11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements

January 8th 2007

Recommendation:

Based on 3 level 1 and 10 level 2 studies, the use of supplemental combined vitamins and trace elements should be considered in critically ill patients.

Discussion: The committee noted the strong treatment effect and narrow confidence intervals with respect to a reduction in mortality. Even with the exclusion of one small study that had poor methodological quality (Kuklinksi), the reduction in mortality remained. The committee expressed concern about the differences in the types of antioxidant nutrients used in the studies and the heterogeneity of the trials. Despite the optimal composition and dose of supplemental vitamins and trace elements not being well established, there were no concerns about the safety, feasibility and cost of these nutrients. The committee therefore agreed to make a recommendation that supplemental combined vitamins and trace elements should be considered. These nutrients are currently being investigated and we await the results of ongoing studies to strengthen the clinical recommendations.

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+ 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	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	2+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2+
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2+

11.1 Topic: Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements **January 8th 2007**

Question: Does the addition of Supplemental Combined Vitamins and Trace Elements result in improved outcomes in the critically ill patient?

Summary of evidence: There were 3 level 1, 10 level 2 and 1 unpublished manuscript reviewed that compared various antioxidants either as single nutrients (selenium) or as a combination of nutrients (selenium, copper, zinc, vit. A, C & E, N-acetylcysteine) given by various routes (IV/parenteral, enteral, oral). 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 and the data listed here represent the data from the latter study (intent to treat). 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 as Berger 2001a and Berger 2001b respectively.

Mortality: Twelve studies reported on mortality and when the results of these were aggregated, antioxidant supplementation was associated with a significant reduction in mortality (RR = 0.59, 95 % confidence intervals 0.59, 0.82, p <0.0001) . When a meta-analysis was done without the Kuklinski study (poor methodological score), antioxidant supplementation was still associated with a significant reduction in mortality (RR = 0.70, 95 % CI 0.59, 0.83, p<0.0001). See page 11.1-7.

Infections: When all the 5 studies that reported on infectious complications were aggregated, antioxidant supplementation had no significant effect on infectious complications (RR = 0.90, 95 % confidence intervals 0.65-1.24, p = 0.51). See page 11.1-8.

LOS: When the 5 studies that reported on ICU LOS and the 3 studies that reported on hospital LOS were meta- analyzed, antioxidant supplementation had no effect on ICU length of stay (SMD = - 0.10, 95% CI -0.46,0.26, p=0.50) but had no significant affect on hospital LOS (SMD = -0.18, 95 % confidence intervals –0.62 - 0.26, p = 0.42). See page 11.1-8.

Ventilator days: When the 3 studies that reported ventilator days were meta-analyzed, antioxidant supplementation had no effect on ventilator days (SMD = -0.36, 95 % confidence intervals –1.27 - 0.56, p = 0.45). See page 11.1-9.

Other complications: not reported

Conclusions:

1) Antioxidant Nutrients i.e. combined vitamins and trace elements are associated with a significant reduction in mortality in critically ill patients.
2) Antioxidant Nutrients i.e. combined vitamins and trace elements have no effect on infectious complications in critically ill patients.
3) Antioxidant Nutrients i.e. combined vitamins and trace elements have no effect on ICU LOS in critically ill patients.
4) Antioxidant Nutrients i.e. combined vitamins and trace elements have no effect on hospital LOS or ventilator days.

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 Supplemental Combined Vitamins And Trace Elements 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	ICU 0/8 (0)	ICU 8/9 (89)	NA	NA
2) Maderazo 1991	Blunt Trauma N = 46	C.Random: yes ITT: yes Blinding: double (7)	200 mg Ascorbic acid, then ↑ 500 mg + 50 mg α tocopherol in 100 mls of D5W vs. 100 mls of D5W**. (Experimental group divided into 2 groups, 200 mg ascorbic acid vs. 50 mg α tocopherol) .Given as 2 hr infusions from Day 0-7. (All groups received enteral nutrition or po intake)	NA	NA	13/28 (46)	5/18 (28)
3) Young 1996	Severely head injured patients, ventilated N = 68	C.Random: yes ITT: yes Blinding: double (7)	12 mg elemental zinc via PN, then progressing to oral zinc from 0- 15 days vs. 2.5 mg elemental zinc, then progressing to oral placebo	4/33 (12)	9/35 (26)	NA	NA
4) 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
5) 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) from day 0- 8, 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
6) 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, from Day 0-7 vs. none	0/9	0/9	5/9 (56)	8/9 (89)
7) 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)	hospital 7/21 (33)	hospital 11/21 (52)	NA	NA

Table 1. (Continued) Randomized Studies Evaluating Combined Vitamins And Trace Elements in Critically Ill Patients

Study	Population	Methods score	Intervention	Mortality # (%)† Experimental	Mortality # (%)† Control	Infections # (%)‡ Experimental	Infections # (%)‡ Control
8) Preiser 2000	Mixed ICU N = 51	C.Random: not sure ITT: no Blinding: single (7)	Antioxidant rich formula via EN (133 μg /100 ml vit. A, 13 mg/100 mls Vit C & 4.9 mg/100 ml Vit E) vs isonitrogenous, isocaloric standard formula (67 μg /100 ml vit. A, 5 mg/100 mls Vit C and 0.81 mg/100 mls Vit E) from Day 0- 7	ICU 3/20 (15) hospital 8/20 (40)	ICU 3/17 (18) hospital 6/17 (35)	3/20 (15)	1/17 (6)
9) Berger 2001	Trauma patients, surgical ICU N = 32	C.Random: yes ITT: no Blinding: doube blind (9)	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 for 1st 5 days after injury (All groups received EN)	a) Selenium alone 2/9 (22) b) Sel+zinc+α tocopherol 0/11 (0)	1/11 (9)	a) Selenium alone 5/9 (56) b)Sel+zinc+α tocopherol 3/11 (27)	5/12 (42)
10) Nathens 2002	General Surgical/Trauma ICU N=770	C.Random: not sure ITT: no Blinding: no (7)	α tocopherol 1000 IU q 8 h via naso or orogastric tube and Ascorbic acid 1000 mg q 8 h via IV vs. standard care	ICU 3/301 (1) Hospital 5/301(2) 28 day 4/301 (1)	ICU 9/294 (3) Hospital 9/294(3) 28 day 7/294 (2)	36/301 (12)	44/294 (15)
11) Berger 2002	Burns > 20 % BSA N = 17	N/A	100 mls of Copper (59 μmol) + Selenium (380 μg) + zinc (574 μmol) within 12hrs of injury vs NaCl (0.9%) from admission for 14-21 days.	1/9 (11)	1/8 (13)	NA	NA
12) Crimi 2004	Mixed ICU N = 224	C.Random: not sure ITT: no Blinding: no (7)	Vit C (500 mg), Vit E (400 IU) within 72 hrs for 10 days vs. isotonic saline (all groups received EN)	28 day 49/112 (44)	28 day 76/112 (68)	NA	NA
13) 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)

Table 1. (Continued) Randomized Studies Evaluating Combined Vitamins And Trace Elements 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) Maderazo 1991	NA	NA	NA	NA	NA	NA	NA	NA
3) Young 1996	NA	NA	NA	NA	NA	NA	NA	NA
4) Zimmerman 1997	NA	NA	NA	NA	NA	NA	NA	NA
5) 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
6) 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)
7) Angstwurm 1999	NA	NA	9 (3-23)	10 (1-43)	NA	NA	NA	NA
8) Preiser 2000	5 (3-26)	5 (3-18)	NA	NA	NA	NA	NA	NA
9) Berger 2001	a) ICU 8.0 ± 4.0 (9) Hospital 82 ± 78 (9) b) ICU 5.8 ±4.4 (11) Hospital 60 ± 48 (11)	ICU 8.6 ± 8.1 (12) Hospital 64 ± 39 (12)	a) 6.2 ± 3.5 (9) b) 4.1 ±3.6 (11)	4.2 ± 5.2 (11)	NA	NA	Organ failure 6/20 (30)	4/11 (36)
10) Nathens 2002	ICU 5.3 (mean) Hospital 14.6 (mean)	ICU 6.4 (mean) Hospital 15.1 (mean)	3.7 (mean)	4.6 (mean)	NA	NA	Multi Organ Failure 8/301 (3)	18/ 294 (6)
11) Berger 2002	ICU 39 ± 7 (9)	ICU 38 ± 12 (8)	NA	NA	NA	NA	NA	NA
12) Crimi 2004	Hospital 26.5 (mean)	Hospital 27.5 (mean)	6.2 ± 2.3 (112)	8.9 ± 1.8 (112)	NA	NA	Multi Organ Failure 24/112 (21)	26/112 (23)
13) Angstwurm 2007	ICU 15.1 ± 10 (116)	ICU 12.7± 9 (122)	NA	NA	NA	NA	change in Logistic Organ dysfunction -2.6 ± 4.7	-2.0 ± 4.0

Selenium: 1 μg = 0.0126 μmol.

* data pertaining to the group receiving selenium alone is presented as Berger 2001a and the data for the group receiving Selenium + α tocopherol + zinc is presented as Berger 2001b.

** Maderazo 1991: only data pertaining to the group receiving Ascorbic acid + α tocopherol vs. placebo presented here

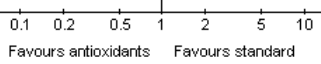
C.Random: concealed randomization ‡ refers to the # of patients with infections unless specified NA: not available

ITT: intent to treat † presumed hospital mortality unless otherwise specified ± ( ) : mean ± Standard deviation (number)

Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 01 Mortality

Study or sub-category	Antioxidants n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Berger '98	1/10	0/10		0.30	3.00 [0.14, 65.90]	1998
Berger 2001a	2/9	1/12		0.57	2.67 [0.28, 25.04]	2001
Berger 2001b	0/11	1/12		0.29	0.36 [0.02, 8.04]	2001
Berger 2002	1/9	1/8		0.42	0.89 [0.07, 12.00]	2002
Crimi	49/112	76/112		47.05	0.64 [0.50, 0.82]	2004
Porter	0/9	0/9			Not estimable	1999
Preiser	8/20	6/17		4.04	1.13 [0.49, 2.62]	2000
Kuklinski	0/8	8/9		0.39	0.07 [0.00, 0.98]	1991
Zimmerman	3/20	8/20		2.06	0.38 [0.12, 1.21]	1997
Nathens	5/301	9/294		2.43	0.54 [0.18, 1.60]	2002
Young	4/33	9/35		2.45	0.47 [0.16, 1.38]	1996
Angstwurm	7/21	11/21		5.34	0.64 [0.31, 1.32]	1999
Angstwurm 2007	46/116	61/122		34.67	0.79 [0.60, 1.06]	2007
Total (95% CI)	679	681		100.00	0.69 [0.59, 0.82]	

Total events: 126 (Antioxidants), 191 (standard)
Test for heterogeneity: Chi² = 9.82, df = 11 (P = 0.55), I² = 0%
Test for overall effect: Z = 4.24 (P < 0.0001)

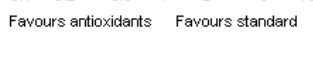


Sensitivity Analysis without Kuklinski

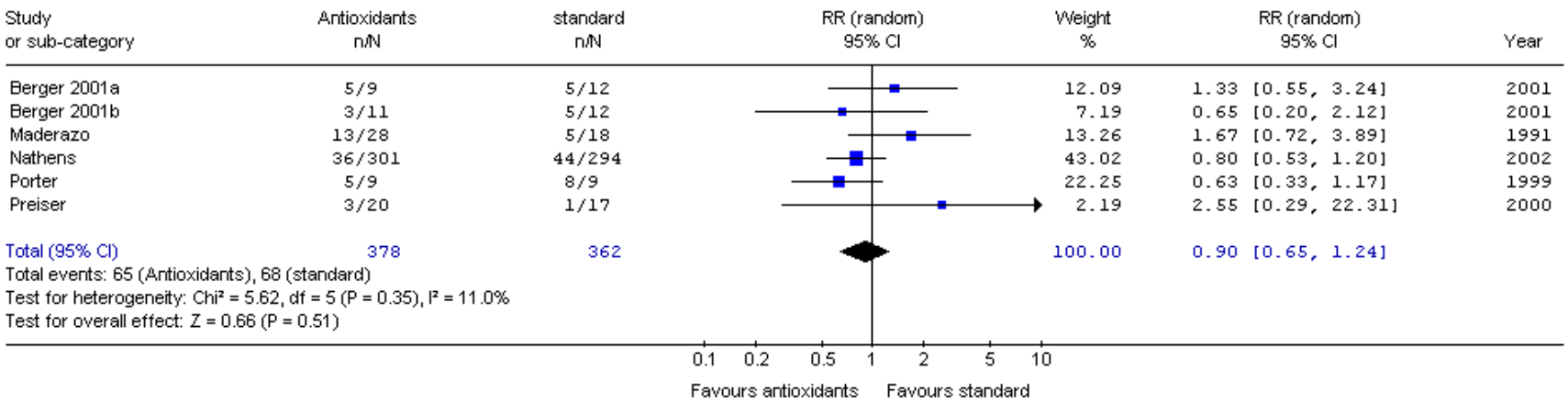
Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 01 Mortality

Study or sub-category	Antioxidants n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Berger '98	1/10	0/10		0.30	3.00 [0.14, 65.90]	1998
Berger 2001a	2/9	1/12		0.57	2.67 [0.28, 25.04]	2001
Berger 2001b	0/11	1/12		0.30	0.36 [0.02, 8.04]	2001
Berger 2002	1/9	1/8		0.42	0.89 [0.07, 12.00]	2002
Crimi	49/112	76/112		47.23	0.64 [0.50, 0.82]	2004
Porter	0/9	0/9			Not estimable	1999
Preiser	8/20	6/17		4.06	1.13 [0.49, 2.62]	2000
Zimmerman	3/20	8/20		2.07	0.38 [0.12, 1.21]	1997
Nathens	5/301	9/294		2.44	0.54 [0.18, 1.60]	2002
Young	4/33	9/35		2.45	0.47 [0.16, 1.38]	1996
Angstwurm	7/21	11/21		5.36	0.64 [0.31, 1.32]	1999
Angstwurm 2007	46/116	61/122		34.81	0.79 [0.60, 1.06]	2007
Total (95% CI)	671	672		100.00	0.70 [0.59, 0.83]	

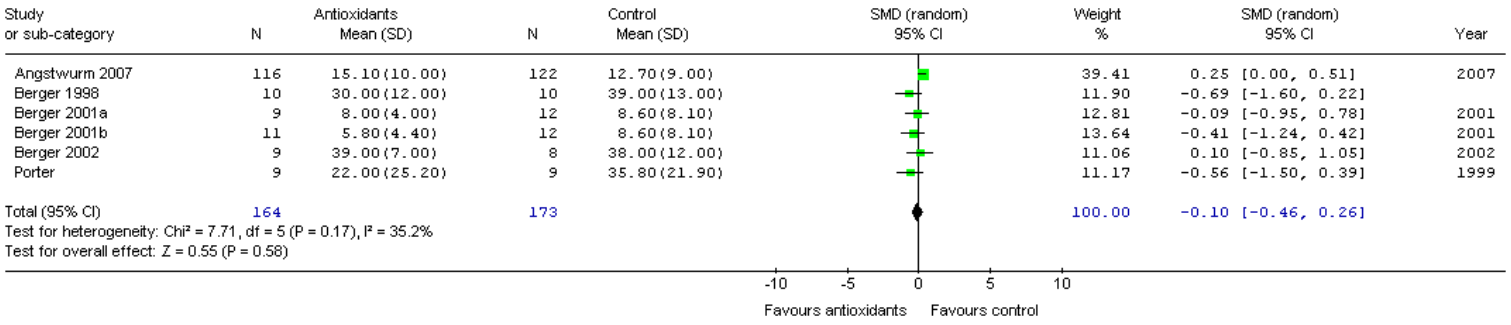
Total events: 126 (Antioxidants), 183 (standard)
Test for heterogeneity: Chi² = 6.74, df = 10 (P = 0.75), I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)



Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 02 Infectious Complications



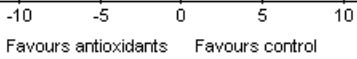
Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 03 ICU Length of Stay



Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 04 Hospital Length of Stay

Study or sub-category	Antioxidants N	Antioxidants Mean (SD)	Control N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Berger 1998	10	54.00(27.00)	10	66.00(31.00)		24.50	-0.40 [-1.28, 0.49]	
Berger 2001a	9	82.00(78.00)	12	64.00(39.00)		25.48	0.29 [-0.58, 1.16]	2001
Berger 2001b	11	60.00(48.00)	12	64.00(39.00)		28.77	-0.09 [-0.91, 0.73]	2001
Porter	9	31.30(23.40)	9	49.00(30.00)		21.25	-0.63 [-1.58, 0.33]	1999
Total (95% CI)	39		43			100.00	-0.18 [-0.62, 0.26]	

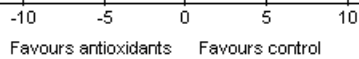
Test for heterogeneity: Chi² = 2.26, df = 3 (P = 0.52), I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)



Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 05 Ventilator Days

Study or sub-category	Antioxidants N	Antioxidants Mean (SD)	Control N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Berger 1998	10	9.00(10.00)	10	12.00(9.00)		22.81	-0.30 [-1.18, 0.58]	
Berger 2001a	9	6.20(3.50)	12	5.40(6.50)		23.06	0.14 [-0.72, 1.01]	2001
Berger 2001b	11	4.10(3.60)	12	5.40(6.50)		23.70	-0.24 [-1.06, 0.59]	2001
Crimi	112	6.20(2.30)	112	8.90(1.80)		30.42	-1.30 [-1.59, -1.01]	2004
Total (95% CI)	142		146			100.00	-0.49 [-1.29, 0.31]	

Test for heterogeneity: Chi² = 16.63, df = 3 (P = 0.0008), I² = 82.0%
Test for overall effect: Z = 1.20 (P = 0.23)



TOPIC: 11.1 Antioxidant Strategies: Single and Multimodal (combined)

(Reviewers: Ulrich Suchner, Minto Jain, Deborah Schroter-Noppe, Carmen Christman, Brian Jurewitsch, Shannon Mackenzie)

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill ventilated patients (no elective surgical patients)
Intervention :TPN and /or 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.	Porter (selenium, Vit E, C and N-acetylcysteine)	Am Surgeon 1999	√		
2.	Berger (selenium & trace elements)	Am J Clin Nutr 1998	√		
3.	Berger (selenium, zinc & α tocopherol)	Int Care Med 2001	√		
4.	Angstwurm (selenium)	CCMedicine 1999	√		
5.	Kuklinski (selenium)	Gestame Inn Med 1991	√		
6.	Zimmermann (selenium)	Medi Klinik 1997	√		
7.	Preiser (vit A, C & E)	CCMedicine 2000	√		
8.	Maderazo (vit C, vit E)	J. Trauma 1991	√		
9.	Galley (NAC, vit C, vit E)	Free Rad Bio Med 1997		√	Only 6 hr duration of intervention
10.	Nathens (vit E, vit C)	Ann Surg 2002	√		
11.	Young (zinc)	J of Neurotrauma 1996	√		
12.	Tanaka (vit C)	Arch Surgery 2000		√	pseudorandomized
13.	Barquist (folate)	J Trauma 1998		√	Not RCT
14.	Zhang (vit E)	Burns 1992		√	Not RCT
15.	Mingjian (vit E)	Burns 1992		√	Not RCT
16.	Cerwanka (vitamins)	Gastroenterology 1998		√	Not RCT
17.	Cerwanka (vitamins)	Free Rad Res 1999		√	Not RCT
18.	Keith	Am J Clin Nut 2001		√	Not ICU patients

	(vit E)				
19.	Sisto (Vit E,C)	Ann Thorac Surg 1995		√	Not ICU patients
20.	Faure (zinc)	Biol Trace Elem Res 1991		√	No Significant outcomes
21.	Rock (vit A)	J Burn Care Rehab 1997		√	No significant outcomes
22.	R**ümelin (Vit C)**	ESPEN Congress Abstract 2001		√	No significant outcomes
23	Molnar (NAC)	Inten Care Med 1998		√	NAC alone
24.	Yamaguchi (selenium)	Stroke 1998		√	Not ICU patients
25.	Saito (selenium)	Neurosurgery 1998		√	Not ICU patients
26..	Ogawa (selenium)	Cerebrovas Dis 1999		√	Not ICU patients
27.	Kuklinski (selenium)	Z. Gesamte Inn Med 1992		√	Not RCT
28.	Kuklinski (selenium)	Med Klin 1995		√	Not RCT
29.	Berger (cu, se, zinc)	J Trauma 1996		√	Not RCT
30.	G**ä**rtner (se)	Med Klein 1994		√	Not RCT
31.	Lehmann (se)	Z. Ernährungsriss 1998		√	Not RCT
32.	Börner (se)	Med Klein 1999		√	Not ICU adult patients
33.	Uden (se, Vit A, E)	Alim Pharmac Ther 1990		√	Not ICU patients
34.	Uden (se, Vit A, E)	Alim Pharmac Ther 1992		√	Not ICU patients
35.	Sawyer (se, NAC, vit E,C)	C.C. Medicine 1989		√	Abstract only
36.	Berger (se, cu, zinc)	Nutrition 1994		√	Not RCT
37.	Heaney (se, vit A,E,C)	J Clin Endocrin Met 1999		√	Not ICU patients
38.	Spapen (NAC)	Chest 1998		√	NAC alone
39.	Domenighetti (NAC)	J Crit Care 1997		√	NAC alone
40.	Bernard (NAC)	Chest 1997		√	NAC alone
41.	Ortolani	Am J Resp Care 2000		√	NAC alone and Glutathione
42.	Crimi	Anesth Analg. 2004	√		
43.	Angstwurm 2007 (selenium)	CCMed 2007	√		

I = included, E = excluded

Reference List

1. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005 Mar;31(3):327-37.

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

3. 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

4. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, Radella F, Garcia I, Maier RV (2002) Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 236:814-822

5. Kuklinski B, Buchner M, Schweder R, Nagel R (1991) Akute Pancreatitis-eine “Free Radical Disease:. Letalitatssenkung durch Natriumselenit (Na2SeO3)-Therapie. Z. gestame Inn Med 46:S145-149

6. 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

7. 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

8. 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

9. Preiser JC, Van Gossum A, Berré J, Vincent JL, Carpentier Y (2000)
Enteral feeding with a solution enriched with antioxidant vitamins A, C, E enhances the resistance to oxidative stress. Crit Care Med 28:3828-3832

10. 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

11. Maderazo EG, Woronick CL, Hickingbotham N, Jacobs L, Bhagavan HN (1991) A randomized trial of replacement antioxidant vitamin therapy for neutrophil locomotory dysfunction in blunt trauma. J Trauma 31:1142-1150

12. Berger MM, Baines M, Wardle CA, Cayeux MC, Chiolero R, Shenkin A (2002) Trace element supplements modulate tissue levels, antioxidant status and clinical course after major burns - preliminary results. Clin Nutr 21 (suppl 1):66

13. Berger MM, Cavadini C, Chioléro R, Dirren H (1996): Copper, selenium, and zinc status and balances after major trauma. J Trauma 40:103-109

14. Kuklinski B, Buchner M, Muller T, Schweder R (1992) [Anti-oxidative therapy of pancreatitis--an 18-month interim evaluation] Z Gesamte Inn Med 47:239-245

15. Kuklinski B, Zimmermann T, Schweder R (1995) Letalitätssenkung der akuten Pankreatitis mit Natriumselenit . [Decreasing mortality in acute pancreatitis with sodium selenite. Clinical results of 4 years antioxidant therapy], Med Klin 90 (Suppl. I):36-41

16. Barquist E, Kirton O, Windsor J, Hudson-Civetta J, Lynn M, Herman M, Civetta J (1998) The impact of antioxidant and splanchnic-directed therapy on persistent uncorrected gastric mucosal pH in the critically injured trauma patient. J Trauma 44:355-360

17. Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S (2000) Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. Arch Surg 135:326-331

18. Cerwenka H, Bacher H, Werkgartner G, El-Shabrawi A, Quehenberger F, Hauser H, Mischinger HJ (1998) Antioxidant Treatment during Liver Resection for Alleviation of Ischemia- Reperfusion Injury. Hepatogastroenterology 45:777-782

19. Heaney AP, Sharer N, Rameh B, Braganza JM, Durrington PN (1999) Prevention of recurrent pancreatitis in familial lipoprotein lipase deficiency with high-dose antioxidant therapy. J Clin Endocrinol Metab 84:1203-1205

20. Keith ME, Jeejeebhoy KN, Langer A, Kurian R, Barr A, O'Kelly B, Sole MJ (2001) A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. Am J Clin Nutr 73:219-224

21. Sisto T, Paajanen H, Metsä-Ketelä T, Harmoinen A, Nordback I, Tarkka M (1995) Pretreatment with antioxidants and allopurinol diminishes cardiac onset events in coronary artery bypass grafting. Ann Thorac Surg 59:1519-1523

22. Uden S, Bilton D, Nathan L, Hunt LP, Mains C, Braganza JM (1990) Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. Aliment Pharmacol Therap 4: 357-371

23. Uden S, Schofield D, Miller PF, Day JP, Bottiglier T, Braganza JM (1992) Antioxidant therapy for recurrent pancreatitis: biochemical profiles in a placebo-controlled trial. Aliment Pharmacol Ther 6:229-240

24. Watters JM, Vallerand A, Kirkpatrick SM, Abbott HE, Norris S, Wells G, Barber GG (2002) Limited effects of micronutrient supplementation on strength and physical function after abdominal aortic aneurysmectomy. Clin Nutr 21:321-327

25. Berger MM, Cavadini C, Chioléro R, Guinchard S, Krupp S, Dirren H (1994) Influence of large intakes of trace elements on recovery after major burns. Nutrition 10:327-334

26. Faure H, Peyrin JC, Richard MJ, Favier A (1991) Parenteral supplementation with zinc in surgical patients corrects postoperative serum-zinc drop. Biol Trace Elem Res 30:37-45

27. Rock CL, Dechert RE, Khilnani R, Parker RS, Rodriguez JL (1997) Carotenoids and antioxidant vitamins in patients after burn injury, J Burn Care Rehabil 18:269-278

28. Rümelin A, Dörr, S, Depta A, Fauth U (2001) Preoperative oral ascorbic acid (AA) and postoperative plasma levels of AA, Clin Nutr 20 (suppl 3):47

29. Sawyer MA, Mike JJ, Chavin K, Marino PL (1989) Antioxidant therapy and survival in ARDS. Crit Care Med 17: S153 (abstract)

30. Galley HF, Howdle PD, Walker BE, Webster NR (1997) The effects of intravenous antioxidants in patients with septic shock. Free Radic Biol Med 23:768-774

31. Ortolani O, Conti A, Raffaele De Gaudio A, Moraldi E, Cantini Q, Novelli G (2000) The effect of glutathione and N-acetylcysteine on lipoperoxidative damage in patients with early septic shock. Am J Respir Crit Care Med 161:1907-1911

32. Molnar Z, MacKinnon KL, Shearer E, Lowe D, Watson ID (1998) The effect of N-acetylcysteine on total serum anti-oxidant potential and urinary albumin excretion in critically ill patients. Intensive Care Med 24:230-235

33. Angstwurm MW, Engelmann L, Zimmermann T, Lehmann C et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med. 2007 ;35(1):118-26.