7.2 Early vs. Delayed Supplemental Parenteral Nutrition

There were no new randomized controlled trials since the 2015 update, but functional status outcomes have been added to the summary of evidence.

Question: Does the use of early vs delayed supplemental parenteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There was 1 level 1 study reviewed that compared early initiation of parenteral nutrition (day 3) with late initiation (day 8 if insufficient enteral intake by day 7) in adults in the (ICU) to supplement insufficient enteral nutrition. This trial is confounded by the fact that patients in the early group received high dose insulin to achieve tight glycemic control along with IV dextrose until day 3 when PN started. There is evidence that the groups separated early (by day 3-4, see Table 2 of primary publication) before the PN started so some of the harm may be due to IV glucose/insulin, not the PN.

Mortality: Early supplemental PN vs late had no effect on ICU mortality (RR 1.04, 95% CI 0.83, 1.30, p=0.72), hospital mortality (RR 1.04, 95% CI 0.88, 1.23, p=0.61), or 90-day mortality (RR 1.00, 95% CI 0.85, 1.18, p=0.99).

Infections: Early supplemental PN vs late was associated with a significant increase in all infectious complications (RR1.15, 95% CI 1.04, 1.27, p=0.008). The early PN group had a significantly higher incidence of sepsis (RR 1.23, 95% CI 1.00, 1.53, p=0.05) compared to the late PN group.

LOS & ventilator days: Early supplemental PN vs late was associated with significantly longer lengths of stay in ICU (p=0.02), significantly longer LOS in hospital (p=0.004) and significantly longer time spent on mechanical ventilation (p=0.02) compared to late initiation of supplemental PN.

Costs: Early vs late supplemental PN resulted in significantly higher total health care costs per patient (p=0.04).

Functional Status: Early vs late supplemental PN had no difference on 6 minute walk distance or activities of daily living at hospital discharge (p=0.57 and 0.31, respectively).

Compared to late initiation of PN (day 8) in patients receiving EN:

1) Early supplemental PN has no effect on mortality in critically ill patients.
2) Early supplemental PN may be associated with an increase in infectious complications in critically ill patients.
3) Early supplemental PN may be associated with a longer ICU and hospital length of stay in critically ill patients.
4) Early supplemental PN may be associated with an increase in duration of ventilation in critically ill patients.
5) Early supplemental PN may be associated with higher total health care costs per patient.

6) Early supplemental PN has no effect on functional status outcomes in critically ill patients.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating early vs delayed supplemental PN in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				EN + PN	EN	EN + PN	EN
1) Casaer 2011	Critically ill from 7 ICUs Admitted with a nutrition risk ≥3 based on Nutrition Risk Screening (NRS) N=4640	C.Random: Yes ITT: Yes Blinding: No (11)	EN + early PN (20% IV glucose; kcal target day 1=400kcal, day 2=800 kcal, Day 3 initiate PN with goal of 100% caloric goal with EN+PN; caloric needs based on IBW, PN d/c if kcal via EN ≥80% requirements, restarted if EN ≤50%) vs EN + late PN (Late initiation; 5% glucose IV equal to PN group to match hydration) If EN sufficient >7 days, PN added on day 8 to reach kcal requirements) Non-isocaloric/isonitrogenous	**ICU** 146/2312 (6) RR 1.04, 95% CI 0.83, 1.30 p=0.72 **Hospital** 251/2312 (11) RR 1.04, 95% CI 0.88, 1.23 p=0.61 **90-day** 255/2312 (11) RR 1.00, 95% CI 0.85, 1.18 p=0.99	**ICU** 141/2328 (6) **Hospital** 242/2328 (10) **90-day** 257/2328 (11)	**Total** 605/2312 (26) RR 1.15, 95% CI 1.04, 1.27 p=0.008	**Total** 531/2328 (23)

Table 1. Randomized studies evaluating early vs delayed supplemental PN in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Physical Function	
	EN + PN	EN	EN + PN	EN	EN + PN	EN	EN + PN	EN
1) Casaer 2011	**ICU** 4 (2-9) p=0.02 **Hospital** 16 (9-29) p=0.004	**ICU** 3 (2-7) **Hospital** 14 (9-27)	2 (1-5) p=0.02	2 (1-5)	**Mean total incremental health care cost, Euros (IQR)** 17973 (8749-18677) P=0.04	16863 (8793-17774)	**6 Minute Walk Test Distance at hospital discharge, metres (IQR)** 283 (205-336), n=603 P=0.57 **Independent in all activities of daily living at hospital discharge, no. (%)** 752/996 (75.5) P=0.31	277 (210-345), n=624 779/1060 (73.5

ITT: intent to treat
ICU: intensive care unit
† presumed hospital mortality unless otherwise specified
C. Random: concealed randomization
RR: relative risk; CI: confidence interval
EN: enteral nutrition
LOS: length of stay
PN: parenteral nutrition
NR: not reported
‡ refers to the # of patients with infections unless specified

References

Included Studies

1. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011 Aug 11;365(6):506-17. Epub 2011 Jun 29. PubMed PMID: 21714640.

Excluded Articles

#	Reason excluded	Citation
1	Subanalysis of Casaer 2011	Langouche L, Vander Perre S, Marques M, Boelen A, Wouters PJ, Casaer MP, Van den Berghe G. Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its relation with outcome: a randomized, controlled clinical study. J Clin Endocrinol Metab. 2013 Mar;98(3):1006-13.
2	Duplicate analysis of Casaer	Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Güiza FG, Wouters PJ, Mesotten D, Van den Berghe G. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013 Oct;41(10):2298-309.
3	Secondary analysis of Casaer 2011	Greet Hermans; Michael P Casaer; Beatrix Clerckx; Fabian Güiza; Tine Vanhullebusch; Sarah Derde; Philippe Meersseman; Inge Derese; Dieter Mesotten; Pieter J Wouters; Sophie Van Cromphaut; Yves Debaveye; Rik Gosselink; Jan Gunst; Alexander Wilmer; Greet Van den Berghe; Ilse Vanhorebeek. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. The Lancet Respiratory Medicine (October 2013), 1 (8), Supplement 2, pg. 621-629.
4	Subanalysis of Casaer 2011, no new relevant data	Vanwijngaerden YM, Langouche L, Brunner R, Debaveye Y, Gielen M, Casaer M, Liddle C, Coulter S, Wouters PJ, Wilmer A, Van den Berghe G, Mesotten D. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. Hepatology. 2014 Jul;60(1):202-10.