Vitamins and Trace Elements:

Are they relevant in the critically ill?

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Wat doen jullie?

- welke supplementen?
- wanneer?
- bij EN/bij PN?

Pharmaconutrition
Immune-modulating feeds

What do you mean?

Fish oil

Glutamine

Arginine

Antioxydants

Vitamins

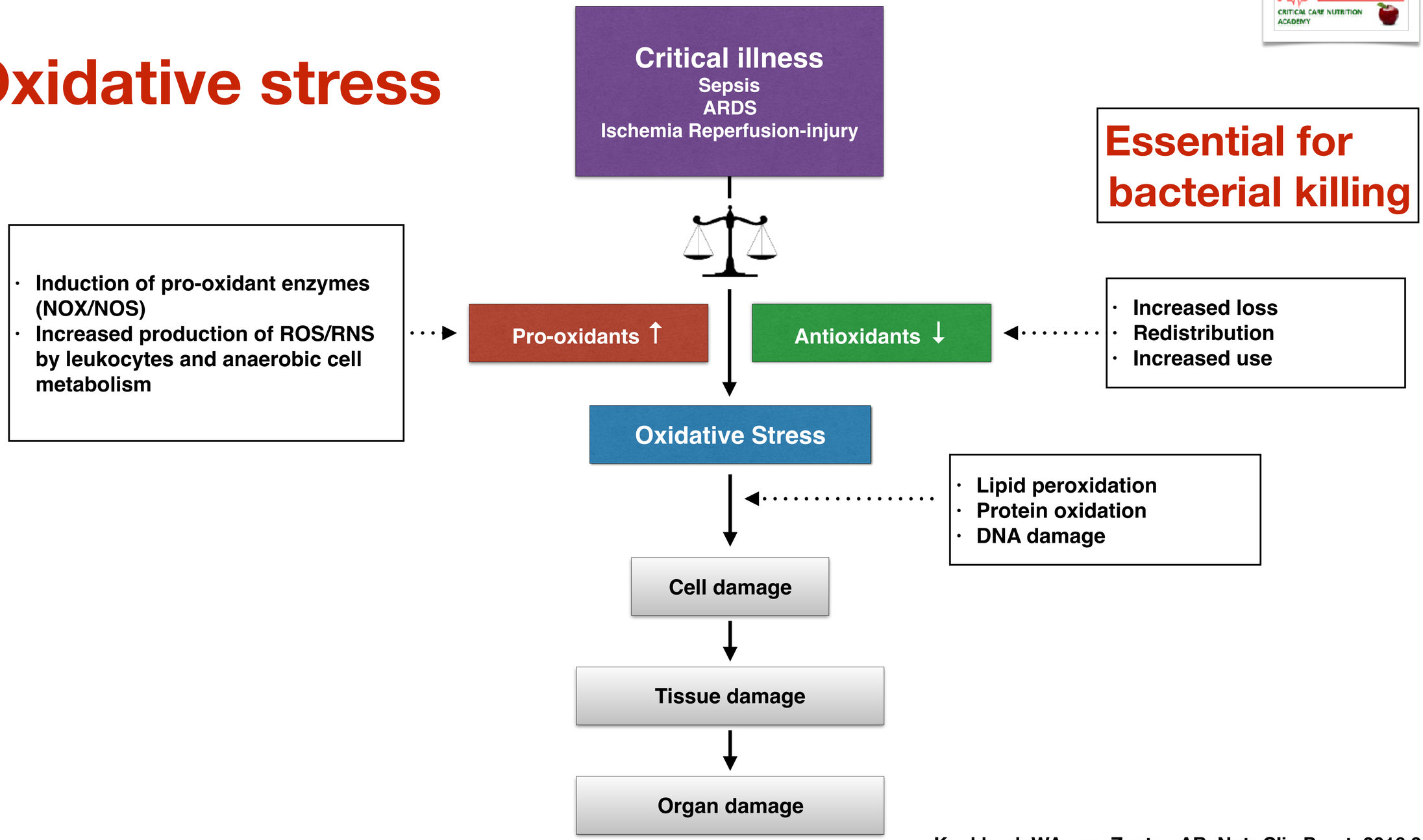
Selenium

Why not mix it?

Critical illness is a state of immunosuppression and inflammation.

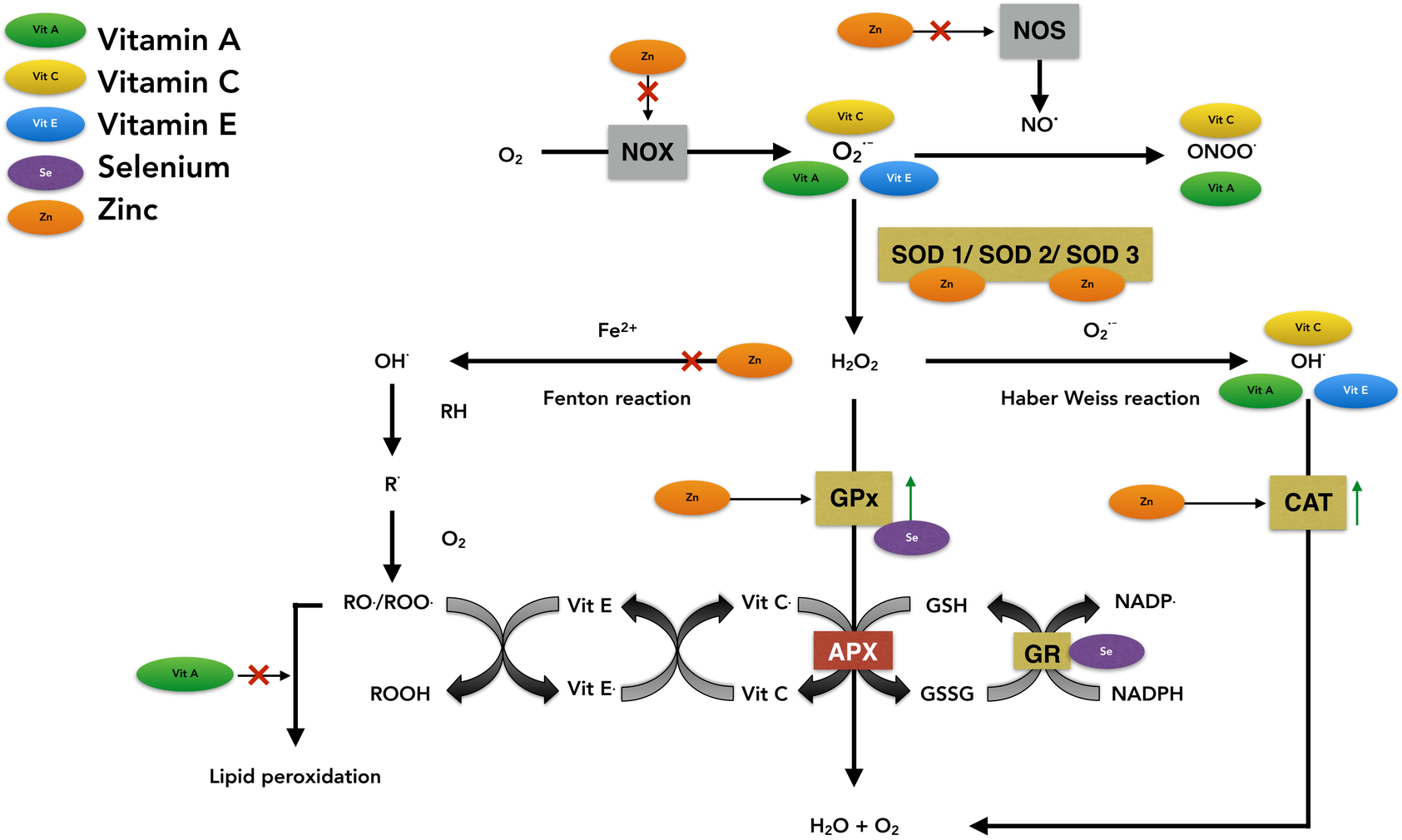
Immune modulating diets or feeds are to enhance the host immune response and/or suppress inflammation in order to improve clinically relevant outcomes such as infectious morbidity, mortality and length of stay.

Oxidative stress



Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.

Antioxidant Network: Vitamins and trace elements



Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.

Vitamin deficiency

A state or condition resulting from the lack of or inability to use one or more vitamins.

The symptoms and manifestations of each deficiency vary, depending on the specific function of the vitamin in promoting growth and development and maintaining body health.

Pharmaconutrition in ICU: Challenges

Lack of substrate

- **Are low plasma levels reflecting deficiency?**
- **Third-spacing & Protein binding**
- **Insufficient intake**

Inability to use

- **No studies on downstream effects in ICU patients**
- **Adaptive response?**

Better Outcome

- **What end point?**
- **ICU morbidity and mortality strong noise to signal ratio**

Vitamin D in critically ill

nasogastric tube 1 dose of 540 000 IU followed monthly doses of 90000 IU for 5 months

492 ICU patients with vitamin D deficiency (≦20 ng/ml)

included

n=249 Vitamin D3	n=243 placebo

analysis

n=237 Vitamin D3	n=238 placebo

Primary outcome HLOS. Secondary outcomes ICU LOS, percentage of patients with 25-hydroxyvitamin D levels >30 ng/mL at day 7, hospital mortality, and 6-month mortality.

All patients

	Vit D3	Placebo	Hazard Ratio	P-value
HLOS, median	20.1	19.3		0.98
Hospital mortality (%)	28.3	35.3	0.81 [0.58-1.11]	0.18
6-months mortality	35.0	42.9	0.78 [0.58-1.09]	0.09

Amrein K et al. JAMA 2014

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Primary outcome HLOS. Secondary outcomes ICU LOS, percentage of patients with 25-hydroxyvitamin D levels >30 ng/mL at day 7, hospital mortality, and 6-month mortality.

severe vitamin D deficiency (≤12 ng/mL) subgroup analysis was specified (n=200)

	Vit D3	Placebo	Hazard Ratio	P-value
HLOS, median	20.1	19.0		0.98
Hospital mortality (%)	28.6	46.1	0.56 [0.35-0.90]	0.04
6-months mortality	34.7	50.0	0.60 [0.39-0.93]	0.12

Amrein K et al. JAMA 2014

Low Selenium plasma levels: Good or Bad in critical illness?

Se **Selenium**

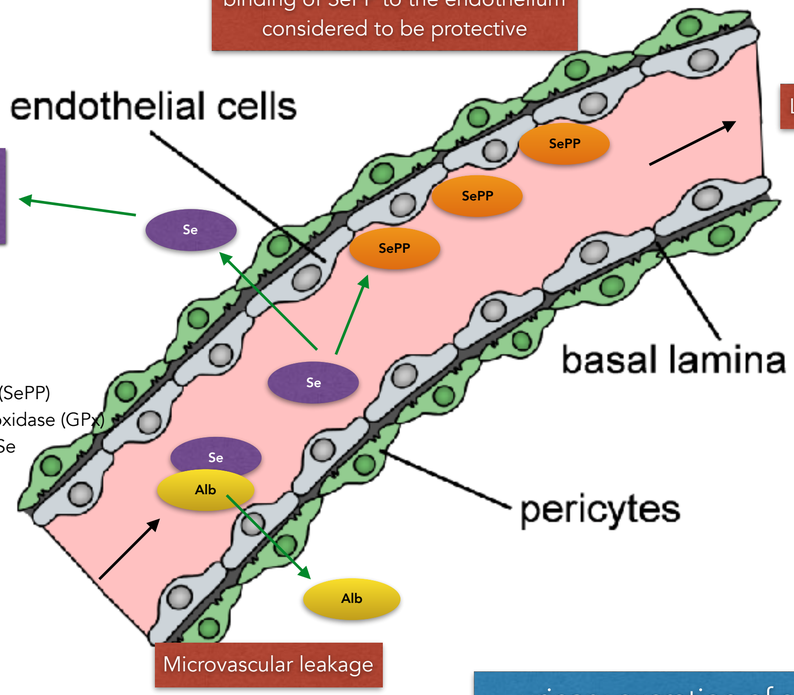
SePP **Selenoprotein P**

Alb **Albumin**

Vit C **Vitamin C**

enzymatic cofactor of over 30 selenoproteins

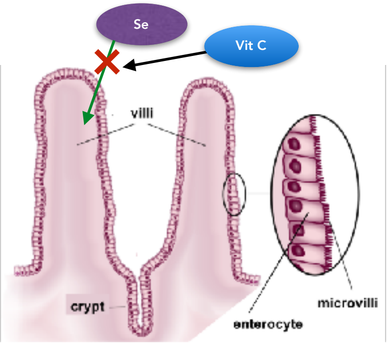
binding of SePP to the endothelium considered to be protective

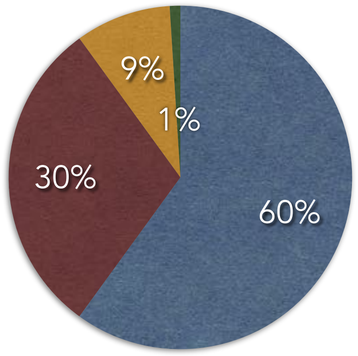


Low total plasma Se

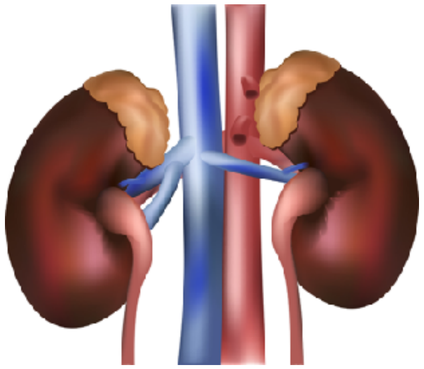
protein synthesis and immune cell proliferation

Selenium with ascorbic acid significantly lowers the enteral absorption of selenium





Selenium homeostasis is controlled by renal regulation



urinary excretion of selenium increases during a catabolic state, despite low serum selenium plasma concentrations

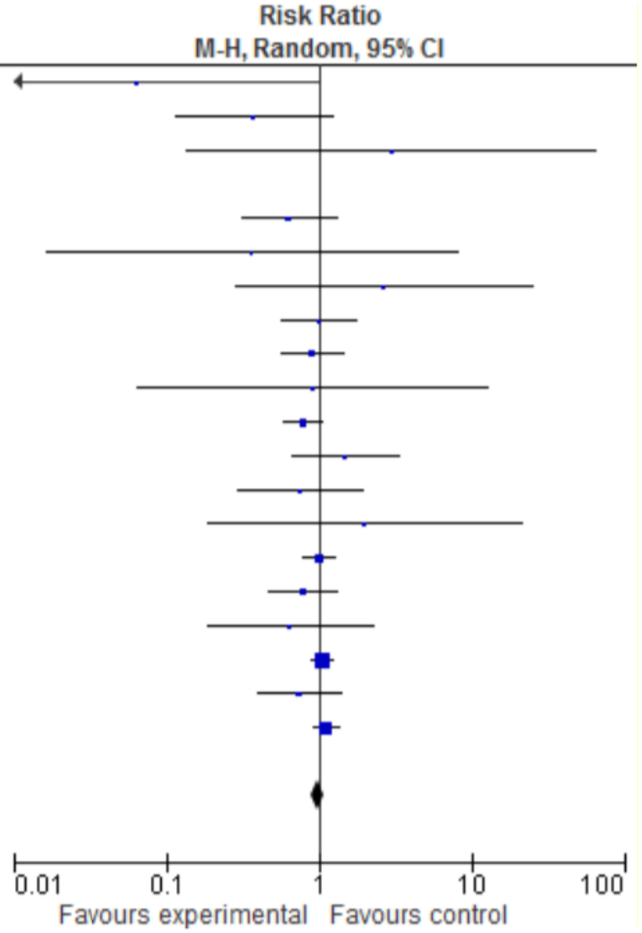
Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.

Clinical studies IV selenium, mortality

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kuklinski	0	8	8	9	0.1%	0.07 [0.00, 0.98]	1991
Zimmerman	3	20	8	20	0.6%	0.38 [0.12, 1.21]	1997
Berger 1998	1	10	0	10	0.1%	3.00 [0.14, 65.90]	1998
Porter	0	9	0	9		Not estimable	1999
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Berger 2001b	0	11	1	12	0.1%	0.36 [0.02, 8.04]	2001
Berger 2001a	2	9	1	12	0.2%	2.67 [0.28, 25.04]	2001
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Mishra	11	18	15	22	4.0%	0.90 [0.56, 1.43]	2007
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
Angstwurm 2007	46	116	61	122	10.5%	0.79 [0.60, 1.06]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
González	6	34	8	34	1.0%	0.75 [0.29, 1.93]	2009
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Andrews	84	251	84	251	14.2%	1.00 [0.78, 1.28]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Manzanares 2011	3	15	5	16	0.6%	0.64 [0.18, 2.22]	2011
Heyland	216	617	199	601	35.2%	1.06 [0.90, 1.24]	2013
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Bloos	152	543	137	546	22.0%	1.12 [0.92, 1.36]	2015
Total (95% CI)		**1962**		**1956**	**100.0%**	**0.99 [0.90, 1.08]**	
Total events	590		597				

Heterogeneity: Tau² = 0.00; Chi² = 17.89, df = 18 (P = 0.46); I² = 0%

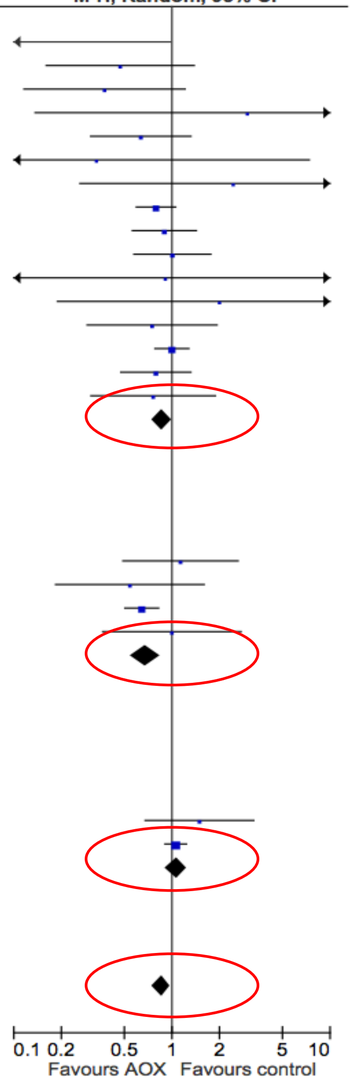
Test for overall effect: Z = 0.27 (P = 0.79)



IV selenium no effect on mortality, length of stay in ICU, hospital or mechanical ventilation. With the Bloos infection data, the effect on infections was reduced to a trend. Subgroup analyses failed to show a difference in infections between the studies of monotherapy vs combined, loading dose vs no loading dose or high vs lower dose of IV selenium supplementation.

Antioxidants in critically ill patients

Study or Subgroup	AOX Events	AOX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
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	1.5%	0.47 [0.16, 1.38]	1996
Zimmerman	3	20	8	20	1.3%	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	3.0%	0.64 [0.31, 1.32]	1999
Berger 2001b	0	11	1	11	0.2%	0.33 [0.02, 7.39]	2001
Berger 2001a	2	9	1	11	0.4%	2.44 [0.26, 22.80]	2001
Angstwurm 2007	46	116	61	122	12.7%	0.79 [0.60, 1.06]	2007
Mishra	11	18	15	22	6.5%	0.90 [0.56, 1.43]	2007
Forceville	14	31	13	29	4.8%	1.01 [0.58, 1.76]	2007
Berger 2007	1	11	1	10	0.3%	0.91 [0.07, 12.69]	2007
El-Attar	2	40	1	40	0.3%	2.00 [0.19, 21.18]	2009
González	6	34	8	34	1.9%	0.75 [0.29, 1.93]	2009
Andrews	84	251	84	251	14.9%	1.00 [0.78, 1.28]	2010
Valenta	19	75	24	75	5.6%	0.79 [0.48, 1.32]	2011
Manzanares	5	15	7	16	2.0%	0.76 [0.31, 1.89]	2011
Subtotal (95% CI)		**703**		**716**	**55.7%**	**0.86 [0.74, 0.99]**	
Total events	205		252				
Heterogeneity: Tau² = 0.00; Chi² = 12.05, df = 15 (P = 0.68); I² = 0%							
Test for overall effect: Z = 2.05 (P = 0.04)							
1.1.2 AOX via EN							
Preiser	8	20	6	17	2.4%	1.13 [0.49, 2.62]	2000
Nathens	5	301	9	294	1.5%	0.54 [0.18, 1.60]	2002
Crimi	49	112	76	112	14.9%	0.64 [0.50, 0.82]	2004
Schneider	6	29	6	29	1.7%	1.00 [0.37, 2.74]	2011
Subtotal (95% CI)		**462**		**452**	**20.4%**	**0.68 [0.54, 0.85]**	
Total events	68		97				
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 3 (P = 0.50); I² = 0%							
Test for overall effect: Z = 3.35 (P = 0.0008)							
1.1.3 AOX via PN & EN							
Porter	0	9	0	9		Not estimable	1999
Berger 2008	14	102	9	98	2.6%	1.49 [0.68, 3.29]	2008
Heyland	216	617	199	601	21.3%	1.06 [0.90, 1.24]	2012
Subtotal (95% CI)		**728**		**708**	**23.9%**	**1.07 [0.92, 1.25]**	
Total events	230		208				
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%							
Test for overall effect: Z = 0.88 (P = 0.38)							
Total (95% CI)		**1893**		**1876**	**100.0%**	**0.86 [0.75, 0.99]**	
Total events	503		557				
Heterogeneity: Tau² = 0.02; Chi² = 26.22, df = 21 (P = 0.20); I² = 20%							
Test for overall effect: Z = 2.16 (P = 0.03)							
Test for subgroup differences: Chi² = 11.26, df = 2 (P = 0.004), I² = 82.2%							



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.

Micronutrients

Dietary elements	RDA/AI	Insufficiency	Excess
Quantity elements			
Potassium	4700 mg	hypokalemia	hyperkalemia
Chlorine	2300 mg	hypochloremia	hyperchloremia
Sodium	1500 mg	hyponatremia	hypernatremia
Calcium	1300 mg	hypocalcaemia	hypercalcaemia
Phophorus	700 mg	hypophosphatemia	hyperphosphatemia
Magnesium	420 mg	Hypomagnesemia/deficiency	hypermagnesemia
Essential trace elements			
Zinc	11 mg	zinc deficiency	zinc toxicity
Iron	18 mg	anaemia	iron overload disorder
Mangenese	2.3 mg	manganese deficiency	manganism
Copper	900 µg	copper deficiency	copper toxicity
Iodine	150 µg	iodine deficiency	iodism
Selenium	55 µg	selenium deficiency	selenosis
Molybdenum	45 µg	molybdenum deficiency	

	Vitamin	RDA	Deficiency disease	Upper Level	Overdose disease
Vitamin A	Retinol, retinal, and beta-carotene	900 µg	Night-blindness, Hyperkeratosis, and Keratomalacia	3,000 µg	Hypervitaminosis A
Vitamin B1	Thiamine	1.2 mg	Beriberi, Wernicke-Korsakoff syndrome	N/D	Drowsiness or muscle relaxation with large doses.
Vitamin B2	Riboflavin	1.3 mg	Ariboflavinosis	N/D	
Vitamin B3	Niacin, niacinamide	16.0 mg	Pellagra	35.0 mg	Liver damage (doses > 2g/day) and other problems
Vitamin B5	Pantothenic acid	5.0 mg	Paresthesia	N/D	Diarrhea; possibly nausea and heartburn
Vitamin B6	Pyridoxine, pyridoxamine, pyridoxal	1.3–1.7 mg	Anemia peripheral neuropathy.	100 mg	Impairment of proprioception, nerve damage (doses > 100 mg/day)
Vitamin B7	Biotin	30.0 µg	Dermatitis, enteritis	N/D	
Vitamin B9	Folic acid, folinic acid	400 µg	Deficiency during pregnancy is associated with birth defects, such as neural tube defects	1,000 µg	May mask symptoms of vitamin B12 deficiency; other effects.
Vitamin B12	Cyanocobalamin, hydroxycobalamin, methylcobalamin	2.4 µg	Megaloblastic anemia	N/D	Acne-like rash [causality is not conclusively established].
Vitamin C	Ascorbic acid	90.0 mg	Scurvy	2,000 mg	Vitamin C megadosage
Vitamin D	Cholecalciferol	5.0 - 10 µg	Rickets and Osteomalacia	50 µg	Hypervitaminosis D
Vitamin E	Tocopherols, tocotrienols	15.0 mg	Deficiency is very rare; mild hemolytic anemia in newborn infants	1,000 mg	Increased congestive heart failure seen in one large randomized study
Vitamin K	phylloquinone, menaquinones	120 µg	Bleeding diathesis	N/D	Increases coagulation in patients taking warfarin

Verhoogde behoefte bij ernstige ziekte

Vitamine/Mineraal	RDA	Ernstige ziekte
Vit A	1000 IU	10,000 IU
Vit D	400 IU	400 IU
Vit E	M 15 IU F 12 IU	400 IU
Vit K	1 ug/kg	1mg
Vit B1	Min. 1mg/dag	10 mg
Vit B2	1.2 mg/dag	10 mg
Niacine	M 18mg , F 14 mg	200 mg
Vit B6	M 2 mg , F 1.6 mg	20 mg
Pantotheen Zuur	geschat 4-7mg	100 mg
Vit B12	2 ug/dag	20 ug
Biotine	geschat 30-100ug	5 mg
Foliumzuur	M 200ug/dag, F 180 ug/dag	2 mg
Vitamin C	60 mg	1000 mg
Selenium	M 70 ug/dag F 55ug/dag	100 ug
Zink	M 15 mg , F 12 mg	50 mg

Suppletie zonder deficiëntie bevordert geen genezing

DeBiasse en Wilmore New Horizons 1994

Characteristics of the study groups

Study group	Number	Gender	Age	APACHE II	Hospital mortality
		M : F*	± SD (years)	± SD	(n)
ICU	24	16 : 8	68 ± 8	21.2 ± 8.8	9
Medical	12	7 : 5	67 ± 9	24.8 ± 8.6	6
Surgical	12	9 : 3	70 ± 6	17.6 ± 7.7	3
Controls	18	10 : 8	67 ± 7	-	-

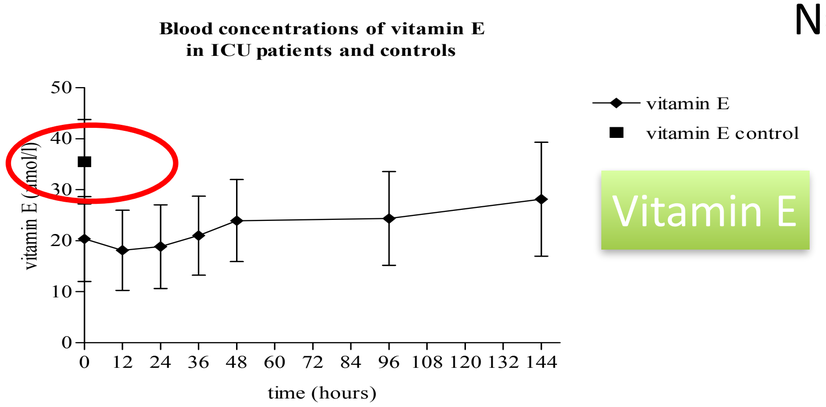
*M=Males, F=Females

Admission Serum Micronutrients

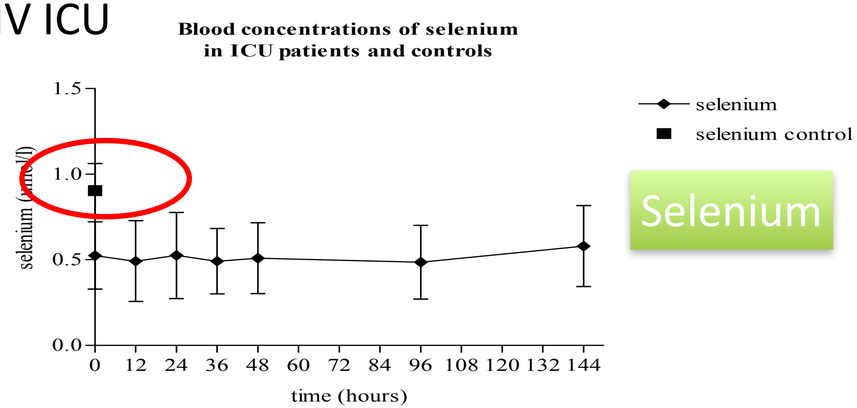
24 ICU patients & 18 age-matched controls

Micronutrient	ICU	Medical patients	Surgical patients	Controls	ICU – Controls (p-value)	Medical – Surgical (p-value)
Selenium (µmol/l)	0.52 (0.44-0.61)	0.58 (0.43-0.72)	0.47 (0.38-0.57)	0.90 (0.83-0.98)	<0.0001	0.21
B-Carotene (µmol/l)	0.19 (0.13-0.24)	0.21 (0.12-0.31)	0.16 (0.09-0.22)	0.44 (0.34-0.54)	<0.0001	0.29
Vitamin C (µmol/l)	22 (15-29)	18 (8-28)	27 (16-38)	47 (35-60)	0.0004	0.18
Vitamin E (µmol/l)	20 (17-24)	21 (16-26)	20 (14-25)	36 (31-40)	<0.0001	0.67
Vitamin B_1 (nmol/l)	138 (122-153)	140 (118-162)	136 (111-160)	123 (112-134)	0.12	0.78
Vitamin B_6 (nmol/l)	50 (40-60)	49 (36-62)	51 (35-68)	50 (41-59)	0.98	0.79

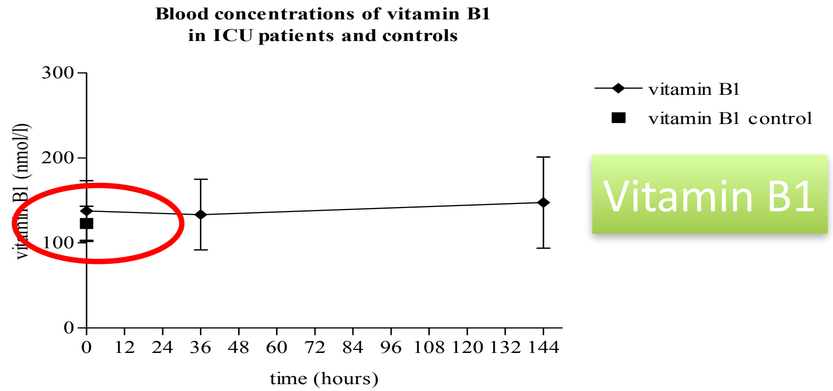
N=24 MV ICU



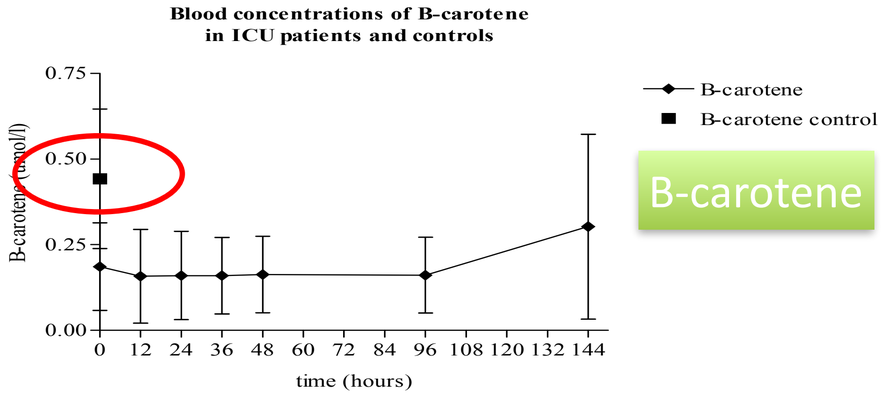
Vitamin E



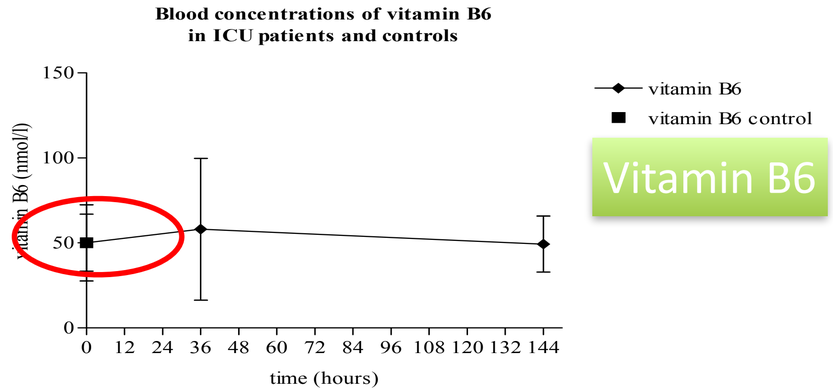
Selenium



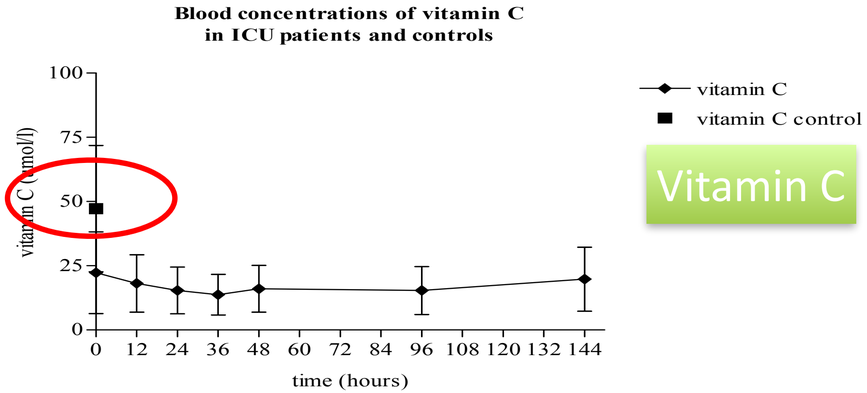
Vitamin B1



B-carotene



Vitamin B6



Vitamin C

Recommended daily allowances in adult ICU patients

Micro-nutrient (MN)	RDA for oral feeding (daily)[144,145]	Recommendations for PN			Proposed supplements (in addition to MNs provided by feeding)		
		AMA 1979[146,147]	Shenkin 1995[148]	FDA 2000[149]	Berger 2006[41] Major trauma (5d)	Berger 2006[41] Major burns (14-21d)	Fuhrman 2002 (/d)[150]
Vitamin C (mg)	60	100	100	200	1000 (IV)	1000 (IV)	500 – 3000
Vitamin E (mg)	8 – 10	10	10	10	100 (EN)	100 (EN)	400 (IV) 40 – 1000 (EN)
Selenium (µg)	55 – 70	30 – 60	60	-	300 (IV)	500 (IV)	100 – 400
Zinc (mg)	12 – 15	2.5 – 4	6.5	-	20 (IV)	30 (IV)	10 – 30
Copper (mg)	2	0.5 – 1.5	1.3	-	-	4 (IV)	-

AMA: American Medical Association; d: day; EN: Enteral nutrition; FDA: Food and Drug Administration; IV: Intravenous; MN: Micronutrient; PN: Parenteral nutrition; RDA: Recommended dietary allowance

Visser J. Nutrition 2011; 27(7-8):745-58.

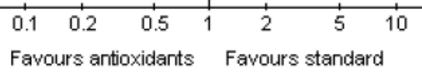
Antioxydants vitamins and trace elements

selenium, copper, zinc, vit. A, C & E, N-acetylcysteine

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

Study or sub-category	Antioxidants n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Kuklinski	0/8	8/9		0.40	0.07 [0.00, 0.98]	1991
Young	4/33	9/35		2.45	0.47 [0.16, 1.38]	1996
Zimmerman	3/20	8/20		2.07	0.38 [0.12, 1.21]	1997
Berger '98	1/10	0/10		0.31	3.00 [0.14, 65.90]	1998
Angstwurm	7/21	11/21		5.18	0.64 [0.31, 1.32]	1999
Porter	0/9	0/9			Not estimable	1999
Preiser	8/20	6/17		3.98	1.13 [0.49, 2.62]	2000
Berger 2001a	2/9	1/12		0.58	2.67 [0.28, 25.04]	2001
Berger 2001b	0/11	1/12		0.30	0.36 [0.02, 8.04]	2001
Nathens	5/301	9/294		2.43	0.54 [0.18, 1.60]	2002
Crimi	49/112	76/112		31.62	0.64 [0.50, 0.82]	2004
Angstwurm 2007	46/116	61/122		25.54	0.79 [0.60, 1.06]	2007
Berger 2007	1/11	1/10		0.42	0.91 [0.07, 12.69]	2007
Forceville	14/31	13/29		8.45	1.01 [0.58, 1.76]	2007
Mishra	11/18	15/22		11.72	0.90 [0.56, 1.43]	2007
Berger 2008	14/102	9/98		4.45	1.49 [0.68, 3.29]	2008
Total (95% CI)	832	832		100.00	0.76 [0.64, 0.91]	

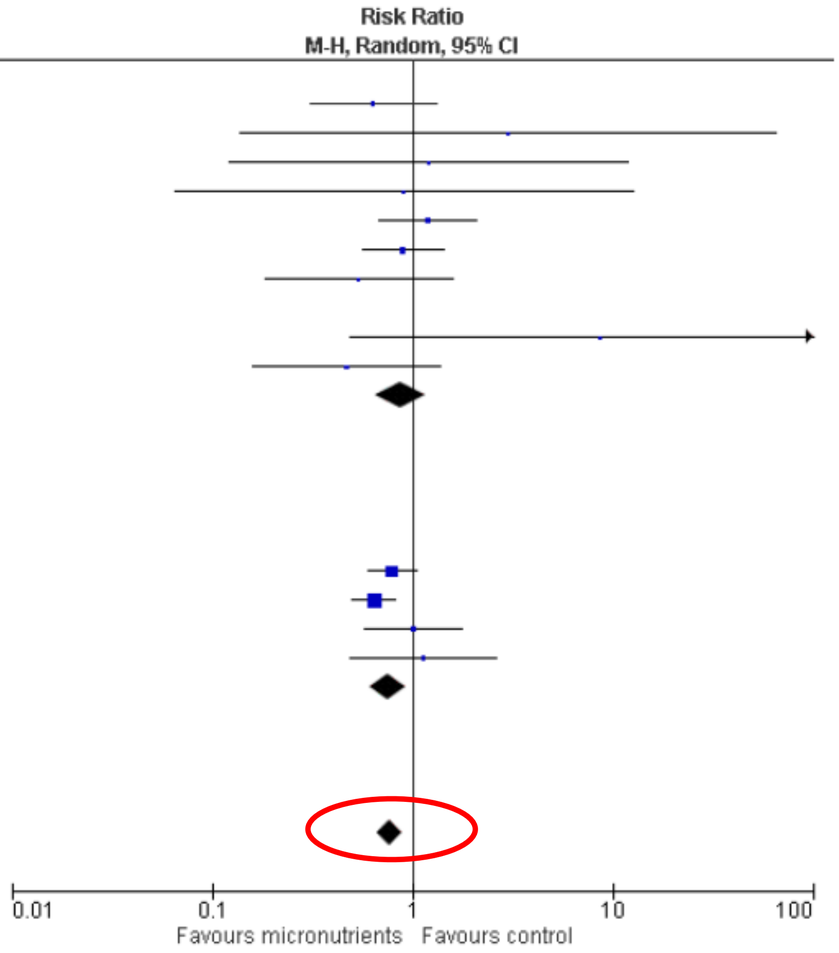
Total events: 165 (Antioxidants), 228 (standard)
Test for heterogeneity: Chi² = 15.10, df = 14 (P = 0.37), I² = 7.3%
Test for overall effect: Z = 3.09 (P = 0.002)



Lower mortality and shorter duration mechanical ventilation

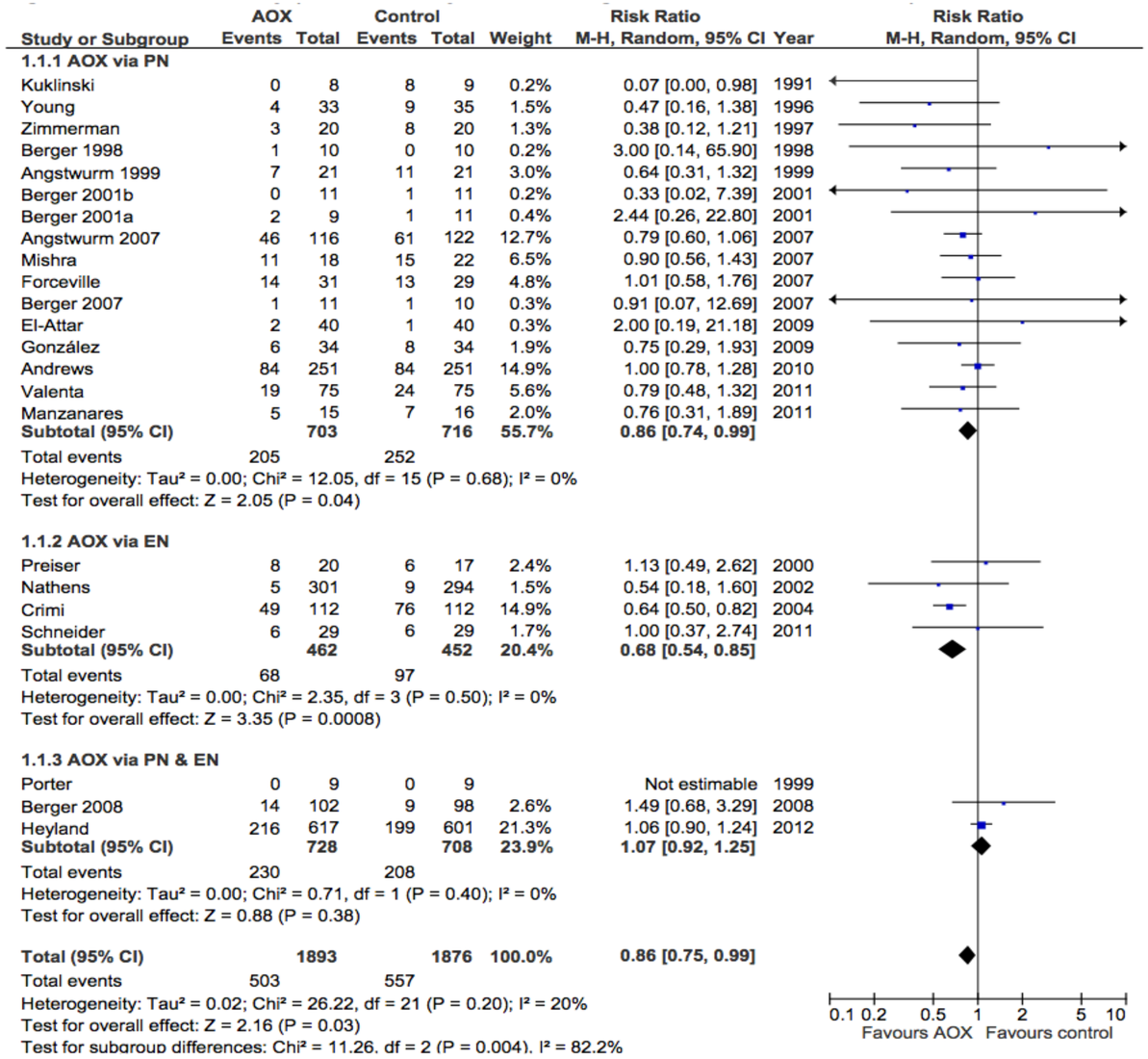
Micronutrient supplementation in ICU patients: mortality

Study or Subgroup	Micronutrients Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Hospital						
Angstwurm 1999	7	21	11	21	4.1%	0.64 [0.31, 1.32]
Berger 1998	1	10	0	10	0.2%	3.00 [0.14, 65.90]
Berger 2001	2	20	1	12	0.4%	1.20 [0.12, 11.87]
Berger 2007	1	11	1	10	0.3%	0.91 [0.07, 12.69]
Galley 1997	11	16	8	14	7.0%	1.20 [0.69, 2.11]
Mishra 2007	11	18	15	22	10.2%	0.90 [0.56, 1.43]
Nathens 2002	5	301	9	294	1.9%	0.54 [0.18, 1.60]
Porter 1999	0	9	0	9		Not estimable
Siriwardena 2007	4	22	0	21	0.3%	8.61 [0.49, 150.72]
Young 1996	4	33	9	35	1.9%	0.47 [0.16, 1.38]
Subtotal (95% CI)		**461**		**448**	**26.3%**	**0.88 [0.66, 1.17]**
Total events	46		54			
Heterogeneity: Tau² = 0.00; Chi² = 7.14, df = 8 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
1.1.2 28 day						
Angstwurm 2007	46	116	61	122	26.9%	0.79 [0.60, 1.06]
Crimi 2004	49	112	76	112	36.6%	0.64 [0.50, 0.82]
Forceville 2007	14	31	13	29	7.0%	1.01 [0.58, 1.76]
Preiser 2000	8	20	6	17	3.1%	1.13 [0.49, 2.62]
Subtotal (95% CI)		**279**		**280**	**73.7%**	**0.76 [0.62, 0.93]**
Total events	117		156			
Heterogeneity: Tau² = 0.01; Chi² = 3.61, df = 3 (P = 0.31); I² = 17%						
Test for overall effect: Z = 2.68 (P = 0.007)						
Total (95% CI)		**740**		**728**	**100.0%**	**0.78 [0.67, 0.90]**
Total events	163		210			
Heterogeneity: Tau² = 0.00; Chi² = 11.68, df = 12 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Test for subgroup differences: Not applicable						



Visser J. Nutrition 2011; 27(7-8):745-58.

Antioxydants including selenium



Study or Subgroup	AOX Events	AOX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
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	1.5%	0.47 [0.16, 1.38]	1996
Zimmerman	3	20	8	20	1.3%	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	3.0%	0.64 [0.31, 1.32]	1999
Berger 2001b	0	11	1	11	0.2%	0.33 [0.02, 7.39]	2001
Berger 2001a	2	9	1	11	0.4%	2.44 [0.26, 22.80]	2001
Angstwurm 2007	46	116	61	122	12.7%	0.79 [0.60, 1.06]	2007
Mishra	11	18	15	22	6.5%	0.90 [0.56, 1.43]	2007
Forceville	14	31	13	29	4.8%	1.01 [0.58, 1.76]	2007
Berger 2007	1	11	1	10	0.3%	0.91 [0.07, 12.69]	2007
El-Attar	2	40	1	40	0.3%	2.00 [0.19, 21.18]	2009
González	6	34	8	34	1.9%	0.75 [0.29, 1.93]	2009
Andrews	84	251	84	251	14.9%	1.00 [0.78, 1.28]	2010
Valenta	19	75	24	75	5.6%	0.79 [0.48, 1.32]	2011
Manzanares	5	15	7	16	2.0%	0.76 [0.31, 1.89]	2011
Subtotal (95% CI)		**703**		**716**	**55.7%**	**0.86 [0.74, 0.99]**	
Total events	205		252				
Heterogeneity: Tau² = 0.00; Chi² = 12.05, df = 15 (P = 0.68); I² = 0%							
Test for overall effect: Z = 2.05 (P = 0.04)							
1.1.2 AOX via EN							
Preiser	8	20	6	17	2.4%	1.13 [0.49, 2.62]	2000
Nathens	5	301	9	294	1.5%	0.54 [0.18, 1.60]	2002
Crimi	49	112	76	112	14.9%	0.64 [0.50, 0.82]	2004
Schneider	6	29	6	29	1.7%	1.00 [0.37, 2.74]	2011
Subtotal (95% CI)		**462**		**452**	**20.4%**	**0.68 [0.54, 0.85]**	
Total events	68		97				
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 3 (P = 0.50); I² = 0%							
Test for overall effect: Z = 3.35 (P = 0.0008)							
1.1.3 AOX via PN & EN							
Porter	0	9	0	9		Not estimable	1999
Berger 2008	14	102	9	98	2.6%	1.49 [0.68, 3.29]	2008
Heyland	216	617	199	601	21.3%	1.06 [0.90, 1.24]	2012
Subtotal (95% CI)		**728**		**708**	**23.9%**	**1.07 [0.92, 1.25]**	
Total events	230		208				
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%							
Test for overall effect: Z = 0.88 (P = 0.38)							
Total (95% CI)		**1893**		**1876**	**100.0%**	**0.86 [0.75, 0.99]**	
Total events	503		557				
Heterogeneity: Tau² = 0.02; Chi² = 26.22, df = 21 (P = 0.20); I² = 20%							
Test for overall effect: Z = 2.16 (P = 0.03)							
Test for subgroup differences: Chi² = 11.26, df = 2 (P = 0.004), I² = 82.2%							

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.

Use of antioxydants in this septic pancreatitis patient may be considered

Antioxydants/vitamins/trace elements/selenium

- Consider to use Antioxydants/vitamins/trace elements/selenium in all ICU patients
- RDA is available in 1500 mL of EN
- Many patients do not reach this targets for days

vitamins&trace elements during CVVH

- water soluble vitamins and trace elements are lost into ultra filtrate
- depending on UF production and filter
- suggestion: double in dosages for normal patients.

ESPEN ICU guidelines

- **Recommendation 34: To enable substrate metabolism, micronutrients (i.e. trace elements and vitamins) should be provided daily with PN.**

- **Grade of recommendation: B – strong consensus (100 % agreement)**

- **Recommendation 35: Antioxidants as high dose monotherapy should not be administered without proven deficiency.**

- **Grade of recommendation: B – strong consensus (96 % agreement)**

ESPEN ICU guidelines

- **Recommendation 36: In critically ill patients with measured low plasma levels (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) vitamin D3 can be supplemented.**

- **Grade of recommendation: GPP- consensus (86 % agreement)**

- **Recommendation 37: In critically ill patients with measured low plasma levels (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) a high dose of vitamin D3 (500,000 UI) as a single dose can be administered within a week after admission.**

- **Grade of recommendation: 0 – consensus (86 % agreement)**

Conclusions

- Micronutrient targets in ICU patients are unknown
- Many ICU patients have low ICU admission micronutrient levels
- During the first days intake of micronutrients is insufficient
- Supplementation of multivitamins and trace elements can be used to meet RDA
- Use of pharmacological dosages is unclear
- Supplements can be provided IV or enteral