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 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 I²=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 I²=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 I²=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 I²=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 0.86, 95% CI 0.75, 0.99, p=0.03, heterogeneity l^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 l^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 I²=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 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 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 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 I²=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 I²=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 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=0.31).

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 I²=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 \pm 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 I²=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 I²=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 I²=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 \pm 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 I²=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 I²=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 I²=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.

Study	Population	Methods Score	Intervention
Studies in which antioxid	ants 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 μ g/day) vs. placebo (Selenium group randomized further to two groups: 500 μ g Selenium alone vs. 500 μ g 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).

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 $\mu mol)$ + Selenium (375 μgm + zinc (574 $\mu mol)$ 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 μ g Selenium IV x 3 days followed by 316 μ g x 3 days, 158 μ g x 3 days and 31.6 μ g thereafter vs. 31.6 μ g 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 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			

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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, 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 da 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			

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 (1000m Vit E (1000 IU) q8h as a bolus via EN vs placebo q8h as a bolus via EN. <i>Note: 2 intervention groups</i>		
Studies in which antioxid	ants were delivered simulta	neously 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 III Patients (continued)

Study	Mortality Experimental Control		Infections Experimental Control		LOS Experimental Control		Ventilator Days Experimental 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	B.1 ± 1.1 (2-5) ICU per patient 30 ± 12 (10) 39 Hospital H 54 ± 27 (10) 66		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 ICU 3/11 (27) ICU ICU ICU 5.8 ± 4.4 (11) 8.6 ± 8.1 (1 Hospital Hospital 60 ± 48 (11) 64 ± 39 (1*) 64 ± 39 (1*) 100 ± 10		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	$3.6\pm1.3~\text{per pt}$	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)	Superinfection 2/29 (7) Hospital 25 (7-68)		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	1.8 ± 1.6 ICU per patient 21.3 ± 16.2 (18)		NR	NR

12) El-Attar 2009	ICU 2/40 (5)	ICU 1/40 (3)	VAP 5/36 (14)	VAP NR 7/34 (21)		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 ICU 13.2 15.1 (IQR 7.8, 23.7) (IQR 8.3, 24 Hospital Hospital 29.8 31.2 (IQR 14.7, 52.4) (IQR 15.1-5)		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 VAP ICU 15 (20) 7/16 (44) 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 antioxid	ants 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)	/17 (6) 5 (3-26)		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 ICU 5.3 (mean) 6.4 (n Hospital Hos 14.6 (mean) 15.1 (n		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 <u>+</u> 11	Hospital 27 <u>+</u> 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	$\label{eq:constraint} \begin{array}{c} \mbox{Vit+acetylcysteine} & \mbox{ICU} \\ 13.0 \pm 10.5 (23) & \mbox{Hospital} \\ 24.0 \pm 20.8 (23) & \mbox{No acetylcysteine} & \mbox{ICU} \\ 12.9 \pm 9.0 (27) & \mbox{Hospital} \\ 21.2 \pm 13.7 (27) & \mbox{Combined}^{\star} & \mbox{ICU} \\ 12.946 \pm 9.72 (50) & \mbox{Hospital} \\ 22.488 \pm 17.32 (50) & \mbox{Hospital} \\ \end{array}$	ICU 19.1 <u>+</u> 16.0 (22) Hospital 22.6 <u>+</u> 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 antioxid	lants were deliver	ed simultaneously	y 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	e unit	VAP: ventilator	associated pneumonia	L	.OS: length of stay	

Table 2. QOL Outcomes

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

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

NS: not significant

	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
1.1.1 AOX via PN								
Kuklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]	1991	←
Young	4	33	9	35	1.2%	0.47 [0.16, 1.38]	1996	
Zimmerman	3	20	8	20	1.0%	0.38 [0.12, 1.21]	1997	
Berger 1998	1	10	0	10	0.2%	3.00 [0.14, 65.90]	1998	
Angstwurm 1999	7	21	11	21	2.4%	0.64 [0.31, 1.32]	1999	
Berger 2001	0	11	1	11	0.1%	0.33 [0.02, 7.39]	2001	· · · · · · · · · · · · · · · · · · ·
Forceville	14	31	13	29	3.9%	1.01 [0.58, 1.76]	2007	
Angstwurm 2007	46	116	61	122	10.0%	0.79 [0.60, 1.06]	2007	
Berger 2007	1	11	1	10	0.2%	0.91 [0.07, 12.69]	2007	<→
Mishra	11	18	15	22	5.2%	0.90 [0.56, 1.43]	2007	
El-Attar	2	40	1	40	0.3%	2.00 [0.19, 21.18]	2009	
González	6	34	8	34	1.5%	0.75 [0.29, 1.93]	2009	
Andrews	84	251	84	251	11.8%	1.00 [0.78, 1.28]	2010	-
Valenta	19	75	24	75	4.5%	0.79 [0.48, 1.32]	2011	
Manzanares	5	15	7	16	1.6%	0.76 [0.31, 1.89]	2011	
Woth	9	21	11	19	3.2%	0.74 [0.40, 1.38]	2014	
Bloos	152	543	137	546	14.3%	1.12 [0.92, 1.36]	2015	
Subtotal (95% CI)		1258		1270	61.5%	0.93 [0.83, 1.04]		•
Total events	364		399					
Heterogeneity: Tau² =	: 0.00; Chi	² = 16.1	11, df = 1	6 (P = (0.45); I² =	1%		
Test for overall effect:	Z = 1.23 ((P = 0.2	2)					
1.1.2 AOX via EN								
Preiser	8	20	6	17	1.9%	1.13 [0.49, 2.62]	2000	
Nathens	5	301	9	294	1.2%	0.54 [0.18, 1.60]	2002	
Crimi	49	112	76	112	11.8%	0.64 [0.50, 0.82]	2004	
Schneider	6	29	6	29	1.3%	1.00 [0.37, 2.74]	2011	
Howe	17	50	10	22	3.4%	0.75 [0.41, 1.36]	2015	
Subtotal (95% CI)		512		4/4	19.7%	0.69 [0.56, 0.85]		•
Total events	85		107					
Heterogeneity: Tau ² =	0.00; Chi	² = 2.4	3, df = 4 (P = 0.6	6); I² = 0%	6		
Test for overall effect:	Z= 3.47 ((P = 0.0	1005)					
1.1.3 AOX via PN & El	N							
Porter	0	9	0	9		Not estimable	1999	
Berger 2008	14	102	9	98	2.1%	1.49 [0.68, 3.29]	2008	
Hevland	216	617	199	601	16.7%	1.06 [0.90, 1.24]	2012	-
Subtotal (95% CI)		728		708	18.8%	1.07 [0.92, 1.25]		◆
Total events	230		208					
Heterogeneity: Tau ² =	0.00; Chi	² = 0.7 ¹	1, df = 1 (P = 0.4	0); l² = 0%	6		
Test for overall effect:	Z = 0.88 ((P = 0.3	18)					
Total (95% CI)		2498		2452	100.0%	0.88 [0.78, 1.00]		◆
Total events	679		714					
Heterogeneity: Tau² =	0.02; Chi	r = 30.3	33, df = 2	3 (P = (0.14); I ^z =	24%		
Test for overall effect:	Z = 2.03 ((P = 0.0	14)					Eavours AOX Eavours control

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

Test for subgroup differences: Chi² = 11.06, df = 2 (P = 0.004), l² = 81.9%

_	AOX	AOX Control			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
1.2.1 High mortality										
Kuklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]	1991	←		
Young	4	33	9	35	1.2%	0.47 [0.16, 1.38]	1996			
Zimmerman	3	20	8	20	1.0%	0.38 [0.12, 1.21]	1997			
Angstwurm 1999	7	21	11	21	2.4%	0.64 [0.31, 1.32]	1999			
Crimi	49	112	76	112	11.8%	0.64 [0.50, 0.82]	2004			
Mishra	11	18	15	22	5.2%	0.90 [0.56, 1.43]	2007			
Forceville	14	31	13	29	3.9%	1.01 [0.58, 1.76]	2007			
Angstwurm 2007	46	116	61	122	10.0%	0.79 [0.60, 1.06]	2007			
González	6	34	8	34	1.5%	0.75 [0.29, 1.93]	2009			
Andrews	84	251	84	251	11.8%	1.00 [0.78, 1.28]	2010	+		
Valenta	19	75	24	75	4.5%	0.79 [0.48, 1.32]	2011			
Schneider	6	29	6	29	1.3%	1.00 [0.37, 2.74]	2011			
Manzanares	5	15	7	16	1.6%	0.76 [0.31, 1.89]	2011			
Heyland	216	617	199	601	16.7%	1.06 [0.90, 1.24]	2012			
Woth	9	21	11	19	3.2%	0.74 [0.40, 1.38]	2014			
Howe	17	50	10	22	3.4%	0.75 [0.41, 1.36]	2015			
Bloos	152	543	137	546	14.3%	1.12 [0.92, 1.36]	2015			
Subtotal (95% CI)		1994		1963	94.1%	0.86 [0.75, 0.99]		•		
Total events	648		687							
Heterogeneity: Tau² =	0.02; Chi	≈ = 26.3	35, df = 1	6 (P = 1	0.05); I² =	39%				
Test for overall effect:	Z = 2.16 ((P = 0.0	13)							
1.2.2 Low mortality										
1.2.2 Low mortality										
Berger 1998	1	10	U	10	0.2%	3.00 [0.14, 65.90]	1998			
Porter	U	9	U	9	4.000	Not estimable	1999			
Preiser Dammen 2004	8	20	6	17	1.9%	1.13 [0.49, 2.62]	2000			
Berger 2001	0	11	1	11	0.1%	0.33 [0.02, 7.39]	2001			
Nathens Dawrau 2007	5	301	9	294	1.2%	0.54 [0.18, 1.60]	2002			
Berger 2007	1	11	1	10	0.2%	0.91 [0.07, 12.69]	2007			
Berger 2008	14	102	9	98	2.1%	1.49 [0.68, 3.29]	2008			
El-Allar Subtotal (05% Cl)	2	40 504	1	40	0.3%	2.00 [0.19, 21.18]	2009			
Total quanta	24	J04	27	405	3.370	1.10 [0.00, 1.77]				
Hotorogonoity: Touã-	0.00 Chi	8-24	27 7 df = 67	0-07	SV 18 - 00	<i>,</i>				
Test for overall effect:	Z = 0.38 ((P=0.7	7, ui = 6 ('0)	F = 0.7	5), 17 = 03	ο				
T-4-1 (05% OB				0.450	400.05	0.00 0 70 4.000				
Total (95% CI)		2498		2452	100.0%	0.88 [0.78, 1.00]		▼		
Total events	679		714			-				
Heterogeneity: Tau ² =	0.02; Chi	f = 30.3	33, df = 2	3 (P = I	U.14); I ² =	24%		0.1 0.2 0.5 1 2 5 10		
Test for overall effect:	Z = 2.03 ((P = 0.0	14)					Favours AOX Favours control		

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

Test for subgroup differences: $Chi^2 = 0.93$, df = 1 (P = 0.34), $I^2 = 0\%$

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

	AOX	(Cont	rol		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 2001	3	11	3	11	0.3%	1.00 [0.26, 3.91]	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	14.5%	0.86 [0.71, 1.04]	2010	
Manzanares	3	15	7	16	0.4%	0.46 [0.14, 1.45]	2011	
Bloos	319	543	323	546	56.4%	0.99 [0.90, 1.10]	2015	
Subtotal (95% CI)		972		980	72.9%	0.96 [0.88, 1.05]		•
Total events	444		471					
Heterogeneity: Tau ² =	0.00; Ch	i ^z = 3.83	2, df = 5 (P = 0.5	8); I ^z = 0%	1		
Test for overall effect: .	Z = 0.95 ((P = 0.3	(4)					
1.3.2 AOX via FN								
Maderazo	13	28	5	18	0.8%	16710723891	1001	
Preiser	3	20	1	17	0.0%	2 55 0 29 22 31	2000	
Nathens	36	301	44	294	3.3%	0.80 (0.53, 1.20)	2000	
Subtotal (95% CI)		349		329	4.2%	1.10 [0.60, 2.04]	2002	
Total events	52		50					
Heterogeneity: Tau ² =	0.12: Ch	i ^z = 3.20).df=2(P = 0.2	0): I² = 389	%		
Test for overall effect:	Z = 0.32	(P = 0.7	'5)		-)			
1.3.3 AOX via PN & El		_	_	_				
Porter	5	9	8	9	1.4%	0.63 [0.33, 1.17]	1999	
Berger 2008	36	102	34	98	3.9%	1.02 [0.70, 1.48]	2008	
Heyland	168	617 729	181	601 709	17.6%	0.90 [0.76, 1.08]	2012	
Sublotal (95% CI)	200	120		100	22.970	0.90 [0.77, 1.05]		\mathbf{T}
i otal events	209 0.00:05	R 4 7	223 2 46 - 27	D – 0 4				
Test for overall offect:	0.00; CN 7 = 1 20 -	E = 1.7. (P = 0.4	∠,ui=∠(0)	r = 0.4	2), 17 = 0%			
restion overall ellect.	2 - 1.301	(F – 0.1	9)					
Total (95% CI)		2049		2017	100.0%	0.94 [0.88, 1.02]		•
Total events	705		744					
Heterogeneity: Tau² =	0.00; Ch	i ^z = 9.16	3, df = 11	(P = 0.	61); I ^z = 09	%	Ę	
Test for overall effect: .	Z=1.49)	(P = 0.1	4)	-			U	J.T. U.Z. U.S. T. Z. S. 1U Eavoure AOX, Eavoure control
Test for subgroup diffe	erences:	Chi ² = ().70, df=	2 (P =	0.71), I ^z =	0%		Favours AOA Favours condor

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

	AOX		Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 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	14.5%	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	17.6%	0.90 [0.76, 1.08]	2012	- - <u>+</u>
Bloos	319	543	323	546	56.4%	0.99 [0.90, 1.10]	2015	
Subtotal (95% CI)		1542		1536	89.7%	0.95 [0.88, 1.03]		•
Total events	604		642					
Heterogeneity: Tau² =	0.00; Ch	i² = 3.71	7, df = 4 (P = 0.4	4); I² = 0%	1		
Test for overall effect:	Z = 1.29 ((P = 0.2	20)					
1.4.2 I ow mortality								
Porter	5	q	8	q	1 4 %	0.63/0.33/1.171	1999	
Preiser	3	20	1	17	0.1%	2 55 0 29 22 31	2000	
Berger 2001	3	11	3	11	0.3%	1 00 0 26 3 91	2000	
Nathens	36	301	44	294	3.3%		2002	
Berger 2008	36	102	34	98	3.9%	1.02 [0.70, 1.48]	2008	_
El-Attar	5	36	7	34	0.5%	0.67 [0.24, 1.92]	2009	
Subtotal (95% CI)	-	479		463	9.5%	0.86 [0.68, 1.10]		•
Total events	88		97					
Heterogeneity: Tau ² =	0.00; Ch	i ² = 3.1∶	2. df = 5 (P = 0.6	8); I ² = 0%	1		
Test for overall effect:	Z=1.21	(P = 0.2)	22)		-,,,			
		`						
1.4.4 Mortality not rep	ported							
Maderazo	13	28	5	18	0.8%	1.67 [0.72, 3.89]	1991	
Subtotal (95% CI)		28		18	0.8%	1.67 [0.72, 3.89]		
Total events	13		5					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 1.19	(P = 0.2	23)					
Total (05% CI)		2040		2017	100.0%	0.04 [0.99, 4.02]		▲
Total (55% Cl)	705	2045	744	2017	100.0%	0.54 [0.00, 1.02]		•
i otal events Natava vanaity Zevi?	705	7 - 0.4	/44 C -16 - 44	(n – e	C43-17 - 04	w.		
Heterogeneity: Tau* =	0.00; Ch	r= 9.11 /n = 0.4	o, ur = 11 - AN	(P = 0.	01); i*= 0'	70		0.1 0.2 0.5 1 2 5 10
Test for overall effect:	∠=1.491	(P = 0.1 Alian	4) 2.22 - 46	a (n	0.040 17	4.4.200		Favours AOX Favours control
lest for subgroup diff	erences:	Chif=:	2.33, at =	Z (P =	0.31), F=	14.3%		

Figure 5. ICU LOS

	A	VOX	Control				Mean Difference			Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI		
1.5.1 AOX via PN												
Berger 1998	30	12	10	39	13	10	1.9%	-9.00 [-19.97, 1.97]	1998	·		
Berger 2001	5.8	4.4	11	8.6	8.1	11	6.9%	-2.80 [-8.25, 2.65]	2001			
Berger 2007	35	27	11	47	37	10	0.3%	-12.00 [-39.94, 15.94]	2007	← →		
Mishra	21.3	16.2	18	20.8	21.8	18	1.5%	0.50 [-12.05, 13.05]	2007	·		
Angstwurm 2007	15.1	10	116	12.7	9	122	22.7%	2.40 [-0.02, 4.82]	2007			
Manzanares	14	11	15	13	6	16	5.3%	1.00 [-5.30, 7.30]	2011			
Subtotal (95% CI)			181			187	38.5%	-0.20 [-3.47, 3.07]		-		
Heterogeneity: Tau ² = 4	4.77; Chi	i ^z = 7.1	9, df =	5 (P = 0	.21); l ^a	'= 30%						
Test for overall effect: Z	(= 0.12	(P = 0.	90)									
1.5.2 AOX via EN												
Schneider	29.8	26	29	26.5	19.6	29	1.6%	3.30 [-8.55, 15.15]	2011	,		
Howe	12.946	9.72	50	19.1	16	22	4.2%	-6.15 [-13.36, 1.05]	2015			
Subtotal (95% CI)			79			51	5.8%	2.65 [-11.60, 6.31]				
Heterogeneity: Tau ² = 1	9.65: CI	hi² = 1	.78. df=	= 1 (P =	0.18):	$ ^{2} = 449$	%					
Test for overall effect: Z	. = 0.58 ((P = 0.	56)		//							
1.5.3 AOV via DN 8. EN												
Dortor		25.2		25.0	24.0		0.50	40.001.05.04.0.041	4000	•		
Porter Barrar 2000	22	25.2	400	35.8	21.9	9	0.5%	-13.80[-35.61, 8.01]	1999			
Berger 2008	5.8	0.4	102	0.4 40.0	0.7	98	34.1%	0.40[-1.14, 1.94]	2008			
Heyland Subtotal (05% CI)	14.2	22.1	729	13.8	23.1	709	21.1% 55.7%	0.40 [-2.17, 2.97]	2012	L		
Subtotal (55% CI)	0.00	2 4 0	120		4.01.17	- 00	55.170	0.55[-0.57, 1.07]		T		
Teet for everall effect: 7	1.00, Chi 1.00, Chi	(T = 1.0)2, ui = cov	2 (P = 0	.44), 17	-= 0%						
restior overall effect. Z	. = 0.52 ((= 0.	00)									
Total (95% CI)			988			946	100.0%	0.16 [-1.38, 1.69]		•		
Heterogeneity: Tau² = 1	l.18; Chi	i ^z = 12	.59, df=	= 10 (P =	= 0.25)	; I ² = 21	1%					
Test for overall effect: Z	. = 0.20 ((P = 0.	84)							-10 -5 0 5 10 Eavours AOX Eavours control		
Test for subgroup diffe	rences:	Chi ^z =	0.49, d	lf = 2 (P	= 0.78), I² = 0	%					

Figure 6. Hospital LOS

	1	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
1.6.1 AOX via PN										
Berger 1998	54	27	10	66	31	10	1.5%	-12.00 [-37.48, 13.48]	1998	· · · · · · · · · · · · · · · · · · ·
Berger 2001	60	48	11	64	39	11	0.7%	-4.00 [-40.55, 32.55]	2001	← →
Subtotal (95% CI)			21			21	2.2%	-9.38 [-30.29, 11.52]		
Heterogeneity: Tau² =	0.00; Chi	² = 0.12	2, df = 1	(P = 0.7)	72); I 2 =	= 0%				
Test for overall effect:	Z=0.88 (P = 0.3	8)							
1.6.2 AOX via EN										
Schneider	44.4	36.6	29	47.2	48.1	29	2.0%	-2.80 [-24.80, 19.20]	2011	
Nogueira	30	11	11	27	11	24	15.4%	3.00 [-4.85, 10.85]	2013	
Howe	22.488	17.32	50	22.6	15.5	22	14.6%	-0.11 [-8.17, 7.95]	2015	
Subtotal (95% CI)			90			75	32.0%	1.22 [-4.23, 6.67]		
Heterogeneity: Tau² =	0.00; Chi	² = 0.43	3, df = 2	(P = 0.8)	31); I² =	= 0%				
Test for overall effect:	Z = 0.44 (P = 0.6	6)							
1.6.3 AOX via PN & E	N									
Porter	31.3	23.4	9	49	30	9	1.5%	-17.70 [-42.56, 7.16]	1999	←
Berger 2008	23	20	102	26	20	98	30.9%	-3.00 [-8.54, 2.54]	2008	_
Hevland	31.2	50.2	617	29.5	44.8	601	33.3%	1.70 [-3.64, 7.04]	2012	
Subtotal (95% CI)			728			708	65.8%	-1.40 [-6.89, 4.09]		
Heterogeneity: Tau ² =	8.76; Chi	² = 3.22	2, df = 2	(P = 0.2)	20); i² =	= 38%				
Test for overall effect:	Z=0.50 (P = 0.6	2)							
T-4-1 (054) OD							400.00			
Total (95% CI)			839	_		804	100.0%	-0.45 [-3.53, 2.64]		🛨
Heterogeneity: Tau ² =	0.00; Chi	² = 4.90), df = 7	(P = 0.6	57); I² =	:0%				-20 -10 0 10 20
Test for overall effect:	Z=0.28 (P = 0.7	8)							Favours AOX Favours control
Test for subgroup diff	erences: (Chi²=1	1.18, df	= 2 (P =	0.56),	I² = 0%	6			

Figure 7. Duration of mechanical ventilation

	4	AOX		Co	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
1.7.1 AOX via PN										
Berger 1998	9	10	10	12	9	10	5.3%	-3.00 [-11.34, 5.34]	1998	· · · · · · · · · · · · · · · · · · ·
Berger 2001	4.1	3.6	11	4.2	5.2	11	13.7%	-0.10 [-3.84, 3.64]	2001	
Berger 2007	7.6	6	11	12.6	6	10	10.1%	-5.00 [-10.14, 0.14]	2007	← • • · · · · · · · · · · · · · · · · ·
El-Attar	9.4	7.3	40	17.8	7.6	40	15.2%	-8.40 [-11.67, -5.13]	2009	←
Manzanares	10	8	15	9	4	16	11.6%	1.00 [-3.50, 5.50]	2011	
Subtotal (95% CI)			87			87	56.0%	-3.18 [-7.28, 0.93]		
Heterogeneity: Tau² =	15.63; C	≥hi² = '	15.99, (df=4 (P	= 0.0	03); I ² =	75%			
Test for overall effect:	Z = 1.52	(P = 0	1.13)							
1.7.2 AOX via EN										
Crimi	6.2	2.3	112	8.9	1.8	112	22.7%	-2.70 [-3.24, -2.16]	2004	+
Schneider	30.5	19.2	21	27.2	18.1	19	3.1%	3.30 [-8.26, 14.86]	2011	
Subtotal (95% CI)			133			131	25.8%	-2.59 [-4.15, -1.04]		-
Heterogeneity: Tau² =	0.56; Cł	ni² = 1.	.03, df=	= 1 (P = 0	0.31);	I ^z = 3%				
Test for overall effect:	Z = 3.27	(P = 0	1.001)							
1.7.3 AOX via PN & E	N									
Heyland	10.9	21.4	617	10.5	19.7	601	18.3%	0.40 [-1.91, 2.71]	2012	
Subtotal (95% CI)			617			601	18.3%	0.40 [-1.91, 2.71]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.34	(P = 0	1.73)							
Total (05% CI)			027			040	100.0%	2 27 [4 46 0 00]		
	C 10. 01		0J1		0.00	019	700.0%	-2.21 [-4.40, -0.09]		
Heterogeneity: Tau* =	5.40; Cr 7 = 2.04	$11^{-} = 2$	4.76,01 COM	= / (P =	0.001	08); I==	72%			-10 -5 0 5 10
Test for overall effect:	∠= ∠.04	(P=1	1.04)	-16 D (D		0) 17	CO 100			Favours AOX Favours control
Test for subgroup dim	erences:	. Unit:	= 4.92,	ui = 2 (P	r = 0.0	9), ITE	59.4%			

Table 3. 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 pancreatitisan 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.
11	Only 6 hr duration of intervention	Galley HF, Howdle PD, Walker BE, Webster NR (1997) The effects of intravenous antioxidants in patients with septic shock. Free Radic Biol Med 23:768-774
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.
17	Not ICU pts	Yamaguchi T, Sano K, Takakura K, Saito I, Shinohara Y, Asano T, Yasuhara H. Ebselen Study Group. Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. Stroke. 1998 Jan;29(1):12-7.

18	Not ICU pts	Cerwenka H, Khoschsorur G, Bacher H, Werkgartner G, El-Shabrawi A, Quehenberger F, Rabl H, Mischinger HJ. Normothermic liver ischemia and antioxidant treatment during hepatic resections. Free Radic Res. 1999 Jun:30(6):463-9.
19	Not ICU pts	Ogawa A, Yoshimoto T, Kikuchi H, Sano K, Saito I, Yamaguchi T, Yasuhara H. Ebselen in acute middle cerebral artery occlusion: a placebo-controlled, double-blind clinical trial. Cerebrovasc Dis. 1999 Mar-Apr;9(2):112-8.
20	NAC alone and Glutathione	Ortolani O, Conti A, De Gaudio AR, Moraldi E, Cantini Q, Novelli G. The effect of glutathione and N-acetylcysteine on lipoperoxidative damage in patients with early septic shock. Am J Respir Crit Care Med. 2000 Jun;161(6):1907-11.
21	Pseudorandomized	Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. Arch Surg 2000 135:326-331
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
23	Not ICU pts	Keith ME, Jeejeebhoy KN, Langer A, Kurian R, Barr A, O'Kelly B, Sole MJ (2001) A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. Am J Clin Nutr 73:219-224
24	No clinical outcomes	Rümelin A, Dörr, S, Depta A, Fauth U (2001) Preoperative oral ascorbic acid (AA) and postoperative plasma levels of AA. Clin Nutr 20 (suppl 3):47
25	Elective surgery pts	Watters JM, Vallerand A, Kirkpatrick SM, Abbott HE, Norris S, Wells G, Barber GG (2002) Limited effects of micronutrient supplementation on strength and physical function after abdominal aortic aneurysmectomy. Clin Nutr 21:321-327
26	Elective surgery pts	Angdin M, Settergren G, Starkopf J, Zilmer M, Zilmer K, Vaage J. Protective effect of antioxidants on pulmonary endothelial function after cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2003 Jun;17(3):314-20.
27	Not ICU pts	Lassnigg A, Punz A, Barker R, Keznickl P, Manhart N, Roth E, Hiesmayr M. Influence of intravenous vitamin E supplementation in cardiac surgery on oxidative stress: a double-blinded, randomized, controlled study. Br J Anaesth. 2003 Feb;90(2):148-54.
28	Elective surgery & cancer pts	Bartels M, Biesalski HK, Engelhart K, Sendlhofer G, Rehak P, Nagel E. Pilot study on the effect of parenteral vitamin E on ischemia and reperfusion induced liver injury: a double blind, randomized, placebo-controlled trial. Clin Nutr. 2004 Dec;23(6):1360-70.
29	Meta-analysis	Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005 Mar;31(3):327-37.
30	Not ICU pts	Ullegaddi R, Powers HJ, Gariballa SE. Antioxidant supplementation with or without B-group vitamins after acute ischemic stroke: a randomized controlled trial. JPEN J Parenter Enteral Nutr. 2006 Mar-Apr;30(2):108-14.
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.
33	Elective surgery pts	Matzi V, Lindenmann J, Muench A, Greilberger J, Juan H, Wintersteiger R, Maier A, Smolle-Juettner FM. The impact of preoperative micronutrient supplementation in lung surgery. A prospective randomized trial of oral supplementation of combined alpha-ketoglutaric acid and 5-hydroxymethylfurfural. Eur J Cardiothorac Surg. 2007 Nov;32(5):776-82. Epub 2007 Sep 4.
34	Not ICU patients, used NAC in combination	Siriwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, Hardman JG, Jamdar S. Randomised, double blind, placebo controlled trial of intravenous antioxidant (n-acetylcysteine, selenium, vitamin C) therapy in severe acute pancreatitis. Gut. 2007 Oct;56(10):1439-44. Epub 2007 Mar 13.

35	Elective surgery pts	van Stijn MF, Ligthart-Melis GC, Boelens PG, Scheffer PG, Teerlink T, Twisk JW, Houdijk AP, van Leeuwen PA. Antioxidant enriched enteral nutrition and oxidative stress after major gastrointestinal tract surgery. World J Gastroenterol. 2008 Dec 7;14(45):6960-9.
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.
37	Not ICU pts	Bansal D, Bhalla A, Bhasin DK, Pandhi P, Sharma N, Rana S, Malhotra S. Safety and efficacy of vitamin-based antioxidant therapy in patients with severe acute pancreatitis: a randomized controlled trial. Saudi J Gastroenterol. 2011 May-Jun;17(3):174-9.
38	Systematic review	Visser J, Labadarios D, Blaauw R. Micronutrient supplementation for critically ill adults: a systematic review and meta-analysis. Nutrition. 2011 Jul-Aug;27(7-8):745-58.
39	Not ICU pts	Moreno C. Langlet P. Hittelet A. Lasser L. Degre D. Evrard S. Colle I. Lemmers A. Deviere J. Le Moine O. Journal of Hepatology. 2010;53(6):1117-22
40	Meta-analyses	Huang TS, Shyu YC, Chen HY, Lin LM, Lo CY, Yuan SS, Chen PJ. Effect of Parenteral Selenium Supplementation in Critically III Patients: A Systematic Review and Meta-Analysis. PLoS One. 2013;8(1):e54431.
41	Not a RCT	Kočan L, Vašková J, Vaško L, Simonová J, Simon R, Firment J. Selenium adjuvant therapy in septic patients selected according to Carrico index. Clin Biochem. 2014 Oct;47(15):44-50.
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 III Patients. Int J Mol Sci. 2017 Apr 3;18(4). pii: E759.