11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements

There are no new randomized controlled trials since the 2015 updates and hence there are no changes to the following summary of evidence.

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

Summary of evidence: Of the 28 studies included, there were eight level 1 and twenty level 2 studies reviewed that compared various antioxidants either as single nutrients (zinc, selenium) or as a combination of nutrients (selenium, copper, zinc, vit. A, C & E, N-acetylcysteine) given by various routes (IV/parenteral, enteral, combined parenteral and enteral). 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 (selenium alone and selenium combined with zinc and α tocopherol compared to placebo) and the data presented here are for the combined group only. Refer to topic 11.2 Parenteral Selenium (alone or in combination) for the results of both groups combined and subgroup analyses including the monotherapy group only. Howe 2015 also had two intervention arms (Vit C+E and Vit C+E+N-acetylcysteine) and the data for the two intervention arms has been combined in this meta-analysis.

Mortality: Twenty-five studies reported on mortality and when the results were aggregated, antioxidant supplementation was associated with a significant reduction in overall mortality (RR 0.88, 95% CI 0.78, 1.00, p=0.04, heterogeneity I^2=24%; figure 1). Linder (2004) and Nogueira (2013) were excluded from the meta-analyses because the type of mortality was not specified but appeared to be 90 days and mortality was only reported as a percent of total deaths, respectively. The following subgroup analyses were completed:

> **Antioxidant delivery method:** When the 17 studies which delivered antioxidants intravenously were sub-grouped and analysed, antioxidant supplementation was not associated with a reduction in overall mortality (RR 0.93, 95% CI 0.83, 1.04, p=0.22, heterogeneity I^2=1%; figure 1). When the 5 studies which delivered antioxidants via enteral nutrition were sub-grouped and analysed, antioxidant supplementation was associated with a significant reduction in overall mortality (RR 0.69, 95% CI 0.56, 0.85, p=0.0005, heterogeneity I^2=0%; figure 1). When the data from the subgroup comprised of the 3 studies which delivered antioxidants enterally and intravenously were aggregated, antioxidant supplementation had no effect on overall mortality (RR 1.07, 95% CI 0.92, 1.25, p=0.38, heterogeneity I^2=0%; figure 1). The test for subgroup differences was significant (p=0.004).
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> **Mortality (higher vs. lower mortality in control group):** Subgroup analysis showed that antioxidant supplementation was associated with a significant reduction in overall mortality among patients with higher risk of death (>10% mortality in the control group) (RR 0.86, 95% CI 0.75, 0.99, p=0.03, heterogeneity I^2=39%; figure 2). There was no significant effect observed for trials of patients with a lower mortality in the control group (RR 1.10, 95% CI 0.68, 1.77, p=0.70, heterogeneity I^2=0%; figure 2). The test for subgroup differences was not significant (p=0.34).

Infections: When the 12 studies that reported on the number of patients with infectious complications were aggregated, antioxidant supplementation was associated with a trend towards reduction in overall infections (RR 0.94, 95% CI 0.88, 1.02, p=0.14, heterogeneity I^2=0%; figure 3). The following subgroup analyses were completed:

Antioxidant delivery method: When a subgroup analysis based on 6 studies which delivered antioxidants intravenously was done, antioxidant supplementation was not associated with a reduction in infectious complications (RR 0.96, 95% CI 0.88, 1.04, p=0.35, heterogeneity I^2=0%; figure 3). When a subgroup analysis based on 3 studies which delivered antioxidants via enteral nutrition was done, antioxidant supplementation had no effect on infectious complications (RR 1.10, 95% CI 0.60, 2.04, p=0.75, heterogeneity I^2=38%; figure 3). When a third subgroup analysis based on 3 studies which delivered antioxidants enterally and intravenously was done, antioxidant supplementation was associated with a trend towards a reduction in infectious complications (RR 0.90, 95% CI 0.77, 1.05, p=0.19, heterogeneity I^2=0%; figure 3). The test for subgroup differences was not significant (p=0.71).

Infections (higher vs. lower mortality in control group): Subgroup analysis showed that antioxidant supplementation was associated with a trend in a reduction in infectious complications among patients with higher risk of death (>10% mortality in the control group) (RR 0.95, 95% CI 0.88, 1.03, p=0.20, heterogeneity I^2=0%; figure 4). There was no significant effect observed for patients in trials with a lower mortality in the control group (RR 0.86, 95% CI 0.68, 1.10, p=0.22, heterogeneity I^2=0%; figure 4). The Maderazo study was not included in the analysis since it does not report on mortality. The test for subgroup differences was not significant (p=0.31).

ICU length of stay: When the 11 studies that reported ICU length of stay as a mean ± standard deviation were aggregated, antioxidant supplementation had no effect on ICU length of stay (WMD 0.16, 95% CI -1.38, 1.69, p=0.84, heterogeneity I^2=21%; figure 5). The following subgroup analysis was completed:

Antioxidant delivery method: The result was the same for each of the 3 subgroups: six studies which delivered antioxidants intravenously (WMD -0.20, 95% CI -3.47, 3.07, p=0.90, heterogeneity I^2=30%; figure 5), two studies which delivered antioxidants via enteral nutrition (WMD -2.65, 95% CI -11.60, 6.31, p=0.56; figure 5), and three studies which delivered antioxidants enterally and intravenously (WMD 0.35, 95% CI -0.97, 1.67, p=0.60, heterogeneity I^2=0%; figure 5). The test for subgroup differences was not significant (p=0.78).

Hospital length of stay: When the 8 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, antioxidant supplementation had no effect on hospital length of stay (WMD -0.45, 95% CI -3.53, 2.64, p=0.78, heterogeneity I^2=0%; figure 6). The following subgroup analysis was completed:

Antioxidant delivery method: The result was the same for each of the 3 of the subgroups: two studies which delivered antioxidants intravenously (WMD -9.38, 95% CI -30.29, 11.52, p=0.38, heterogeneity I^2=0%; figure 6), two studies which delivered antioxidants via

enteral nutrition (WMD 1.22, 95% CI -4.23, 6.67, p=0.66; figure 6), and 3 studies in which antioxidants were delivered enterally and parenterally (WMD -1.40, 95% CI -6.89, 4.09, p=0.62, heterogeneity I^2=38%; figure 6). The test for subgroup differences was not significant (p=0.59).

Duration of mechanical ventilation: When the 8 studies that reported duration of ventilation as a mean ± standard deviation were aggregated, antioxidant supplementation was associated with a significant reduction in duration of ventilation (WMD -2.27, 95% CI -4.46, -0.09, p=0.04, heterogeneity I^2=72%; figure 7). The following subgroup analysis was completed:

Antioxidant delivery method: In the subgroup of 5 studies in which antioxidants were delivered intravenously, antioxidant supplementation was associated with a trend towards a reduction in duration of ventilation (WMD -3.18, 95% CI -7.28, 0.93, p=0.13, heterogeneity I^2=78%; figure 7). In the 2 studies where antioxidants were delivered via enteral nutrition, antioxidant supplementation was associated with a significant reduction in duration of ventilation (WMD -2.59, 95% CI -4.15, -1.04, p=0.001, heterogeneity I^2=3%; figure 7). In the subgroup consisting of 1 study in which antioxidants were delivered enterally and intravenously, no effect was observed (WMD 0.40, 95% CI -1.91, 2.71, p=0.73; figure 7). There was a trend towards a difference between the subgroups (p=0.09).

Quality of Life (QOL) Outcomes: Berger 2008 and Andrews 2011 reported on QOL outcomes. Berger 2008 conducted the SF-36 questionnaire at 3 months and found a trend towards improved physical activity score in the antioxidant group. There was no difference between the groups for physical limitation, physical pain and perceived health scores. Andrews 2011 completed the SF-12 physical and mental composite scale score and the EQ-5D instrument at 3 and 6 months with survivors and found no significant different between scores.

Conclusions:

1) Antioxidant nutrients are associated with a reduction in overall mortality in critically ill patients.
2) Antioxidant nutrients may be associated with a reduction in overall infectious complications in critically ill patients.
3) Antioxidant nutrients have no effect on ICU length of stay in critically ill patients.
4) Antioxidant nutrients have no effect on hospital length of stay in critically ill patients.
5) Antioxidant nutrients are associated with a reduction in duration of ventilation in critically ill patients.
6) Antioxidant nutrients are not associated with improvements in QOL in critically ill patients.

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
Studies in which antioxidants were delivered via PN			
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
2) 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
3) Zimmerman 1997	Patients with SIRS, APACHE > 15 and multiorgan 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
4) 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) from day 0- 8, all received early EN
5) 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)
6) Berger 2001	Trauma patients, surgical ICU N=32	C. Random: yes ITT: no Blinding: double 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)
7) Lindner 2004	Patients with acute pancreatitis admitted to the ICU N=70	C. Random: not sure ITT: no Blinding: single (9)	IV sodium selenite dose of 2000 μg on day 1, 1000 μg on days 2-5, and 300 μg from day 6 until discharge vs placebo (isotonic 0.9% IV NaCl solution).

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)
9) Berger 2007	Burns > 20 % TBSA N=21	C.Random: not sure ITT: yes Blinding: no (8)	IV 100 ml 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.
10) 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)
11) 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).
12) El-Attar 2009	COPD patients N=80	C.Random: yes ITT: yes Blinding: yes (12)	IV selenium as sodium selenite 100 μg/day, zinc 2 mg/day and manganese 0.4 mg/day vs. none. TE were administered during the period on mechanical ventilation
13) González 2009	Medical/surgical ICU pts N=68	C.Random: yes ITT: yes Blinding: double (7)	day 1 sodium selenite 1000μg , day 2 sodium selenite 500 μg and thereafter 200 μg during seven additional days vs selenite 100 μg/d
14) Andrews 2011	Mixed ICU N=502	C. Random: yes ITT: yes Blinding: double (13)	500μg selenium supplemented PN (12.5g nitrogen, 2000kcal) vs. standard PN (12.5g nitrogen, 2000kcal) initiated after ICU admission (actual median 2.6 days) for 7 days (actual duration, mean 4.1 days).
15) Manzanares 2011	Septic or trauma patients N=31	C. Random: not sure ITT: no (except mortality) Blinding: single (9)	IV Selenium supplementation loading dose 2000 μg (2 hours) on day 1 followed by 1600μg/day for 10 days vs. NaCl as placebo

16) Valenta 2011	Patients with sepsis or SIRS N=150	C. Random: not sure ITT: yes Blinding: no (8)	IV Selenium supplementation loading dose 1000 μg on day 1 followed by 500μg/day for 5-14 days + <75μg/day of Na-selenite added to PN. vs. NaCl + <75μg/day of Na-selenite added to PN.
17) Woth 2014	Mixed ICU, severe septic pts w multi-organ failure N=40	C. Random: not sure ITT: yes Blinding: no (6)	1000-μg/30 minutes loading dose of Na selenite and 1000-μg/die treatment for a maximum of 14 days vs control group (not described).
18) Bloos, 2016	Multicentre Mixed ICU pts with severe sepsis or septic shock in last 24 hrs. N=1180	C. Random: yes ITT: yes Blinding: double (12)	IV loading dose of 1000 μg sodium selenite followed by continuous IV of 1000 μg sodium selenite daily until ICU discharge or for 21 days, whichever comes first vs placebo (0.9% sodium chloride).
Studies in which antioxidants were delivered via EN			
19) 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 ml of D5W vs. 100 ml 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)
20) 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 ml Vit C & 4.9 mg/100 ml Vit E) vs. isonitrogenous, isocaloric standard formula (67 μg /100 ml vit. A, 5 mg/100 ml Vit C and 0.81 mg/100 ml Vit E) from Day 0- 7
21) 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
22) 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)
23) Schneider 2011	ICU patients with sepsis or SIRS N=58	C.Random: not sure ITT: yes Blinding: single blind (8)	Fresenius Kabi Intestamin (300μg selenium, zinc 20mg, vitamin C 1500mg, Vitamin E 500mg) vs. Fresubin original plus 250mL water delivered via duodenal tube and initiated within first 48h of ICU admission. Both groups received Fresenius Kabi original fiber and supplemental PN if <60% adequacy

24) Nogueira 2013	ICU pts requiring EN (80% post-op, 20% medical) N=70	C.Random: not sure ITT: no Blinding: no (4)	'Hospital routine' EN + 10 000 IU retinol acetate, 400 mg vit E, 600 mg vit C vs 'hospital routine' EN. *Note: 'hospital routine' not defined in article.*
25) Howe 2015	Mechanically ventilated ICU patients N=72	C.Random: not sure ITT: no Blinding: no (4)	Vit C (1000mg) + Vit E (1000 IU) + N-acetylcysteine (400 mg) q8h as a bolus via EN vs Vit C (1000mg) + Vit E (1000 IU) q8h as a bolus via EN vs placebo q8h as a bolus via EN. *Note: 2 intervention groups*
Studies in which antioxidants were delivered simultaneously via PN and EN			
26) 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 g of N-acetylcysteine (NAC) q 6 hrs via nasogastric or oral route, from Day 0-7 vs. none
27) 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)
28) Heyland 2013	Multicentre mixed ICUs N=1218	C.Random: yes ITT: yes Blinding: double (12)	500 μg selenium via PN + 300 μg selenium, 20 mg zinc, 10 mg beta carotene, 500 mg vitamin E, 1500 mg vitamin C via EN vs. placebo via PN and EN

D5W: dextrose 5% in water
TBSA: total body surface area

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

Study	Mortality		Infections		LOS		Ventilator Days	
	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control
Studies in which antioxidants were delivered via PN								
1) Kuklinski 1991	ICU 0/8 (0)	ICU 8/9 (89)	NR	NR	NR	NR	NR	NR
2) Young 1996	4/33 (12)	9/35 (26)	NR	NR	NR	NR	NR	NR

3) Zimmerman 1997	3/20 (15)	8/20 (40)	NR	NR	NR	NR	NR	NR
4) Berger 1998	1/10 (10)	0/10 (0)	1.9 ± 0.9 (1-4) per patient	3.1 ± 1.1 (2-5) per patient	**ICU** 30 ± 12 (10) **Hospital** 54 ± 27 (10)	**ICU** 39 ± 13 (10) **Hospital** 66 ± 31 (10)	9 ± 10 (10)	12 ± 9 (10)
5) Angstwurm 1999	**Hospital** 7/21 (33)	**Hospital** 11/21 (52)	NR	NR	NR	NR	9 (3-23)	10 (1-43)
6) Berger 2001	**Se+AT+Zn** 0/11 (0)	1/11 (9)	**Se+AT+Zn** 3/11 (27)	3/11 (27)	**Se+AT+Zn ICU** 5.8 ± 4.4 (11) **Hospital** 60 ± 48 (11)	**ICU** 8.6 ± 8.1 (11) **Hospital** 64 ± 39 (11)	**Se+AT+Zn** 4.1 ± 3.6 (11)	4.2 ± 5.2 (11)
7) Linder 2004	**Not specified** 5/32 (15.6)	**Not specified** 3/35 (8.6)	NA	NA	**Hospital** 24 (9-44)	**Hospital** 26 (11-46)	NA	NA
8) Angstwurm 2007	**28-day** 46/116 (40)	**28-day** 61/122 (50)	**HAP** 10/116 (9)	**HAP** 10/122 (8)	**ICU** 15.1 ± 10 (116)	**ICU** 12.7 ± 9 (122)	NR	NR
9) Berger 2007	1/11 (9)	1/10 (10)	2.1 ± 1.0 per pt	3.6 ± 1.3 per pt	**ICU** 35 ± 27 (11)	**ICU** 47 ± 37 (10)	7.6 ± 6 (11)	12.6 ± 6 (10)
10) Forceville 2007	**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)	**Superinfection** 2/29 (7)	**ICU** 21 (7-40) **Hospital** 25 (7-68)	**ICU** 18 (10-31) **Hospital** 33 (11-51)	19 (7-34)	14 (8-23)
11) Mishra 2007	**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)	1.5 ± 1.9 per patient	1.8 ± 1.6 per patient	**ICU** 21.3 ± 16.2 (18)	**ICU** 20.8 ± 21.8 (18)	NR	NR

12) El-Attar 2009	**ICU** 2/40 (5)	**ICU** 1/40 (3)	**VAP** 5/36 (14)	**VAP** 7/34 (21)	NR	NR	9.4 ± 7.3 (40)	17.8 ± 7.6 (40)
13) González 2009	**Hospital** 6/34 (18)	**Hospital** 8/34 (24)	NR	NR	**Hospital** 12(12-14)	**Hospital** 17(14-20)	9 (7-12)	13 (8-14)
14) Andrews 2011	**ICU** 84/251 (33) **6-month** 107/251 (43)	**ICU** 84/251 (33) **6-month** 114/251 (45)	**Confirmed** 104/251 (41)	**Confirmed** 121/251 (48)	**ICU** 13.2 (IQR 7.8, 23.7) **Hospital** 29.8 (IQR 14.7, 52.4)	**ICU** 15.1 (IQR 8.3, 28.4) **Hospital** 31.2 (IQR 15.1-57.8)	NR	NR
15) Manzanares 2011	**ICU** 3/15 (20) **Hospital** 5/15 (33)	**ICU** 5/16 (31) **Hospital** 7/16 (44)	**VAP** 3/15 (20)	**VAP** 7/16 (44)	**ICU** 14 ± 11 (15)	**ICU** 13 ± 6 (16)	10 ± 8 (15)	9 ± 4 (16)
16) Valenta 2011	**28-day** 19/75 (25)	**28-day** 24/75 (32)	NR	NR	NR	NR	NR	NR
17) Woth 2014	**In 14 day study period** 9/21 (43)	**In 14 day study period** 11/19 (58)	**Gram negative** 8/21 (38) **Gram positive** 3/21 (14) **Fungal** 1/21 (5)	**Gram negative** 3/19 (16) **Gram positive** 2/19 (11) **Fungal** 0/19 (0)	**NR**	NR	NR	NR
18) Bloos, 2016	**28 day** 152/543 (28) **90 day** 198/543 (38)	**28 day** 137/546 (25) **90 day** 201/546 (38)	**Secondary infections, Day 14** 243/543 (44.7%) **Secondary infections, Day 21** 319/543 (58.8%)	**Secondary infections, Day 14** 269/546 (49.3%) **Secondary infections, Day 21** 323/546 (59.2%)	**ICU** 11 (5-22) **Hospital** 26 (16-42)	**ICU** 12 (6-24) **Hospital** 29 (17-50)	2 (0-5)	2 (0-5)
Studies in which antioxidants were delivered via EN								
19) Maderazo 1991	NR	NR	13/28 (46)	5/18 (28)	NR	NR	NR	NR

20) Preiser 2000	**ICU** 3/20 (15) **Hospital** 8/20 (40)	**ICU** 3/17 (18) **Hospital** 6/17 (35)	3/20 (15)	1/17 (6)	5 (3-26)	5 (3-18)	NR	NR
21) Nathens 2002	**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)	**ICU** 5.3 (mean) **Hospital** 14.6 (mean)	**ICU** 6.4 (mean) **Hospital** 15.1 (mean)	3.7 (mean)	4.6 (mean)
22) Crimi 2004	**28-day** 49/112 (44)	**28-day** 76/112 (68)	NR	NR	**Hospital** 26.5 (mean)	**Hospital** 27.5 (mean)	6.2 ± 2.3 (112)	8.9 ± 1.8 (112)
23) Schneider 2011	6/29 (21)	6/29 (21)	**From day 8** 13/26 (50)	**From day 8** 9/24 (38)	**ICU** 29.8 ± 26 (29) **Hospital** 44.4 ± 36.6 (29)	**ICU** 26.5 ± 19.6 (29) **Hospital** 47.2 ± 48.1 (29)	30.5 ± 19.2 (21)	27.2 ± 18.1 (19)
24) Nogueira 2013	25% of total deaths Actual data not reported	75% of total deaths Actual data not reported	NR	NR	**Hospital** 30 ± 11	**Hospital** 27 ± 11	28% of vent needs Actual data not reported	72% of vent needs Actual data not reported
25) Howe 2015	**Vit+acetylcysteine** **All cause** 8/23 (35) **No acetylcysteine** **All cause** 9/27 (33)	**All cause** 10/22 (45)	NR	NR	**Vit+acetylcysteine** **ICU** 13.0 ± 10.5 (23) **Hospital** 24.0 ± 20.8 (23) **No acetylcysteine** **ICU** 12.9 ± 9.0 (27) **Hospital** 21.2 ± 13.7 (27) **Combined*** **ICU** 12.946 ± 9.72 (50) **Hospital** 22.488 ±17.32 (50)	**ICU** 19.1 ± 16.0 (22) **Hospital** 22.6 ± 15.5 (22)	**Vit+acetylcysteine** Mean 12 days Median 6 days **No acetylcysteine** Mean 10 days Median 6 days P=0.74 across 2 intervention groups	Mean 19 days Median 15 days P=0.02 across 3 groups
Studies in which antioxidants were delivered simultaneously via PN and EN								

26) Porter 1999	0/9	0/9	5/9 (56)	8/9 (89)	**ICU** 22 ± 25.2 (9) **Hospital** 31.3 ± 23.4 (9)	**ICU** 35.8 ± 21.9 (9) **Hospital** 49 ± 30 (9)	NR	NR
27) Berger 2008	**ICU** 8/102 (8) **Hospital** 14/102 (14) **3-month** 14/602 (14)	**ICU** 5/98 (5) **Hospital** 9/98 (9) **3-month** 11/98 (11)	36/102 (35)	34/98 (35)	**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
28) Heyland 2013	**Hospital** 216/617 (35) **14-day** 154/617 (25) **28-day** 190/617 (31) **3-month** 239 (36) **6-month** 250 (40)	**Hospital** 199/601 (33) **14-day** 132/601 (22) **28-day** 173/601 (29) **3-month** 222 (36) **6-month** 235(41)	**All** 168/617 (27) **VAP** 71/617 (12)	**All** 181/601 (30) **VAP** 95/601 (16)	**ICU** 14.2 ± 22.7 (617) **Hospital** 31.2 ± 50.2 (617)	**ICU** 13.8 ± 23.1 (601) **Hospital** 29.5 ± 44.8 (601)	10.9 ± 21.4 (617)	10.5 ± 19.7 (601)

*Calculated from individual group data ICU: Intensive care unit VAP: ventilator associated pneumonia LOS: length of stay

Table 2. QOL Outcomes

Study	QOL Outcomes
27) Berger 2008	**AOX** **Control** **Short Form (SF) 36-item health survey at 3 months** **Physical Activity Score** 24.2 ± 4.9 22.8 ± 5.7, p=0.14 **Physical Limitation** 5.8 ± 1.4 5.5 ± 1.5, p=NS **Physical Pain** 8.9 ± 2.4 9.0 ± 2.7, p=NS **Perceived Health** 18.9 ± 4.5 19.2 ± 4.1, p=NS

14) Andrews 2011	**Gln**	**Gln+Se**	**Se**	**Neither**
		SF-12 PCS at 3 months		
	35.2 ± 9.8 (49)	33.3 ± 11.1 (50)	33.9 ± 9.8 (52)	36.6 ± 11.6 (59)
		SF-12 PCS at 6 months		
	35.9 ± 9.3 (45)	35.9 ± 10.9 (43)	36.3 ± 10.0 (46)	39.9 ± 10.5 (53)
		SF-12 MCS at 3 months		
	420 ± 11.8 (49)	40.3 ± 12.0 (50)	41.9 ± 11.9 (52)	42.2 ± 12.2 (59)
		SF-12 MCS at 6 months		
	43.4 ± 11.9 (45)	44.8 ± 11.9 (43)	44.1 ± 11.6 (46)	43.3 ± 12.1 (53)
		EQ-5D at 3 months		
	0.47 ± 0.41 (52)	0.51 ± 0.35 (52)	0.49 ± 0.35 (55)	0.56 ± 0.34 (61
		EQ-5D at 6 months		
	0.53 ± 0.35 (49)	0.60 ± 0.30 (51)	0.53 ± 0.33 (47)	0.63 ± 0.28 (55)

NS: not significant

Figure 1. Overall Mortality (with sub-analyses according to routes of administration)

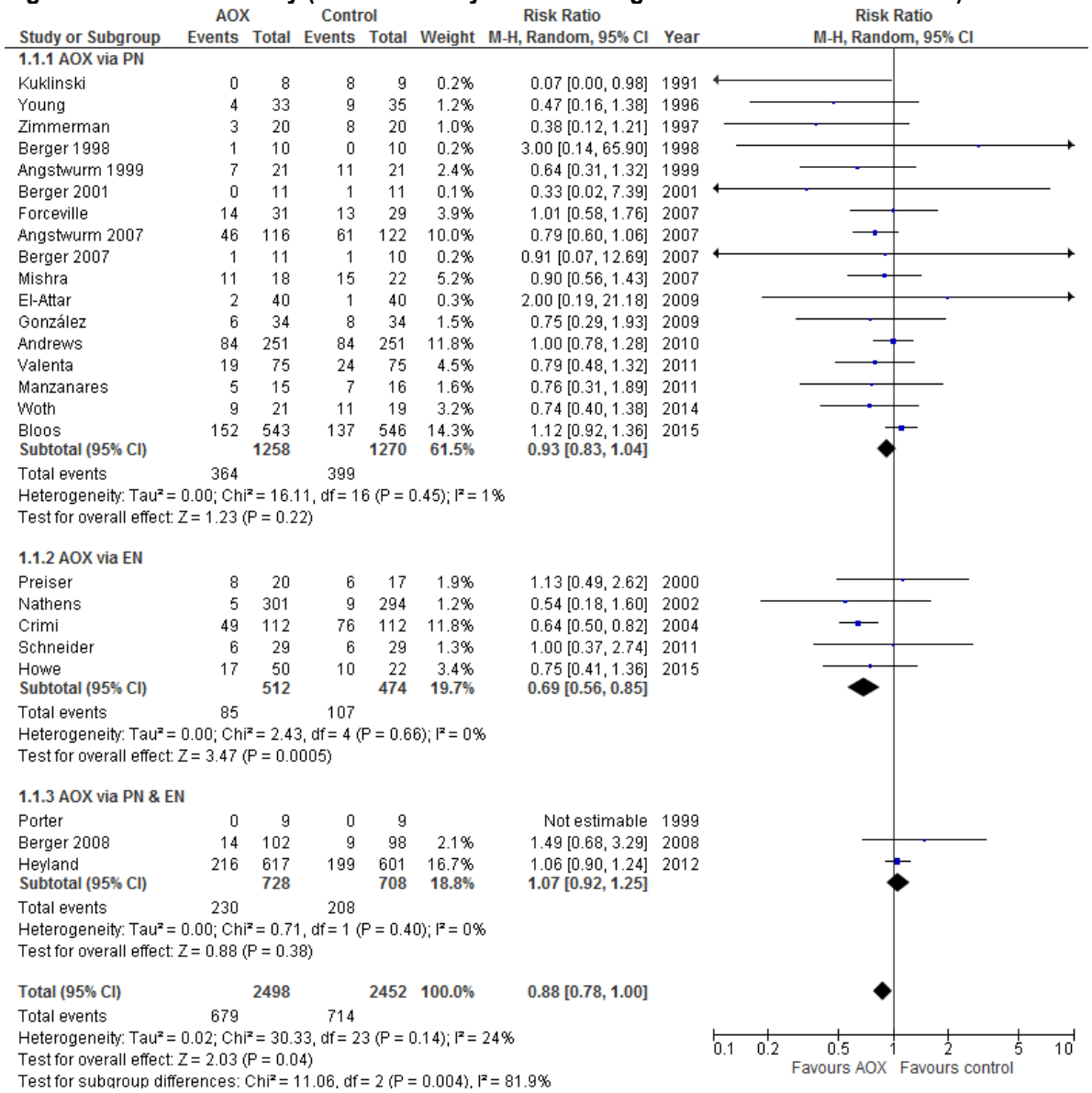


Figure 2: Mortality (with sub-analyses according to high (>10%) or low mortality in the control group)

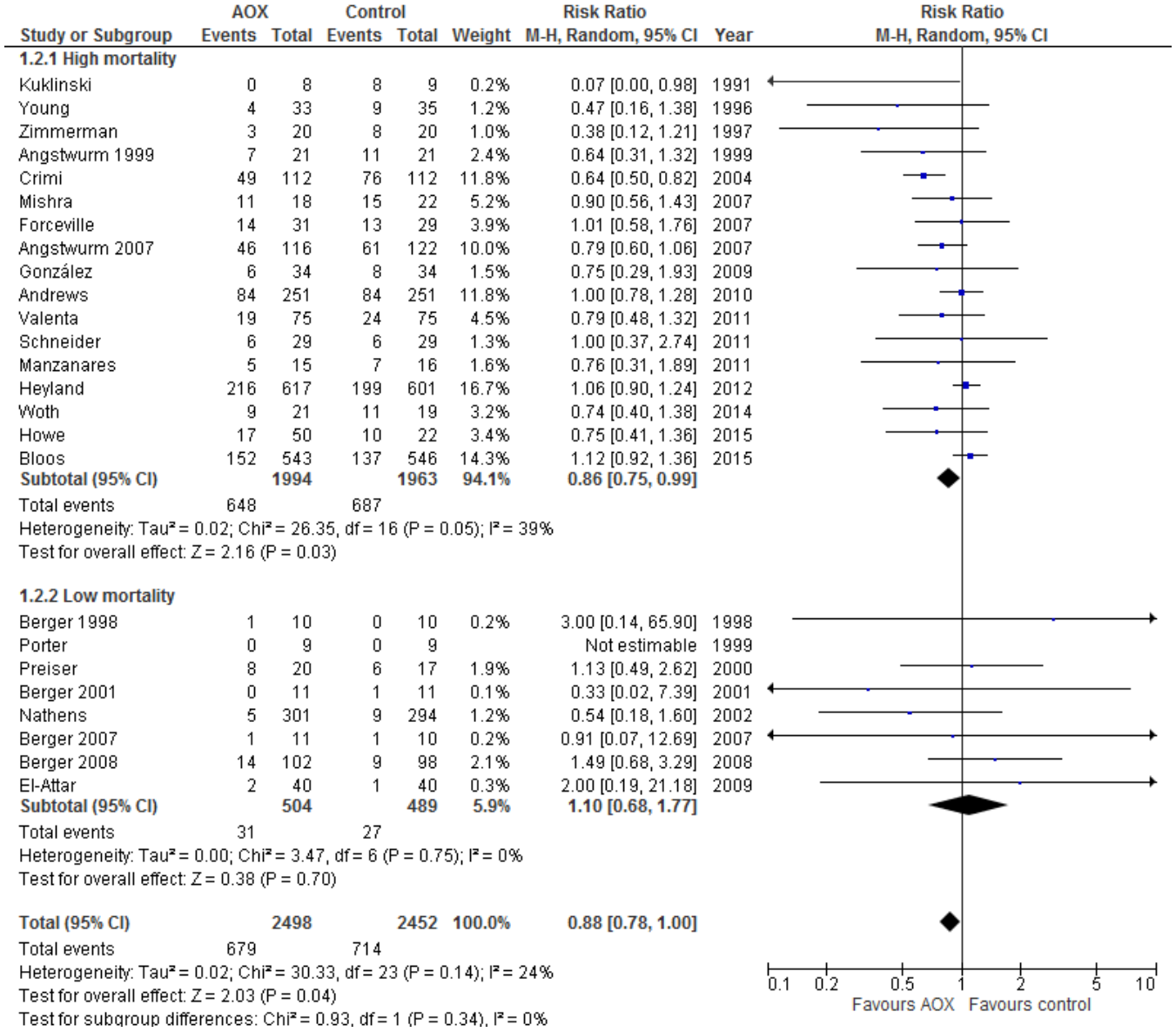


Figure 3. Infections (with sub-analyses according to routes of administration)

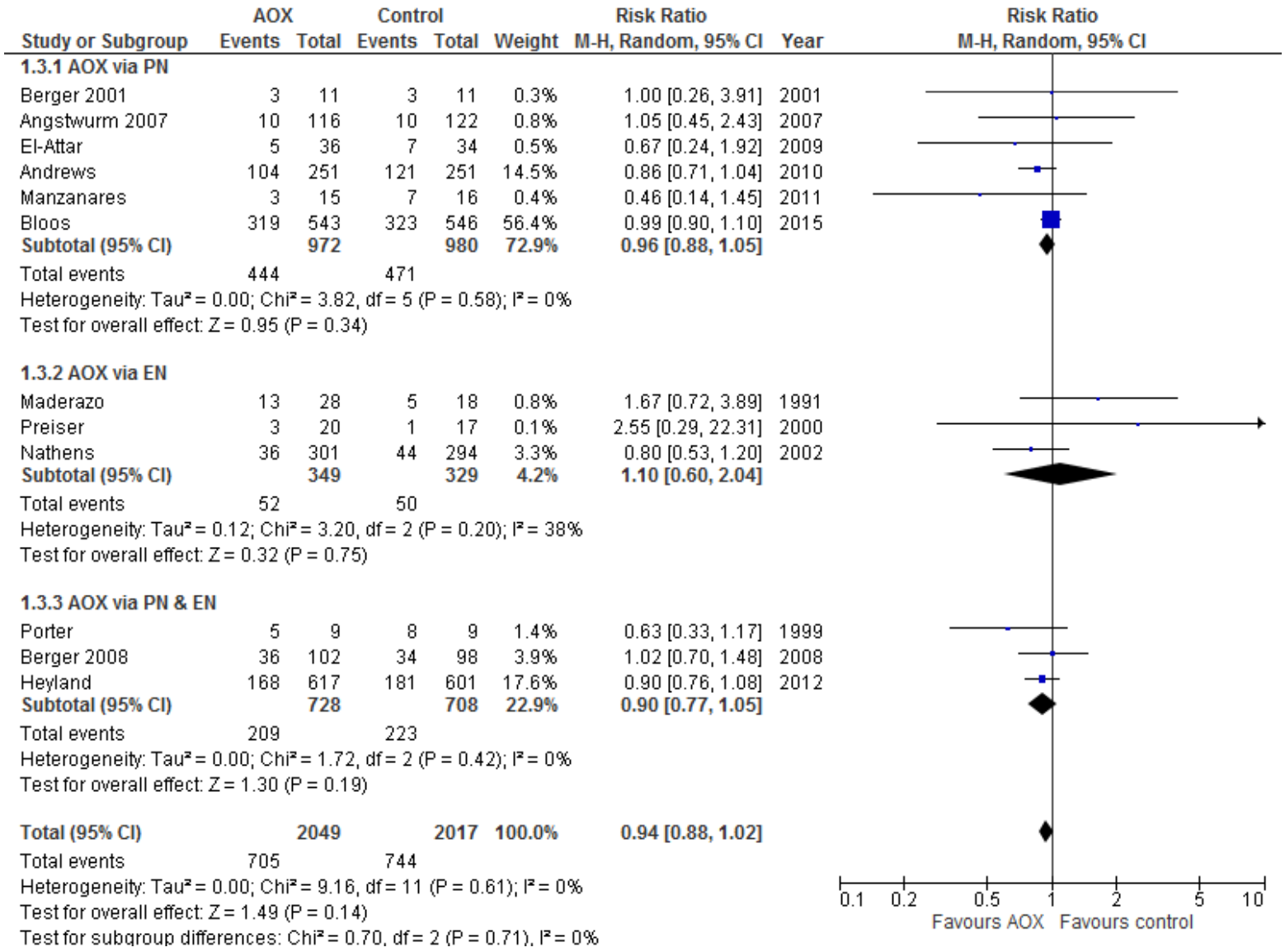


Figure 4. Infections (with sub-analyses according to high (>10%) or low mortality in the control group)

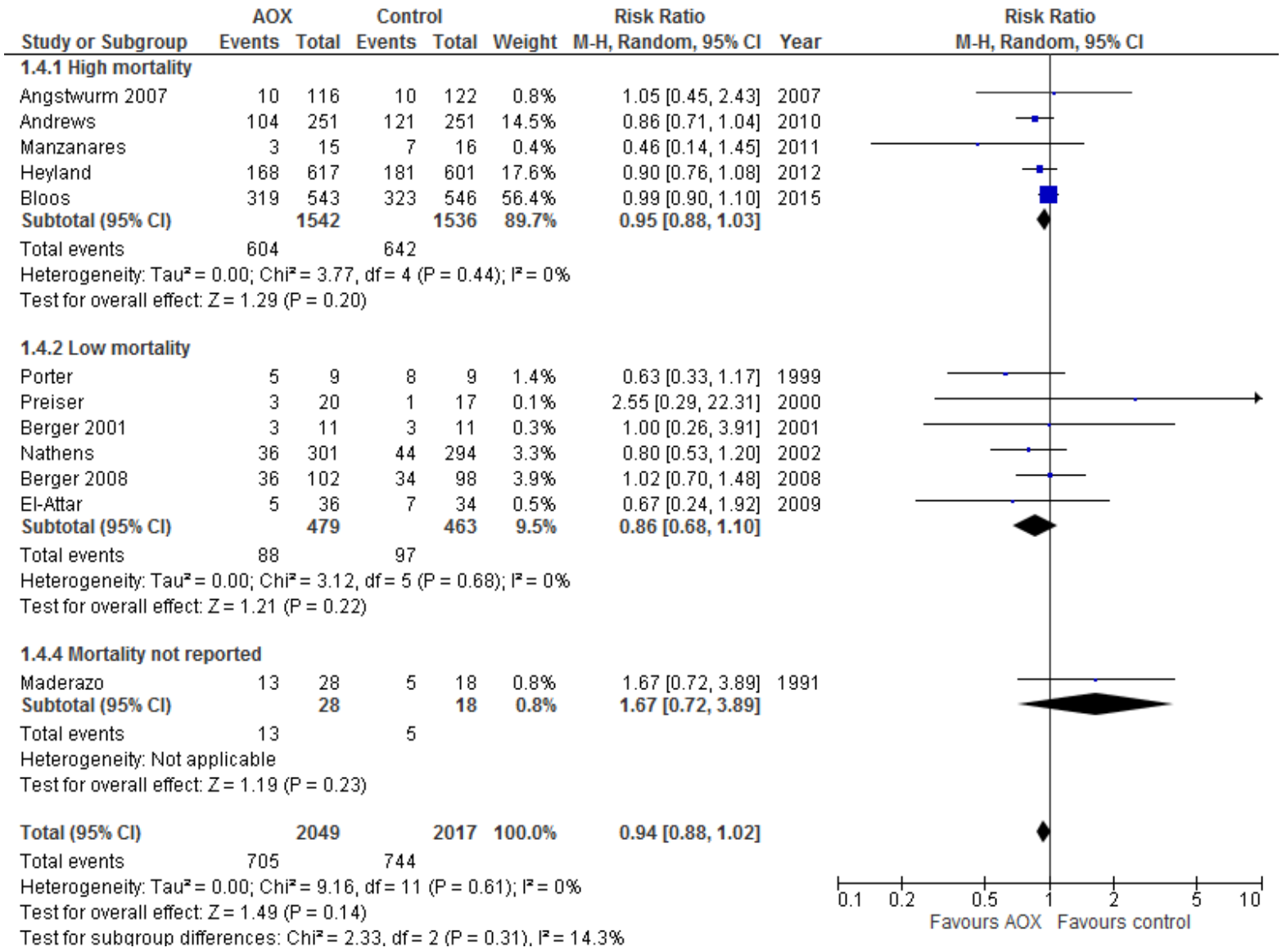


Figure 5. ICU LOS

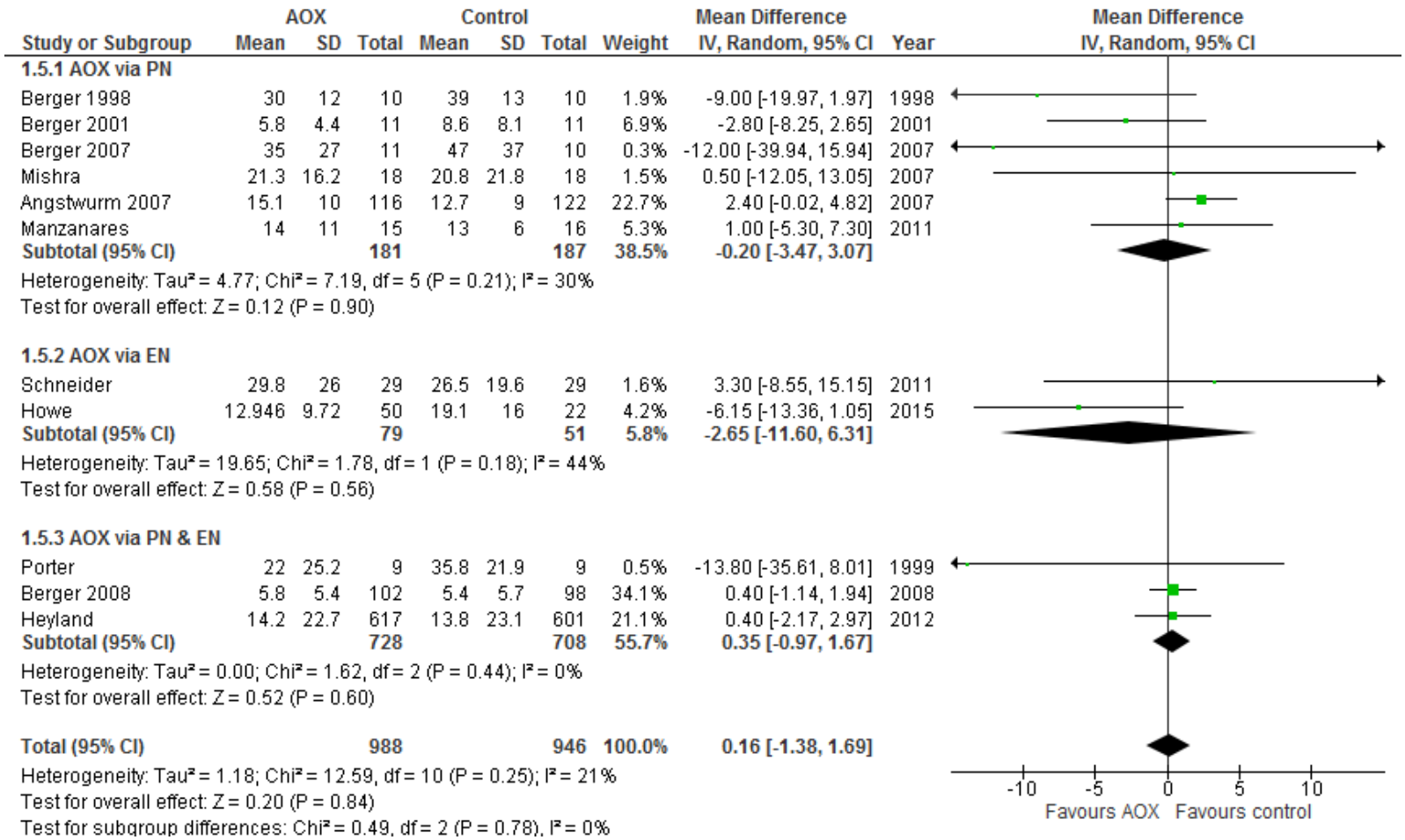


Figure 6. Hospital LOS

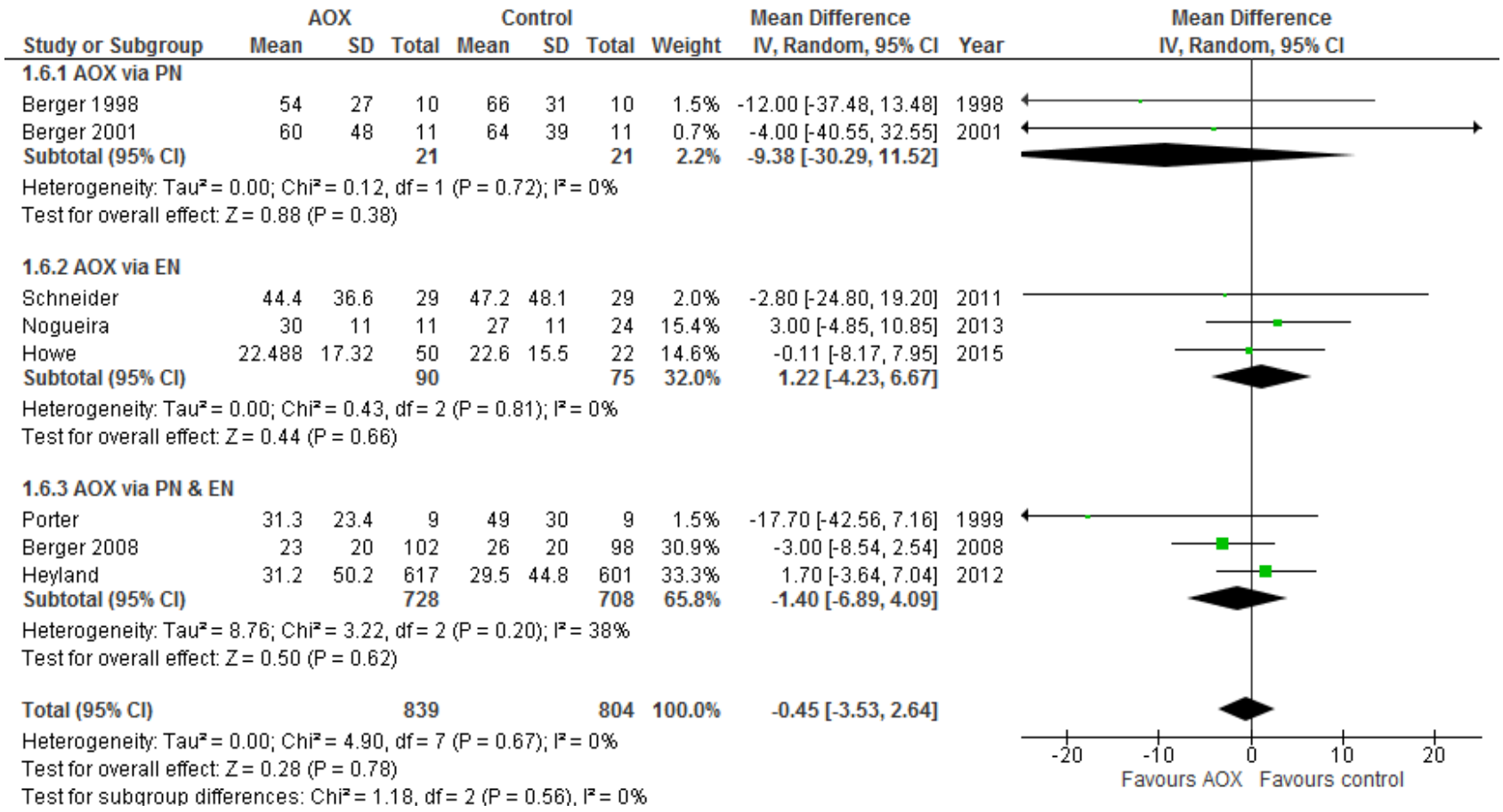
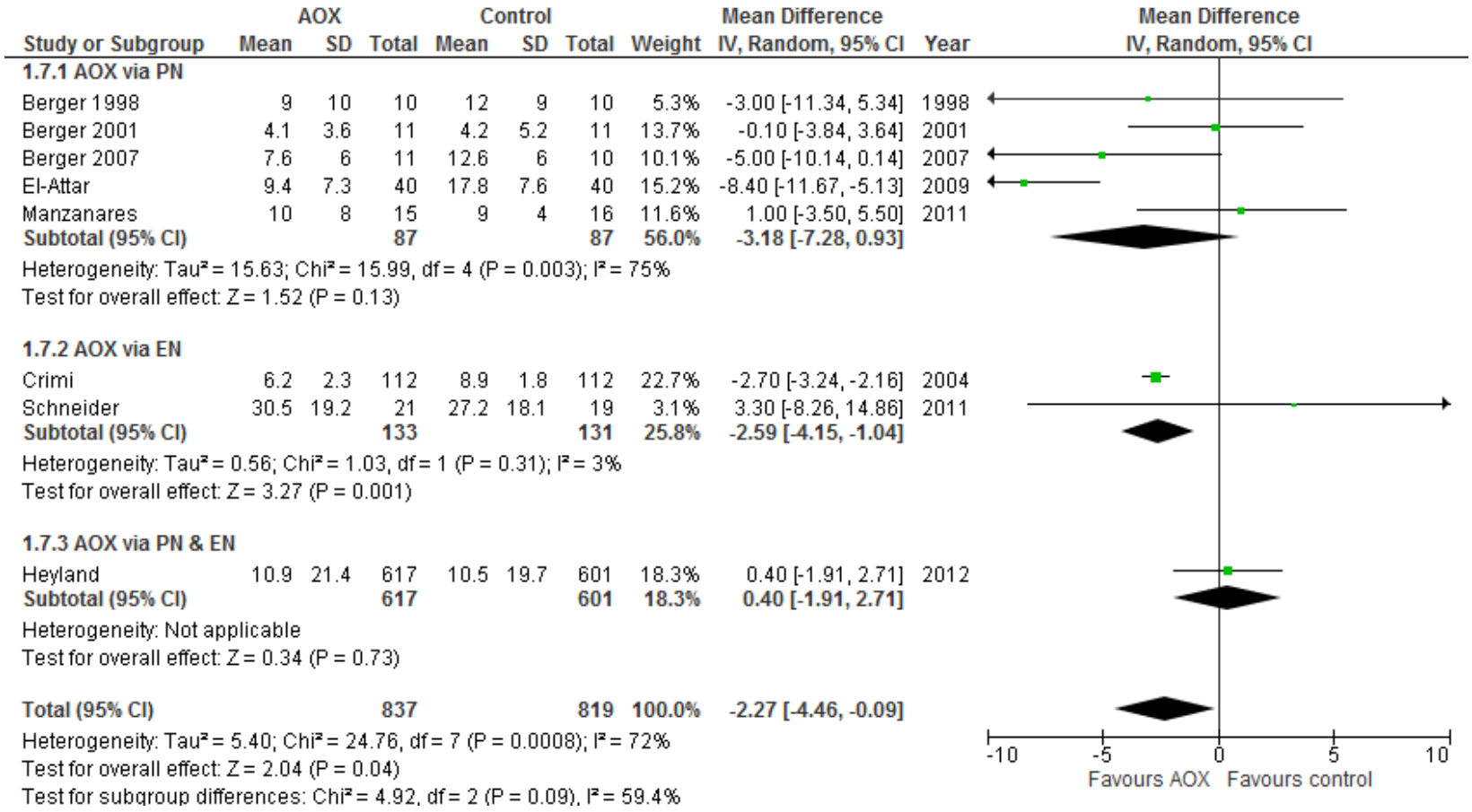


Figure 7. Duration of mechanical ventilation



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Excluded Articles

#	Reason excluded	Citation
1	Abstract only	Sawyer MA, Mike JJ, Chavin K, Marino PL (1989) Antioxidant therapy and survival in ARDS. Crit Care Med 17: S153 (abstract)
2	Not ICU pts	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
3	No clinical outcomes	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
4	Observational study of Kuklinski 1991	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
5	No clinical outcomes	Ortolani O, Gratino F, Leone D, Russo F, Tufano R. [Usefulness of the prevention of oxygen radical damage in the critical patient using the parenteral administration of reduced glutathione in high doses] [Article in Italian] Boll Soc Ital Biol Sper. 1992 Apr;68(4):239-44.
6	Not ICU pts	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
7	Not ICU pts	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
8	Same as Berger 1998	Berger MM, Cavadini C, Chioléro R, Dirren H (1996): Copper, selenium, and zinc status and balances after major trauma. J Trauma 40:103-109
9	NAC alone	Bernard GR, Wheeler AP, Arons MM, Morris PE, Paz HL, Russell JA, Wright PE. A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group. Chest. 1997 Jul;112(1):164-72.

10	NAC alone	Domenighetti G, Suter PM, Schaller MD, Ritz R, Perret C. Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. J Crit Care. 1997 Dec;12(4):177-82.
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12	No clinical outcomes	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
13	Not ICU pts	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
14	NAC alone	Molnar Z, MacKinnon KL, Shearer E, Lowe D, Watson ID. The effect of N-acetylcysteine on total serum anti-oxidant potential and urinary albumin excretion in critically ill patients. Intensive Care Med. 1998 Mar;24(3):230-5.
15	Not ICU pts	Saito I, Asano T, Sano K, Takakura K, Abe H, Yoshimoto T, Kikuchi H, Ohta T, Ishibashi S. Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1998 Feb;42(2):269-77; discussion 277-8.
16	NAC alone	Spapen H, Zhang H, Demanet C, Vleminckx W, Vincent JL, Huyghens L. Does N-acetyl-L-cysteine influence cytokine response during early human septic shock? Chest. 1998 Jun;113(6):1616-24.
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22	Same as Berger 2001 [Int Care Med]	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
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31	Same as Berger AJCN 2007	Berger MM, Baines M, Raffoul W, Benathan M, Chiolero RL, Reeves C, Revelly JP, Cayeux MC, Sénéchaud I, Shenkin A. Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. Am J Clin Nutr. 2007 May;85(5):1293-300.
32	Systematic review & meta-analysis, Not ICU pts	Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA. 2007 Feb 28;297(8):842-57.
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36	High dose Se vs low dose Se	Manzanares W, Biestro A, Galusso F, Torre MH, Mañáy N, Facchin G, Hardy G. High-dose selenium for critically ill patients with systemic inflammation: pharmacokinetics and pharmacodynamics of selenious acid: a pilot study. Nutrition. 2010 Jun;26(6):634-40. Epub 2010 Jan 15.
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42	No clinical outcomes	Mistraletti G, Paroni R, Umbrello M, D'Amato L, Sabbatini G, Taverna M, Formenti P, Finati E, Favero G, Bonomini F, Rezzani R, Reiter RJ, Iapichino G. Melatonin Pharmacological Blood Levels Increase Total Antioxidant Capacity in Critically Ill Patients. Int J Mol Sci. 2017 Apr 3;18(4). pii: E759.