10.1 Strategies to Optimize Parenteral Nutrition and Minimize Risks: Dose of PN March 2013

There are no new randomized controlled trials since the 2009 update and hence there are no changes to the following summary of evidence.

Recommendations: *Based on 4 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when parenteral nutrition is indicated for short term use (< 10 days), low dose parenteral nutrition should be considered. There are insufficient data to make recommendations about the use of low dose parenteral nutrition in the following patients: those requiring PN for long term (> 10 days); obese critically ill patients and malnourished critically ill patients. Practitioners will have to weigh the safety and benefits of low dose PN on an individual case-by-case basis in these latter patient populations.*

Discussion: Our recommendation on low dose PN is in the context of our earlier recommendation that EN be used preferentially to PN and that strategies to maximize EN be utilized prior to initiating PN. The issue of low dose PN is only relevant to those patients tolerating some (inadequate) EN where practitioners, on a case-by case basis are deliberating about adding PN (see section 1 and 7 i.e. EN vs PN and combination EN + PN). Given the inconsistencies in the definition of low dose PN amongst the studies included, the committee could not agree upon a specific definition. It was agreed that low dose PN could be achieved by either withholding lipids or reducing carbohydrate load. The committee had concerns about including the trial (Ahrens et al) that compared 27 Kcal/kg/day to 37 kcal/kg/day in the meta-analysis as the lower dose group from this study had substantially greater calories than the lower dose group of the other studies. When a sensitivity analysis was done without this paper, there was a large treatment effect on infectious complications. There was no evidence from the studies that showed low dose PN was harmful. Low dose parenteral nutrition may be equivalent to standard PN with respect to cost and feasibility. Two of the studies excluded malnourished patients (McCowen, Ahrens) and the committee was concerned about the paucity of data in this population and also about the safety and unknown effects of long term Low dose parenteral nutrition. The committee decided that while the concerns regarding low dose parenteral nutrition and essential fatty acid deficiency were probably minimal for those patients tolerating some EN and requiring PN for short term (< 10 days), this cannot be extrapolated to those who have an absolute contraindication to EN and need PN for a longer duration.

Semi Quantitative Scoring

Values	Definition	2009 Score: (0,1,2,3)	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	3* (infection)	0* (mortality) 2* (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	2*	1*
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	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	0	0
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	3	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	1	1
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	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	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3	3
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	2	2

*The 2009 scoring for effect size, confidence intervals and validity were corrected in December 2012

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Question: Does the dose of parenteral nutrition affect the outcome of critically ill patients?

Summary of evidence: Four level 2 studies have evaluated this question. Choban et al looked at low dose feeding in obese patients specifically. In the McCowen and Batistella studies, the control group was also given lipids as a source of calories. Ahrens et al studied the effect of a higher lipid, lower CHO parenteral solution (27 Kcals/kg/day) vs. a higher CHO, lower lipid PN solution (37 Kcal/kg/day)

Mortality: A meta-analysis of all 4 studies showed no effect on mortality (RR 0.61, 95 % CI 0.20,1.85, p = 0.4) (figure 1). This did not change when a sensitivity analysis was done without Ahrens et al (RR = 0.78, 95%CI 0.17, 3.56, p = 0.7) (figure 2) or without McCowen (RR = 0.65, 95% CI 0.10,4.05, p =0.6) (figure 3).

Infections: Three studies reported on the number of patients with infections. Batistella et al found a significant reduction in pneumonia in the low dose PN group ($p < 0.05$) and in the McCowen et al study, low dose PN was associated with a trend towards a reduction in infections (p = 0.2) while Ahrens et al found no significant difference in the number of patients with infectious complications (p = 0.4). When these 3 studies were aggregated, low dose PN has no effect on infectious complications (RR = 0.73, 95%CI 0.41,1.31, p = 0.3) (figure 4). In a sensitivity analysis without the Ahrens, low dose PN was associated with a significant reduction in infectious complications (RR=0.63, 95 % CI-0.42,0.93, p = 0.02) (figure 5).

LOS: A significantly shorter ICU stay (p = 0.02) and hospital stay (p = 0.03) was observed in trauma patients receiving low dose PN (Batistella). No differences in LOS were seen in the other three other studies (McCowen, Choban, Ahrens).

Ventilator days: Were reported in 2 studies. Significantly fewer ventilated days (p = 0.01) were observed in trauma patients receiving low dose PN (no lipids) compared to those receiving higher dose PN (with lipids) (Battistella). No differences were observed between the groups in surgical critically ill patients (Ahrens).

Other complications: Incidence of hypergylcemia was similar in the low dose and standard groups (McCowen), but significantly lower in the Ahrens et al study.

Conclusions:

1) Low dose parenteral nutrition without lipids maybe associated with a reduction in infections in critically ill patients.
2) Insufficient data to comment on the effects of low dose parenteral nutrition in obese 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 Dose of Parenteral Nutrition In Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡		RR (CI)**
				Low dose	High dose	Low dose	High dose	
1) Ahrens 2003 unpublished	Surgical+ICU patients N=40	C:Random: not sure ITT: no Blinding: no (7)	Low dose PN (lipids/CHO) Pro 1.61g/kg/d±0.13, 27 kcal/kg/d vs. Standard PN, (lipids/CHO) Pro 1.53±0.26g/kg/d 37 kcaL/kg/d	1/20 (5)	3/20 (15)	5/20 (25)	2/20 (10)	2.50 (0.28-2.52)
2) Battistella 1997	Polytrauma patients N=60	C:Random: not sure ITT: no Blinding: no (8)	Lipid-free PN, Pro: 1.6g/kg/d 28.5kcal/kg/d vs. Standard PN (lipids/CHO), Pro 1.6g/kg/d 37kcal/kg/d	2/27 (7)	0/30 (0)	Pneumonia 13/27 (48) Line Sepsis 5/27 (19) Total # infections per group 39/27	Pneumonia 22/30 (73) Line Sepsis 13/30 (43) Total # infections per group 72/30	Pneumonia 0.66 (0.42-1.03) Line Sepsis 0.43 (0.18-1.04)
3) Choban 1997	ICU & hospital obese patients, ICU patients N=13	C: Random: yes ITT: yes Blinding: no (10)	Low dose PN (low lipids/CHO) Pro 2g/kg/d, 22kcal/kg/d vs. Standard PN, (low lipids/CHO) Pro 2 g/kg/d, 36 kcal/kg/d	Hospital 0/6 (0)	Hospital 2/7 (29)	NA	NA	NA
4) McCowen 2000	Probable ICU patients (mostly ventilated) N=48	C:Random: not sure ITT: no Blinding: no (6)	Low dose PN (no lipids), Pro 1.5 g/d, 14 kcal/kg/d vs. Standard PN (lipids,CHO), Pro 1.5 g/d, 18 kcal/kg/d	2/21 (10)	3/19 (16)	6/21 (29)	10/19 (53)	0.54 (0.24-1.21)

Table 1. Randomized Studies Evaluating Dose of Parenteral Nutrition In Critically Ill Patients (continued)

Study	LOS days		Ventilator days		Hyperglycemic Episodes	
	Low dose PN	StandardPN				
1) Ahrens 2003 [unpublished]	14 (10-21) ICU 15 (11-26) hospital	14(10-37) ICU 25 (15-39) hospital	10 (4-15)	19 (4-35)	Low dose ≥200 mg/dl: 0 ≥300mg/dl: 0 ≥400mg/dl: 0 # pts with hyperglycemia 5/20 (25 %)	Standard ≥200mg/dl: 33.1%(0-58.4) ≥300mg/dl: 5 % (0-13.8) ≥400 mg/dl: 0% (0-1.5) # pts with hyperglycemia 14/20 (70%)
2) Battistella 1997	18±12 (27) ICU 27 ±16 (27) hospital	29±22 (30) ICU 39±24 (30) hospital	15 ±12 (27)	27 ± 21 (30)	NA	NA
3) Choban 1997	48±30 (6) hospital	45±38 (7) hospital	NA	NA	NA	NA
4) McCowen 2000	19±14 (21)	17±15 (19)	NA	NA	20%	26%

C. Random: concealed randomization
ITT: intent to treat
† presumed ICU mortality unless otherwise specified
±():mean±Standard deviation (number)
‡ refers to the # of patients with infections
** RR= relative risk, CI=Confidence Intervals

Figure 1. Mortality (with Ahrens)

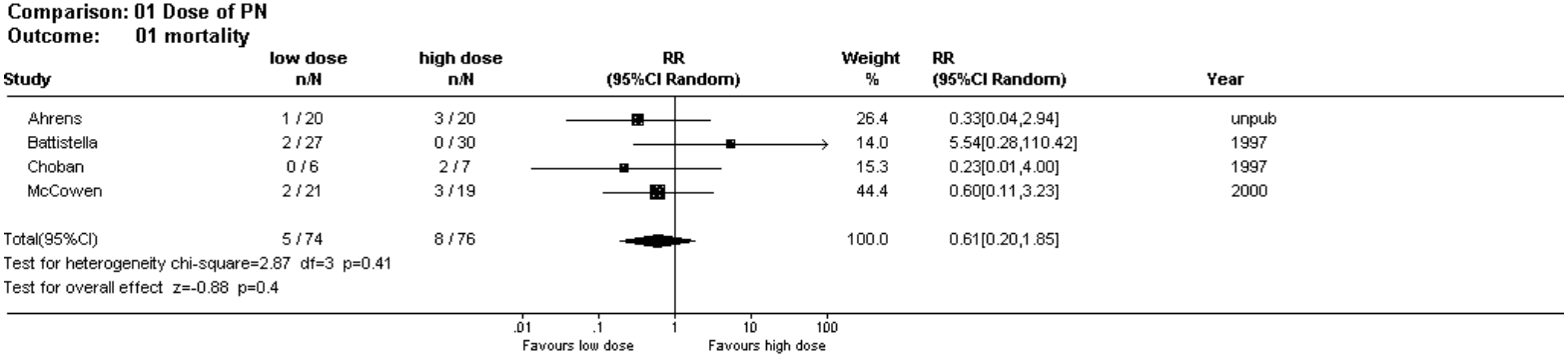

Figure 2. Sensitivity Analysis (Without Ahrens)

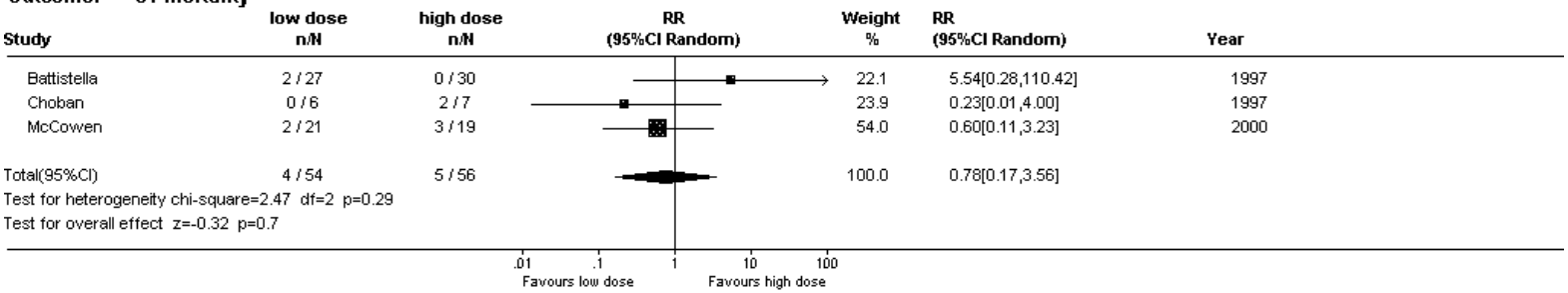

Figure 3. Sensitivity Analysis (without McCowen)

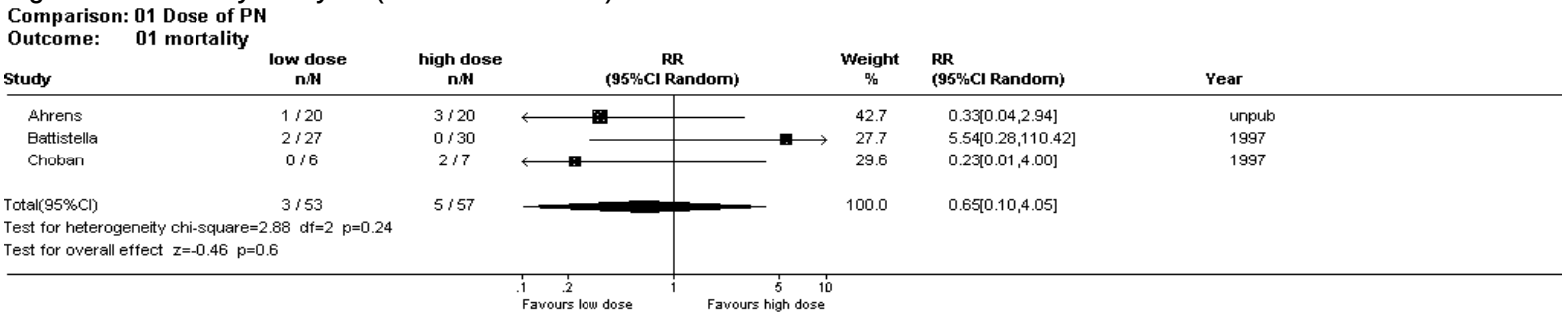

Figure 4.

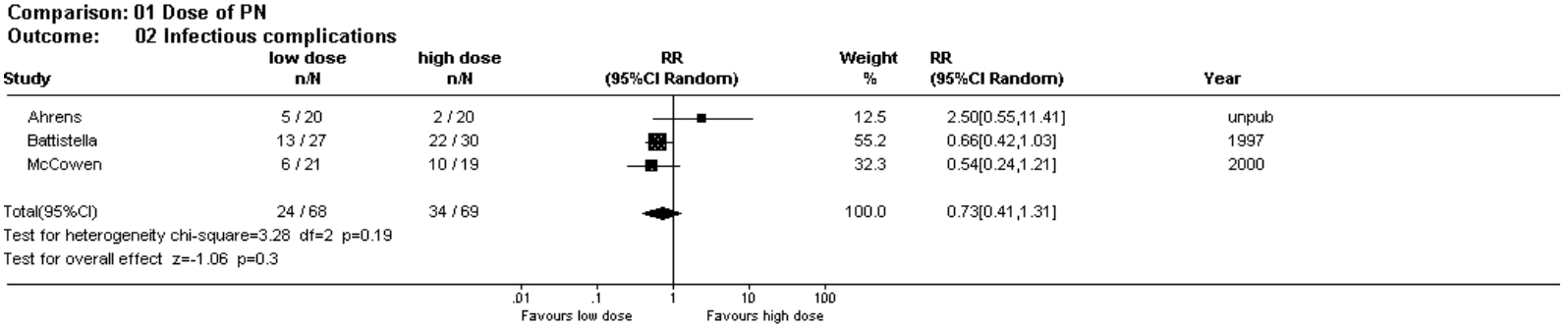

Figure 5. Sensitivity Analysis (without Ahrens)