11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements June 28th 2005

Recommendation:

Based on 4 level 1 and 7 level 2 studies, the use of supplemental combined vitamins and trace elements and 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	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	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 December 5th, 2003

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, 8 level 2 and one 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: Eleven studies reported on mortality and when the results of these were aggregated, antioxidant supplementation was associated with a significant reduction in mortality (RR = 0.65, 95 % confidence intervals 0.53-0.80, 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 = 0.66, 95 % CI 0.53-0.81, 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*)*.

LOS: When the 4 studies that reported on ICU LOS and the 3 studies that reported on hospital LOS were meta- analyzed, antioxidant supplementation was associated with a trend towards a reduction in ICU length of stay (SMD = - 0.33, 95 % confidence intervals –0.73 - 0.07, p = 0.11) but had no significant affect on hospital LOS (SMD = -0.18, 95 % confidence intervals –0.62 - 0.26, p = 0.42).

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).

Other complications: not reported

Conclusions:

1) Antioxidant Nutrients are associated with a significant reduction in mortality in critically ill patients.
2) Antioxidant Nutrients have no effect on infectious complications in critically ill patients.
3) Antioxidant Nutrients are associated with a trend toward reduced ICU LOS in critically ill patients.
4) Antioxidant Nutrients 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)

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

Study	Population	Methods score	Intervention	Mortality # (%)†		Infections # (%)‡	
				Experimental	Control	Experimental	Control
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
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 (1.7) 28 day 4/301 (1.3)	ICU 9/294 (3.1) Hospital 9/294 (3.1) 28 day 7/294 (2.4)	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

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)

Selenium: 1 μg = 0.0126 μmol.

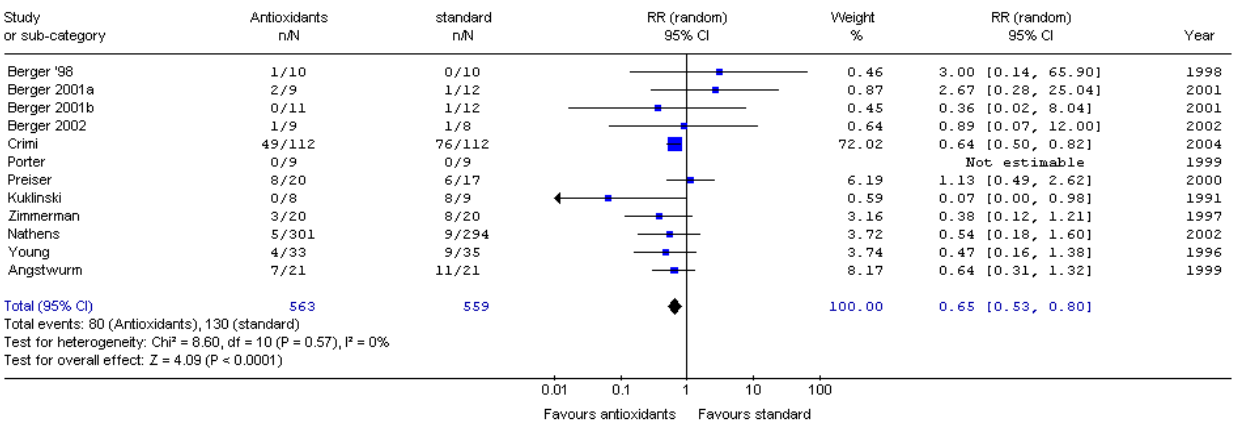
* data pertaining to the group receiving selenium alone is presented as Berger 2001a and the data for the group receiving Selenium + α tocopherol + zinc is presented as Berger 2001b.

** 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

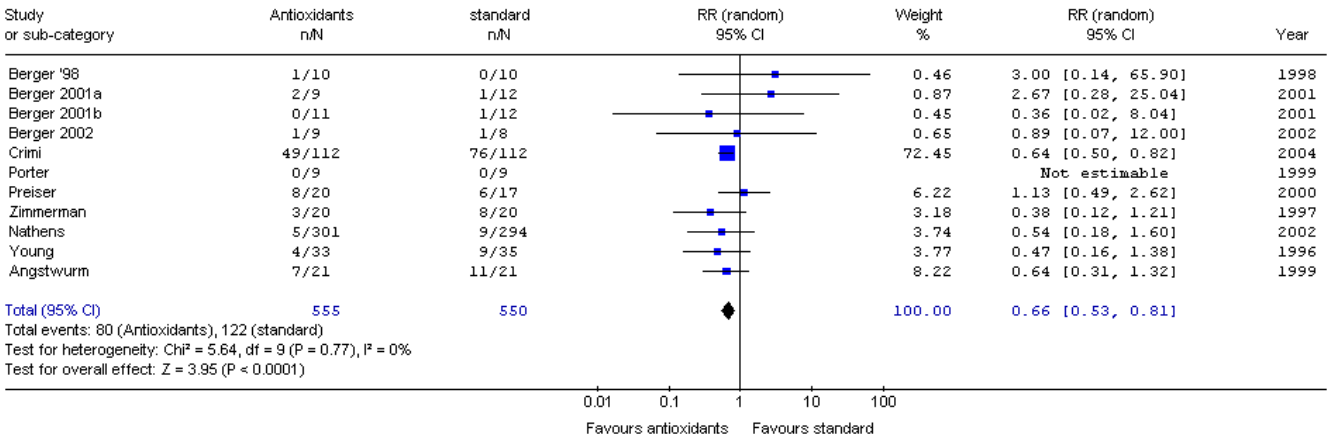
ITT: intent to treat † presumed hospital mortality unless otherwise specified ± ( ) : mean ± Standard deviation (number)

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

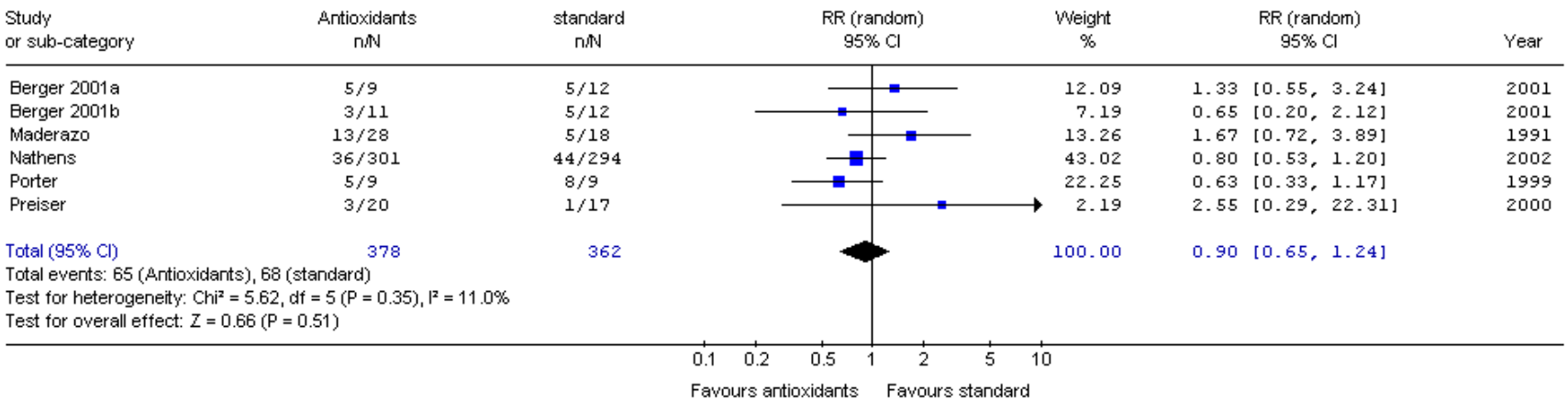


Sensitivity Analysis without Kuklinski

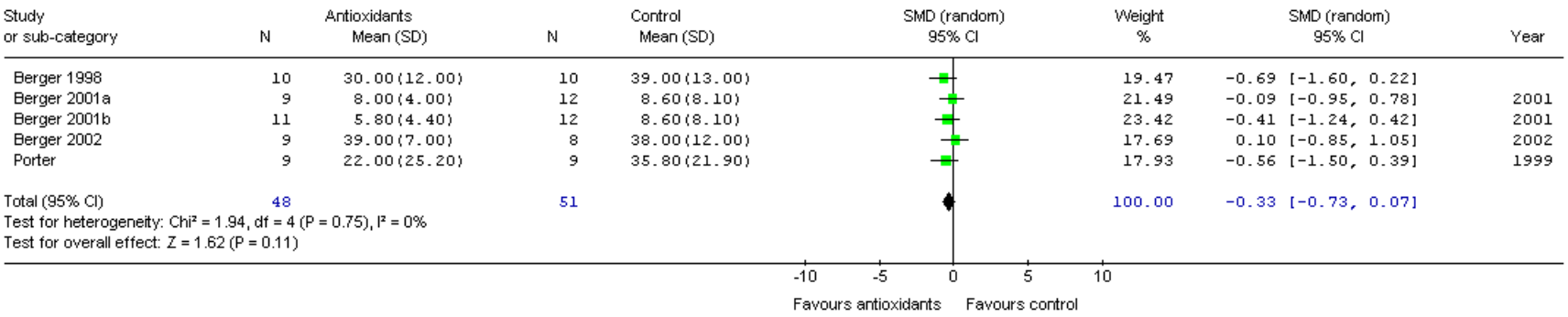
Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 01 Mortality



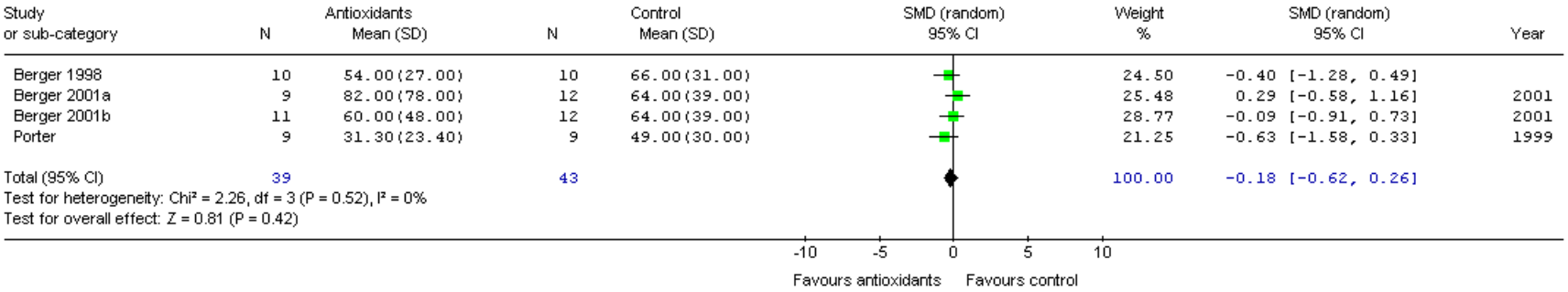
Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 02 Infectious Complications



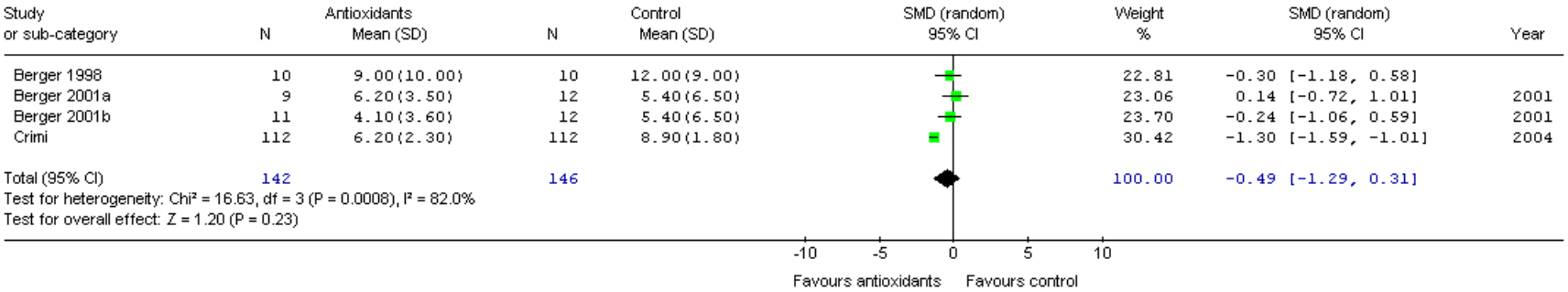
Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 03 ICU Length of Stay



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



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



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.

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	√		
29.	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	√		

I = included, E = excluded

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