11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements

August 2015

2015 Recommendation: Based on 8 level 1 and 19 level 2 studies, we do not recommend the use of supplemental combined vitamins and trace elements in critically ill patients.

2015 Discussion: The committee noted that with the addition of 3 new trials (Nogueira 2013, Bloos in submission, Woth 2014), there were no significant treatment effects, only a trend towards reduction in mortality, infections, and duration of mechanical ventilation. The committee noted that enterally administered supplemental antioxidants seemed to exert the most positive effect on mortality; however the committee felt that a clinical recommendation on this subgroup result alone was not warranted as the results were driven by largely one study (Crimi). 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 also concerns raised about the safety of these micronutrients (REDOXS and METAPLUS studies) particularly in the setting of renal failure. Because of the lack of significant treatment effect and emerging safety concerns, the committee downgraded their recommendation and recommended against the routine use of supplemental antioxidants in critically ill patients.

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

Semi Quantitative Scoring

Value	Definition	2009 Score (0,1,2,3)	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listeda higher score indicates a larger effect size	2	1 (mortality) 1 (infections)	1 (mortality) 0 (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)	2 (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 outcomesa higher score indicates presence of more of these features in the trials appraised	2	3	2
Homogeneity or Reproducibility	Similar direction of findings among trialsa higher score indicates greater similarity of direction of findings among trials	2	1	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	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	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	3
Low cost	Estimated cost of implementing the intervention listeda higher score indicates a lower cost to implement the intervention in an average ICU	2	2	2
Feasible	Ease of implementing the intervention listeda higher score indicates greater ease of implementing the intervention in an average ICU	2	2	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listeda higher score indicates a lower probability of harm	2	2	1

11.1 Supplemental Antioxidant Nutrients: Combined Vitamins and Trace Elements

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 27 studies included, there were eight level 1 and nineteen 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-five studies reported on mortality and when the results were aggregated, antioxidant supplementation was associated with a trend towards a reduction in overall mortality (RR 0.89, 95% CI 0.79, 1.01, p=0.06, heterogeneity $l^2=25\%$; 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. When the 17 studies which delivered antioxidants via parental nutrition were sub-grouped and analysed, antioxidant supplementation was not associated with a reduction in overall mortality (RR 0.93, 95% CI 0.83, 1.05, p=0.25, heterogeneity $l^2=0\%$; figure 1). When the 4 studies which delivered antioxidants via enteral nutrition were sub-grouped and analysed, antioxidant supplementation in overall mortality (RR 0.68, 95% CI 0.54, 0.85, p=0.0008, heterogeneity $l^2=0\%$; figure 1). 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 $l^2=0\%$; figure 1). The test for subgroup differences was significant (p=0.005).

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, 1.00, p=0.04, heterogeneity $l^2=42\%$; 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 $l^2=0\%$; figure 2). The test for subgroup differences was not significant (p=0.27).

Infections: When the 13 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 0.95, 95% CI 0.88, 1.02, p=0.14, heterogeneity I²=0%; figure 3). When a subgroup analysis based on 7 studies which delivered antioxidants via parental nutrition was done, antioxidant supplementation was not associated with a reduction in infectious complications (RR 0.96, 95% CI 0.88, 1.05, p=0.35, heterogeneity I²=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 0.96, 95% CI 0.88, 1.05, p=0.35, heterogeneity I²=0%; figure 3).

1.10, 95% CI 0.60, 2.04, p=0.75, heterogeneity I²=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 I²=0%; figure 3). The test for subgroup differences was not significant (p=0.70).

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 I²=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 I²=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=0.33).

ICU length of stay: When the 10 studies that reported ICU length of stay as a mean \pm 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 I²=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 I²=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 I²=0%; figure 5). The test for subgroup differences was not significant (p=0.87).

Hospital length of stay: When the 7 studies that reported hospital length of stay as a mean \pm standard deviation were aggregated, antioxidant supplementation had no effect on hospital length of stay (WMD -0.44, 95% CI -3.77, 2.89, p=0.80, heterogeneity I²=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 I²=0%; figure 6), and one study which delivered antioxidants via enteral nutrition (WMD 2.34, 95% CI -5.05, 9.74, p=0.53; 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 I²=38%; figure 6). The test for subgroup differences was not significant (p=0.61).

Duration of mechanical ventilation: When the 8 studies that reported duration of ventilation as a mean \pm 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 I²=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 I²=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 I²=3%; figure 7). There was a trend towards a difference between the subgroups (p=0.10). **Conclusions:**

- 1) Antioxidant nutrients are associated with a trend towards a reduction in overall mortality in critically ill patients.
- 2) Antioxidant nutrients are associated with a trend towards 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 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.

Study	Population	Methods Score	Intervention
Studies in which antioxid	dants 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 μ g x 3 days, 285 μ g x 3 days and 155 μ g x 3 days and 35 μ g thereafter) vs. low dose selenium (35 μ g/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 1 st 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).

Table 1. Randomized Studies Evaluating Supplemental Combined Vitamins And Trace Elements in Critically III Patients

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 $\mu g/day$, 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 1000 μg , day 2 sodium selenite 500 μg and thereafter 200 μg during seven additional days vs selenite 100 $\mu g/d$
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

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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, In Submission	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 antioxid	ants were delivered via EN		
19) Maderazo 1991	Blunt Trauma N=46	C. Random: yes ITT: yes Blinding: double (7)	200 mg Ascorbic acid, then \uparrow 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

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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.
Studies in which antioxid	dants were delivered simulta	neously via PN and EN	
25) 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
26 Berger 2008	Mixed ICU N=200	C.Random: not sure ITT: yes Blinding: no (10)	IV Selenium supplementation loading dose 540 μ g/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)
27) 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 III Patients (continued)

Study	Mort Experimental	ality Control	Infec Experimental	tions Control	LC Experimental)S Control	Ventilat Experimental	or Days Control
Studies in which antioxic	lants were deliver	ed 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
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, In submission		·	·	Confider	ntial data		·	·

Studies in which antioxi	dants were deliver	ed 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	25% of total deaths Actual data not reported	75% of total deaths Actual data not reported	NR	NR	Hospital 30 <u>+</u> 11	Hospital 27 <u>+</u> 11	28% of vent needs Actual data not reported	72% of vent needs Actual data not reported
Studies in which antioxi	dants were deliver	ed simultaneously	via PN and EN					
25) 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
26) 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

27) Heyland 2013 Hospital 216/617 (35) Hospital 199/601 (33) 14-day 14-day 154/617 (25) 132/601 (22) 28-day 28-day 190/617 (31) 173/601 (29) 3-month 3-month 239 (36) 222 (36) 6-month 6-month 250 (40) 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)
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tudy or Subarous	AOX	-	Contr		Weight	Risk Ratio	Vaar		Risk Ratio M-H, Random,	-	
tudy or Subgroup	Events	rotal	events	rotal	Weight	M-H, Random, 95% C	rear		M-H, Random,	90% GI	
				6	0.00/	0.07 (0.00.0.00)	4004	-			
luklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]		•			
oung	4	33	9	35	1.2%	0.47 [0.16, 1.38]					
immerman	3	20	8	20	1.1%	0.38 [0.12, 1.21]		_			
erger 1998	1	10	0	10	0.2%	3.00 [0.14, 65.90]					
ngstwurm 1999	7	21	11	21	2.6%	0.64 [0.31, 1.32]					
lerger 2001a	2	9	1	11	0.3%	2.44 [0.26, 22.80]				-	
erger 2001b	0	11	1	11	0.2%	0.33 [0.02, 7.39]					-
ngstwurm 2007	46	116	61	122	10.4%	0.79 [0.60, 1.06]					
lishra	11	18	15	22	5.4%	0.90 [0.56, 1.43]					
erger 2007	1	11	1	10	0.2%	0.91 [0.07, 12.69]		•			-
orceville	14	31	13	29	4.0%	1.01 [0.58, 1.76]					
Bonzález	6	34	8	34	1.6%	0.75 [0.29, 1.93]				_	
l-Attar	2	40	1	40	0.3%	2.00 [0.19, 21.18]				-	-
ndrews	84	251	84	251	12.1%	1.00 [0.78, 1.28]			-+-		
fanzanares	5	15	7	16	1.7%	0.76 [0.31, 1.89]	2011			_	
/alenta	19	75	24	75	4.7%	0.79 [0.48, 1.32]					
Voth	9	21	11	19	3.4%	0.74 (0.40, 1.38)	2014				
loos									ا م		
iubtotal (95% CI)		1267		1281	64.0%	0.93 [0.83, 1.05]			•		
otal events	366		400								
leterogeneity: Tau ² = (est for overall effect: 2	Z = 1.16 (5)								
est for overall effect: 2		P = 0.2									
est for overall effect: 2 .1.2 AOX via EN Preiser	8	P = 0.2	6	17	2.0%	1.13 [0.49, 2.62]	2000				
est for overall effect: 2 .1.2 AOX via EN Preiser lathens	8	P = 0.2 20 301				1.13 [0.49, 2.62] 0.54 [0.18, 1.60]					
est for overall effect: 2 .1.2 AOX via EN Preiser	8	P = 0.2	6	17	2.0%		2002			-	
est for overall effect: 2 .1.2 AOX via EN Preiser lathens	8	P = 0.2 20 301	6 9	17 294	2.0% 1.2%	0.54 [0.18, 1.60]	2002 2004				
est for overall effect: 2 .1.2 AOX via EN reiser lathens crimi cchneider	8 5 49	P = 0.2 20 301 112 29	6 9 76	17 294 112 29	2.0% 1.2% 12.1% 1.4%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74]	2002 2004				
est for overall effect: 2 .1.2 AOX via EN reiser lathens crimi cchneider subtotal (95% CI)	8 5 49 6	20 301 112 29 462	6 9 76 6 97	17 294 112 29 452	2.0% 1.2% 12.1% 1.4% 16.8%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74]	2002 2004				
est for overall effect: 2 .1.2 AOX via EN Preiser lathens crimi cichneider subtotal (95% CI) total events	8 5 49 6 68 0.00; Chi ²	20 301 112 29 462 = 2.35	6 9 76 6 97 , df = 3 (P	17 294 112 29 452	2.0% 1.2% 12.1% 1.4% 16.8%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74]	2002 2004			 	
est for overall effect: 2 .1.2 AOX via EN reiser lathens crimi schneider subtotal (95% CI) otal events leterogeneity: Tau ² = (leterogeneity: Tau ² = (.1.3 AOX via PN & EB	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0	6 9 76 6 97 , df = 3 (P 008)	17 294 112 29 452 = 0.50	2.0% 1.2% 12.1% 1.4% 16.8%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85]	2002 2004 2011			- -	
est for overall effect: 2 .1.2 AOX via EN reiser lathens crimi cchneider subtotal (95% CI) rotal events leterogeneity: Tau ² = (leterogeneity: Tau ² = (.1.3 AOX via PN & E) Porter	8 5 49 6 8 0.00; Chi ² Z = 3.35 (I N	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9	6 9 76 6 97 , df = 3 (F 008)	17 294 112 29 452 = 0.50	2.0% 1.2% 12.1% 1.4% 16.8%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable	2002 2004 2011 1999				
est for overall effect: 2 .1.2 AOX via EN Preiser lathens cimi cichneider subtotal (95% CI) fotal events leterogeneity: Tau ² = (est for overall effect: 2 .1.3 AOX via PN & EP Porter lerger 2008	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f N 0 14	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102	6 9 76 6 97 , df = 3 (P 008) 0 9	17 294 112 29 452 = 0.50 9 98	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29]	2002 2004 2011 1999 2008				
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens cimi ichneider subtotal (95% CI) iotal events leterogeneity: Tau ² = (est for overall effect: 2 .1.3 AOX via PN & El iorter erger 2008 leyland	8 5 49 6 8 0.00; Chi ² Z = 3.35 (I N	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102 617	6 9 76 6 97 , df = 3 (F 008)	17 294 112 29 452 9 = 0.50 9 98 601	2.0% 1.2% 12.1% 1.4% 16.8%)); ² = 0% 2.2% 17.0%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24]	2002 2004 2011 1999 2008				
est for overall effect: 2 .1.2 AOX via EN Preiser lathens cimi ichneider subtotal (95% CI) iotal events leterogeneity: Tau ² = (est for overall effect: 2 .1.3 AOX via PN & EP iorter lerger 2008 leyland subtotal (95% CI)	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f N 0 14 216	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102	6 9 76 6 97 , df = 3 (P 008) 0 9 199	17 294 112 29 452 = 0.50 9 98	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29]	2002 2004 2011 1999 2008				
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens crimi icchneider ubtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 .1.3 AOX via PN & El Porter leerger 2008 legand iubtotal (95% CI) iotal events	8 5 49 6 8 0.00; Chi ² Z = 3.35 (I N 0 14 216 230	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102 617 728	6 9 76 6 97 , df = 3 (F 008) 0 9 199 208	17 294 112 29 452 = 0.50 9 98 601 708	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0% 2.2% 17.0% 19.2%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24]	2002 2004 2011 1999 2008			 	
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens chineider ubtotal (95% CI) iotal events leterogeneity: Tau ² = (.1.3 AOX via PN & E) Porter leegen 2008 leyland ubtotal (95% CI) iotal events leterogeneity: Tau ² = (8 5 49 6 8 0.00; Chi ² Z = 3.35 (I N 0 14 216 230 0.00; Chi ²	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102 617 728 = 0.71	6 9 76 6 97 97 008 9 199 208 , df = 1 (P	17 294 112 29 452 = 0.50 9 98 601 708	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0% 2.2% 17.0% 19.2%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24]	2002 2004 2011 1999 2008				
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens crimi icchneider ubtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 .1.3 AOX via PN & El Porter leerger 2008 legand iubtotal (95% CI) iotal events	8 5 49 6 8 0.00; Chi ² Z = 3.35 (I N 0 14 216 230 0.00; Chi ²	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102 617 728 = 0.71	6 9 76 6 97 97 008 9 199 208 , df = 1 (P	17 294 112 29 452 = 0.50 9 98 601 708	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0% 2.2% 17.0% 19.2%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24]	2002 2004 2011 1999 2008			 	
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens cimii ichneider subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 .1.3 AOX via PN & EP Porter lerger 2008 leyland subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 iotal (95% CI)	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f N 0 14 216 230 0.00; Chi ² Z = 0.88 (f	P = 0.2 20 301 112 29 462 = 2.35 P = 0.0 9 102 617 728 = 0.71	6 9 76 6 97 , df = 3 (P 008) 0 9 199 208 , df = 1 (P 8)	17 294 112 29 452 = 0.50 9 98 601 708 = 0.40	2.0% 1.2% 12.1% 1.4% 16.8%); ² = 0% 2.2% 17.0% 19.2%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24]	2002 2004 2011 1999 2008				
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens cimii ichneider subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 .1.3 AOX via PN & EP iorter lerger 2008 leyland subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 iotal events leterogeneity: Tau ² = (iest for overall effect: 2 iotal events	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f N 0 14 216 230 0.00; Chi ² Z = 0.88 (f 664	$\begin{array}{c} 20\\ 301\\ 112\\ 29\\ 462\\ = 2.35\\ 0\\ 102\\ 617\\ 728\\ = 0.71\\ 9\\ = 0.3\\ 2457 \end{array}$	6 9 76 6 97 , df = 3 (P 008) 0 9 199 208 , df = 1 (P 8) 705	17 294 112 29 452 = 0.50 9 98 601 708 = 0.40 2441	2.0% 1.2% 12.1% 1.4% 16.8% 16.8% 1); ² = 0% 2.2% 17.0% 19.2% 19.2% 100.0%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24] 1.07 [0.92, 1.25]	2002 2004 2011 1999 2008				
iest for overall effect: 2 .1.2 AOX via EN Preiser lathens cimii ichneider subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 .1.3 AOX via PN & EP Porter lerger 2008 leyland subtotal (95% CI) iotal events leterogeneity: Tau ² = (iest for overall effect: 2 iotal (95% CI)	8 5 49 6 8 0.00; Chi ² Z = 3.35 (f N 0 14 216 230 0.00; Chi ² Z = 0.88 (f 664 0.02; Chi ²	20 301 112 29 462 = 2.35 P = 0.0 9 102 617 728 = 0.711 P = 0.3 2457 = 30.5	6 9 76 6 97 , df = 3 (P 008) 0 9 199 208 , df = 1 (P 8) 705 6, df = 23	17 294 112 29 452 = 0.50 9 98 601 708 = 0.40 2441	2.0% 1.2% 12.1% 1.4% 16.8% 16.8% 1); ² = 0% 2.2% 17.0% 19.2% 19.2% 100.0%	0.54 [0.18, 1.60] 0.64 [0.50, 0.82] 1.00 [0.37, 2.74] 0.68 [0.54, 0.85] Not estimable 1.49 [0.68, 3.29] 1.06 [0.90, 1.24] 1.07 [0.92, 1.25]	2002 2004 2011 1999 2008	0.1	•		10

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

study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		N	I-H, Rand	dom, 95	5% CI	
1.2.1 High mortality						, ,				ć			
Kuklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]	1991	←			_		
/oung	4	33	9	35	1.2%	0.47 [0.16, 1.38]		-			+		
Zimmerman	3	20	8	20	1.1%	0.38 [0.12, 1.21]					+-		
Angstwurm 1999	7	21	11	21	2.6%	0.64 [0.31, 1.32]					+		
Crimi	49	112	76	112	12.1%	0.64 [0.50, 0.82]							
orceville	14	31	13	29	4.0%	1.01 [0.58, 1.76]					+		
Angstwurm 2007	46	116	61	122	10.4%	0.79 [0.60, 1.06]				-	+		
∕lisĥra	11	18	15	22	5.4%	0.90 [0.56, 1.43]					• 		
3onzález	6	34	8	34	1.6%	0.75 [0.29, 1.93]						_	
Andrews	84	251	84	251	12.1%	1.00 [0.78, 1.28]				_	┿─		
/alenta	19	75	24	75	4.7%	0.79 [0.48, 1.32]	2011				+-		
vlanzanares	5	15	7	16	1.7%	0.76 [0.31, 1.89]						-	
Schneider	6	29	6	29	1.4%	1.00 [0.37, 2.74]			-				
Heyland	216	617	199	601	17.0%	1.06 [0.90, 1.24]	2012				-		
Noth	9	21	11	19	3.4%	0.74 [0.40, 1.38]	2014		-	•	+		
Bloos													
Subtotal (95% CI)		1944		1941	93.4%	0.86 [0.75, 1.00]							
Fotal events Heterogeneity: Tau ² =	•			5 (P = (0.04); I² =	42%							
Heterogeneity: Tau² = Fest for overall effect:	0.03; Ch		38, df = 1	5 (P = (0.04); I ^z =	42%							
	0.03; Ch		38, df = 1				1998	_					,
Heterogeneity: Tau ² = Fest for overall effect: I .2.2 Low mortality	: 0.03; Chi Z = 2.03 ((P = 0.0	38, df = 1 4)	5 (P = 1 10 9	0.04); I² = 0.2%	42% 3.00 (0.14, 65.90) Not estimable		_					+
Heterogeneity: Tau ² = Fest for overall effect: I .2.2 Low mortality Berger 1998	: 0.03; Chi Z = 2.03 (1	P = 0.0	38, df = 1 4) 0	10		3.00 [0.14, 65.90]	1999						 -
Heterogeneity: Tau ² = Fest for overall effect: I.2.2 Low mortality Berger 1998 Porter	: 0.03; Chi Z = 2.03 (1 0	(P = 0.0 10 9	38, df = 1 4) 0 0	- 10 9	0.2%	3.00 [0.14, 65.90] Not estimable	1999 2000	_			-		→
Heterogeneity: Tau ² = Fest for overall effect: I.2.2 Low mortality Berger 1998 Porter Preiser	: 0.03; Chi Z = 2.03 (1 0 8	P = 0.0 10 9 20	38, df = 1 4) 0 0 6	10 9 17	0.2%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62)	1999 2000 2001	-			-		→ →
Heterogeneity: Tau ² = Fest for overall effect: I.2.2 Low mortality Berger 1998 Porter Preiser Berger 2001a	: 0.03; Chi Z = 2.03 (1 0 8 2	P = 0.0 10 9 20 9	38, df = 1 4) 0 6 1	10 9 17 11	0.2% 2.0% 0.3%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39)	1999 2000 2001 2001	_			· · · · · · · · · · · · · · · · · · ·		 → _→ _
Heterogeneity: Tau ² = Fest for overall effect: 1.2.2 Low mortality Berger 1998 Porter Preiser Berger 2001a Berger 2001b	: 0.03; Chi Z = 2.03 (1 0 8 2 0	P = 0.0 10 9 20 9 11	38, df = 1 4) 0 6 1 1	10 9 17 11 11	0.2% 2.0% 0.3% 0.2%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80)	1999 2000 2001 2001 2002	- +			·		 → _ _ _
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens	: 0.03; Chi Z = 2.03 (1 0 8 2 0 5	P = 0.0 10 9 20 9 11 301	38, df = 1 4) 0 6 1 1 9	10 9 17 11 11 294	0.2% 2.0% 0.3% 0.2% 1.2%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60)	1999 2000 2001 2001 2002 2007	- 			· · · ·		 →
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007	: 0.03; Chi Z = 2.03 (1 0 8 2 0 5 1	P = 0.0 10 9 20 9 11 301 11	38, df = 1 4) 0 6 1 1 9 1	10 9 17 11 11 294 10	0.2% 2.0% 0.3% 0.2% 1.2% 0.2%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69)	1999 2000 2001 2001 2002 2007 2008				· · · · · · · · · · · · · · · · · · ·		 →
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007 Berger 2008	0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14	P = 0.0 10 9 20 9 11 301 11 102	38, df = 1 4) 0 6 1 1 9 1 9	10 9 17 11 11 294 10 98	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29)	1999 2000 2001 2001 2002 2007 2008	- 			· · · · · · · · · · · · · · · · · · ·		 → _→
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007 Berger 2008 El-Attar	0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14	P = 0.0 10 9 20 9 11 301 11 102 40	38, df = 1 4) 0 6 1 1 9 1 9	10 9 17 11 294 10 98 40	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18)	1999 2000 2001 2001 2002 2007 2008						 →
Heterogeneity: Tau ² = Test for overall effect: I.2.2 Low mortality Berger 1998 Porter Preiser Berger 2001 a Berger 2001 b Nathens Berger 2007 Berger 2008 EI-Attar Subtotal (95% CI) Total events	0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14 2 33	P = 0.0 10 9 20 9 11 301 11 102 40 513	38, df = 1 4) 0 0 6 1 1 9 1 9 1 28	10 9 17 11 294 10 98 40 500	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3% 6.6%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18) 1.14 [0.71, 1.81]	1999 2000 2001 2001 2002 2007 2008						 → - →
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007 Berger 2008 El-Attar Subtotal (95% CI)	0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14 2 33 : 0.00; Chi	P = 0.0 10 9 20 9 11 301 102 40 513 ² = 3.9 ²	38, df = 1 4) 0 0 6 1 1 9 1 9 1 28 4, df = 7 (10 9 17 11 294 10 98 40 500	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3% 6.6%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18) 1.14 [0.71, 1.81]	1999 2000 2001 2001 2002 2007 2008						 → _ → _
Heterogeneity: Tau ² = Fest for overall effect: Berger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007 Berger 2008 EI-Attar Subtotal (95% CI) Fotal events Heterogeneity: Tau ² =	0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14 2 33 : 0.00; Chi	P = 0.0 10 9 20 9 11 301 102 40 513 ² = 3.9 ²	38, df = 1 4) 0 0 6 1 1 9 1 9 1 28 4, df = 7 (9)	10 9 17 11 294 10 98 40 500 P = 0.7	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3% 6.6%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18) 1.14 [0.71, 1.81]	1999 2000 2001 2001 2002 2007 2008	- 					→ - - -
Heterogeneity: Tau ² = Fest for overall effect: Serger 1998 Porter Preiser Berger 2001a Berger 2001b Nathens Berger 2007 Berger 2008 EI-Attar Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = Fest for overall effect: Fotal (95% CI) Fotal events	: 0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14 2 33 : 0.00; Chi Z = 0.54 (664	P = 0.0 10 9 20 9 11 301 11 102 40 513 P = 0.5 2457	38, df = 1 4) 0 0 6 1 1 9 1 28 4, df = 7 (9) 705	10 9 17 11 294 10 98 40 500 P = 0.7 2441	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3% 6.6% 9); I ² = 0%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18) 1.14 (0.71, 1.81)	1999 2000 2001 2001 2002 2007 2008						 → - - -
Heterogeneity: Tau ² = Test for overall effect: 1.2.2 Low mortality Berger 1998 Porter Preiser Berger 2001 a Berger 2001 b Nathens Berger 2007 Berger 2008 EI-Attar Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI)	: 0.03; Chi Z = 2.03 (1 0 8 2 0 5 1 14 2 33 : 0.00; Chi Z = 0.54 (664	P = 0.0 10 9 20 9 11 301 11 102 40 513 P = 0.5 2457	38, df = 1 4) 0 0 6 1 1 9 1 28 4, df = 7 (9) 705	10 9 17 11 294 10 98 40 500 P = 0.7 2441	0.2% 2.0% 0.3% 0.2% 1.2% 0.2% 2.2% 0.3% 6.6% 9); I ² = 0%	3.00 (0.14, 65.90) Not estimable 1.13 (0.49, 2.62) 2.44 (0.26, 22.80) 0.33 (0.02, 7.39) 0.54 (0.18, 1.60) 0.91 (0.07, 12.69) 1.49 (0.68, 3.29) 2.00 (0.19, 21.18) 1.14 (0.71, 1.81)	1999 2000 2001 2001 2002 2007 2008						 \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow

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

	AOX	(Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.3.1 AOX via PN								
Berger 2001a	5	9	5	12	0.7%	1.33 [0.55, 3.24]	2001	
Berger 2001b	3	11	5	12	0.4%	0.65 [0.20, 2.12]	2001	
Angstwurm 2007	10	116	10	122	0.8%	1.05 [0.45, 2.43]	2007	
El-Attar	5	36	7	34	0.5%	0.67 [0.24, 1.92]	2009	
Andrews	104	251	121	251	14.4%	0.86 [0.71, 1.04]	2010	
Manzanares	3	15	7	16	0.4%	0.46 [0.14, 1.45]	2011	
Bloos								
Subtotal (95% CI)		981		993	73.1%	0.96 [0.88, 1.05]		•
Total events	449		478					
Heterogeneity: Tau ² =	0.00; Chi	² = 4.76	6, df = 6 (P = 0.5	7); I ² = 0%)		
Test for overall effect: 2	Z = 0.93 (P = 0.3	5)					
1.3.2 AOX via EN								
Maderazo	13	28	5	18	0.8%	1.67 [0.72, 3.89]	1991	
Preiser	3	20	1	17	0.1%	2.55 [0.29, 22.31]		
Nathens	36	301	44	294	3.3%	0.80 [0.53, 1.20]		
Subtotal (95% CI)		349		329	4.2%	1.10 [0.60, 2.04]		
		349		329	4.270	1.10 [0.00, 2.04]		
	52	349	50	329	4.2%	1.10 [0.00, 2.04]		
Total events	52 0.12; Chi	_						
Total events Heterogeneity: Tau² =	0.12; Chi	z = 3.20), df = 2 (
Total events Heterogeneity: Tau² = Test for overall effect: 2	0.12; Chi Z = 0.32 (z = 3.20), df = 2 (
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN	0.12; Chi Z = 0.32 (² = 3.20 P = 0.7), df = 2 (5)	P = 0.2	0); I² = 38'	%	1999	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter	0.12; Chi Z = 0.32 (I 5	² = 3.20 P = 0.7 9), df = 2 (5) 8	P = 0.2 9	0); I² = 38' 1.4%	% 0.63 [0.33, 1.17]		
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008	0.12; Chi Z = 0.32 (I	² = 3.20 P = 0.7 9 102), df = 2 (5) 8 34	P = 0.2 9 98	0); I ^z = 38' 1.4% 3.8%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland	0.12; Chi Z = 0.32 (I 5 36	² = 3.20 P = 0.7 9), df = 2 (5) 8	P = 0.2 9	0); I² = 38' 1.4%	% 0.63 [0.33, 1.17]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI)	0.12; Chi Z = 0.32 (I 5 36	² = 3.2(P = 0.7 9 102 617), df = 2 (5) 8 34	P = 0.2 9 98 601	0); I² = 38' 1.4% 3.8% 17.5%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events	0.12; Chi Z = 0.32 (I 5 36 168 209	² = 3.20 P = 0.7 9 102 617 728), df = 2 (5) 8 34 181 223	P = 0.2 9 98 601 708	0); I² = 38 1.4% 3.8% 17.5% 22.7%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events Heterogeneity: Tau ² =	0.12; Chi Z = 0.32 (I 5 36 168 209 0.00; Chi	² = 3.20 P = 0.7 9 102 617 728 ² = 1.72), df = 2 (5) 8 34 181 223 2, df = 2 (P = 0.2 9 98 601 708	0); I² = 38 1.4% 3.8% 17.5% 22.7%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	0.12; Chi Z = 0.32 (I 5 36 168 209 0.00; Chi	² = 3.20 P = 0.7 9 102 617 728 ² = 1.72), df = 2 (5) 8 34 181 223 2, df = 2 (P = 0.2 9 8 601 708 P = 0.4	0); I² = 38 1.4% 3.8% 17.5% 22.7%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Total (95% CI) Total events	0.12; Chi Z = 0.32 (I 5 36 168 209 0.00; Chi	² = 3.20 P = 0.7 9 102 617 728 ² = 1.72 P = 0.1), df = 2 (5) 8 34 181 223 2, df = 2 (P = 0.2 9 8 601 708 P = 0.4	0); I² = 38 1.4% 3.8% 17.5% 22.7% 2); I² = 0%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05]	2008	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Total (95% CI) Total events	0.12; Chi Z = 0.32 (1 36 168 209 0.00; Chi Z = 1.30 (710	² = 3.2(P = 0.7 9 102 617 728 ² = 1.7(P = 0.1 2058), df = 2 (5) 8 34 181 223 2, df = 2 (9) 751	P = 0.2 9 88 601 708 P = 0.4 2030	0); I ² = 38 ⁴ 1.4% 3.8% 17.5% 22.7% 2); I ² = 0% 100.0%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05] 0.95 [0.88, 1.02]	2008 2012	
Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.3.3 AOX via PN & EN Porter Berger 2008 Heyland Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Total (95% CI)	0.12; Chi Z = 0.32 (1 5 36 168 209 0.00; Chi Z = 1.30 (710 0.00; Chi	² = 3.20 P = 0.7 9 102 617 728 ² = 1.72 P = 0.1 2058 ² = 10.7), df = 2 (5) 8 34 181 223 2, df = 2 (9) 751 12, df = 1	P = 0.2 9 88 601 708 P = 0.4 2030	0); I ² = 38 ⁴ 1.4% 3.8% 17.5% 22.7% 2); I ² = 0% 100.0%	% 0.63 [0.33, 1.17] 1.02 [0.70, 1.48] 0.90 [0.76, 1.08] 0.90 [0.77, 1.05] 0.95 [0.88, 1.02]	2008 2012	0.1 0.2 0.5 1 2 5 10 Favours AOX Favours control

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

5	•			,		5	5 .		5 5 17
	AO	K	Cont	rol		Risk	Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Rand	om, 95% Cl	Year	M-H, Random, 95% Cl
1.4.1 High mortality									
Angstwurm 2007	10	116	10	122	0.8%	1.05	[0.45, 2.43]	2007	
Andrews	104	251	121	251	14.4%	0.86	[0.71, 1.04]	2010	
Manzanares	3	15	7	16	0.4%	0.46	[0.14, 1.45]	2011	
Heyland	168	617	181	601	17.5%	0.90	[0.76, 1.08]	2012	-+-
Bloos									
Subtotal (95% CI)		1542		1536	89.0%	0.95	[0.88, 1.03]		•
Total events	604		642						
Heterogeneity: Tau ² =				P = 0.4	4); I ^z = 0%)			
Test for overall effect: .	Z = 1.29 ((P = 0.2	20)						
1.4.2 Low mortality									
Porter	5	9	8	9	1.4%	ca ()	[0.33, 1.17]	1000	
Preiser	3	20	1	17	0.1%		0.29, 22.31]		
Berger 2001b	3	11	5	12	0.4%		[0.20, 2.12]		
Berger 2001a	5	9	5	12	0.7%		[0.55, 3.24]		
Nathens	36	301	44	294	3.3%		[0.53, 1.20]		
Berger 2008	36	102	34	98	3.8%		[0.70, 1.48]		
El-Attar	5	36	7	34	0.5%		[0.24, 1.92]		
Subtotal (95% CI)	Ŭ	488		476	10.2%		[0.69, 1.10]	2000	•
Total events	93		104						
Heterogeneity: Tau ² =		i² = 4.1	8. df = 6 (P = 0.6	5): I ² = 0%)			
Test for overall effect: .			•		-//				
1.4.4 Mortality not rep			_						
Maderazo Subtotal (95% CI)	13	28 28	5	18 18	0.8% 0.8%		[0.72, 3.89] [0.72, 3.89]	1991	
Total events	13		5						
Heterogeneity: Not ap									
Test for overall effect: .	•	(P = 0.2)	23)						
			-						
Total (95% CI)		2058		2030	100.0%	0.95	[0.88, 1.02]		•
Total events	710		751						
Heterogeneity: Tau ² =				2 (P = 0	0.61); I^z = (0%			
Test for overall effect: .		`							Favours AOX Favours control
Test for subgroup diffe	oroncoc.	Chi² = 1	2 20 df=	2 (P = 1)	0.33) 17=	Q 796			, around not in around condition

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

Figure 5. ICU LOS

		AOX		С	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
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	<u>ا ا ا ا ا ا ا ا ا ا ا ا ا ا ا ا ا ا ا </u>
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	<u> </u>
Subtotal (95% CI)			190			198	32.4%	0.08 [-2.47, 2.62]		•
Heterogeneity: Tau ² =	2.36; CI	hi² = 7	.49, df=	= 6 (P =	0.28);	l ² = 20°	%			
Test for overall effect:	Z = 0.06	(P = 0	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 ap	plicable									
Test for overall effect:	Z = 0.55	(P = 0	0.59)							
1.5.3 AOX via PN & E	N									
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: Tau ² =	0.00; Cl	hi ² = 1	.62, df=	= 2 (P =	0.44);	l² = 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: Tau ² =	0.00; CI	hi ² = 9	.49. df=	= 10 (P :	= 0.49)); I^z = 0 9	%			
Test for overall effect:	•		•		,					-10 -5 Ó Ś 10
Test for subgroup diff				df = 2/0	P = 0.8	(7), I ² =	0%			Favours AOX Favours control
		/								

Figure 6. Hospital LOS

	A	AOX		Control Mean Difference						Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.6.1 AOX via PN										
Berger 1998	54	27	10	66	31	10	1.7%	-12.00 [-37.48, 13.48]	1998	·
Berger 2001a	82	78	9	64	39	11	0.4%	18.00 [-37.93, 73.93]	2001	· · · · · · · · · · · · · · · · · · ·
Berger 2001b	60	48	11	64	39	11	0.8%	-4.00 [-40.55, 32.55]	2001	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)			30			32	2.9%	-6.03 [-25.61, 13.55]		
Heterogeneity: Tau ² =	•		•	= 2 (P =	0.63);	I ² = 0%				
Test for overall effect:	Z = 0.60	(P = 0).55)							
1.6.2 AOX via EN										
Schneider	44.4	36.6	29	47.2	48.1	29	2.3%	-2.80 [-24.80, 19.20]	2011	
Noqueira	30	11	11	27	11	24	18.0%	3.00 [-4.85, 10.85]		
Subtotal (95% CI)			40			53	20.3%	2.34 [-5.05, 9.74]		
Heterogeneity: Tau ² =	0.00; Ch	ni z = 0.	.24, df=	= 1 (P =	0.63);	I ² = 0%				
Test for overall effect:	Z=0.62	(P = 0).53)							
1.6.3 AOX via PN & E	N									
Porter		23.4	9	49	30	9	1.8%	-17.70 [-42.56, 7.16]	1999	·
Berger 2008	23	20.4	102	26	20	98	36.1%	-3.00 [-8.54, 2.54]	2008	_ _
Hevland	31.2		617	29.5		601	38.9%	1.70 [-3.64, 7.04]		
Subtotal (95% CI)	01.2	-	728	20.0		708	76.8%	-1.40 [-6.89, 4.09]	2012	
Heterogeneity: Tau ² =	8.76: Ch	ni ² = 3.	22. df=	= 2 (P =	0.20):	l ² = 389	%			
Test for overall effect:					/1					
		,								
Total (95% CI)			798			793	100.0%	-0.44 [-3.77, 2.89]		•
Heterogeneity: Tau ² =	0.00; Ch	ni² = 5.	.31, df=	= 7 (P =	0.62);	l ² = 0%				-20 -10 0 10 20
Test for overall effect:	Z = 0.26	(P = 0)).80)							-20 -10 0 10 20 Favours AOX Favours control
Test for subaroup diff	erences:	: Chi ≇∍	= 0.97,	df = 2 (F	^o = 0.6	1), I ² =	0%			

Figure 7. Duration of mechanical ventilation

		AOX		C	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.7.1 AOX via PN										
Berger 1998	9	10	10	12	9	10	4.8%	-3.00 [-11.34, 5.34]	1998	3 ←
Berger 2001a	6.2	3.5	9	4.2	5.2	11	11.9%	2.00 [-1.83, 5.83]	2001	
Berger 2001b	4.1	3.6	11	4.2	5.2	11	12.2%	-0.10 [-3.84, 3.64]	2001	_
Berger 2007	7.6	6	11	12.6	6	10	9.1%	-5.00 [-10.14, 0.14]	2007	* +
El-Attar	9.4	7.3	40	17.8	7.6	40	13.4%	-8.40 [-11.67, -5.13]	2009	; ←
Manzanares Subtotal (95% CI)	10	8	15 <mark>96</mark>	9	4	16 <mark>98</mark>	10.4% <mark>61.8%</mark>	1.00 [-3.50, 5.50] - 2.22 [-6.07, 1.62]	2011	
Heterogeneity: Tau ² =	= 17.19; 0	Chi²=	22.67,	df = 5 (P	= 0.00	004); I ^z	= 78%			
Test for overall effect:										
1.7.2 AOX via EN										
Crimi	6.2	2.3	112	8.9	1.8	112	19.4%	-2.70 [-3.24, -2.16]	2004	•
Schneider Subtotal (95% CI)	30.5	19.2	21 133	27.2	18.1	19 131	2.9% 22.2%	3.30 [-8.26, 14.86] - 2.59 [-4.15, -1.04]	2011	•
Heterogeneity: Tau² = Test for overall effect:				= 1 (P =	0.31);	I² = 3%				
1.7.3 AOX via PN & E	N									
Heyland Subtotal (95% CI) Heterogeneity: Not ap	10.9 oplicable		617 <mark>617</mark>	10.5	19.7	601 <mark>601</mark>	15.9% <mark>15.9%</mark>	0.40 [-1.91, 2.71] <mark>0.40 [-1.91, 2.71]</mark>	2012	
Test for overall effect:	Z=0.34	(P = (0.73)							
Total (95% CI)			846			830	100.0%	-1.76 [-3.87, 0.36]		-
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	Z= 1.63	(P = ().10)							-10 -5 0 5 Favours AOX Favours control