## 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,  $\alpha$  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	Intervention	Mortality	y # (%)†	Infections # (%)‡		
	· opanacion	(score)		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*	surgical ICU ITT: no vs placebo		(All groups received enteral	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.		μmol) vs NaCl (0.9%) from admission for 5-15 days. Both	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)

LOS	days	Ventilat	or days	Co	st	Other	
Experimental	Control	Experimental	Control	Experimental	Control	Experimental Control	
NR	NR	NR	NR	NR	NR	NR	
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	
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	<b>Organ failure</b> 3/11 (27) 4/11 (36)	
ICU 35 ± 27 (11)	ICU 47 ± 37 (10)	7.6 ± 6 (11)	12.6 ± 6 (10)	NR	NR	NR	
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	<b>Vent free days</b> 26.6 ± 5.2	NR	NR	NR	
	CU   30 $\pm$ 12 (10)   Hospital   54 $\pm$ 27 (10)     CU   5.8 $\pm$ 4.4 (11)   Hospital   60 $\pm$ 48 (11)     CU   35 $\pm$ 27 (11)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{ c c c c c c } \hline \textbf{Experimental} & \textbf{Control} & \textbf{Experimental} \\ \hline NR & NR & NR & NR \\ \hline & \textbf{ICU} & \textbf{ICU} & 9 \pm 10 \ (10) \\ \hline 30 \pm 12 \ (10) & 39 \pm 13 \ (10) & \textbf{Hospital} \\ 54 \pm 27 \ (10) & 66 \pm 31 \ (10) & \textbf{ICU} \\ \hline 5.8 \pm 4.4 \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	$ \begin{array}{ c c c c c c c c } \hline \textbf{Experimental} & \textbf{Control} & \textbf{Experimental} & \textbf{Control} \\ \hline \textbf{NR} & \textbf{NR} & \textbf{NR} & \textbf{NR} & \textbf{NR} \\ \hline                                  $	$ \begin{array}{ c c c c c c c c } \hline \textbf{Experimental} & \textbf{Control} & \textbf{Experimental} & \textbf{Control} & \textbf{Experimental} \\ \hline \textbf{NR} & \textbf{NR} & \textbf{NR} & \textbf{NR} & \textbf{NR} & \textbf{NR} \\ \hline \textbf{ICU} & \textbf{ICU} & 39 \pm 13 \ (10) & 39 \pm 13 \ (10) & \textbf{Hospital} & 66 \pm 31 \ (10) & \textbf{ICU} & 5.8 \pm 4.4 \ (11) & \textbf{Hospital} & 61 \pm 6.0 \ (11) & \textbf{Hospital} & 60 \pm 48 \ (11) & 59 \pm 37 \ (11) & \textbf{ICU} & \textbf{35} \pm 27 \ (11) & \textbf{47} \pm 37 \ (10) & \textbf{Vent free days} & \textbf{NR} \\ \hline \textbf{ICU} & \textbf{ICU} & \textbf{ICU} & \textbf{S.8} \pm 5.4 \ (102) & 5.4 \pm 5.7 \ (98) & \textbf{Hospital} & \textbf{Hospital} & \textbf{Hospital} \\ \hline \textbf{Hospital} & \textbf{Hospital} & \textbf{Hospital} & \textbf{NR} \\ \hline  \end{array} $	Experimental   Control   Experimental   Control   Experimental   Control	

C.Random: concealed randomization

ITT: intent to treat ICU: intensive care unit

NR: not reported LOS: length of stay

<sup>\*\*</sup>RR (CI): Relative risk (95 % confidence intervals)

<sup>‡</sup> refers to the # of patients with infections unless specified

<sup>†</sup> presumed hospital mortality unless otherwise specified

<sup>\*</sup> only data pertaining to the selenium + lpha tocopherol + zinc vs placebo groups reported here

<sup>\*\*</sup>RR (CI): Relative risk (95 % confidence intervals)

# Figure 1. Mortality Review: Parenteral Zinc

Comparison: 01 Parenteral Zinc vs control

Outcome: 01 Mortality

Study	Parenteral zinc	Control	RR (random)	Weight	RR (random)	Year	
or sub-category	n <i>i</i> N	n/N	95% Cl	%	95% Cl		
Young 1996	4/33	9/35		70.94	0.47 [0.16, 1.38]	1996	
Berger 1998	1/10	0/10		8.63	3.00 [0.14, 65.90]	1998	
Berger 2001	0/11	1/11	÷ • • • • • • • • • • • • • • • • • • •	8.58	0.33 [0.02, 7.39]	2001	
Berger 2007	1/11	1/10		11.85	0.91 [0.07, 12.69]	2007	
Total (95% CI) Total events: 6 (Parenteral Test for heterogeneity: Ch Test for overall effect: Z =	i <sup>2</sup> = 1.47, df = 3 (P = 0.69), l <sup>2</sup> = 0%	66		100.00	0.58 [0.23, 1.44]		
			0.1 0.2 0.5 1 2  Favours zinc Favours co	5 10			

# Figure 2. Hospital LOS

Review: Parenteral Zinc

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

Study or sub-category	N	Parenteral zinc Mean (SD)	N	Control Mean (SD)			) (random) 95% Cl	Weight %	WMD (random) 95% Cl	Year
Berger 1998	10	54.00(27.00)	10	66.00(31.00)				66.40	-12.00 [-37.48, 13.48]	1998
Berger 2001	11	60.00(48.00)	11	59.00(37.00)			+	33.60	1.00 [-34.81, 36.81]	2001
Total (95% CI) Test for heterogeneity: Ch Test for overall effect: Z =		= 0.56), I <sup>2</sup> = 0%	21			4		100.00	-7.63 [-28.39, 13.13]	
					-100	-50	0 50	100		
						Favours zin	c Favourso	ontrol		

### Figure 3. ICU LOS

Review: Parenteral Zinc

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

Study		Parenteral zinc	Control		Control WMD (random) Weight		Control VVMD (random) Weight		VVMD (random) VVeight		VVMD (random)	
or sub-category	N	Mean (SD)	N	Mean (SD)			95% CI		%	95% CI	Year	
Berger 1998	10	30.00(12.00)	10	39.00(13.00)	4=				25.13	-9.00 [-19.97, 1.97]	1998	
Berger 2001	11	5.80(4.40)	11	6.10(6.00)			-	_	70.04	-0.30 [-4.70, 4.10]	2001	
Berger 2007	11	35.00(27.00)	10	47.00(37.00)	←				4.84	-12.00 [-39.94, 15.94]	2007	
Total (95% CI)	32		31					-	100.00	-3.05 [-9.34, 3.24]		
Test for heterogeneity: Ch	i <sup>2</sup> = 2.61, df = 2 (P	= 0.27), I <sup>2</sup> = 23.5%					_					
Test for overall effect: Z =	= 0.95 (P = 0.34)											
					-10	-5	ó	5	10			
					F	avours zir	nc Favo	ours contr	ol			

#### References Included Articles

- 1. 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. 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.

#### **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.

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