11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements April 2013

2013 Recommendation: *Based on 7 level 1 and 17 level 2 studies, the use of supplemental combined vitamins and trace elements should be considered in critically ill patients.*

2013 Discussion: The committee noted that with the addition of 8 new trials (Lindner 2004, El Attar 2009, González 2009, Andrews 2011, Manzanares 2011, Valenta 2011, Schneider 2011 and Heyland 2013), there was a moderate treatment effect but narrow confidence intervals with respect to a reduction in mortality, infections and a trend towards a reduction in mechanical ventilation similar to a recent systematic review (1). The committee noted that the large REDOXS trial was negative but that the signal of benefit persisted despite its inclusion in the meta-analysis. They considered that the dose of antioxidants in the REDOXS trial may have been insufficient and there is still uncertainty about the optimal composition and dose of supplemental vitamins and trace elements. Concern was expressed about the differences in the types of antioxidant nutrients used in the studies and the heterogeneity of the trials but the high generalizability of the results from many large, multicentre trials was also noted. There were no concerns about the safety, feasibility and cost of these nutrients. The committee therefore agreed to continue with a recommendation that supplemental combined vitamins and trace elements should be considered.

(1) Manzanares W, Dhaliwal R, Jiang X, Murch L, Heyland DK. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care. 2012 Dec 12;16(2):R66

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.

Semi Quantitative Scoring

Value	Definition	2009 Score (0,1,2,3)	2013 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	2	1 (mortality) 1 (infections)
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)	3 (mortality) 3 (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	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2	1
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	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	3
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	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2	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	2

11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements April 2013

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 24 studies included, there were seven level 1 and seventeen 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 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: Twenty-three studies reported on mortality and when the results were aggregated, antioxidant supplementation was associated with a significant reduction in overall mortality (RR 0.86, 95% CI 0.75, 0.0.99, p=0.03, heterogeneity I^2=20%; figure 1). Linder (2004) was excluded from the meta-analyses because the type of mortality was not specified and appeared to be 90 days. When the 15 studies which delivered antioxidants via parental nutrition were sub-grouped and analysed, antioxidant supplementation was associated with a significant reduction in overall mortality as well (RR 0.86, 95% CI 0.74, 0.99, p=0.04, heterogeneity I^2=0%; figure 1). Similarly, when the 4 studies which delivered antioxidants via enteral nutrition were sub-grouped and analysed, antioxidant supplementation was associated with a significant reduction in overall mortality (RR 0.68, 95% CI 0.54, 0.85, p=0.0008, heterogeneity I^2=0%; figure 1). However, when the data from the subgroup comprised of the 3 studies which delivered antioxidants via both enteral and parental nutrition 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).

> 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 0.83, 95% CI 0.71, 0.97, p=0.02, 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 1.14, 95% CI 0.71, 1.81, p=0.59, heterogeneity I^2=0%; figure 2). The test for subgroup differences was not significant (p=0.21).

Infections: When the 11 studies that reported on infectious complications were aggregated, antioxidant supplementation was associated with a significant reduction in overall infections (RR 0.89, 95% CI 0.79, 0.99, p=0.04, heterogeneity I^2=0%; figure 3). When a subgroup analysis based on 5 studies which delivered antioxidants via parental nutrition was done, antioxidant supplementation was associated with a trend towards a reduction in infectious complications (RR 0.86, 95% CI 0.72, 1.03, p=0.09, 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 via both enteral and

parental nutrition 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=0.72).

Infections (higher vs. lower mortality in control group): Subgroup analysis showed that antioxidant supplementation was associated with a significant reduction in infectious complications among patients with higher risk of death (>10% mortality in the control group) (RR 0.88, 95% CI 0.77, 1.00, p=0.05, 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 0.87, 95% CI 0.69, 1.10, p=0.25, 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=0.96).

ICU length of stay: When the 10 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 0.53, 95% CI -0.55, 1.61, p=0.33, heterogeneity I^2=0%; figure 5). The result was the same for each of the 3 subgroups: six studies which delivered antioxidants via parental nutrition (WMD 0.08, 95% CI -2.47, 2.62, p=0.95, heterogeneity I^2=20%; figure 5), one study which delivered antioxidants via enteral nutrition (WMD 3.30, 95% CI -8.55, 15.15, p=0.59; figure 5), and three studies which delivered antioxidants via both enteral and parental nutrition (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=0.87).

Hospital length of stay: When the 6 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 -1.19, 95% CI -4.87, 2.49, p=0.53, heterogeneity I^2=0%; figure 6). The result was the same for 2 of the subgroups: two studies which delivered antioxidants via parental nutrition (WMD -6.03, 95% CI -25.61, 13.55, p=0.55, heterogeneity I^2=0%; figure 6), and one study which delivered antioxidants via enteral nutrition (WMD -2.80, 95% CI -24.80, 19.20, p=0.80; figure 6). However, in the subgroup of 3 studies in which antioxidants were delivered via both enteral and parental nutrition, antioxidant supplementation was associated with a trend towards a reduction in hospital length of stay (WMD -1.408, 95% CI -6.89, 4.09, p=0.62, heterogeneity I^2=38%; figure 6). The test for subgroup differences was not significant (p=0.90).

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 trend towards a reduction in duration of ventilation (WMD -1.76, 95% CI -3.87, 0.36, p=0.10, heterogeneity I^2=74%; figure 7). Subgroup analysis showed that antioxidant supplementation had no effect on duration of ventilation in the subgroup of 5 studies in which antioxidants were delivered via parental nutrition (WMD -2.22, 95% CI -6.07, 1.62, p=0.26, heterogeneity I^2=78%; figure 7), nor in the subgroup consisting of 1 study in which antioxidants were delivered via both enteral and parental nutrition (WMD 0.40, 95% CI -1.91, 2.71, p=0.73; figure 7). However, in the subgroup of 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). There was a trend towards a difference between the subgroups (p=0.10).

Conclusions:

1) Antioxidant nutrients are associated with a significant reduction in overall mortality in critically ill patients.
2) Antioxidant nutrients are associated with a significant 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 trend towards a reduction in duration of ventilation 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.
Studies in which antioxidants were delivered via EN			
17) 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)
18) 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
19) 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
20) 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)
21) 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
Studies in which antioxidants were delivered simultaneously via PN and EN			
22) 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

23) 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)
24) 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	(a) Se alone 2/9 (22) (b) Se+AT+Zn 0/11 (0)	1/11 (9)	(a) Se alone 5/9 (56) (b) Se+AT+Zn 3/11 (27)	5/12 (42)	(a) Se alone ICU 8.0 ± 4.0 (9) Hospital 82 ± 78 (9) (b) Se+AT+Zn ICU 5.8 ± 4.4 (11) Hospital 60 ± 48 (11)	ICU 8.6 ± 8.1 (11) Hospital 64 ± 39 (11)	(a) Se alone 6.2 ± 3.5 (9) (b) 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
Studies in which antioxidants were delivered via EN								
17) Maderazo 1991	NR	NR	13/28 (46)	5/18 (28)	NR	NR	NR	NR
18) 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
19) 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)
20) 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)
21) 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)
Studies in which antioxidants were delivered simultaneously via PN and EN								

22) 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
23) 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
24) 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)

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

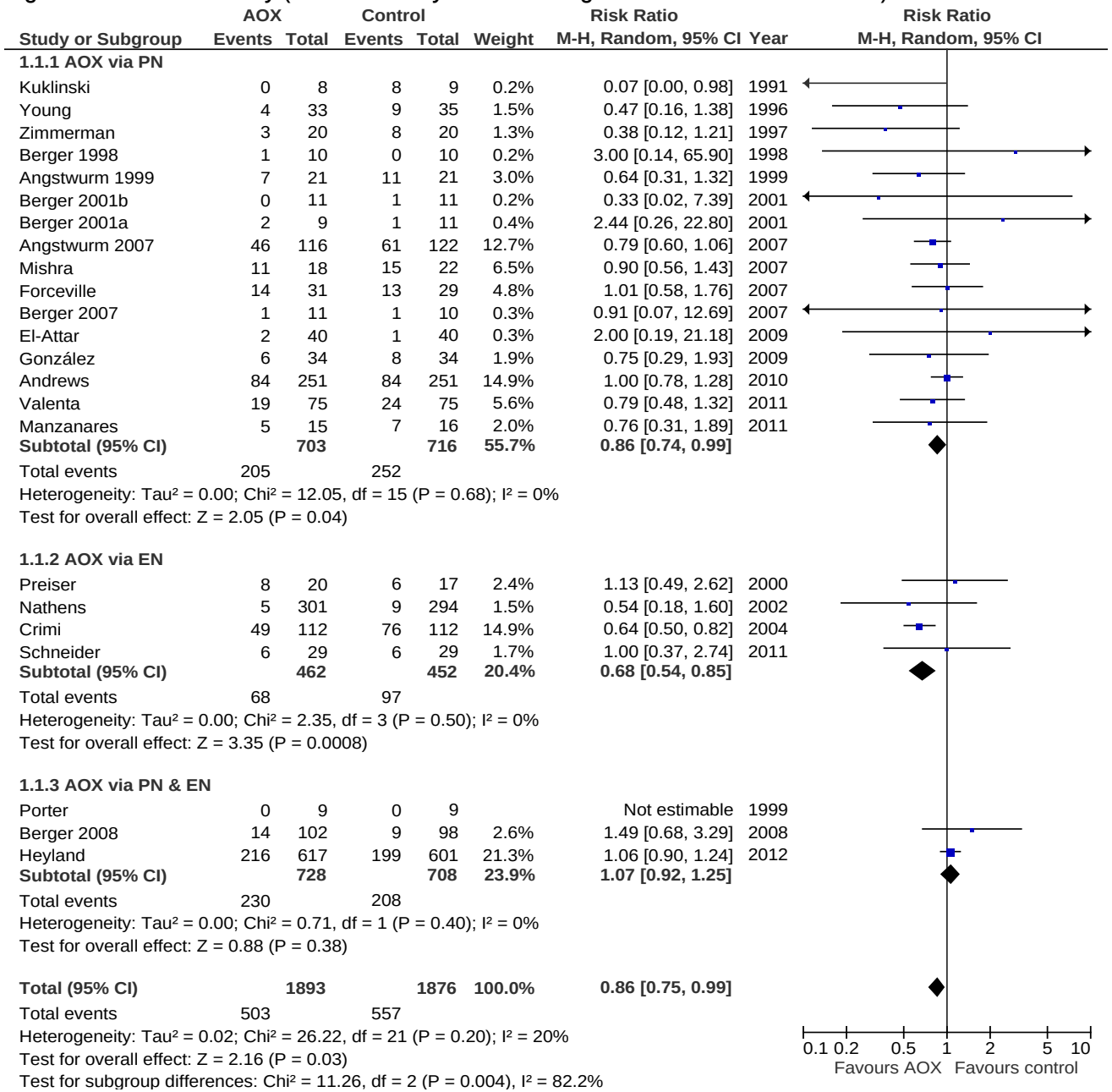

Figure 2: Mortality (with sub-analyses according to high (>10%) or low mortality in the control group)

Study or Subgroup	AOX Events	AOX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 High mortality							
Kuklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]	1991
Young	4	33	9	35	1.5%	0.47 [0.16, 1.38]	1996
Zimmerman	3	20	8	20	1.3%	0.38 [0.12, 1.21]	1997
Angstwurm 1999	7	21	11	21	3.0%	0.64 [0.31, 1.32]	1999
Crimi	49	112	76	112	14.9%	0.64 [0.50, 0.82]	2004
Forceville	14	31	13	29	4.8%	1.01 [0.58, 1.76]	2007
Angstwurm 2007	46	116	61	122	12.7%	0.79 [0.60, 1.06]	2007
Mishra	11	18	15	22	6.5%	0.90 [0.56, 1.43]	2007
González	6	34	8	34	1.9%	0.75 [0.29, 1.93]	2009
Andrews	84	251	84	251	14.9%	1.00 [0.78, 1.28]	2010
Manzanares	5	15	7	16	2.0%	0.76 [0.31, 1.89]	2011
Valenta	19	75	24	75	5.6%	0.79 [0.48, 1.32]	2011
Schneider	6	29	6	29	1.7%	1.00 [0.37, 2.74]	2011
Heyland	216	617	199	601	21.3%	1.06 [0.90, 1.24]	2012
Subtotal (95% CI)		**1380**		**1376**	**92.3%**	**0.83 [0.71, 0.97]**	
Total events	470		529				
Heterogeneity: Tau² = 0.03; Chi² = 21.24, df = 13 (P = 0.07); I² = 39%							
Test for overall effect: Z = 2.30 (P = 0.02)							
1.2.2 Low mortality							
Berger 1998	1	10	0	10	0.2%	3.00 [0.14, 65.90]	1998
Porter	0	9	0	9		Not estimable	1999
Preiser	8	20	6	17	2.4%	1.13 [0.49, 2.62]	2000
Berger 2001b	0	11	1	11	0.2%	0.33 [0.02, 7.39]	2001
Berger 2001a	2	9	1	11	0.4%	2.44 [0.26, 22.80]	2001
Nathens	5	301	9	294	1.5%	0.54 [0.18, 1.60]	2002
Berger 2007	1	11	1	10	0.3%	0.91 [0.07, 12.69]	2007
Berger 2008	14	102	9	98	2.6%	1.49 [0.68, 3.29]	2008
El-Attar	2	40	1	40	0.3%	2.00 [0.19, 21.18]	2009
Subtotal (95% CI)		**513**		**500**	**7.7%**	**1.14 [0.71, 1.81]**	
Total events	33		28				
Heterogeneity: Tau² = 0.00; Chi² = 3.94, df = 7 (P = 0.79); I² = 0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)		**1893**		**1876**	**100.0%**	**0.86 [0.75, 0.99]**	
Total events	503		557				
Heterogeneity: Tau² = 0.02; Chi² = 26.22, df = 21 (P = 0.20); I² = 20%							
Test for overall effect: Z = 2.16 (P = 0.03)							
Test for subgroup differences: Chi² = 1.55, df = 1 (P = 0.21), I² = 35.6%							

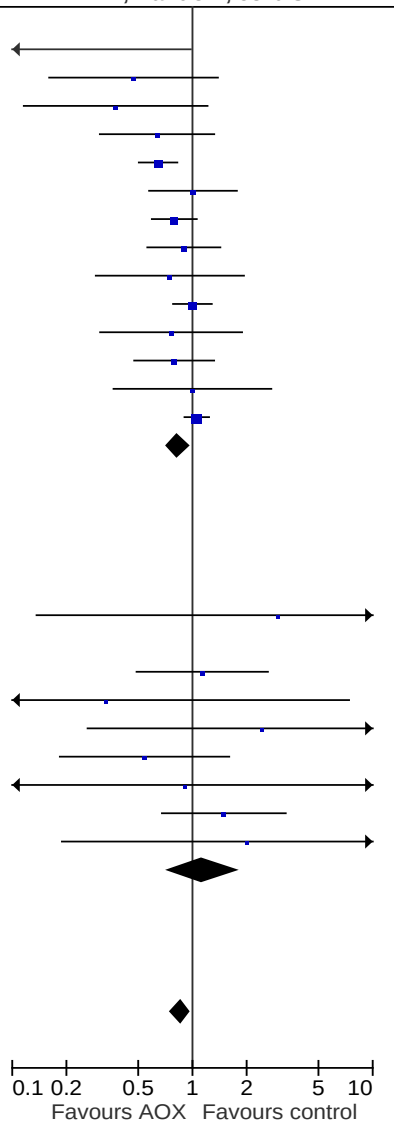

Figure 3. Infections (with sub-analyses according to routes of administration)

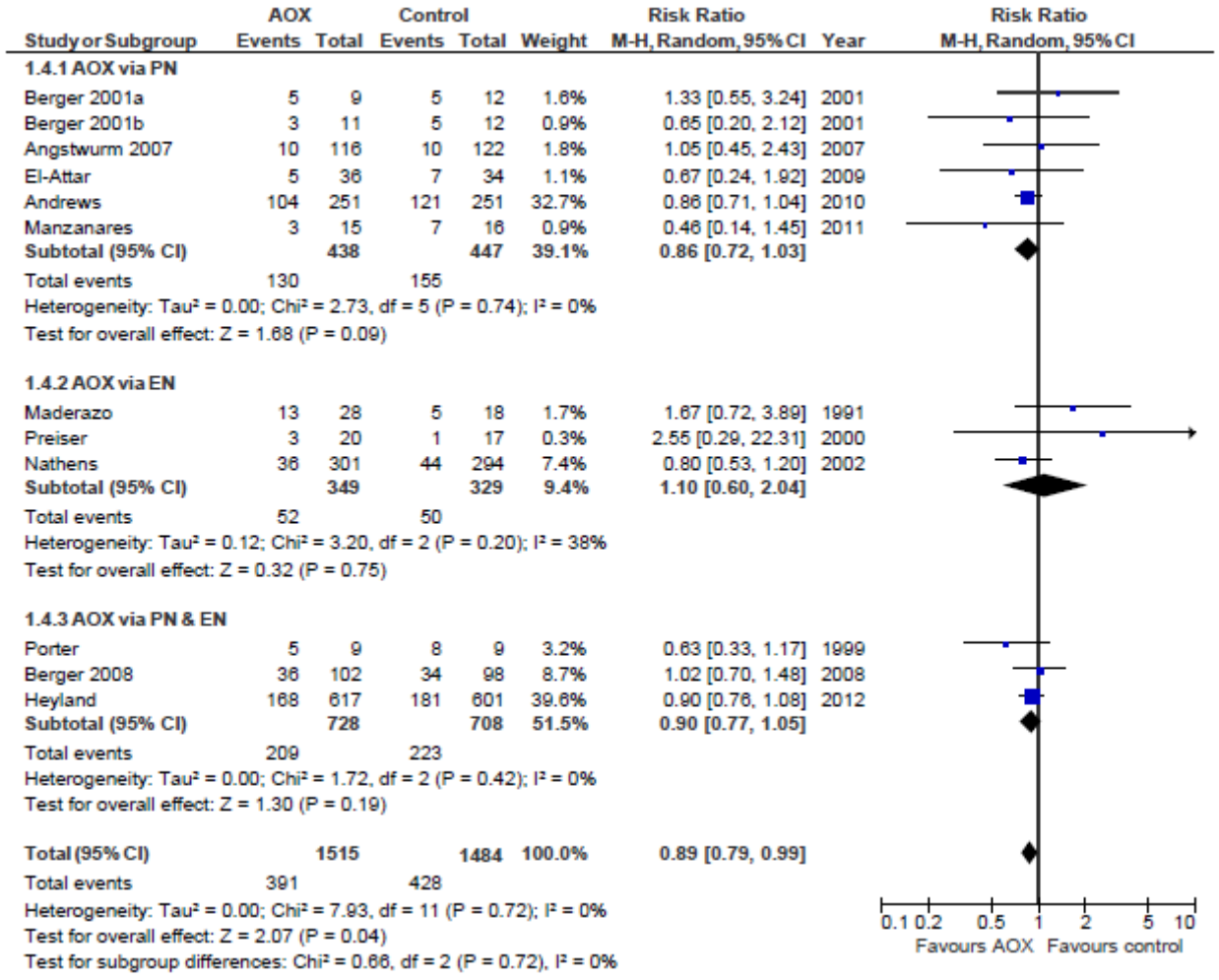

Figure 4. Infections (with sub-analyses according to high (>10%) or low mortality in the control group)

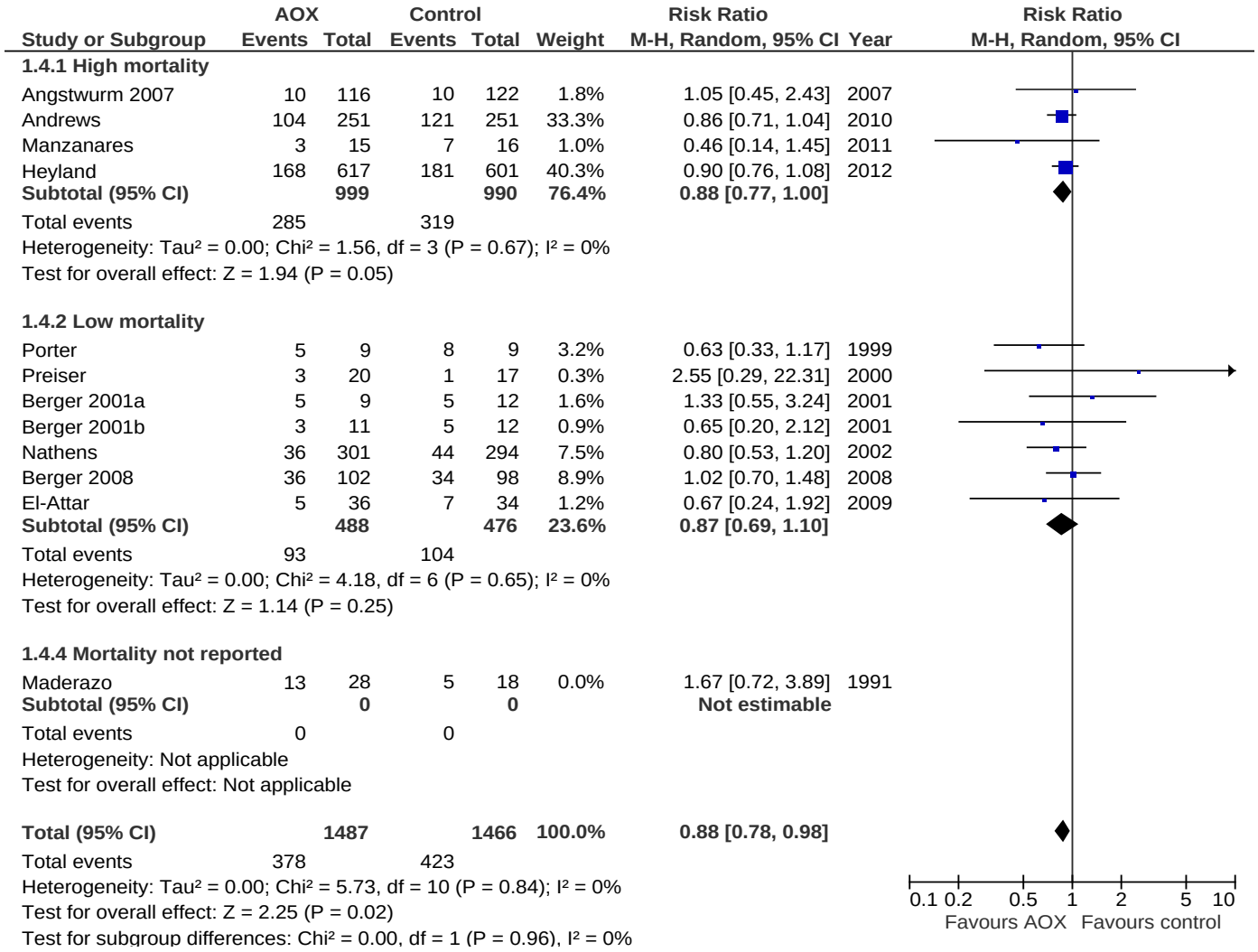

Figure 5. ICU LOS

Study or Subgroup	AOX Mean	AOX SD	AOX Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.5.1 AOX via PN									
Berger 1998	30	12	10	39	13	10	1.0%	-9.00 [-19.97, 1.97]	1998
Berger 2001b	5.8	4.4	11	8.6	8.1	11	3.9%	-2.80 [-8.25, 2.65]	2001
Berger 2001a	8	4	9	8.6	8.1	11	3.9%	-0.60 [-6.05, 4.85]	2001
Angstwurm 2007	15.1	10	116	12.7	9	122	19.8%	2.40 [-0.02, 4.82]	2007
Berger 2007	35	27	11	47	37	10	0.1%	-12.00 [-39.94, 15.94]	2007
Mishra	21.3	16.2	18	20.8	21.8	18	0.7%	0.50 [-12.05, 13.05]	2007
Manzanares	14	11	15	13	6	16	2.9%	1.00 [-5.30, 7.30]	2011
Subtotal (95% CI)			**190**			**198**	**32.4%**	**0.08 [-2.47, 2.62]**	
Heterogeneity: Tau² = 2.36; Chi² = 7.49, df = 6 (P = 0.28); I² = 20%									
Test for overall effect: Z = 0.06 (P = 0.95)									
1.5.2 AOX via EN									
Schneider	29.8	26	29	26.5	19.6	29	0.8%	3.30 [-8.55, 15.15]	2011
Subtotal (95% CI)			**29**			**29**	**0.8%**	**3.30 [-8.55, 15.15]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.55 (P = 0.59)									
1.5.3 AOX via PN & EN									
Porter	22	25.2	9	35.8	21.9	9	0.2%	-13.80 [-35.61, 8.01]	1999
Berger 2008	5.8	5.4	102	5.4	5.7	98	49.0%	0.40 [-1.14, 1.94]	2008
Heyland	14.2	22.7	617	13.8	23.1	601	17.5%	0.40 [-2.17, 2.97]	2012
Subtotal (95% CI)			**728**			**708**	**66.8%**	**0.35 [-0.97, 1.67]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 2 (P = 0.44); I² = 0%									
Test for overall effect: Z = 0.52 (P = 0.60)									
Total (95% CI)			**947**			**935**	**100.0%**	**0.53 [-0.55, 1.61]**	
Heterogeneity: Tau² = 0.00; Chi² = 9.49, df = 10 (P = 0.49); I² = 0%									
Test for overall effect: Z = 0.96 (P = 0.33)									
Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%									

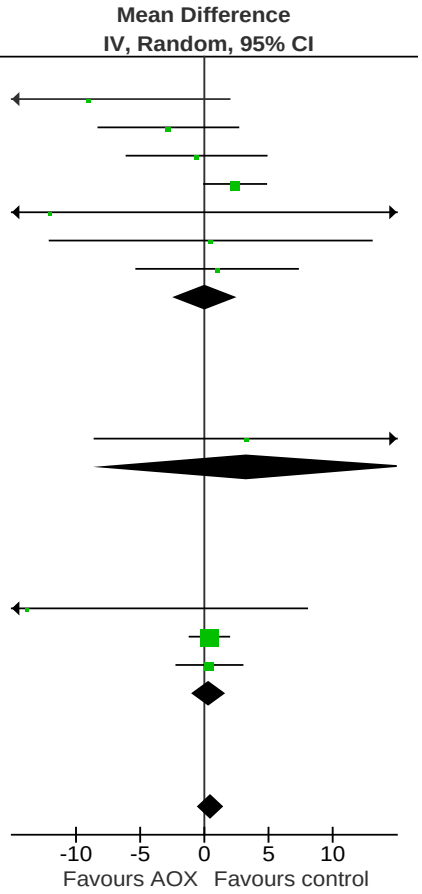

Figure 6. Hospital LOS

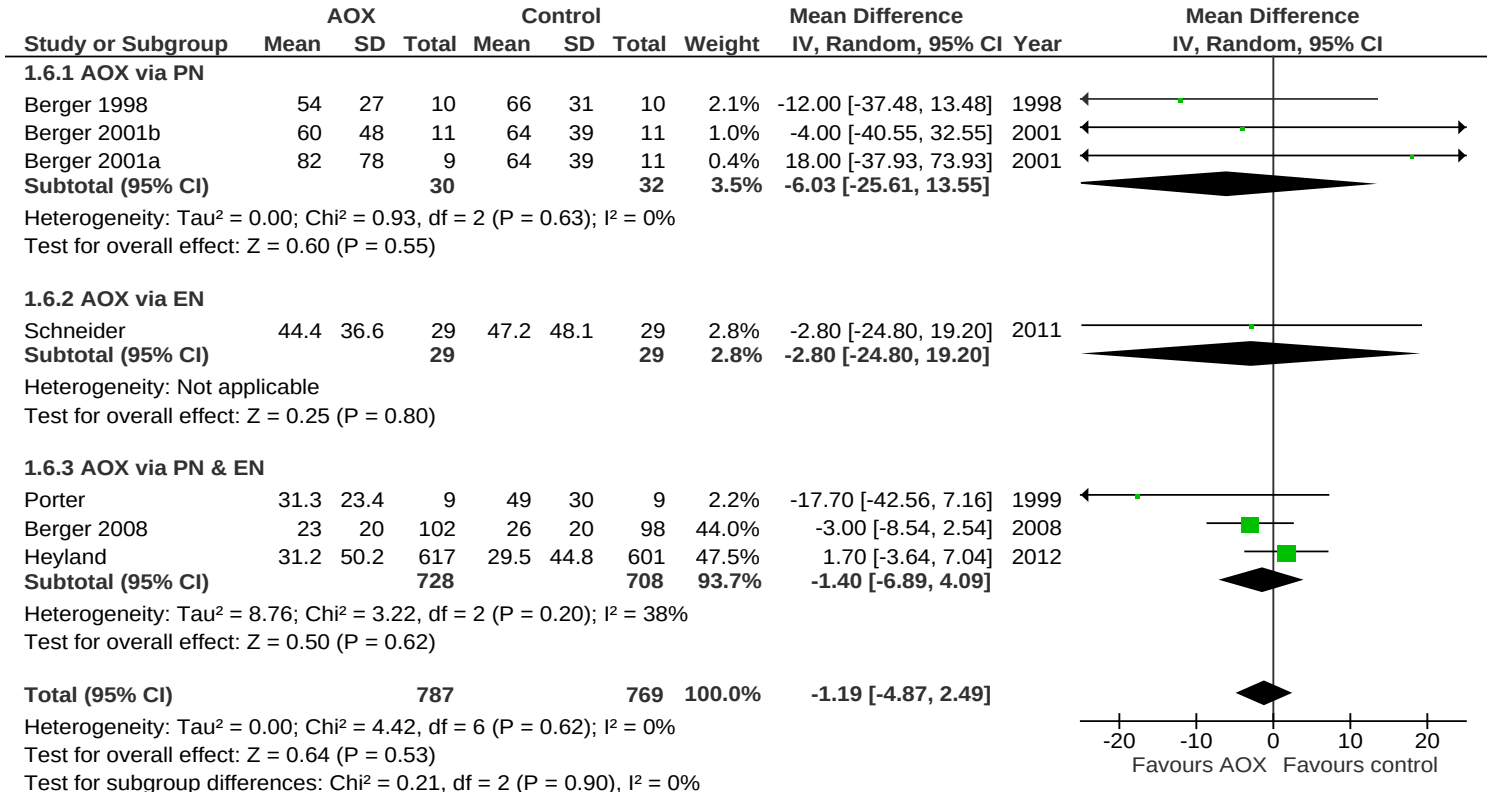

Figure 7. Duration of mechanical ventilation