

## 11.2 Supplemental Antioxidant Nutrients: Parenteral Selenium

June 28<sup>th</sup>, 2005

### Recommendation:

*There are insufficient data to make a recommendation regarding IV/PN selenium supplementation alone or in combination with other antioxidants in critically ill patients.*

**Discussion:** The committee noted the large treatment effect of selenium supplementation with respect to a reduction in mortality with narrow confidence intervals, which was attributed to one small study that had poor methodological quality (Kuklinski). It was noted that without this study, the treatment effect was reduced to a trend towards a reduction in mortality. Given this modest effect, the heterogeneity in the trial designs and high cost, despite favourable safety and feasibility, the committee decided not to put forward a recommendation.

Values	definition	Score: 0, +, ++, +++
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	3+ 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	2+
Homogeneity	similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2+
Safe	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+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3+
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	1+

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**Question:** Does parenteral selenium supplementation (alone or in combination with other antioxidants) result in improved outcomes in the critically ill patient?

**Summary of evidence:** There was 1 level 1 study and 6 level 2 studies reviewed, three that compared selenium supplementation to none (Kuklinski, Zimmerman, Berger 2001), one that compared higher amounts of selenium to low dose selenium (Angstrom) and three (Berger 1998, Porter, Berger 2002) that studied selenium supplementation in addition to other antioxidants (copper, zinc, vit E, C, N-acetylcysteine). In all of the studies selenium was administered via the IV/PN route, in 3 studies patients were on parenteral nutrition, in the other 4, patients were on enteral nutrition. One study was published in 2 parts (Berger et al Intensive Care Medicine 2001;27:91-100 and Berger et al Nutrition Research (21):41-54. This study had two intervention arms i.e. selenium alone and selenium combined with zinc and  $\alpha$  tocopherol compared to placebo and the data are presented in the meta-analysis are from the combined selenium group (combined data).

**Mortality:** When the 7 studies that reported on mortality were aggregated, selenium supplementation was associated with a trend towards a significant reduction in mortality (RR = 0.59 95% CI 0.32,1.08, p = 0.09). When a meta-analysis was done without the Kuklinski study (poor methodological score), this trend towards a reduction in mortality remained (RR = 0.65, 95% CI 0.37, 1.14, p = 0.13). (See figure page 11.2-5).

**Infections:** Only 3 studies reported on infections, Berger 1998 did not report on the number of patients with infections and hence was not included in the meta-analysis. When the other 2 studies were aggregated, selenium supplementation had no effect on infectious complications (RR = 0.78, 95 % confidence intervals 0.49-1.26, p = 0.3).

**LOS and Ventilator days:** Four studies reported on LOS but there were no significant differences between the groups. Ventilator days were also found to be no different between the groups in the 2 studies.

**Other complications:** not reported

### Conclusions:

- 1) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) may be associated with significant reduction in mortality in critically ill patients
- 2) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on infectious complications in the critically ill.

*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 Selenium Supplementation In Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Experimental	Control	Experimental	Control
1) Kuklinski 1991	Patients with acute pancreatic necrosis N = 17	C.Random: not sure ITT: no Blinding: no (4)	PN + selenium supplementation (500 µg /d) vs PN without selenium supplementation	0/8 (0) ICU	8/9 ( 89) ICU	NA	NA
2) Zimmerman 1997	Patients with SIRS, APACHE > 15 and multi organ failure score >6 N = 40	C.Random: no ITT: yes Blinding: no (6)	1000 µg Na-Selenite as a bolus IV then 1000µg Na-Selenite/24 hrs as a continuous infusion over 28 days vs. standard	3/20 (15)	8/20 (40)	NA	NA
3) Berger 1998	Burns > 30 % TBSA N = 20	C.Random: yes ITT: yes Blinding: double blind (12)	IV Copper (40.4 µmol), selenium (159 µg), zinc (406 µmol) + standard trace elements vs. standard trace elements (Copper 20 µmol, selenium 32 µg, 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
4) Porter 1999	Surgical ICU Penetrating trauma patients with injury severity score ≥ 25 N = 18	C.Random: yes ITT: yes Blinding: no (9)	50 µg selenium IV q 6 hrs + 400 IU Vit E, 100 mg Vit. C q 8 hrs and 8 gms of N-acetylcysteine (NAC) q 6 hrs via nasogastric or oral route	0/9	0/9	5/9 (56)	8/9 (89)
5) Angstwurm 1999	Patients with systematic inflammatory response syndrome N = 42	C.Random: not sure ITT: yes Blinding: no (10)	PN with high dose selenium (535 µg x 3 days, 285 µg x 3 days and 155 µg x 3 days and 35 µg thereafter) vs low dose selenium (35 µg/day for duration of study)	7/21 (33) hospital	11/21 (52) hospital	NA	NA
6) Berger 2001*	Trauma patients, surgical ICU N = 32	C.Random: not sure ITT: no Blinding: single (7)	IV Selenium supplementation (500 µg/day ) vs placebo * (Selenium group randomized further to two groups: 500 µg Selenium alone vs 500 µg Selenium + 150 mg α tocopherol + 13 mg zinc) given slowly over 5 days (All groups received EN)	2/20 (10)	1/12 (8)	8/20 (40)	5/12 (42)
7) Berger 2002	Burns > 20 % BSA N = 17	N/A	IV 100 mls of Copper (59 µmol) + Selenium (380 µgm + zinc (574 µmol) vs NaCl (0.9%) from admission for 14-21 days. Both groups were on EN.	1/9 (11)	1/8 (13)	NA	NA

Table 1 (continued). Randomized Studies Evaluating Selenium Supplementation In Critically Ill Patients

Study	LOS days		Ventilator days		Cost		Other	
	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control
1)Kuklinski 1991	NA	NA	NA	NA	NA	NA	NA	NA
2) Zimmerman 1997	NA	NA	NA	NA	NA	NA	NA	NA
3) Berger 1998	30 ± 12 (10) ICU 54 ± 27 (10) hospital	39 ± 13 (10) ICU 66 ± 31 (10) hospital	9 ± 10 (10)	12 ± 9 (10)	NA	NA	NA	N/A
4) Porter 1999	ICU 22 ± 25.2 Hospital 31.3 ± 23.4	ICU 35.8 ± 21.9 Hospital 49 ± 30	NA	NA	NA	NA	Organ dysfunction 0/9 (0) 6/9 (67)	
5) Angstwurm 1999	NA	NA	9 (3-23)	10 (1-43)	NA	NA	NA	NA
6) Berger 2001*	ICU 6.1 ± 3.9 (20) Hospital 68 ± 60(20)	ICU 8.6 ± 8.1 (12) Hospital 64 ± 39 (12)	5.1 ± 3.7 (20)	5.4 ± 6.5 (12)	NA	NA	Organ failure 6/20 (30) 4/11 (36)	
7) Berger 2002	ICU 39 ± 7 (9)	ICU 38 ± 12 (8)	NA	NA	NA	NA	NA	NA

\* Data presented here represent the Combined Selenium group.

C.Random: concealed randomization

ITT: intent to treat

NA: not available

‡ refers to the # of patients with infections unless specified

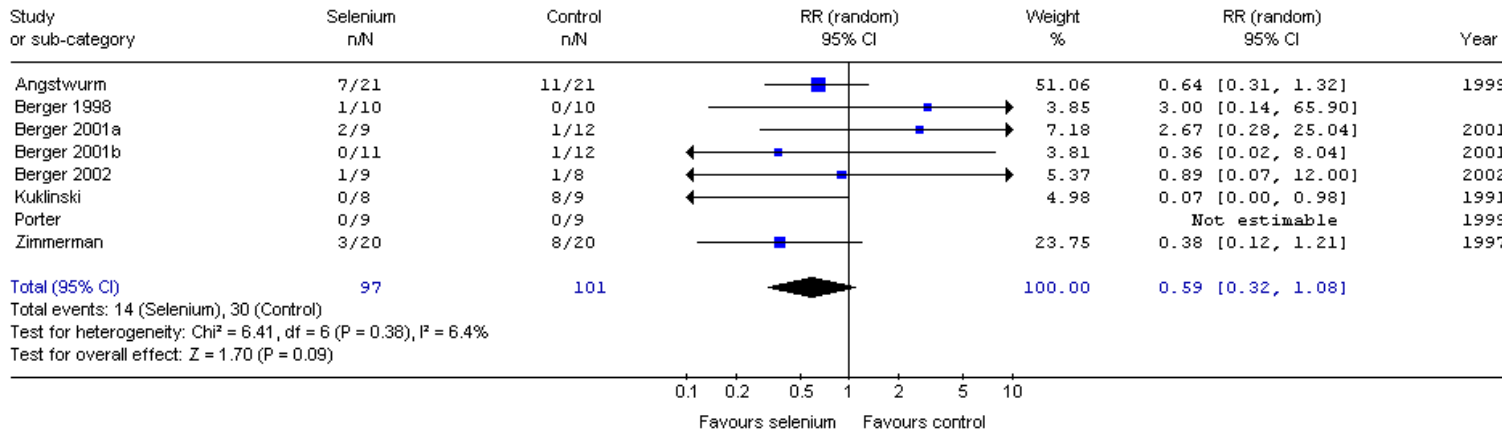
† presumed hospital mortality unless otherwise specified

± ( ) : mean ± Standard deviation (number)

Selenium: 1 µg = 0.0126 µmol.

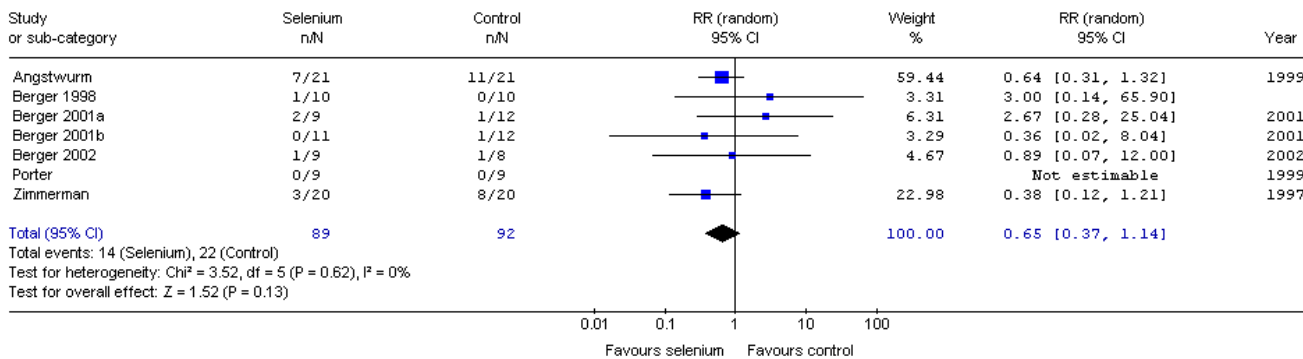
## Mortality with Kuklinski

Review: Antioxidants  
 Comparison: 04 Antioxidants (Selenium; single+ combined)  
 Outcome: 01 Mortality

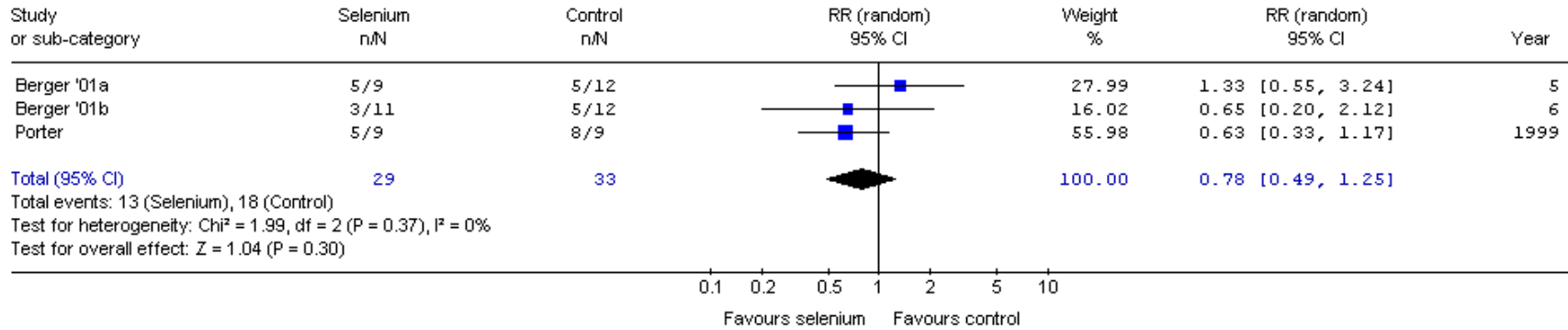


## Sensitivity Analysis without Kuklinski

Review: Antioxidants  
 Comparison: 04 Antioxidants (Selenium; single+ combined)  
 Outcome: 01 Mortality



Review: Antioxidants  
 Comparison: 04 Antioxidants (Selenium; single+ combined)  
 Outcome: 02 Infectious Complications



TOPIC: 11.2 Antioxidant Strategies: Parenteral Selenium (alone or in combination)

*(Reviewers: Ulrich Suchner, Deborah Schroter-Noppe & Carmen Christman)*

Article inclusion log

Criteria for study selection

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

ID #	Author	Journal	I	E	why rejected
97.	1. Porter (selenium, Vit E, C and N-acetylcysteine)	Am Surgeon 1999	√		
30	2. Berger (selenium & trace elements)	Am J Clin Nutr 1998	√		
73	3. Berger (selenium, zinc & α tocopherol)	Int Care Med 2001	√		
9.	4. Angstrum (selenium)	CCMedicine 1999	√		
86.	5. Kuklinski (selenium)	Gestame Inn Med 1991	√		
87.	6. Zimmermann (selenium)	Medi Klinik 1997	√		
	7. Young (zinc)	J of Neurotrauma 1996	√		
	8. Yamaguchi (selenium)	Stroke 1998		√	Not ICU patients
	9. Saito (selenium)	Neurosurgery 1998		√	Not ICU patients
	10. Ogawa (selenium)	Cerebrovas Dis 1999		√	Not ICU patients
	11. Kuklinski (selenium)	Z. Gesamte Inn Med 1992		√	Not RCT
	12. Kuklinski (selenium)	Med Klin 1995		√	Not RCT
	13. Berger (cu, se, zinc)	J Trauma 1996		√	Not RCT
	14. Gärtner (se)	Med Klein 1994		√	Not RCT
	15. Lehmann (se)	Z. Ernährungsriess 1998		√	Not RCT
	16. Börner (se)	Med Klein 1999		√	Not ICU adult patients

	17.	<b>Uden</b> (se, Vit A, E)	Alim Pharmac Ther 1990	√	Not ICU patients
	18.	<b>Uden</b> (se, Vit A, E)	Alim Pharmac Ther 1992	√	Not ICU patients
	19.	<b>Sawyer</b> (se, NAC, vit E,C)	C.C. Medicine 1989	√	Abstract only
	20.	<b>Berger</b> (se, cu, zinc)	Nutrition 1994	√	Not RCT
	21.	<b>Heaney</b> (se, vit A,E,C)	J Clin Endocrin Met 1999	√	Not ICU patients
	22.	<b>Lehmann</b> (se)	Med Klin 1997	√	No significant outcomes
	23.	<b>Berger</b>	Clinical Nutrition 2004	√	No intervention
	24.	<b>Angstwurm</b>	European J Endocrin 2004	√	Duplicate study of #4

I = included, E = excluded

## References

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5. Angstwurm MW, Schottdorf J, Schopohl J, Gaertner R (1999) Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. *Crit Care Med* 27:1807-1813
6. Porter JM, Ivatury RR, Azimuddin K, Swami R (1999) Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized study. *Am Surg* 65:478-483
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14. Lehmann C, Egerer K, Weber M, Krausch D, Wauer H, Newie T, Kox WJ (1997) Effect of selenium administration on various laboratory parameters of patients at risk for sepsis syndrome. *Med Klin* 15 (Suppl 3):14-16