9.3 Composition of Parenteral Nutrition: Zinc (either alone or in combination with other antioxidants) May 27th 2009

Recommendation:
There are insufficient data to make a recommendation regarding IV/PN zinc supplementation in critically ill patients.

Discussion: The committee noted the potentially large treatment effect of zinc enriched PN with respect to a reduction in mortality. The wide confidence intervals weaken this estimate. Safety, cost and feasibility issues were considered to be favourable. The committee noted that in some sub populations of critical illness with high zinc losses (GI fistula, burns, etc) there may be some benefit to zinc supplementation but data are lacking to support a recommendation.

Values	Definition	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
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
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	1
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	2
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	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	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	3

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Question: Does zinc supplementation (via IV/PN) given either alone or in combination with other nutrients result in improved outcomes in the critically ill patient?

Summary of evidence: There were 4 level 2 studies reviewed, one that compared a higher dose of parenteral zinc to a lower dose in ventilated head injured patients (Porter), both groups progressing to oral zinc (higher vs. lower). The other three studies compared IV zinc in combination with other antioxidants (selenium, α tocopherol and/or copper) to placebo.

Mortality: When all three studies were aggregated, zinc supplementation was associated with a trend a reduction in mortality (RR = 0.58, 95 % confidence intervals 0.23-1.44, p = 0.24) (figure1).

Infections: Only reported in two studies, one reported number of infections per patient (Young), hence unable to do a meta-analysis. The other study reported no differences in infectious complications between the two groups (Berger 2001).

Hospital/ICU length of stay, ventilator days:There were no statistical differences between the groups (figure 3, 4).

Cost, other complications: Only one study reported the number of patients with organ failure, which was the same in the group receiving zinc supplementation and none (Berger 2001)

Conclusion:
Zinc supplementation given IV/PN (either alone or in combination with other antioxidants) may be associated with a trend towards a reduction in mortality 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 zinc supplementation in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Experimental	Control	Experimental	Control
1) Young 1996	Severely head injured patients, ventilated N = 68	C.Random: not sure ITT: yes Blinding: double (12)	12 mg elemental zinc via PN, then progressing to oral zinc vs. 2.5 mg elemental zinc, then progressing to oral placebo	4/33 (12)	9/35 (26)	NR	NR
2) Berger 1998	Burns > 30 % TBSA N = 20	C.Random: not sure ITT: yes Blinding: double blind (11)	IV Copper (40.4 μmol), selenium (2.0 μmol), zinc (406 μmol) + standard trace elements vs. standard trace elements elements (Copper 20 μmol, selenium 0.4μmol, zinc 100 μmol) X 8 days, all received early EN	1/10 (10)	0/10 (0)	1.9 ± 0.9 (1-4) per patient	3.1 ± 1.1 (2-5) per patient
3) Berger 2001*	Trauma patients, surgical ICU N = 32	C.Random: not sure ITT: no Blinding: single (7)	IV Selenium + α tocopherol + zinc vs placebo (All groups received enteral nutrition)	0/11 (0)	1/11 (9)	3/11 (27)	3/11 (27)
4) Berger 2007	Burns > 20 % BSA N = 21	C.Random: not sure ITT: yes Blinding: no (8)	IV 100 mls of Copper (59 μmol) + Selenium (375 μgm + zinc (574 μmol) vs NaCl (0.9%) from admission for 5-15 days. Both groups were on EN.	1/11 (9)	1/10 (10)	2.1 ± 1.0 per patient	3.6 ± per patient
5) Berger 2008	Mixed ICU N = 200	C.Random: not sure ITT: yes Blinding: no (10)	IV Selenium supplementation loading dose 540 μg/day + zinc (60 mg) + Vit C 2700 mg + Vit B 305 mg + Vit E enteral 600 mg + Vit E 12.8 mg IV for 2 days followed by half the dose of all vs. standard vitamins. (All groups received EN or PN)	ICU 8/102 (8) Hospital 14/102 (14) 3 month 14/602 (14)	ICU 5/98 (5) Hospital 9/98 (11) 3 month 11/98 (11)	36/102 (35)	34/98 (35)

Table 2. Randomized studies evaluating zinc in critically ill patients

Study	LOS days		Ventilator days		Cost		Other	
	Experimental	control	Experimental	control	Experimental	control	Experimental	control
1) Young 1996	NR	NR	NR	NR	NR	NR	NR	NR
2) Berger 1998	ICU 30 ± 12 (10) Hospital 54 ± 27 (10)	ICU 39 ± 13 (10) Hospital 66 ± 31 (10)	9 ± 10 (10)	12 ± 9 (10)	NR	NR	NR	NR
3) Berger 2001*	ICU 5.8 ± 4.4 (11) Hospital 60 ± 48 (11)	ICU 6.1 ± 6.0 (11) Hospital 59 ± 37 (11)	4.1 ± 3.6 (11)	4.2 ± 5.2 (11)	NR	NR	Organ failure 3/11 (27)	4/11 (36)
4) Berger 2007	ICU 35 ± 27 (11)	ICU 47 ± 37 (10)	7.6 ± 6 (11)	12.6 ± 6 (10)	NR	NR	NR	
5) Berger 2008	ICU 5.8 ± 5.4 (102) Hospital 23 ± 20 (102)	ICU 5.4 ± 5.7 (98) Hospital 26 ± 20 (98)	Vent free days 26.1 ± 5.7	Vent free days 26.6 ± 5.2	NR	NR	NR	

C.Random: concealed randomization
ITT: intent to treat
NR: not reported
‡ refers to the # of patients with infections unless specified
† presumed hospital mortality unless otherwise specified
* only data pertaining to the selenium + α tocopherol + zinc vs placebo groups reported here
**RR (CI): Relative risk (95 % confidence intervals)

Figure 1.

Review: Parenteral Zinc
Comparison: 01 Parenteral Zinc vs control
Outcome: 01 Mortality

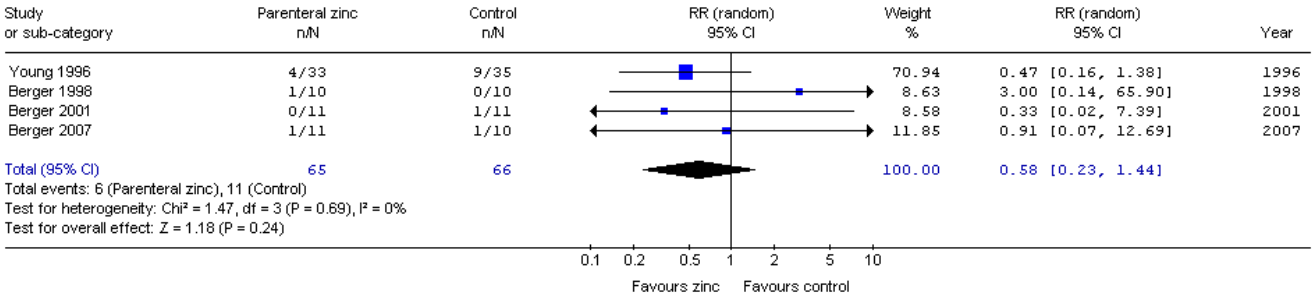


Figure 2.

Review: Parenteral Zinc
Comparison: 01 Parenteral Zinc vs control
Outcome: 02 Hospital Length of Stay

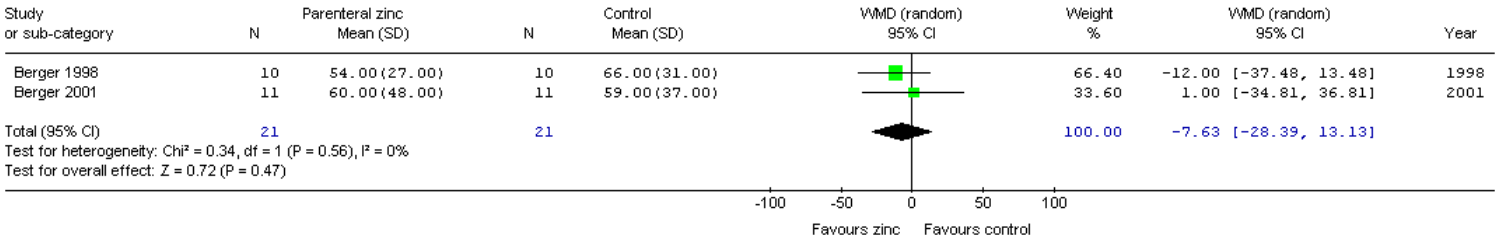
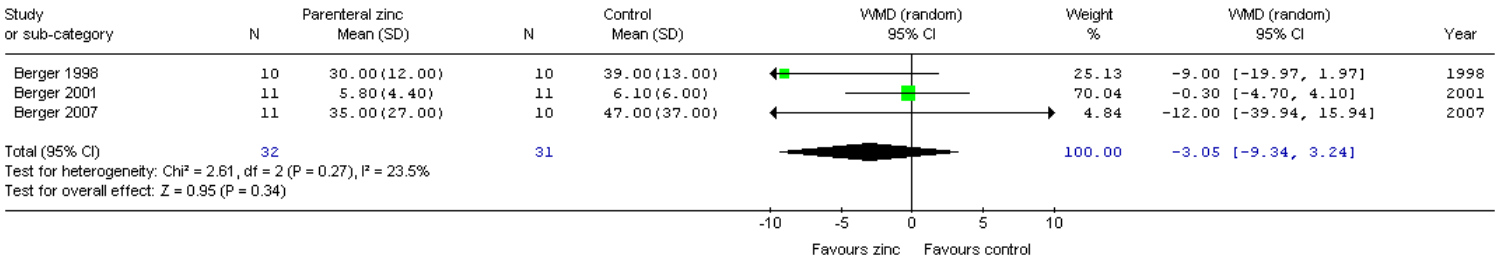


Figure 3.

Review: Parenteral Zinc
Comparison: 01 Parenteral Zinc vs control
Outcome: 03 ICU Length of stay



TOPIC: PN Composition: Zinc (alone or in combination)

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill human patients (no elective sx.)
Intervention: PN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	WhyRejected
1	Young	J of Neurotrauma 1996	√		
2	Berger	Am J Clin Nutr 1998	√		
3	Berger	Int Care Med 2001	√		
4	Berger	Nut Res 2001	√		Same study as Berger 2001: Int Care Med. Data is combined and presented as Berger 2001
5	Berger	Am J Clin Nutr 2007	√		
6	Berger	Critical Care 2008	√		

I = included, E = excluded

Reference List

1. Young B, Ott L, Kasarskis E, Rapp R, Moles K, Dempsey RJ, Tibbs PA, Kryscio R, CcClain C (1996) Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury. J Neurotrauma 13:25-34

2. Berger MM, Spertini F, Shenkin A, Wardle C, Wiesner L, Schindler C, Chioléro RL (1998) Trace element supplementation modulates pulmonary infection rates after major burns: a double-blind, placebo-controlled trial. Am J Clin Nutr 68:365-371

3. Berger MM, Reymond MJ, Shenkin A, Rey F, Wardle C, Cayeux C, Schindler C, Chiolero RL. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial. Intensive Care Med. 2001 Jan;27(1):91-100.

4. Berger MM, Baines M, Chiolero R, Wardle C, Cayeux, Shenkin A (2001) Influence of early trace element and vitamin E supplements on antioxidant status after major trauma: a controlled trial. N. Research 21:41-54

5. Berger MM, Binnert C, Chiolero RL, Taylor W, Raffoul W, Cayeux MC, Benathan M, Shenkin A, Tappy L. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. Am J Clin Nutr. 2007 May;85(5):1301-6.

6. Berger MM, Soguel L, Shenkin A, Revelly JP, Pinget C, Baines M, Chioléro RL. Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma, and subarachnoid hemorrhage patients. Crit Care. 2008;12(4):R101