7.2. Early vs. Delayed Supplemental Parenteral Nutrition May 2015

There were no new randomized controlled trials since the 2013 update and hence there are no changes to the following summary of evidence.

Recommendation: *We strongly recommend that early supplemental PN and high IV glucose not be used in unselected critically ill patients (i.e. low risk patients with short stay in ICU). In the patient who is not tolerating adequate enteral nutrition, there are insufficient data to put forward a recommendation about when parenteral nutrition should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis.*

Discussion: The committee noted that, in contrast to other studies of supplemental PN, this trial focused on the question of timing (early vs. late) and thus it was not combined with the other trials of supplemental PN. The committee noted the large multicentre study that demonstrated worse clinical outcomes with the use of early supplemental parenteral nutrition. There were concerns in the study about the high glucose loading via IV route, and about the population (i.e. low nutritional risk, mostly elective surgical patients, and short ICU length of stay). The committee agreed that a strong recommendation be made not to use early IV glucose and supplemental PN in unselected patients and similar to section 7.0a (Combination Parenteral Nutrition and Enteral Nutrition), they agreed that the use of supplemental PN in patients not tolerating EN may need to assessed on a case-by-case basis.

Semi Quantitative Scoring

Values	Definition	2013 Score: 0, 1, 2,3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	1 (infection)
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	0
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	n/a
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	1
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	3
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre=1, moderate likelihood i.e. multicentre with limited patient population or practice setting=2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings=3)	1
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	1
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	1

7.2 Early vs. Delayed Supplemental Parenteral Nutrition

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.

Mortality: Early vs late supplemental PN had no difference 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).

LOS & ventilator days: Early supplemental PN 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.

Other: 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.

Conclusions:

1) Early vs late PN to supplement EN has no effect on mortality in critically ill patients.
2) Early supplemental PN is associated with an increase in infectious complications in critically ill patients compared to late supplemental PN.
3) Early supplemental PN is associated with significantly longer ICU and hospital length of stay in critically ill patients compared to late supplemental PN.
4) Early supplemental PN is associated with an increase in duration of ventilation in critically ill patients compared to late supplemental PN.

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)	ICU 141/2328 (6)	Total 605/2312 (26)	Total 531/2328 (23)
				RR 1.04, 95% CI 0.83, 1.30 p=0.72		RR 1.15, 95% CI 1.04, 1.27 p=0.008	
				Hospital 251/2312 (11)	Hospital 242/2328 (10)		
				RR 1.04, 95% CI 0.88, 1.23 p=0.61			
				90-day 255/2312 (11)	90-day 257/2328 (11)		
				RR 1.00, 95% CI 0.85, 1.18 p=0.99			

Study	LOS days		Ventilator days		Cost		Other	
	EN + PN	EN	EN + PN	EN	EN + PN	EN	EN + PN	EN
1) Casaer 2011	ICU 4 (2-9)	ICU 3 (2-7)	2 (1-5)	2 (1-5)	NR	NR	NR	
	p=0.02		p=0.02					
	Hospital 16 (9-29)	Hospital 14 (9-27)						
	p=0.004							

† presumed hospital mortality unless otherwise specified
‡ refers to the # of patients with infections unless specified