11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements January 31st 2009

Recommendation:

Based on 3 level 1 and 13 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 1991), 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.

	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	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 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	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
Safety	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

11.1 Topic: Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements January 31st 2009

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, 13 level 2 studies 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: Fifteen studies reported on mortality and when the results of these were aggregated, antioxidant supplementation was associated with a significant reduction in mortality (RR 0.76, 95% CI 0.64, 0.91, p = 0.002) (figure 1). 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 0.76, 95% CI 0.65, 0.88, p = 0.0003) (figure 2).

Infections: When all the 6 studies that reported on infectious complications were aggregated, antioxidant supplementation had no significant effect on infectious complications (RR 0.94, 95%CI 0.75, 1.17, p = 0.56*)* (figure 3).

LOS and Ventilator days: When the 7 studies that reported on ICU LOS and the 4 studies that reported on hospital LOS were meta- analyzed, antioxidant supplementation had no effect on ICU length of stay (WMD 0.12, 95% CI -1.79, 2.03, p = 0.90) and was associated with a trend towards a reduction in hospital LOS (WMD -3.86, 95 % CI -9.07, 1.35, p = 0.15) (figures 4 and 5). When the 3 studies that reported ventilator days were meta-analyzed, antioxidant supplementation was associated with a significant reduction in the duration of ventilation (WMD -2.63, 95% CI -3.16, -2.10, p< 0.0001, no heterogeneity present) (figure 6).

Other complications: The incidence of multi-organ failure/dysfunction was reported to be lower in the combined vitamin/mineral group in the studies that reported on this.

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 and are associated with a trend towards a reduction in hospital LOS in critically ill patients.
4) Antioxidant Nutrients i.e. combined vitamins and trace elements are associated with a significant reduction in 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 from 11 ICUs 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 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
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)
14) Forceville 2007	Septic shock patients from 7 ICUs 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)

15)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
16) 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. (Continued) Randomized Studies Evaluating Combined Vitamins And Trace Elements in Critically Ill Patients

Study	LOS days		Ventilator days		Other	
	Experimental	Control	Experimental	Control	Experimental	Control
1) Kuklinski 1991	NR	NR	NR	NR	NR	NR
2) Maderazo 1991	NR	NR	NR	NR	NR	NR
3) Young 1996	NR	NR	NR	NR	NR	NR
4) Zimmerman 1997	NR	NR	NR	NR	NR	NR
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)	NR	NR
6) 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)
7) Angstwurm 1999	NR	NR	9 (3-23)	10 (1-43)	NR	NR
8) Preiser 2000	5 (3-26)	5 (3-18)	NR	NR	NR	NR

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)	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)	Multi Organ Failure 8/301 (3) 18/ 294 (6)	
11) Berger 2007***	ICU 35 ± 27 (11)	ICU 47 ± 37 (10)	7.6 ± 6 (11)	12.6 ± 6 (10)	NR	NR
12) Crimi 2004	Hospital 26.5 (mean)	Hospital 27.5 (mean)	6.2 ± 2.3 (112)	8.9 ± 1.8 (112)	Multi Organ Failure 24/112 (21) 26/112 (23)	
13) Angstwurm 2007	ICU 15.1 ± 10 (116)	ICU 12.7± 9 (122)	NA	NR	change in Logistic Organ dysfunction -2.6 ± 4.7 -2.0 ± 4.0	
14) 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)	
15) Mishra 2007	ICU 21.3 ± 16.2 (18)	ICU 20.8 ± 21.8 (18)	NR	NR	NR	
16) 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 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
*** Berger 2002 Clin Nutr 21 (suppl 1):66 data replaced by Berger 2007 Am J Clin Nutr data after clarification from author.
***** not included in meta-analysis as a subgroup

C.Random: concealed randomization ‡ Refers to the # of patients with infections unless specified NR: Not reported
ITT: Intent to treat † Presumed hospital mortality unless otherwise specified ± ( ) : Mean ± Standard deviation (number)

Figure 1.

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

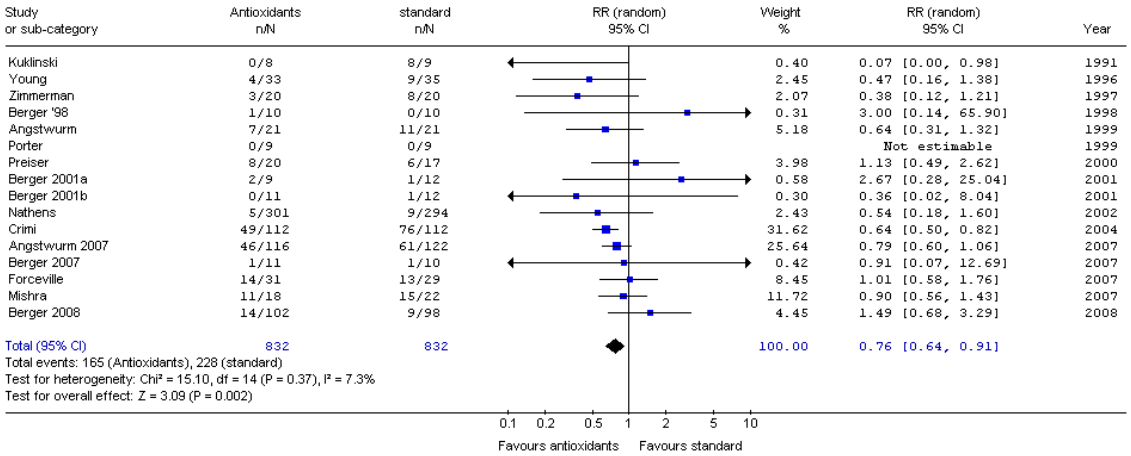


Figure 2. Sensitivity Analysis without Kuklinski

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

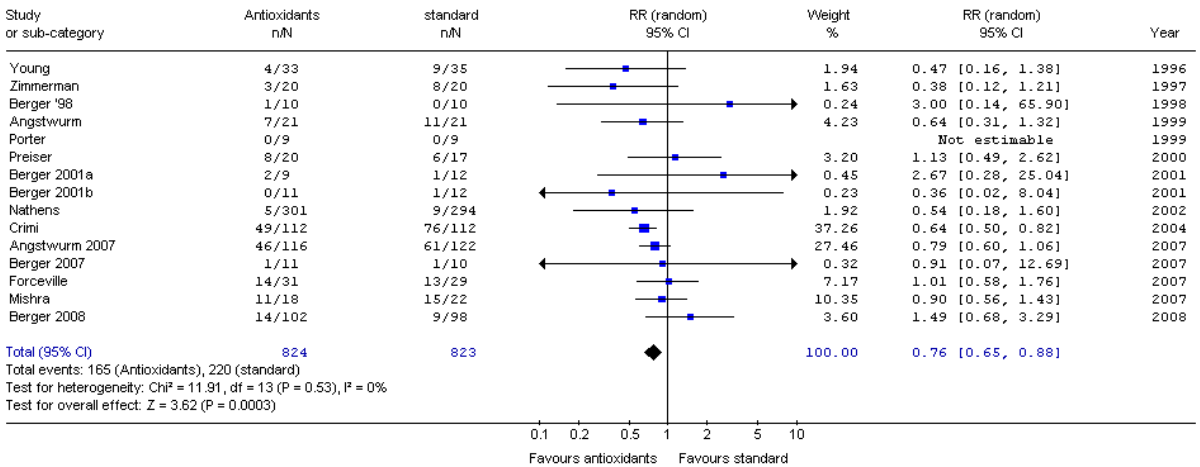


Figure 3.

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

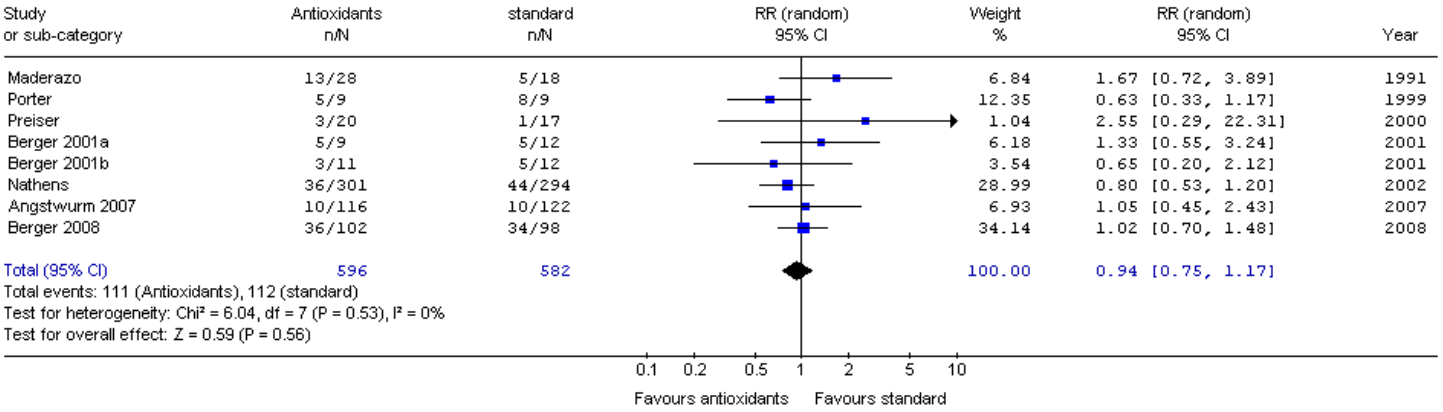


Figure 4.

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

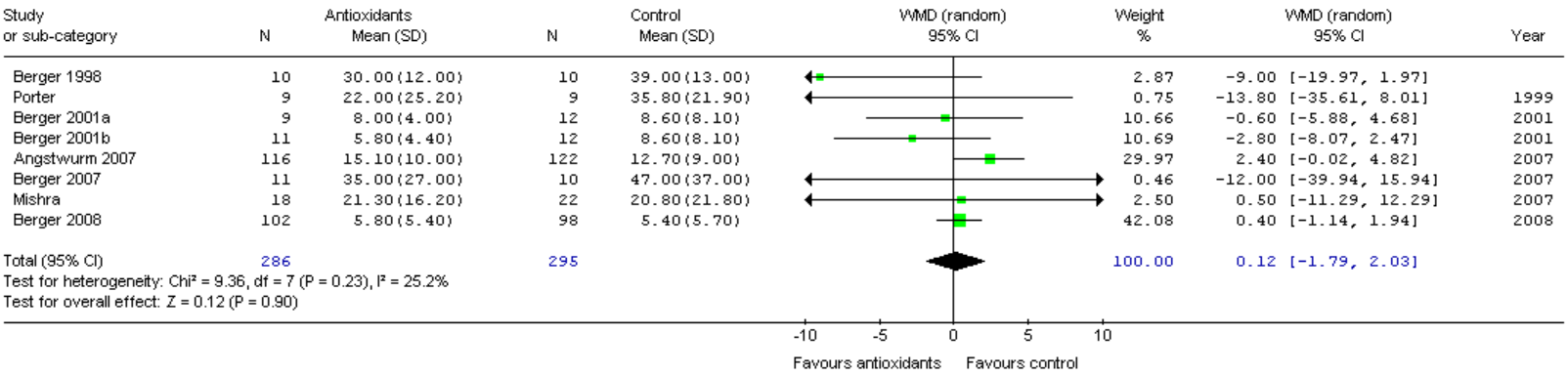


FIGURE 5.

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

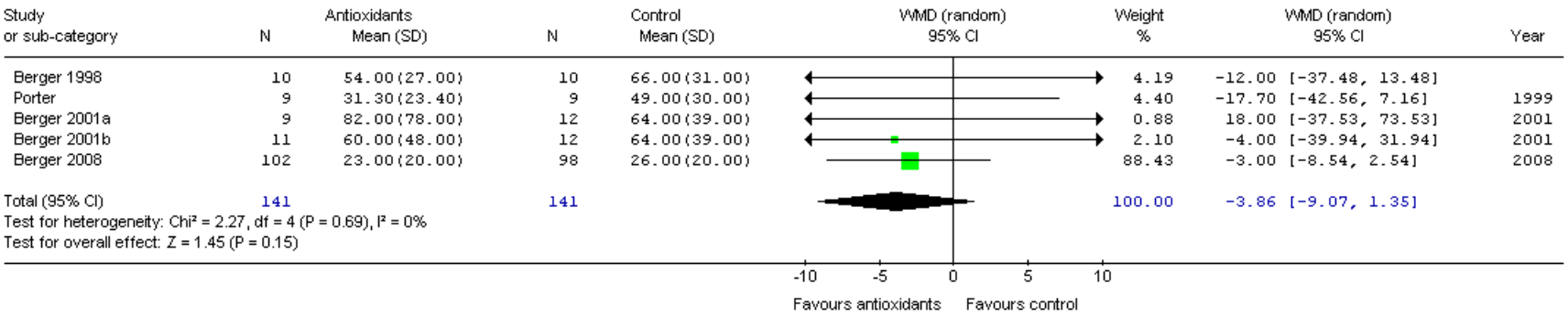
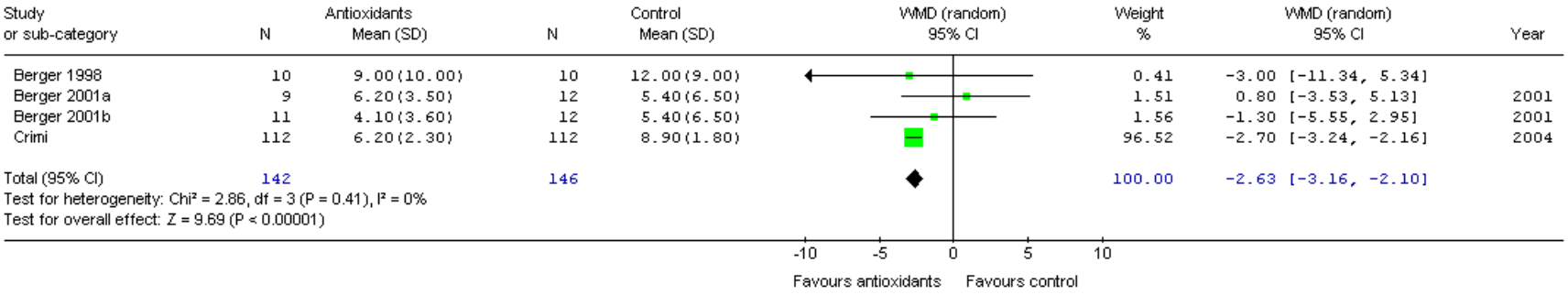


FIGURE 6.

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



TOPIC: 11.1 Antioxidant Nutrients: Combined Vitamins and Trace Elements

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill ventilated patients (no elective surgical patients)
Intervention: PN 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	Sawyer	C.C. Medicine 1989		√	Abstract only
2	Uden	Alim Pharmac Ther 1990		√	Not ICU patients
3	Faure	Biol Trace Elem Res 1991		√	No clinical outcomes
4	Kuklinski	Gestame Inn Med 1991	√		
5	Maderazo	J. Trauma 1991	√		
6	Ortolani	Boll Soc It Biol Sper 1992		√	ICU pts?, No clinical outcomes
7	Uden	Alim Pharmac Ther 1992		√	Not ICU patients
8	Sisto	Ann Thorac Surg 1995		√	Not ICU patients
9	Berger	Clin Nutr 1996		√	Same as Berger 1998
10	Young	J of Neurotrauma 1996	√		
11	Galley	Free Rad Bio Med 1997		√	Only 6 hr duration of intervention
12	Domenighetti	J Crit Care 1997		√	NAC alone
13	Bernard	Chest 1997		√	NAC alone
14	Rock	J Burn Care Rehab 1997		√	No clinical outcomes
15	Zimmermann	Medi Klinik 1997	√		
16	Berger	Am J Clin Nutr 1998	√		
17	Cerwanka	Gastroenterology 1998		√	Not ICU pts
18	Molnar	Inten Care Med 1998		√	NAC alone
19	Saito	Neurosurgery 1998		√	Not ICU patients
20	Spapen	Chest 1998		√	NAC alone
21	Yamaguchi	Stroke 1998		√	Not ICU patients
22	Angstwurm	CCMedicine 1999	√		
23	Cerwanka	Free Rad Res 1999		√	Not ICU pts
24	Ogawa	Cerebrovas Dis 1999		√	Not ICU patients
25	Porter	Am Surgeon 1999	√		
26	Ortolani	Am J Resp Care 2000		√	NAC alone and Glutathione
27	Preiser	CCMedicine 2000	√		
28	Tanaka	Arch Surgery 2000		√	Pseudorandomized
29	Berger	Int Care Med 2001	√		
30	Berger	Nutrition Research 2001		√	Same as Berger 2001 [Int Care Med]

31	Keith	Am J Clin Nut 2001		√	Not ICU patients
32	Rümelin	ESPEN Congress Abstract 2001		√	No clinical outcomes
33	Nathens	Ann Surg 2002	√		
34	Watters	Clinical Nutrition 2002		√	Elective surgery pts
35	Angdin	Journal of Cadiothoracic and Vascular Anesthesia 2003		√	Elective surgery pts
36	Bartels	Clinical Nutrition 2004		√	Elective surgery & cancer pts
37	Crimi	Anesth Analg. 2004	√		
38	Heyland	Intensive Care Med 2005		√	Meta-analysis, Individual studies looked at
39	Ullegaddi	JPEN 2006		√	Not ICU pts
40	Angstwurm 2007	CCMed 2007	√		
41	Bjelakovic	JAMA 2007		√	Systematic review & meta-analysis, Not ICU pts
42	Forceville	Critical Care 2007	√		
43	Mishra	Clinical Nutrition 2007	√		
44	Berger	Critical Care 2008	√		

I = included, E = excluded

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