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

There are no new randomized controlled trials since the 2015 updates and hence there are no changes to the following summary of evidence.

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% CI 0.23, 1.44, p=0.24; figure 1).

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 (figures 3 and 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:

1) Zinc supplementation given IV/PN (either alone or in combination with other antioxidants) may be associated with 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 1. Randomized studies evaluating zinc supplementation in critically ill patients (continued)

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	
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	
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
**RR (CI): Relative risk (95 % confidence intervals)
ITT: intent to treat
ICU: intensive care unit
NR: not reported
LOS: length of stay

‡ 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. Mortality

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

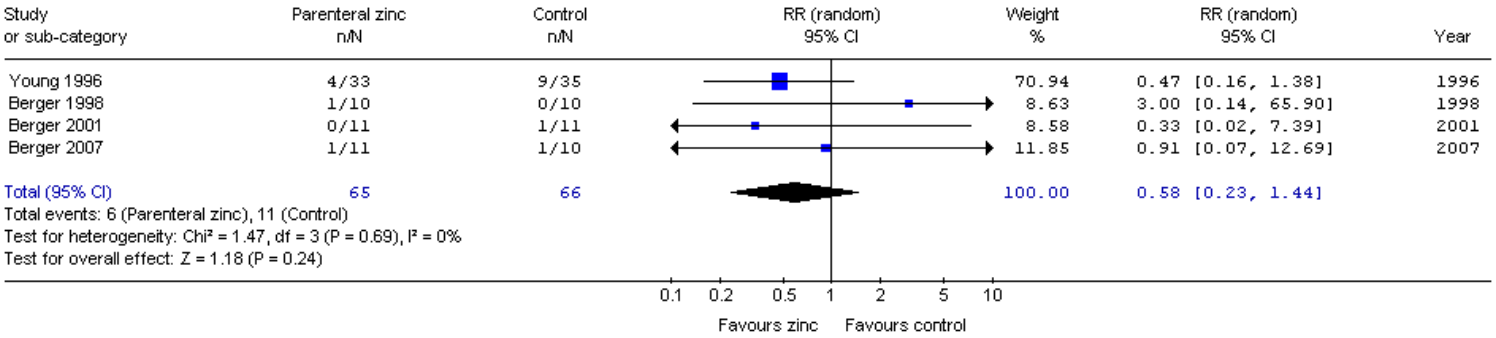

Figure 2. Hospital LOS

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

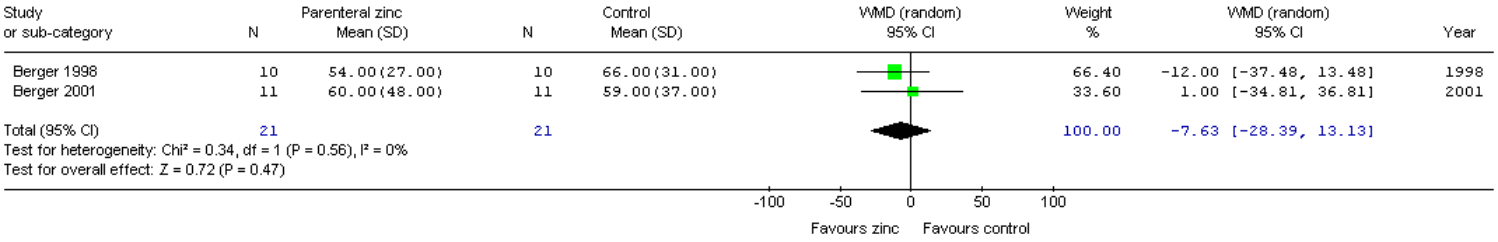

Figure 3. ICU LOS

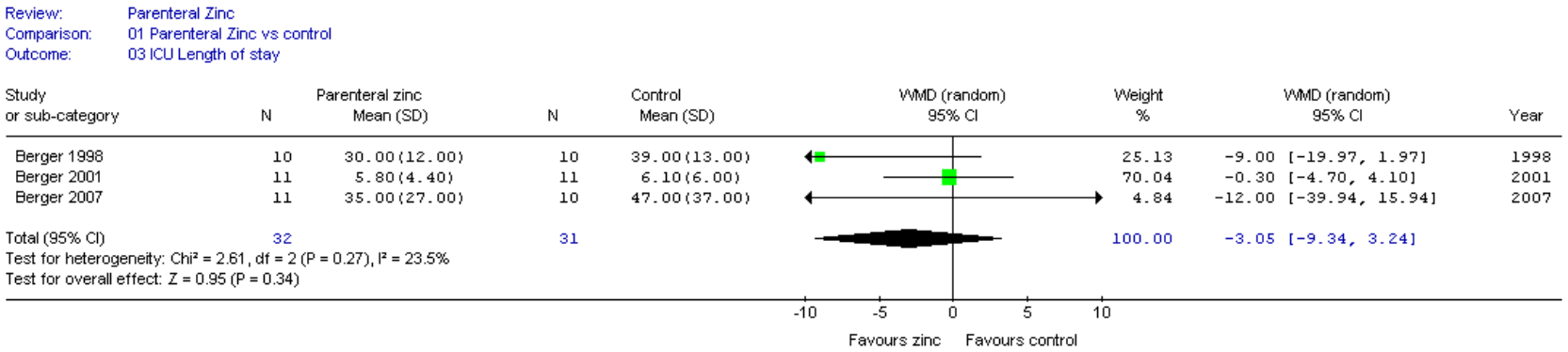

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Same study as Berger 2001: Int Care Med. Data is combined and presented as Berger 2001	Berger MM, Baines M, Chiolero R, Wardle C, Cayeux, Shenkin A. Influence of early trace element and vitamin E supplements on antioxidant status after major trauma: a controlled trial. 2001. N Research 21:41-54
2	Same as Berger AJCN 2007	Berger MM, Baines M, Raffoul W, Benathan M, Chiolero RL, Reeves C, Revelly JP, Cayeux MC, Sénéchaud I, Shenkin A. Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. Am J Clin Nutr. 2007 May;85(5):1293-300.