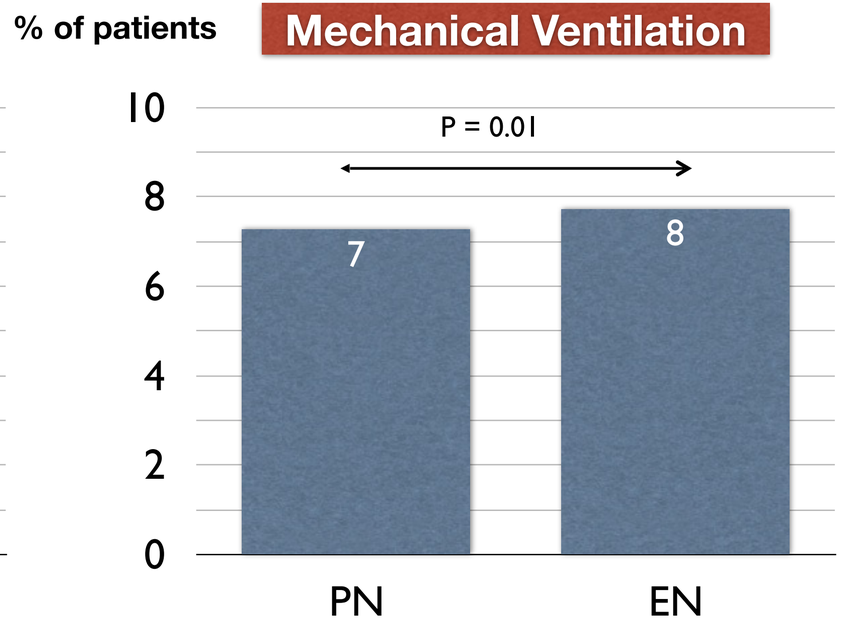
681	676	611	518	435	376	313
682	675	599	480	410	353	301

681	676	611	518	435	376	313
682	675	599	480	410	353	301

Doig, ANZICS, JAMA May 2013

Early PN trial





Reduction in a few Mechanical Ventilation hours did not result in a statistically significant shortening of ICU or hospital LOS

Doig, ANZICS, JAMA May 2013

Conclusions ANZICS trial

- **No significant differences in day-60 mortality or ICU infections.**
- **Patients on early PN required significantly fewer days of invasive mechanical ventilation (0.47 day), but this did not result in a statistically significant shortening of ICU or hospital LOS.**
- **No harm was attributable to the use of early parenteral nutrition in this trial.**

Doig, ANZICS, JAMA May 2013

Conflicting results Early SPN

- **Epanic: Early PN negative effects on ICU discharge survival (no long-term survival difference) & duration of organ failure**
- **SPN trial: no differences, effect on infections questionable**
- **Anzics trial: No major outcome differences, shorter duration of MV 0.4 day and QOL significant but not relevant, 95% of patients tolerate EN within 4.1 days**

Bost *et al. Annals of Intensive Care* 2014, **4**:31
http://www.annalsofintensivecare.com/content/4/1/31

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review

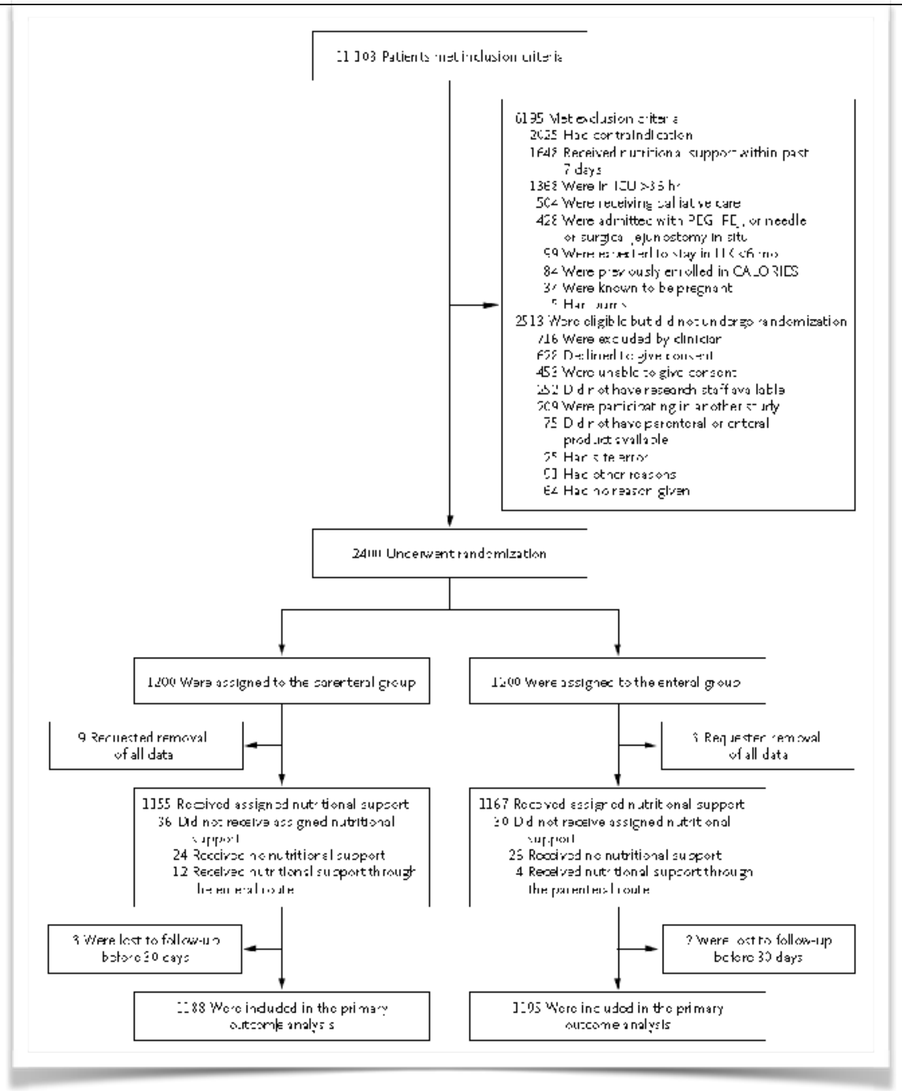
Rianne BC Bost[1], Dave HT Tjan[1] and Arthur RH van Zanten[1,2*]

In adult ICU patients, when full EN support is not possible or fails to reach caloric targets, early administration of SPN compared with late administration (at the end of the first week after ICU admission) does not confer major benefits with respect to morbidity and mortality.

Considering that infectious morbidity and resolution of organ failure may be negatively affected through mechanisms not yet clearly understood, and acquisition costs of PN are higher compared with EN, the early administration of PN cannot be recommended.

Calories trials: to compare EN versus PN, not SPN

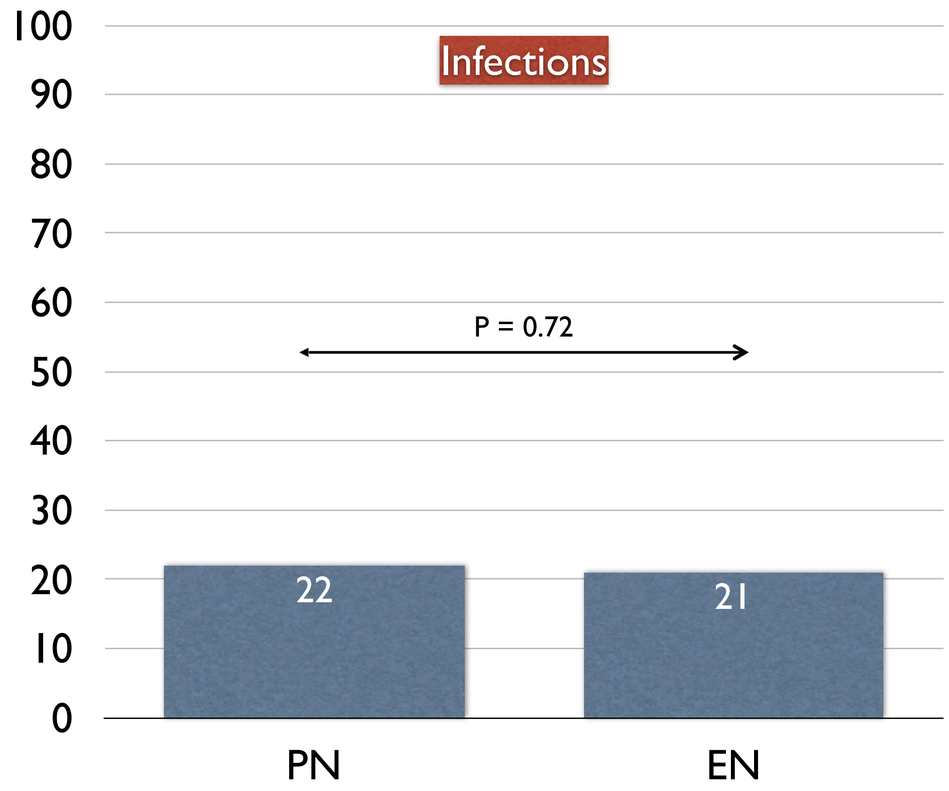
1200 PN

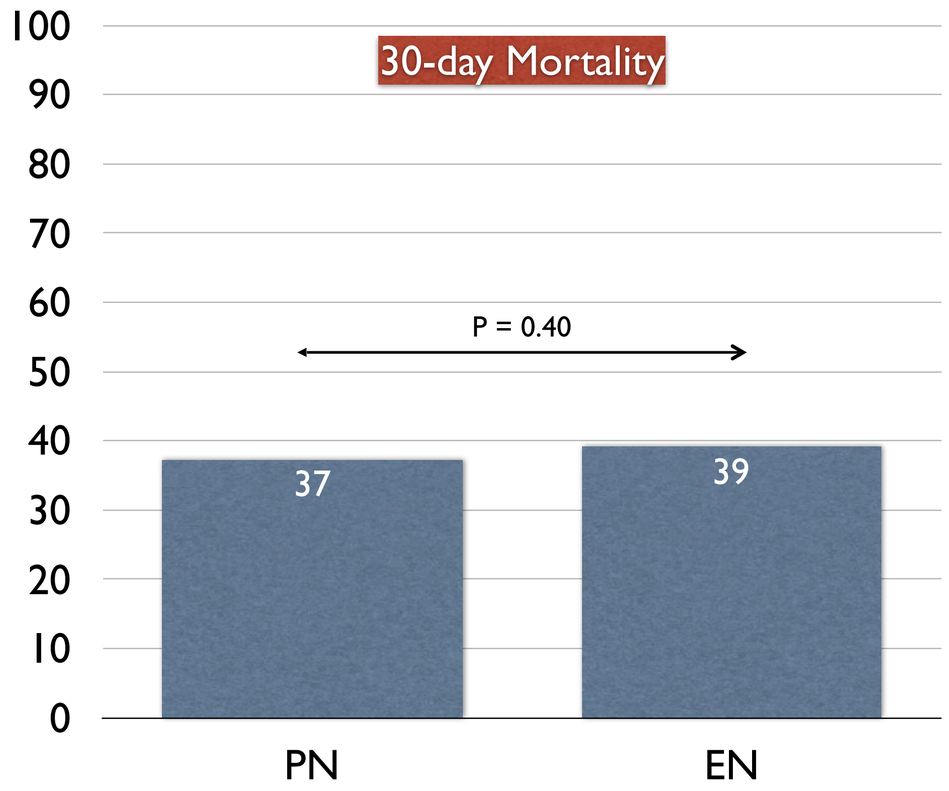


1200 EN

Harvey SE et al. NEJM 2014

Calories trial: mortality and infections

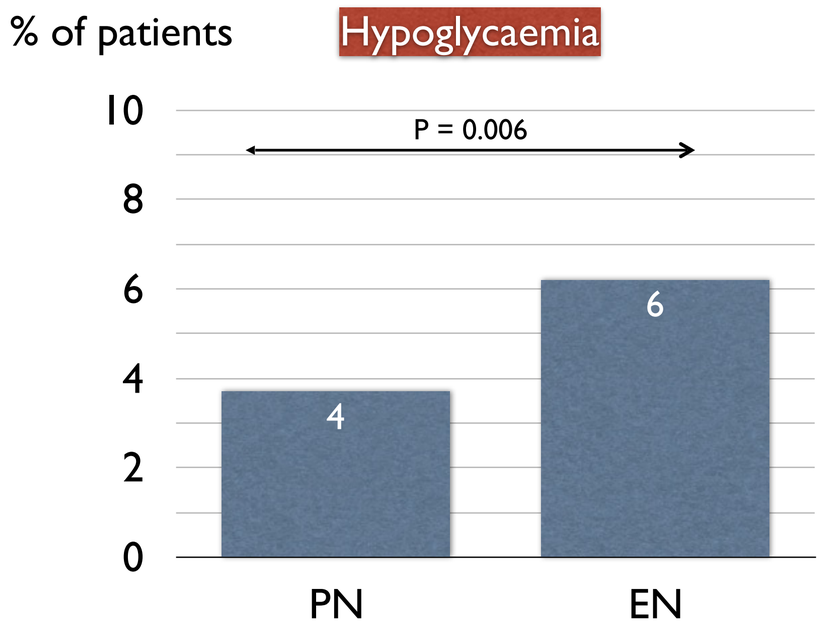


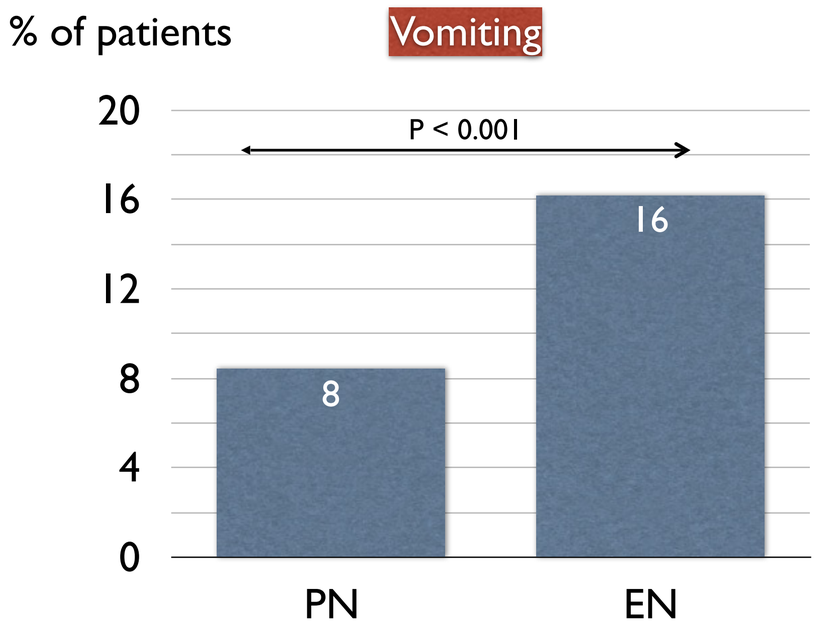


No differences in mean number of treated infectious complications (0.22 vs. 0.21; P = 0.72), 90-day mortality (442/1184 pts [37.3%] vs. 464/1188 pts [39.1%], P = 0.40), and 14 other secondary outcomes, or in rates of adverse events.

Harvey SE et al. NEJM 2014

Calories trial: EEN vs EPN

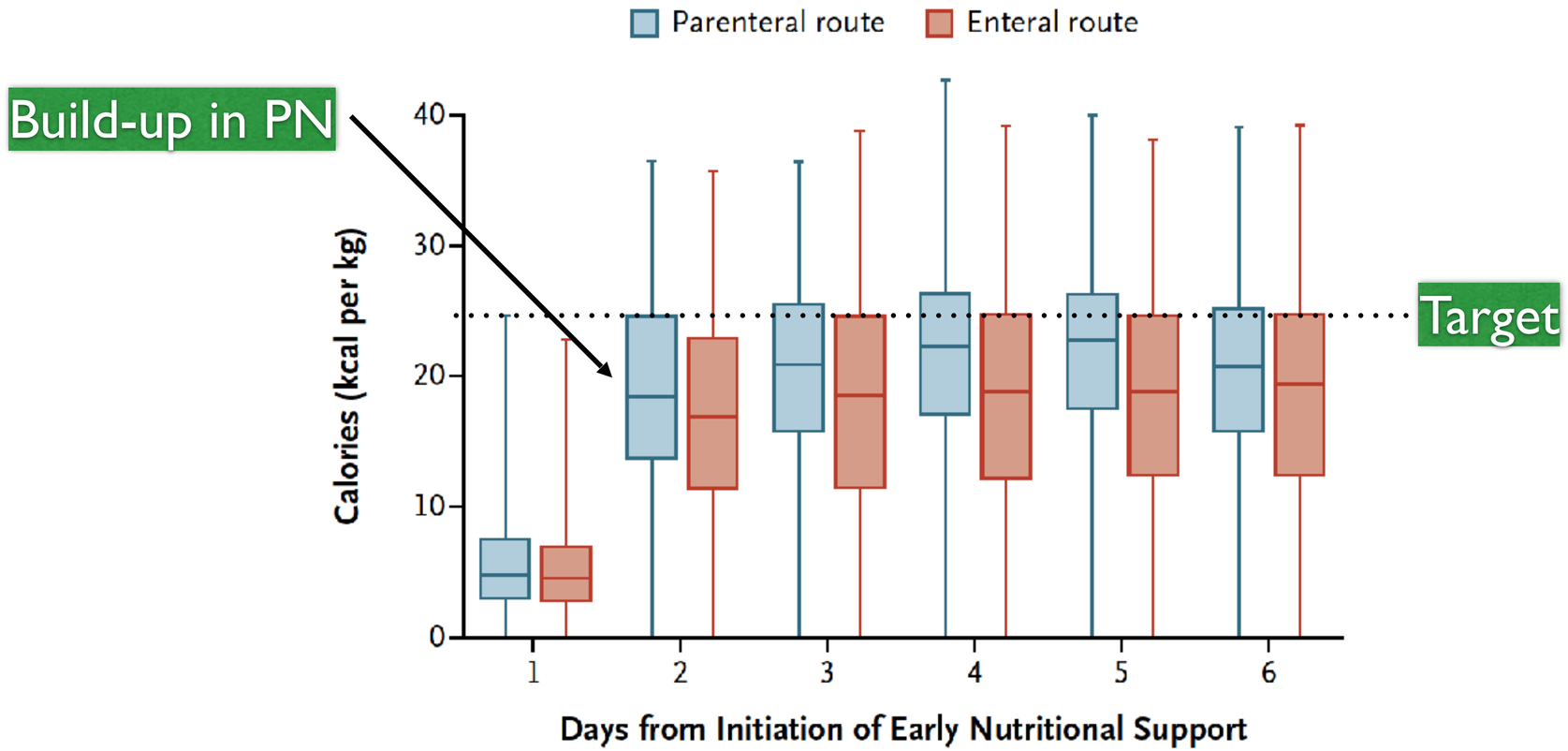




No differences in 14 other secondary outcomes, or in rates of adverse events

Harvey SE et al. NEJM 2014

Unexpected build-up in PN



PN vs. EN total protein intake 3 vs. 3 g/kg, NS
PN vs. EN total energy intake 89 vs. 74 kcal/kg, NS

Harvey SE et al. NEJM 2014

Comments Calories trial

- pragmatic design
- short intervention
- no difference in intake EN vs. PN (both not reaching target)
- relatively high 30-day mortality (33.1 vs 34.2%)
- no difference in outcome (less hypoglycemia and vomiting in PN)

Consequences Calories trial

- Will you start PN in patients with functioning gut?
- Increased infection rates not observed in PN patients
- Due to build-up
- EN is first-line therapy in the ICU
- However, in case we do not reach our targets we should not be afraid to start PN

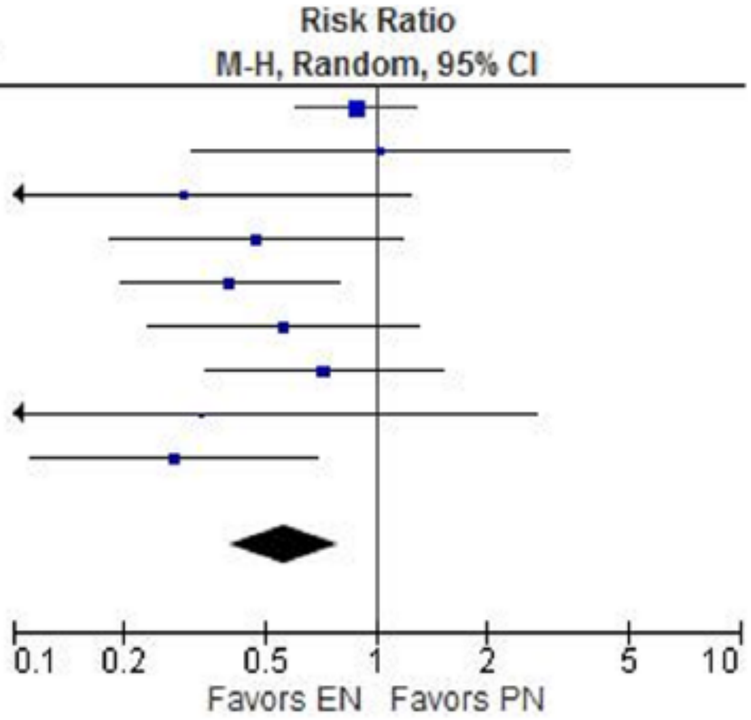
Enteral Nutrition versus Parenteral Nutrition

infectious complications

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams 1986	15	23	17	23	25.0%	0.88 [0.60, 1.30]	1986
Young 1987	5	28	4	23	6.9%	1.03 [0.31, 3.39]	1987
Peterson 1988	2	21	8	25	5.1%	0.30 [0.07, 1.25]	1988
Moore 1989	5	29	11	30	10.2%	0.47 [0.19, 1.19]	1989
Kudsk 1992	9	54	19	45	15.0%	0.39 [0.20, 0.78]	1992
Kalfarentzos 1997	5	18	10	20	11.2%	0.56 [0.23, 1.32]	1997
Woodcock 2001	6	16	11	21	13.5%	0.72 [0.34, 1.52]	2001
Casas 2007	1	11	3	11	2.6%	0.33 [0.04, 2.73]	2007
Chen 2011	5	49	18	49	10.5%	0.28 [0.11, 0.69]	2011
Total (95% CI)		**249**		**247**	**100.0%**	**0.56 [0.39, 0.79]**	
Total events	53		101				

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 12.10$, $df = 8$ ($P = 0.15$); $I^2 = 34\%$

Test for overall effect: $Z = 3.26$ ($P = 0.001$)



A.S.P.E.N./SCCM guidelines 2016

Recent meta-analysis EN vs PN

Elke *et al. Critical Care* (2016) 20:117
DOI 10.1186/s13054-016-1298-1

Critical Care

RESEARCH Open Access

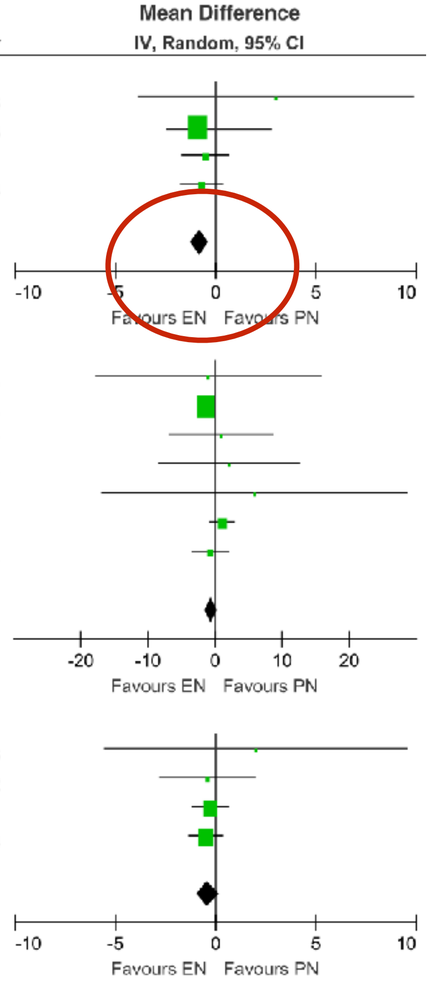
Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials

Gunnar Elke[1], Arthur R. H. van Zanten[2], Margot Lemieux[3], Michele McCall[4], Khursheed N. Jeejeebhoy[5], Matthias Kott[1], Xuran Jiang[3], Andrew G. Day[3] and Daren K. Heyland[3*]

Elke G, Van Zanten AR et al. Crit Care 2016;20:117

EN versus PN: LOS, duration ventilation

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
ICU LOS									
Adams	13	11	19	10	10	17	0.4%	3.00 [-3.86, 9.86]	1986
Peterson	3.7	0.8	21	4.6	1	25	68.6%	-0.90 [-1.42, -0.38]	1988
Chen	9.09	2.75	49	9.6	3.06	49	14.0%	-0.51 [-1.66, 0.64]	2011
Harvey	11.3	12.5	1197	12	13.5	1190	17.0%	-0.70 [-1.74, 0.34]	2014
Total (95% CI)	26.8		**1286**			**1281**	**100.0%**	**-0.80 [-1.23, -0.37]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 3 (P = 0.66); I² = 0%									
Test for overall effect: Z = 3.62 (P = 0.0003)									
Hospital LOS									
Adams	30	21	19	31	29	17	0.3%	-1.00 [-17.71, 15.71]	1986
Peterson	13.2	1.6	21	14.6	1.9	21	62.8%	-1.40 [-2.46, -0.34]	1988
Kudsk	20.5	19.9	51	19.6	18.8	45	1.4%	0.90 [-6.85, 8.65]	1992
Borzotta	39	23.1	28	36.9	14	21	0.8%	2.10 [-8.34, 12.54]	1994
Woodcock	33.2	43	16	27.3	18.7	18	0.2%	5.90 [-16.87, 28.67]	2001
Chen	23.32	5.6	49	22.24	3.27	49	23.6%	1.08 [-0.74, 2.90]	2011
Harvey	26.8	33.2	1186	27.5	33.9	1185	11.0%	-0.70 [-3.40, 2.00]	2014
Total (95% CI)			**1370**			**1356**	**100.0%**	**-0.67 [-1.57, 0.24]**	
Heterogeneity: Tau² = 0.05; Chi² = 6.12, df = 6 (P = 0.41); I² = 2%									
Test for overall effect: Z = 1.44 (P = 0.15)									
Mechanical ventilation									
Adams	12	11	17	10	10	13	0.6%	2.00 [-5.54, 9.54]	1986
Kudsk	2.8	4.9	51	3.2	6.7	45	6.2%	-0.40 [-2.77, 1.97]	1992
Chen	7.95	2.11	49	8.23	2.42	49	43.4%	-0.28 [-1.18, 0.62]	2011
Harvey	8.2	9.3	1197	8.7	11.5	1189	49.8%	-0.50 [-1.34, 0.34]	2014
Total (95% CI)			**1314**			**1296**	**100.0%**	**-0.38 [-0.98, 0.21]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%									
Test for overall effect: Z = 1.27 (P = 0.21)									



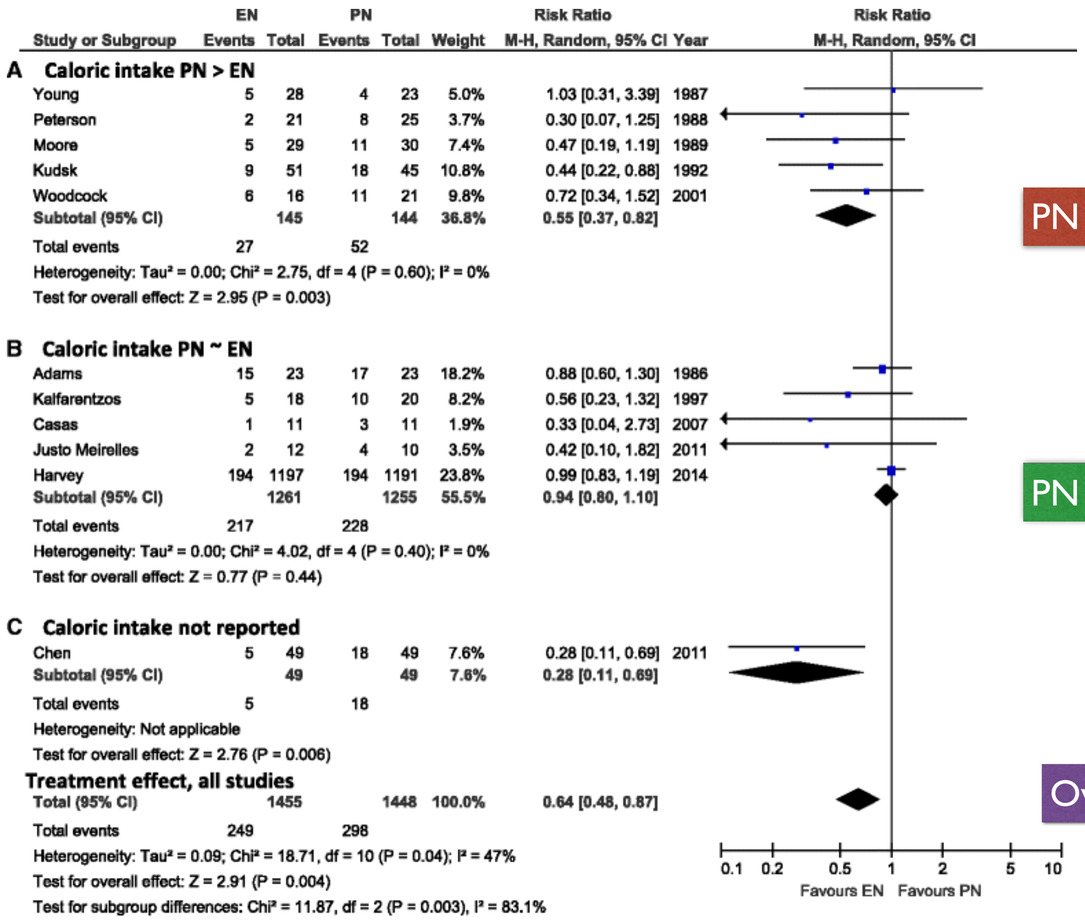
Reduction ICU LOS EN vs PN

No Reduction HLOS EN vs PN

No Reduction Duration Mechanical Ventilation

Elke G, Van Zanten AR et al. Crit Care 2016;20:117

Enteral versus parenteral nutrition in critically ill patients: and updated systematic review and meta-analysis of randomized controlled trials



PN caloric intake > EN caloric intake

PN caloric intake = EN caloric intake

Overall EN less infections than PN

Only more infections in PN trials when caloric dose in PN group is higher

Elke G, Van Zanten AR… Heyland DK. Crit Care 2016;20:117

Try to avoid SPN in low-risk patients

- Combining early PN and EN only for severe malnourished patients (BMI<18.5) or
- Apply only after 8 days of ICU admission in patients failing to achieve enteral targets
- Enhancing early EN and optimizing enteral energy and protein targets is probably the best strategy

Van Zanten AR. Crit Care Med 2011

Late Parenteral Nutrition

- **G1. We suggest that, in the patient at low nutrition risk (eg, NRS 2002 ≤3 or NUTRIC score ≤5), exclusive PN be withheld over the first 7 days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible.**

- **[Quality of Evidence: Very Low]**

Studies until 31 december 2013

A.S.P.E.N./SCCM guidelines 2016

Late Parenteral Nutrition

- **G2. Based on expert consensus, in the patient determined to be at high nutrition risk (eg, NRS 2002 ≥5 or NUTRIC score ≥5) or severely malnourished, when EN is not feasible, we suggest initiating exclusive PN as soon as possible following ICU admission.**

- **G3. We recommend that, in patients at either low or high nutrition risk, use of supplemental PN be considered after 7–10 days if unable to meet >60% of energy and protein requirements by the enteral route alone. Initiating Figure 9. Enteral nutrition (EN) with glutamine vs EN with no glutamine, outcome mortality. ICU, intensive care unit. supplemental PN prior to this 7- to 10-day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient.**

Studies until 31 december 2013

A.S.P.E.N./SCCM guidelines 2016

Late Parenteral Nutrition

- **H2. We suggest that hypocaloric PN dosing (≤20 kcal/kg/d or 80% of estimated energy needs) with adequate protein (≥1.2 g protein/kg/d) be considered in appropriate patients (high risk or severely malnourished) requiring PN, initially over the first week of hospitalization in the ICU.**

- **[Quality of Evidence: Low]**

Studies until 31 december 2013

A.S.P.E.N./SCCM guidelines 2016

SPN in high-risk ICU patients

Wischmeyer *et al. Critical Care* (2017) 21:142
DOI 10.1186/s13054-017-1736-8

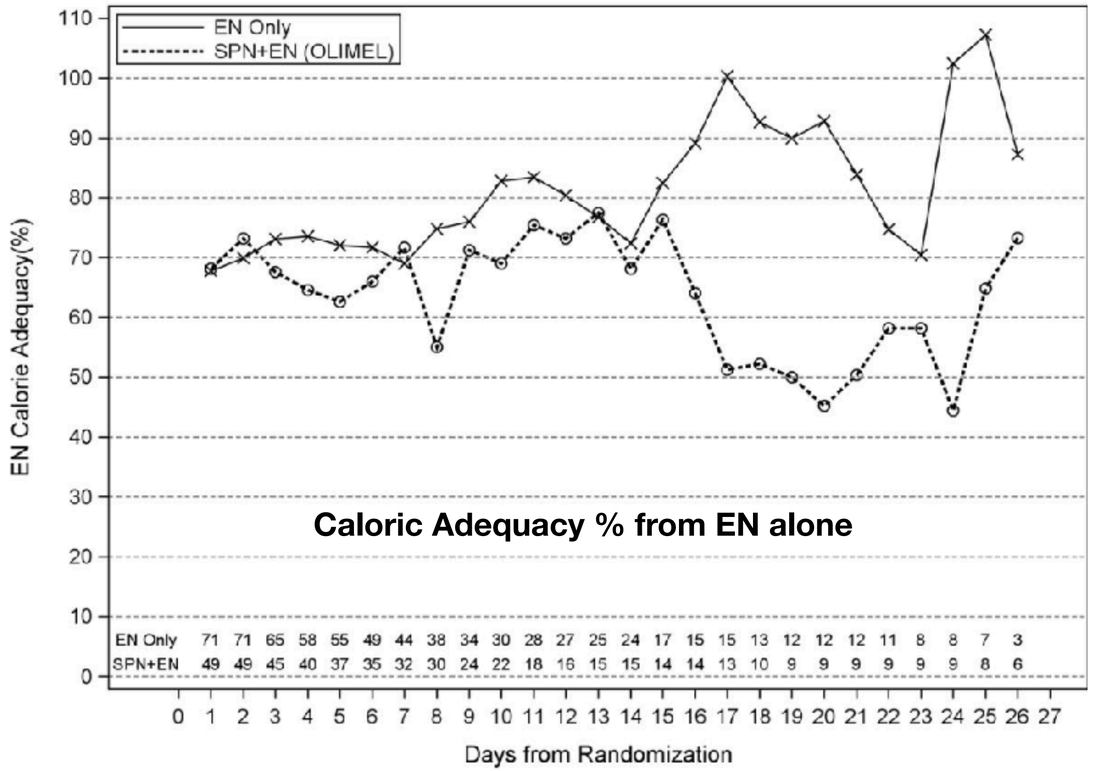
Critical Care

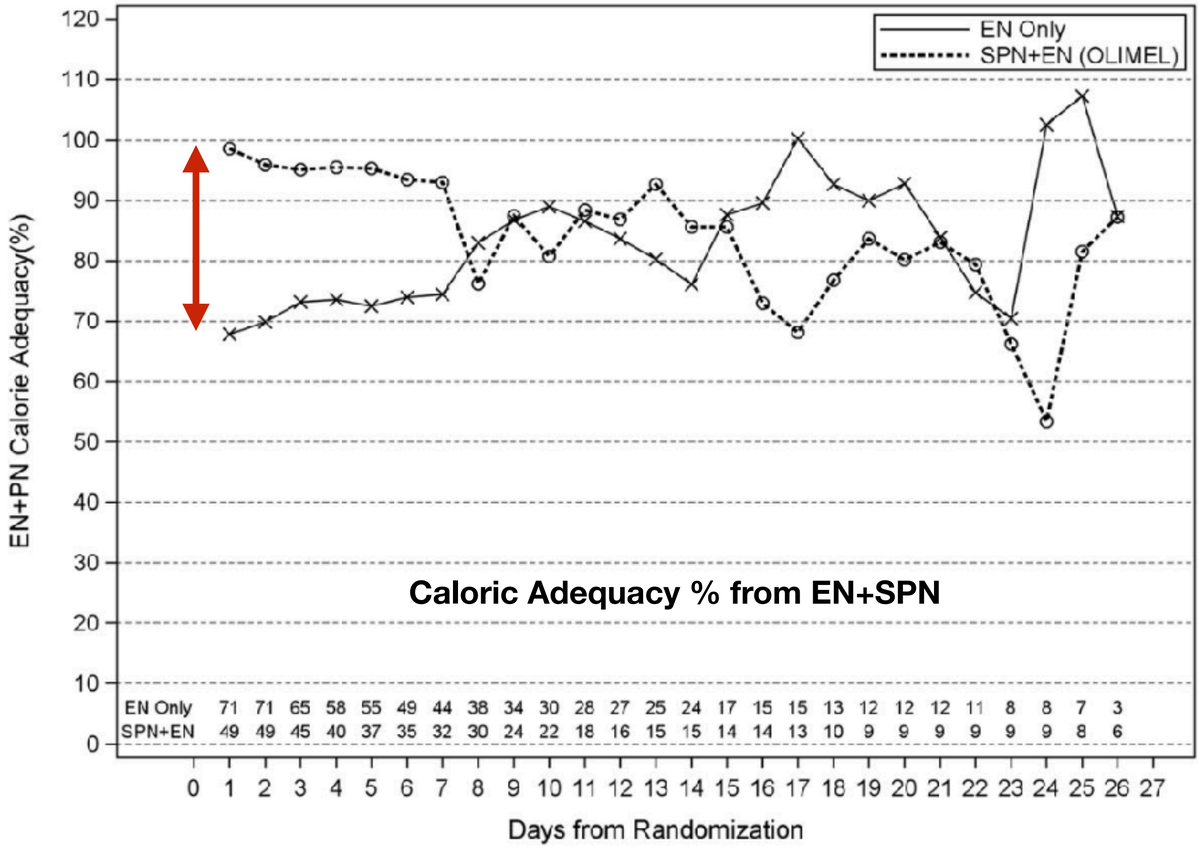
RESEARCH Open Access

A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial

Paul E. Wischmeyer[1*], Michel Hasselmann[2], Christine Kummerlen[2], Rosemary Kozar[3], Demetrios James Kutsogiannis[4], Constantine J. Karvellas[5], Beth Besecker[6], David K. Evans[7], Jean-Charles Preiser[8], Leah Gramlich[9], Khursheed Jeejeebhoy[10], Rupinder Dhaliwal[11], Xuran Jiang[11], Andrew G. Day[11] and Daren K. Heyland[11,12,13]

TOP-UP pilot trial: 71 versus 49 patients





Difference in calories and proteins during first week

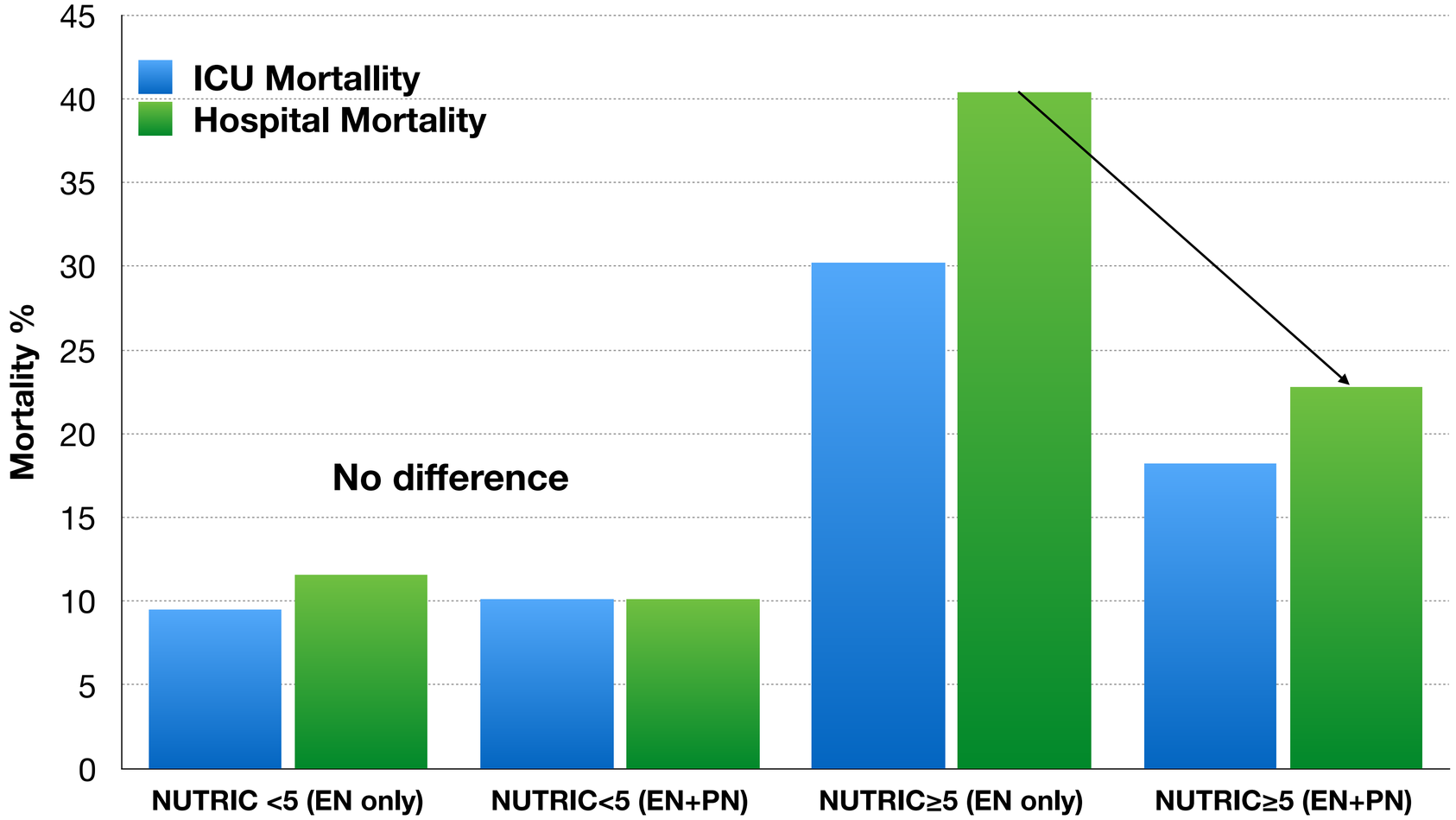
Wischmeyer et al. Critical Care (2017) 21:142

More proteins and calories (20-25%) due to SPN

Calorie prescription	1844 ± 420	1728 ± 444	−116 (−275 to 42)	0.149
Protein prescription	106 ± 30	100 ± 31	−6 (−17 to 6)	0.319
% of prescribed kcal/protein received				
EN only				
Calories first 27 days	70 ± 26	67 ± 25	−3 (−12 to 7)	0.551
Calories first 7 days	68 ± 28	68 ± 27	−1 (−11 to 9)	0.905
Protein first 27 days	66 ± 26	60 ± 23	−5 (−14 to 3)	0.231
Protein in first 7 days	63 ± 26	61 ± 25	−3 (-12 to 7)	0.566
PN + EN				
Calories first 27 days	72 ± 25	90 ± 16	18 (11 to 25)	<0.001
Calories first 7 days	69 ± 28	95 ± 13	26 (18 to 34)	<0.001
Protein first 27 days	68 ± 25	82 ± 19	13 (6 to 21)	<0.001
Protein in first 7 days	64 ± 26	86 ± 16	22 (14 to 29)	<0.001

Wischmeyer et al. Critical Care (2017) 21:142

Effect of SPN
in low and high risk ICU patients according to NUTRIC scores



Wischmeyer et al. Critical Care (2017) 21:142

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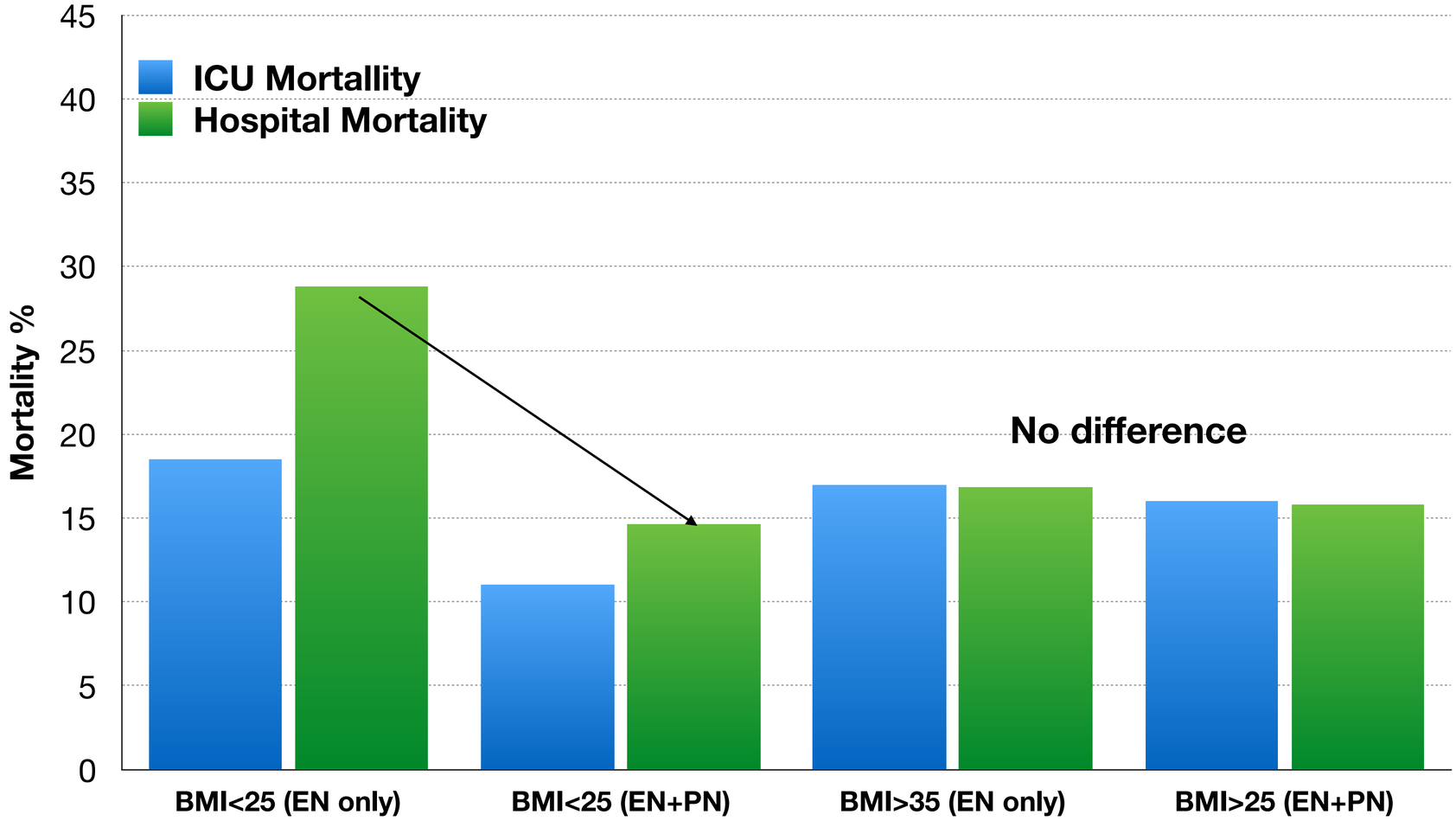

Wischmeyer et al. Critical Care (2017) 21:142

Big scientific debate on this study

2014 Harry M. Vars Award

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

Intensive Nutrition in Acute Lung Injury: A Clinical Trial (INTACT)

Carol A. Braunschweig, PhD, RD[1]; Patricia M. Sheean, PhD, RD[2]; Sarah J. Peterson, MS, RD[3]; Sandra Gomez Perez, MS, RD[4]; Sally Freels, PhD[5]; Omar Lateef, DO[6]; David Gurka, MD, PhD[6]; and Giamila Fantuzzi, PhD[1]

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DOI: 10.1177/0148607114528541
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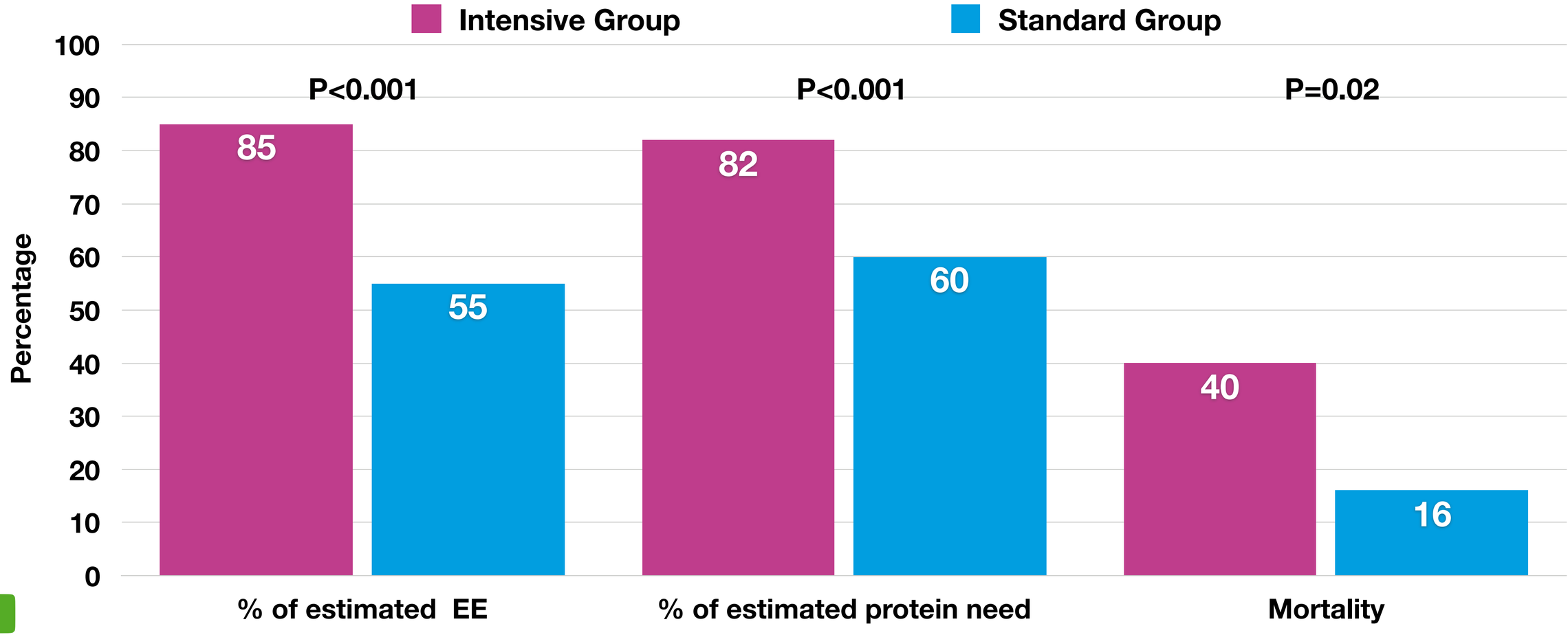
INTACT trial, stopped early (n = 78)

Intensive medical nutrition therapy (IMNT; 30 kcal/kg/day) from acute lung injury diagnosis to hospital discharge



Braunschweig CA, et al. JPEN J Parenter Enteral Nutr. 2015;39:13–20.

Post-hoc analysis INTACT trial

- Higher overall energy intake, higher mortality (OR: 1.14, 95% CI: 1.02, 1.27).
- Patients enrolled for at least 8 days (n = 66), higher early energy intake significantly increased the HR for mortality (HR: 1.17, 95% CI: 1.07, 1.28), higher late energy intake was significantly protective (HR: 0.91, 95% CI: 0.83, 1.0).
- Results were similar for early but not late protein (g/kg) exposure (early-exposure HR: 8.9, 95% CI: 2.3, 34.3; late-exposure HR: 0.15, 95% CI: 0.02, 1.1).
- Threshold analyses indicated early mean intakes >18 kcal/kg significantly increased subsequent mortality.

Braunschweig CA, et al. Am J Clin Nutr 2017;105:411–6.

Intensive Care Med (2017) 43:1637–1647
DOI 10.1007/s00134-017-4880-3

SEVEN-DAY PROFILE PUBLICATION

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

Matilde Jo Allingstrup[1], Jens Kondrup[2], Jørgen Wiis[1], Casper Claudius[1], Ulf Gøttrup Pedersen[1], Rikke Hein-Rasmussen[1], Mads Rye Bjerregaard[1], Morten Steensen[1], Tom Hartvig Jensen[1], Theis Lange[3,4], Martin Bruun Madsen[1], Morten Hylander Møller[1] and Anders Perner[1*]

Methods EAT-ICU study

- Acutely admitted, mechanically ventilated ICU patients expected to stay longer than 3 days in the ICU.
- Early goal-directed nutrition (EGDN) group
  - indirect calorimetry
  - 24-h urinary urea aiming at covering 100% of requirements from the first full trial day using enteral and parenteral nutrition.
- Standard of care group
  - 25 kcal/kg/day by enteral nutrition.
  - If not met by day 7, supplemented with parenteral nutrition.
- Primary outcome: physical component summary (PCS) score of SF-36 at 6 months.

Allingstrup MJ et al. Intensive Care Med (2017) 43:1637–1647

Baseline characteristics

Variable	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)
Age, years	63 (51–72)	68 (52–75)
Male sex, no. (%)	65 (65%)	59 (60%)
Actual body weight, kg	78 (67–90)	80 (70–90)
BMI[a], kg/m^2	22 (20–26)	22 (20–25)
Source of ICU admission, no. (%)		
Emergency department	31 (31%)	30 (30%)
General ward	45 (45%)	38 (38%)
Operating or recovery room	6 (6%)	12 (12%)
Other ICU[b]	10 (10%)	11 (11%)
Other hospital	8 (8%)	8 (8%)
Admission type, no. (%)		
Medical	52 (52%)	43 (43%)
Emergency surgery	43 (43%)	53 (54%)
Elective surgery	5 (5%)	3 (3%)
Diagnoses and procedures, no. (%)		
Haematologic malignancy[c]	13 (13%)	12 (12%)
Multiple trauma	8 (8%)	10 (10%)
Severe sepsis	47 (47%)	47 (47%)
Dialysis on admission	6 (6%)	5 (5%)
Mechanical ventilation	100 (100%)	99 (100%)
Days in hospital before ICU admission, days	0.9 (0.2–4.1)	1.1 (0.2–4.8)
Time from ICU admission to randomisation, h	14 (10–20)	13 (7–20)
Nutrition given in ICU prior to randomisation		
Energy, kcal/day	140 (24–260)	122 (30–275)
Protein, g/day	0 (0–0)	0 (0–0)
SAPS II[d]	47 (37–54)	48 (39–59)
SOFA score[e]	8 (6–11)	8 (5–10)

- 5 years age difference
- low BMI
- 11% other ICU
- otherwise well balanced

Allingstrup MJ et al. Intensive Care Med (2017) 43:1637–1647

Nutrition characteristics in ICU after randomisation

Variable	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)
Measured[a] energy requirement, kcal/day	2069 (1816–2380)	1887 (1674–2244)
Calculated[b] energy requirement, kcal/day	1950 (1750–2125)	1875 (1650–2100)
Energy intake, kcal/day	1877 (1567–2254)	1061 (745–1470)
Energy balance[c], kcal/day	−66 (−157 to −6)	−787 (−1223 to −333)
Measured[d] protein requirement, g/kg/day	1.63 (1.36–2.05)	1.16 (0.89–1.62)
Protein intake, g/kg/day	1.47 (1.13–1.69)	0.50 (0.29–0.69)
Protein balance[c], g/kg/day	−0.28 (−0.76 to 0.11)	−0.69 (−1.02 to −0.38)
Plasma urea, mmol/l	13.5 (8.7–21.9)	9.0 (5.6–14.4)
24-h urinary urea, mmol/day	516 (368–760)	320 (175–482)

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Primary and secondary outcomes

Primary outcome measure	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Adjusted mean difference (95% CI)	*p* value
PCS score at 6 months adjusted for presence of haematologic malignancy, mean (SD)	22.9 (21.8)	23.0 (22.3)	−0.0[a] (−5.9 to 5.8)	0.99

Secondary outcome measures	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Relative risk or mean difference (95% CI)	*p* value
Vital status, no. (%)				
Dead at day 28	20 (20%)	21 (21%)	0.94 (0.55–1.63)	0.83
Dead at day 90	30 (30%)	32 (32%)	0.93 (0.61–1.40)	0.72
Dead at 6 months	37 (37%)	34 (34%)	1.08 (0.74–1.57)	0.70
Length of stay among 6-month survivors, median days (IQR)				
ICU	7 (5–22)	7 (4–11)	NA	0.21
Hospital	30 (12–53)	34 (14–53)	NA	1.00
Percentage of days alive without life support at day 90, median (IQR)				
RRT	100% (97–100)	100% (97–100)	NA	0.64
Mechanical ventilation	86% (39–96)	92% (56–96)	NA	0.27
Inotrope/vasopressor support	96% (82–98)	96% (84–98)	NA	0.67
Time to new organ failure, mean days (SD)	5.4 (0.4)	5.9 (0.5)	NA	0.33[b]
New organ failure in ICU, no. (%)	81 (81%)	77 (78%)	1.04 (0.90–1.20)	0.57
Time to death, mean days (SD)	60 (13)	91 (24)	NA	0.51[c]
New use of RRT in ICU, no. (%)	22 (22%)	17 (17%)	1.28 (0.73–2.26)	0.39
Time to any infection, mean days (SD)	20 (1)	51 (9)	NA	0.80[b]
Nosocomial infections, no. (%)				
Any	19 (19%)	12 (12%)	1.57 (0.80–3.05)	0.18[d]

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EGDN induces more hyperglycemia and insulin use

Secondary outcome measures	Early goal-directed nutrition (*N* = 100)	Standard of care (*N* = 99)	Relative risk or mean difference (95% CI)	*p* value
Cumulative insulin dose in ICU, median IU (IQR)[g]	86 (2–530)	0 (0–39)	262 (71–453)	0.008
No. of patients (%) with at least one episode of				
Blood glucose ≤2.2 mmol/l	2 (2%)	1 (1%)	NA	–[e]
Blood glucose ≥15 mmol/l	52 (52%)	25 (25%)	2.06 (1.40–3.03)	0.0001

- **Protein balance improved from –0.69 to –0.28 in the EGDN group, i.e. by 0.41 g/kg/day.**
- **Plasma urea also increased, (assuming Vd of 60% of weight), increase in plasma urea nitrogen matches the apparent increase in protein balance**
- **This indicates that no net protein gain was obtained with the extra supply of protein.**
- **Reduction of protein load at a plasma urea above 20 mmol/l may explain why no increased in RRT was observed.**

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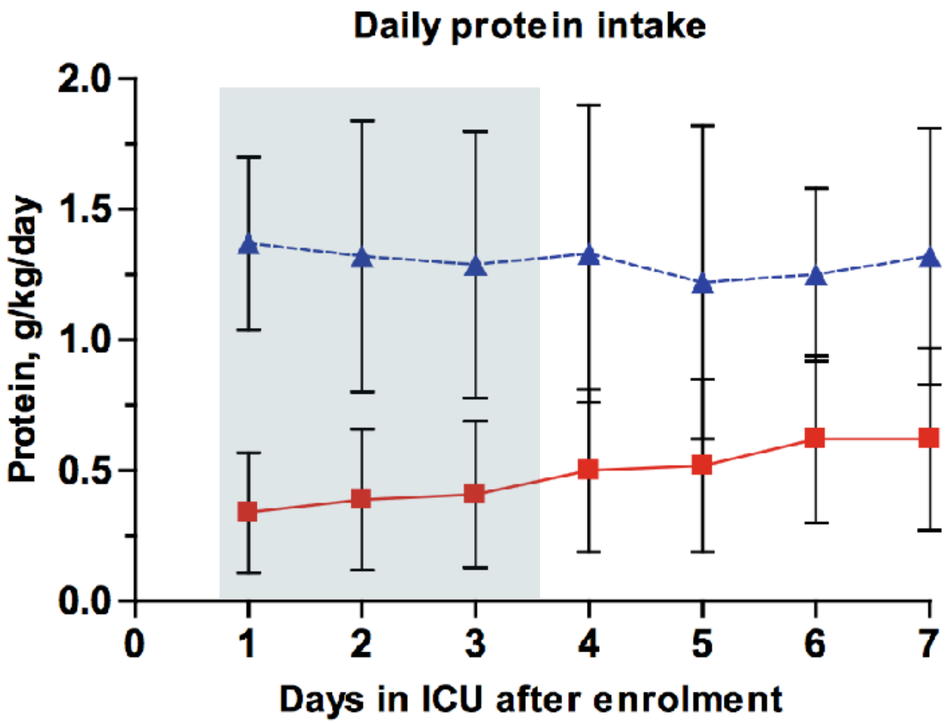
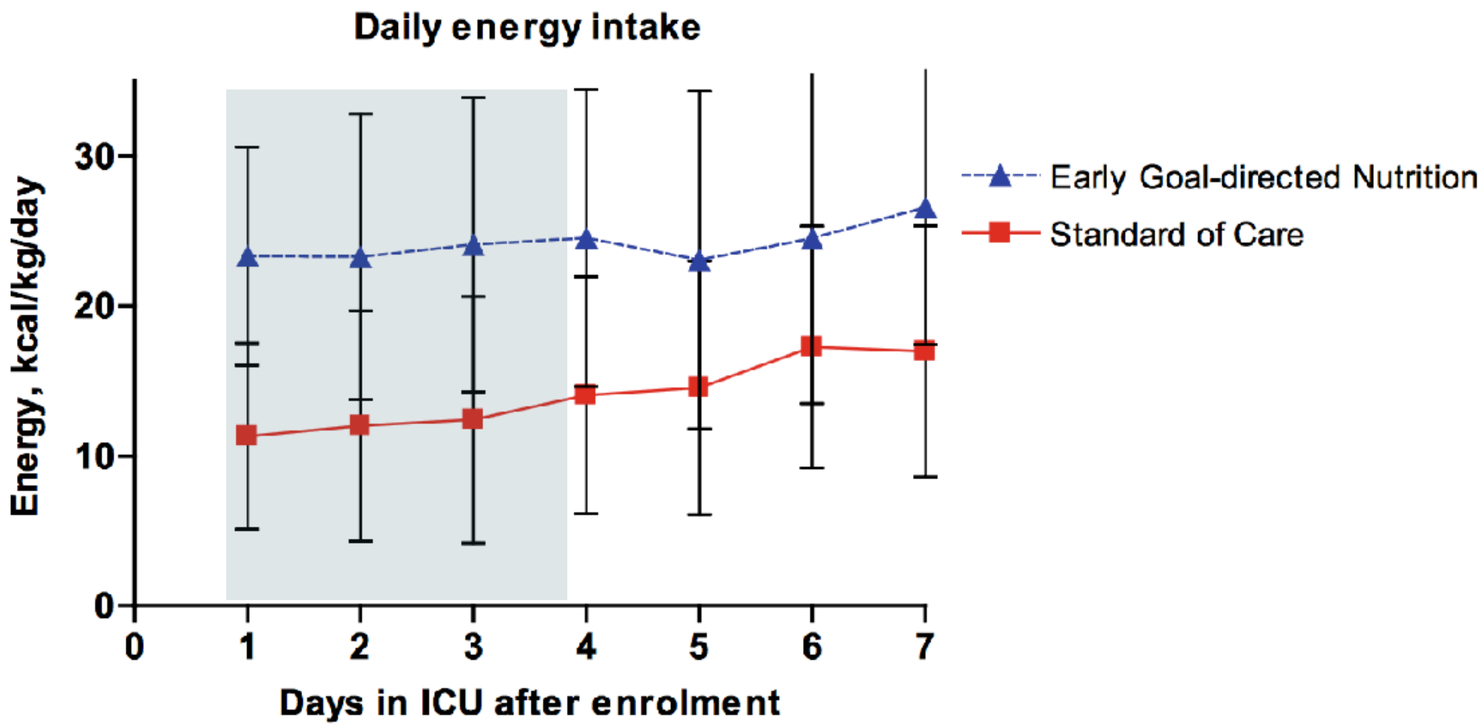
Additional protein and energy by SPN





Period of autophagy suppression

Period of endogenous energy production

Allingstrup MJ et al. Intensive Care Med (2017) 43:1637–1647

ESPEN ICU guidelines 2018

- Recommendation 6: In case of contraindications to oral and EN, PN should be implemented within three to seven days.
- Grade of recommendation: B – consensus (89 % agreement)
- Recommendation 7: Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.
- Grade of Recommendation: 0 – strong consensus (95 % agreement)
- Recommendation 8: To avoid overfeeding, early full EN and PN shall not be used in critically ill patients but shall be prescribed within three to seven days.
- Grade of recommendation: A – strong consensus (100 % agreement)

ESPEN ICU guidelines 2018

- **Recommendation 20: In patients who do not tolerate full dose EN during the first week in the ICU, the safety and benefits of initiating PN should be weighed on a case-by-case basis.**

- **Grade of recommendation: GPP – strong consensus (96.30 % agreement)**

- **Recommendation 21: PN should not be started until all strategies to maximize EN tolerance have been attempted. Grade of recommendation: GPP – strong consensus (95 % agreement)**

Timing nutrition during critical illness is essential