11.2 Supplemental Antioxidant Nutrients: Parenteral Selenium* January 31st 2009

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 that with the evidence from newer trials, the treatment effect of selenium supplementation with respect to a reduction in mortality was small with confidence intervals that overlapped 1.0, and this remain unchanged after the exclusion of one small study that had poor methodological quality (Kuklinski 1991). The committee also expressed concern regarding the heterogeneity in the trial designs, the negative safety reports in other patient populations and the inconsistency in dosing ranges in the critically ill population(1). Given this, the committee felt that there was not enough evidence to support the use of IV/PN selenium supplementation. We await the results of ongoing studies on selenium supplementation in critically ill patients to strengthen the clinical recommendations.

(1) Heyland DK. Selenium supplementation in critically ill patients: can too much of a good thing be a bad thing? Crit Care. 2007;11(4):153.

	Definition	Score 0, 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	2
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 mortality 2 infections
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 or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2
Adequacy of control group	Extent to which the control group represented 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 inconsistencies =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.	2
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
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	2

* refers to parenteral/IV selenium supplementation either alone or combined with other antioxidant nutrients.

11.2 Supplemental Antioxidant Nutrients: Parenteral Selenium January 31st 2009

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 10 level 2 studies reviewed, five that compared selenium supplementation to none (Kuklinski 1991, Zimmerman 1997, Berger 2001, Angstwurm 2007, Forceville 2007), two that compared higher amounts of selenium to low dose selenium (Angstwurm 1999, Mishra 2007) and four (Berger 1998, Porter, Berger 2007, Berger 2008) that studied selenium supplementation in addition to other antioxidants (copper, zinc, vit E, C, N-acetylcysteine). 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 α tocopherol compared to placebo and the data are presented in the meta-analysis are from the combined selenium group (combined data).

Mortality: When the data from all 11 studies were aggregated, selenium supplementation was associated with a trend towards a reduction in mortality (RR 0.84, 95 % CI 0.67, 1.05, p = 0.13) (figure 1). When a meta-analysis was done without the Kuklinski study (poor methodological score), this reduction in mortality remained (RR 0.85, 95 % CI 0.69, 1.64, p = 0.11) (figure 2). When the data from the studies that compared selenium alone to none were aggregated, selenium supplementation had no effect on mortality (RR 0.84, 95 % CI 0.64, 1.11, p = 0.22 (figure 3) and when a sensitivity analysis was done without the Kuklinski study, selenium supplementation alone was associated with a trend towards a reduction in mortality (RR 0.85, 95 % CI 0.69, 1.04, p = 0.12) (figure 4).

Infections: A total of seven studies reported on infections, Berger 1998 and Mishra 2007 did not report on the number of patients with infections while Forceville 2007 reported on a subgroup of infections, hence the data from these studies was not included in the meta-analysis. When the other 4 studies were aggregated, selenium supplementation had no effect on infectious complications (RR 0.93, 95 % CI 0.70, 1.23, p = 0.61) (See figure 5).

LOS and Ventilator days: Seven studies reported on LOS but there were no significant differences between the groups when the data were aggregated (WMD 0.12, 95% CI -1.79, 2.03, p = 0.90)(see figure 6). Ventilator days/ ventilator free days were also found to be no different between the groups in the 4 studies.
Other complications: not reported

Conclusions:

1) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) is associated with a trend towards a 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.
3) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on ICU length of stay.

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 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 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
8) Angstwurm 2007	Multicentre mixed ICUs N =249	C.Random: not sure ITT: no Blinding: double (8)	1000μg Selenium IV within 1 hr followed by 1000μg Selenium for 14 days vs. NaCl (0.9%) (all patients received EN or PN)	28 day 46/116 (40)	28 day 61/122 (50)	New infections (Hospital Acquired Pneumonia) 10/116 (9)	10/122 (8)

9) Forceville 2007	Septic shock patients N = 60	C.Random: not sure ITT: no Blinding: double (8)	4000μg Selenium IV on day 1 followed by 1000μg Selenium for 9 days vs. NaCl (0.9%) (all patients received EN or PN)	28 day 14/31 (45) 6 Month 18/31 (59) 1 year 66%	28 day 13/29 (45) 6 Month 20/29 (68) 1 year 71%	Superinfection** 1/31 (3) 2/29 (7)	
10)Mishra 2007	Septic ICU patients N = 40	C.Random: not sure ITT: yes Blinding: double (9)	474 μg Selenium IV x 3 days followed by 316 μg x 3 days, 158 μg x 3 days and 31.6 μg thereafter vs. 31.6 μg Selenium (all patients received EN or PN).	ICU 8/18 (44) Hospital 11/18 (61) 28 day 8/18 (44)	ICU 11/22 (61) Hospital 15/22 (68) 28 day 11/22 (50)	Infections per patient 1.5 ± 1.9 1.8 ± 1.6	
11) 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 . Started within 24 hrs of admission to ICU. Placebo. (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 (continued). Randomized Studies Evaluating Selenium Supplementation In Critically Ill Patients

Study	LOS days Experimental	 Control	Ventilator days Experimental	 Control	Other Experimental	 Control
1)Kuklinski 1991	NR	NR	NR	NR	NR	NR
2) Zimmerman 1997	NR	NR	NR	NR	NR	NR
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)	NR	NR
4) Porter 1999	ICU 22 ± 25.2 Hospital 31.3 ± 23.4	ICU 35.8 ± 21.9 Hospital 49 ± 30	NR	NR	Organ dysfunction 0/9 (0)	6/9 (67)

5) Angstwurm 1999	NR	NR	9 (3-23)	10 (1-43)	NR	NR
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)	Organ failure 6/20 (30)	4/11 (36)
7) Berger 2007***	ICU 35 ± 27 (11)	ICU 47 ± 37 (10)	7.6 ± 6 (11)	12.6 ± 6 (10)	NR	NR
8) Angstwurm 2007	ICU 15.1 ± 10 (116)	ICU 12.7± 9 (122)	NR	NR	Change in Logistic Organ dysfunction -2.6 ± 4.7	-2.0 ± 4.0
9) Forceville 2007	ICU 21 (7-40) Hospital 25 (7-68)	ICU 18 (10-31) Hospital 33 (11-51)	19 (7-34)	14 (8-23)	Complications 24/31 (78)	16/29 (55)
10) Mishra 2007	ICU 21.3 ± 16.2 (18)	ICU 20.8 ± 21.8 (18)	NR	NR	NR	NR
11) 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

Selenium: 1 μg = 0.0126 μmol

* Data presented here represent the Combined Selenium group.
** not included in meta-analysis as a subgroup
*** Berger 2002 Clin Nutr 21 (suppl 1):66 data replaced by Berger 2007 Am J Clin Nutr data after clarification from author.
C.Random: concealed randomization ‡ refers to the # of patients with infections unless specified
ITT: intent to treat † presumed hospital mortality unless otherwise specified
NR: not reported ± ( ) : mean ± Standard deviation (number)

Figure 1 REVISED Mortality with Kuklinski

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

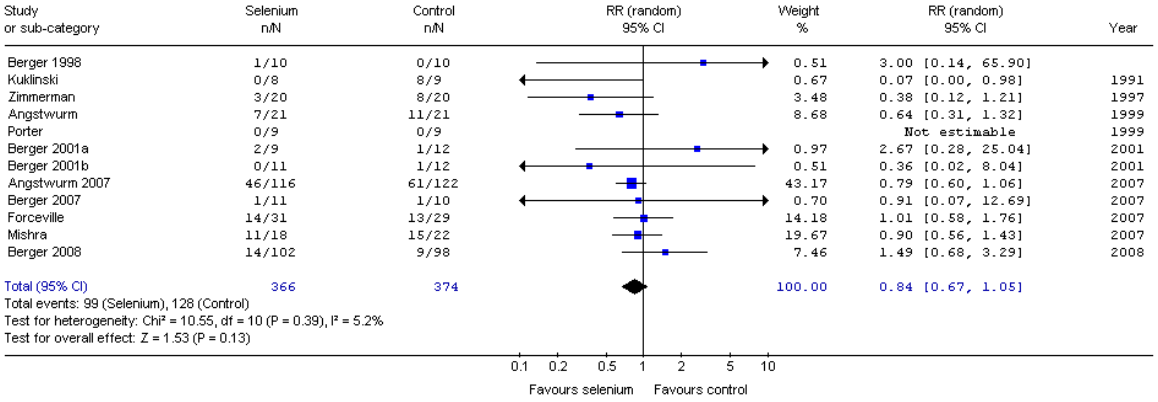


Figure 2. Sensitivity Analysis without Kuklinski

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

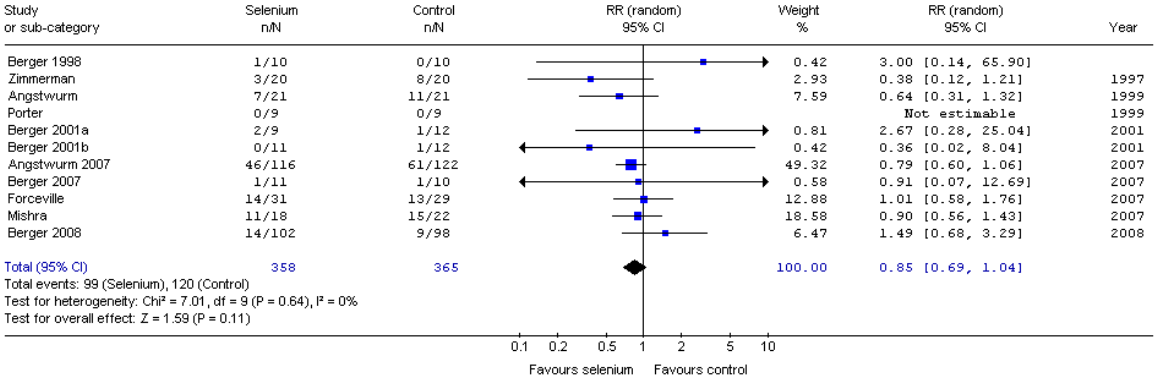


Figure 3. Studies using Parenteral Selenium alone

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

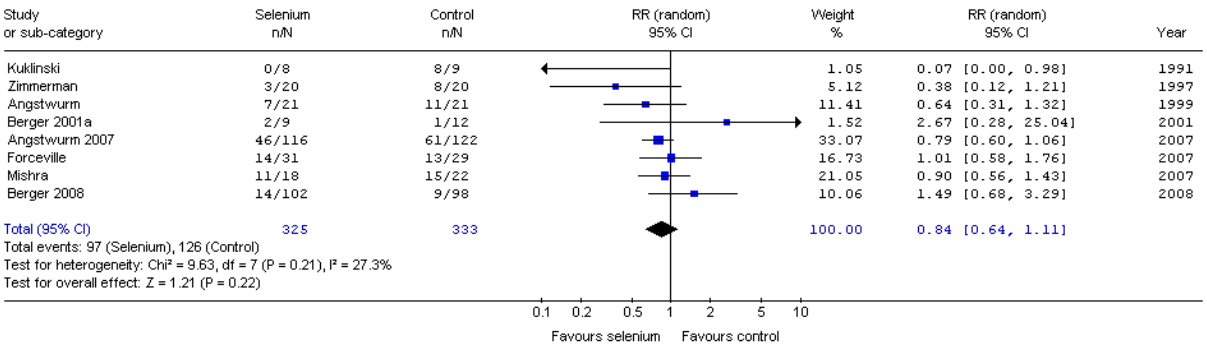


Figure 4. Studies using Parenteral Selenium alone: Sensitivity Analysis without Kuklinski

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

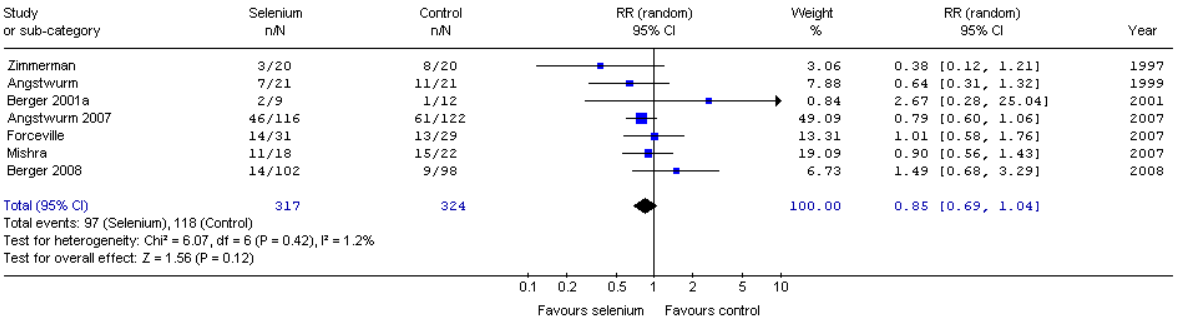


Figure 5.

Review: Antioxidants (Version 01)
Comparison: 04 Antioxidants (Selenium; single+ combined)
Outcome: 02 Infectious Complications

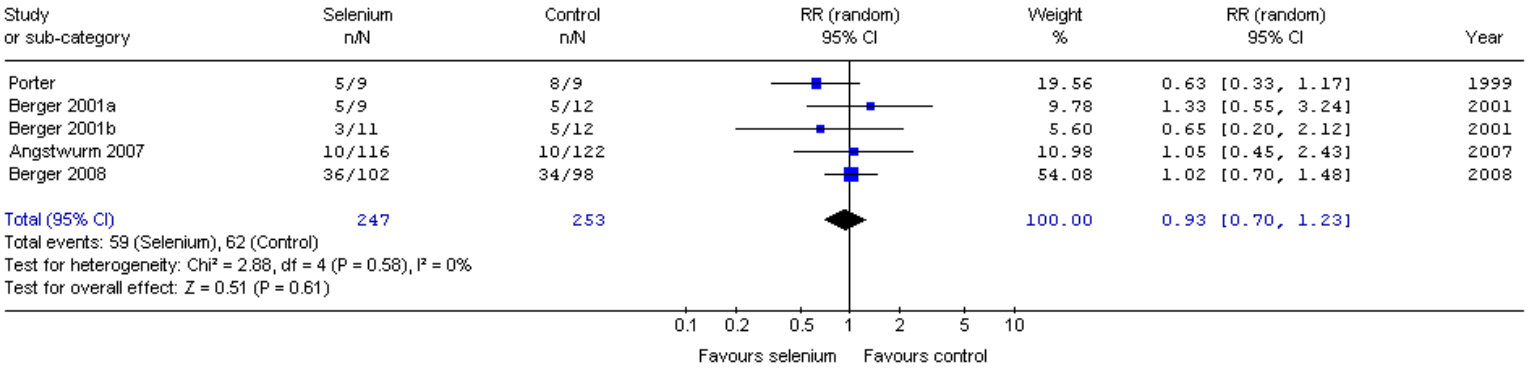
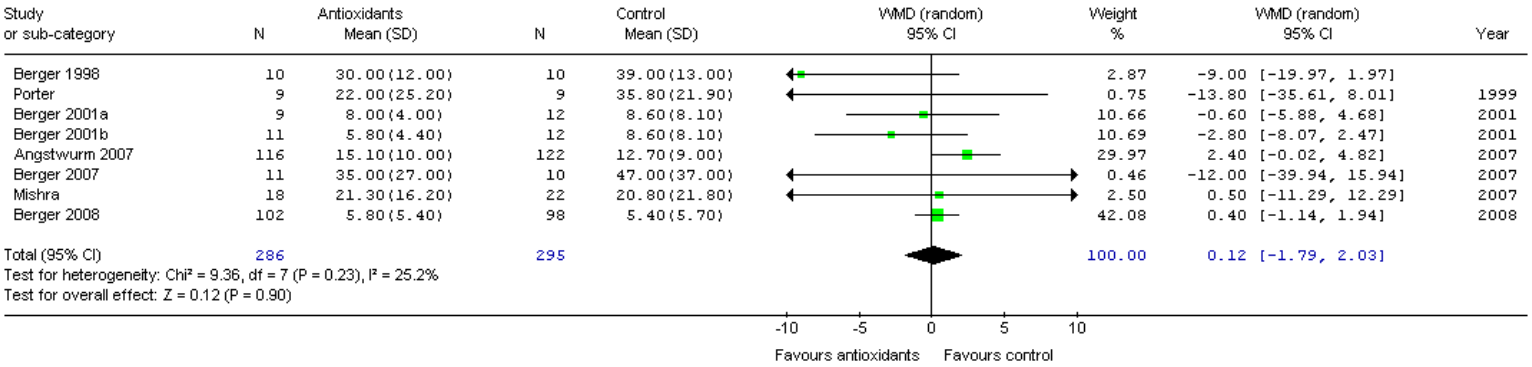


Figure 6.

Review: Antioxidants (Version 01)
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 03 ICU Length of Stay



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

Article inclusion log

Criteria for study selection

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

	Author	Journal	I	E	Why rejected
1	Sawyer(Se, NAC, vit E,C)	C.C. Medicine 1989		√	Abstract only
2	Uden (Se, Vit A, E)	Alim Pharmac Ther 1990		√	Not ICU patients
3	Kuklinski (Selenium)	Gestame Inn Med 1991	√		
4	Uden (Se, Vit A, E)	Alim Pharmac Ther 1992		√	Not ICU patients
5	Young (Zinc)	J of Neurotrauma 1996	√		
6	Lehmann (Se)	Med Klin 1997		√	No clinical outcomes
7	Zimmermann (Selenium)	Medi Klinik 1997	√		
8	Berger (Selenium & trace elements)	Am J Clin Nutr 1998	√		
9	Saito (Selenium)	Neurosurgery 1998		√	Not ICU patients
10	Yamaguchi (Selenium)	Stroke 1998		√	Not ICU patients
11	Angstrum (Selenium)	CCMedicine 1999	√		
12	Heaney (Se, Vit A, E, C)	J Clin Endocrin Met 1999		√	Not ICU patients
13	Ogawa (Selenium)	Cerebrovas Dis 1999		√	Not ICU patients
14	Porter (selenium, Vit E, C and N-acetylcysteine)	Am Surgeon 1999	√		
15	Berger (Selenium, Zinc & α tocopherol)	Int Care Med 2001	√		
16	Berger	Nut Res 2001	√		Same study as Berger 2001: Int Care Med. Data is combined and presented as Berger 2001
17	Angstwurm	European J Endocrin 2004		√	Duplicate study of Angstrum 1999
18	Heyland	Intensive Care Med 2005		√	Meta-analysis, Individual studies looked at
19	Angstwurm (Selenium)	CCMed 2007	√		
20	Forceville	Critical Care 2007	√		
21	Mishra	Clinical Nutrition 2007	√		
22	Berger (Se, other vits)	Critical Care 2008	√		

I = included, E = excluded

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