Is there still a place for antioxidants in the ICU?

Egle Belousoviene MD, PhD

BaltanestIC, 29th September 2023, Tartu


OXYGEN
IS A
BIG DEAL!

Invited Review

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Antioxidant Vitamins and Trace Elements in Critical Illness

W. A. C. (Kristine) Koekkoek, MD[1]; and Arthur R. H. van Zanten, MD, PhD[1]

Nutrition in Clinical Practice
Volume XX Number X
Month 201X 1–18

DOI: 10.1177/0884533616653832
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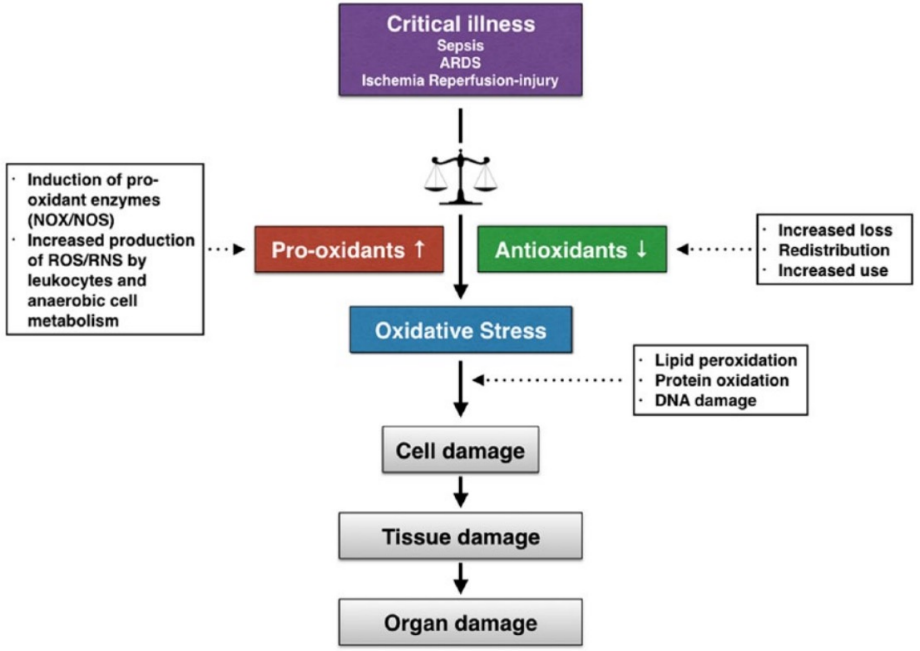

Invited Review

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Antioxidant Vitamins and Trace Elements in Critical Illness

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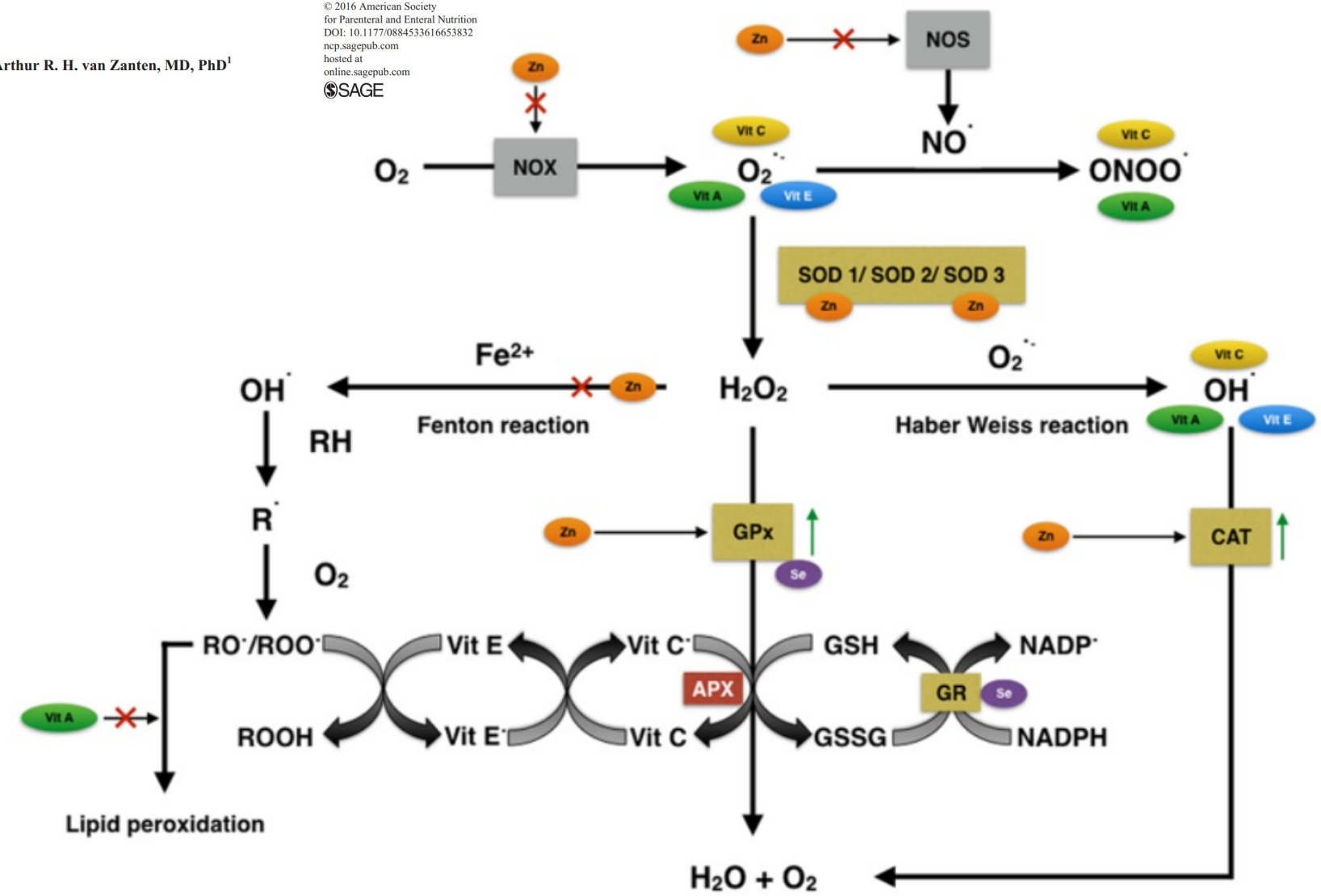
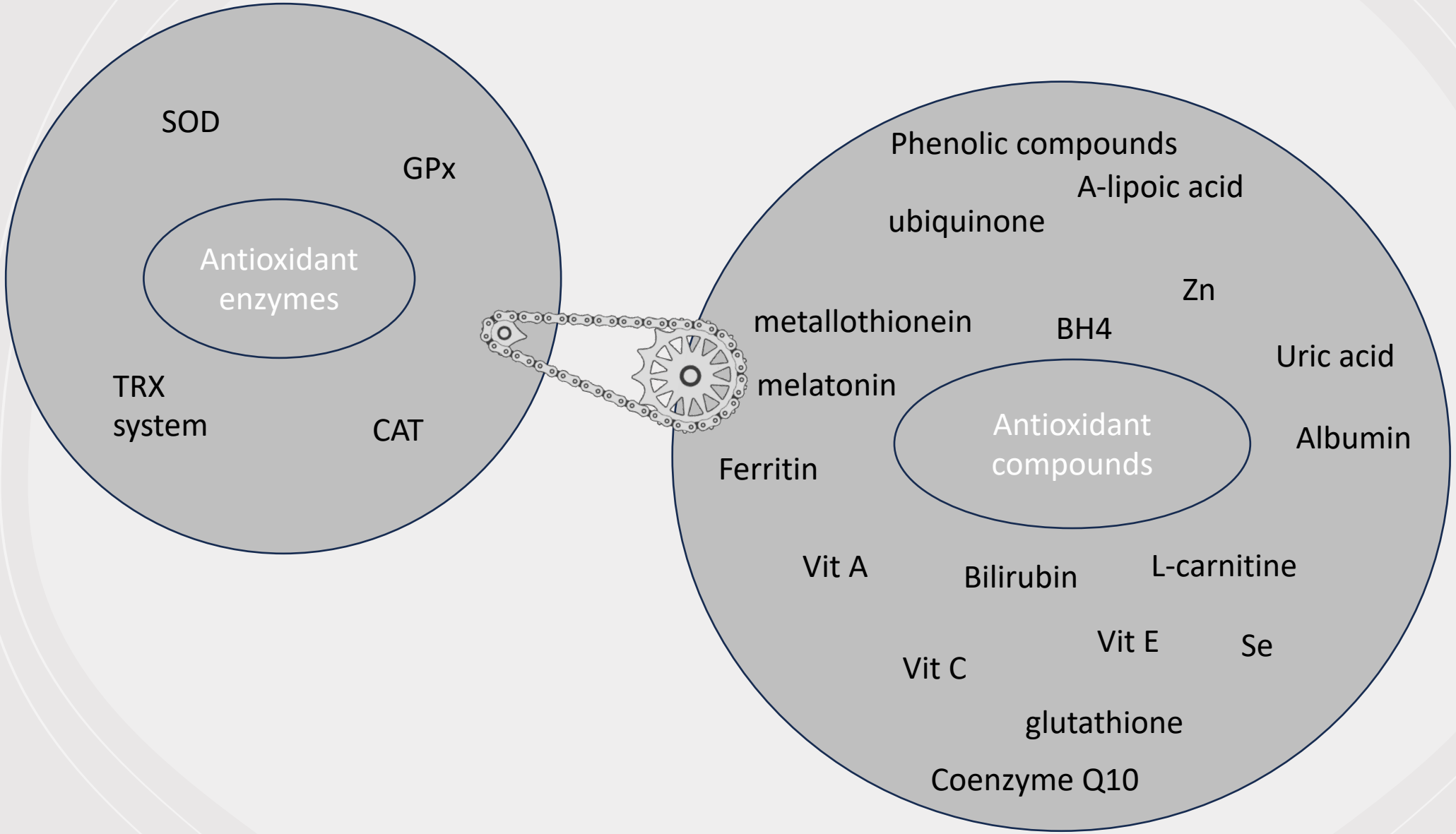



SOD
GPx
Antioxidant enzymes
TRX system
CAT
Phenolic compounds
A-lipoic acid
ubiquinone
Zn
metallothionein
BH4
Uric acid
melatonin
Antioxidant compounds
Albumin
Ferritin
Vit A
Bilirubin
L-carnitine
Vit E
Se
Vit C
glutathione
Coenzyme Q10


NOTHING
CURES ALL ILLS

Antioxidant

Free radical

Healthy cell

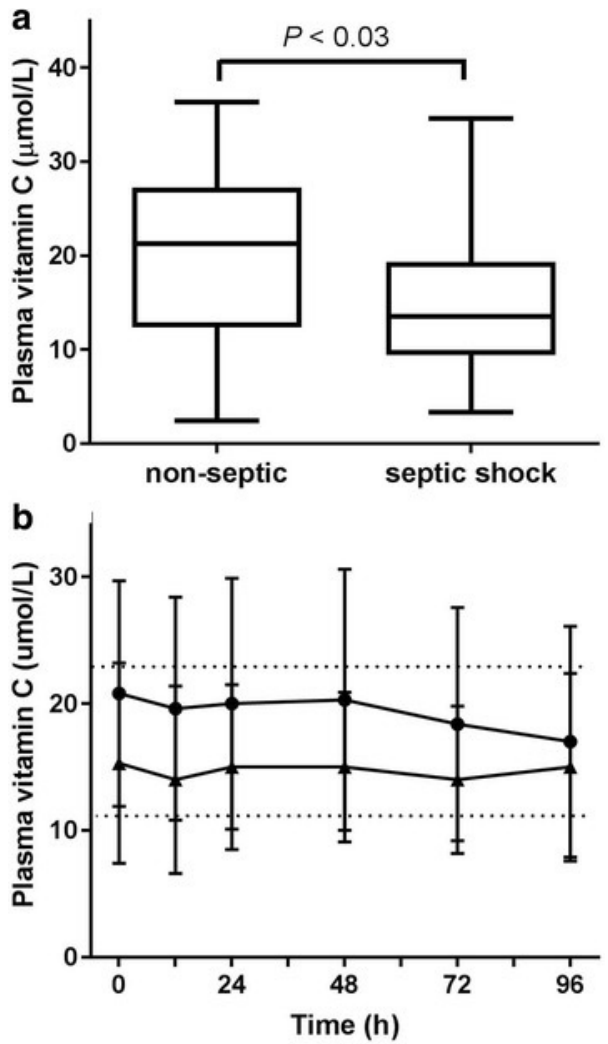
- 13g/d → 100g/d

Crit Care. 2017; 21: 300.
Published online 2017 Dec 11. doi: 10.1186/s13054-017-1891-y
PMCID: PMC5725835
PMID: 29228951

Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes

Anitra C. Carr,[1] Patrice C. Rosengrave,[1] Simone Bayer,[1] Steve Chambers,[1] Jan Mehrtens,[2] and Geoff M. Shaw[2]

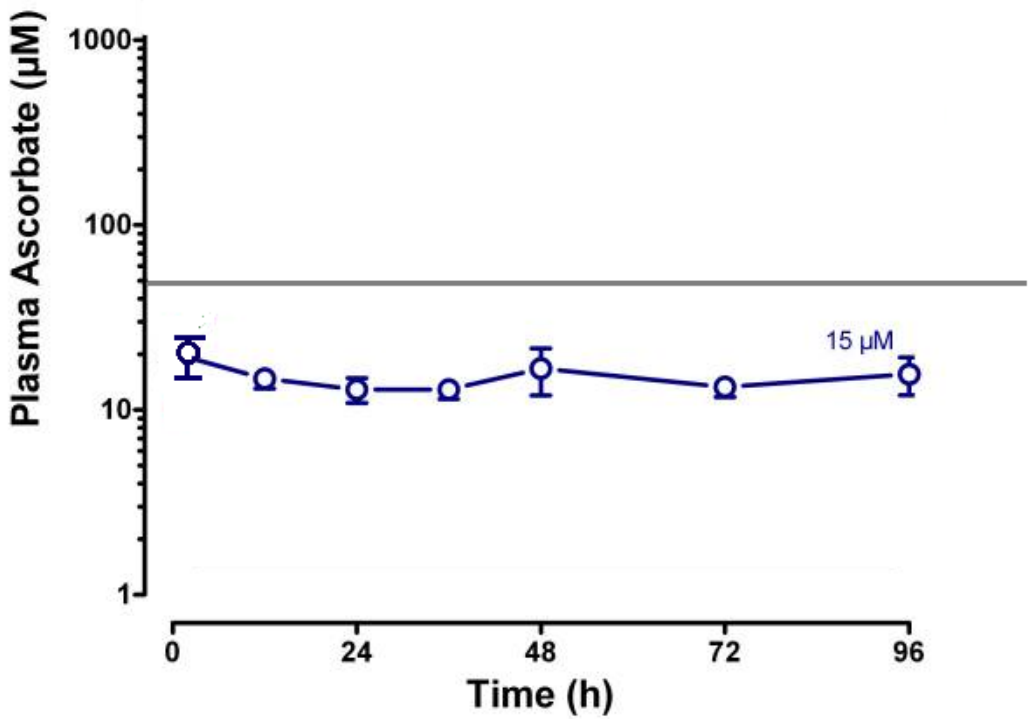
	Hypo (<23µmol/l)	Avitaminosis (<11µmol/l)
Critical illness	68%	32%
Septic shock	88%	38%



J Transl Med. 2014; 12: 32.
Published online 2014 Jan 31. doi: 10.1186/1479-5876-12-32
PMCID: PMC3937164
PMID: 24484547

Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis

Alpha A Fowler, III,[1] Aamer A Syed,[1] Shelley Knowlson,[2] Robin Sculthorpe,[3] Don Farthing,[4] Christine DeWilde,[1] Christine A Farthing,[4] Terri L Larus,[4] Erika Martin,[5] Donald F Brophy,[5] and Seema Gupta[6], Medical Respiratory Intensive Care Unit Nursing



How does it work?

- Antioxidant
- Reduces inflammatory response
- Improves the function of immunocompetent cells
- Inhibits the growth of bacteria
- Improves wound healing
- Cofactor in catecholamines and cortisol synthesis
- Increases sensitivity to catecholamines
- Maintains endothelial function
- Boosts the mood
- Reduces sensitivity to pain

	N	Duration	Dose	Adjuvants	ΔSOFA	Mortality	Time off pressors
Marik's study 2017	94	96 h	6 g/d	Thiamine Hydrocortisone	Improved	Improved	Improved
VITAMINS 2020	216	Until shock resolved	6g/d	Thiamine Hydrocortisone	Improved	No difference	No difference
ACTS 2020	205	96 h	6g/d	Thiamine Hydrocortisone	No difference	No difference	Not reported
VICTOR 2020	88	96 h	6g/d	Thiamine Hydrocortisone	No difference	No difference	Improved
ORANGES 2020	137	96 h	6g/d	Thiamine Hydrocortisone	No difference	No difference	Improved
Wani 2020	100	96 h	6g/d	Thiamine Hydrocortisone	Not reported	No difference	Improved
HYVCTTSSS 2020	80	96 h	6g/d	Thiamine Hydrocortisone	Improved	No difference	No difference
VICTAS 2021	501	96 h	6g/d	Thiamine Hydrocortisone	No difference	No difference	No difference

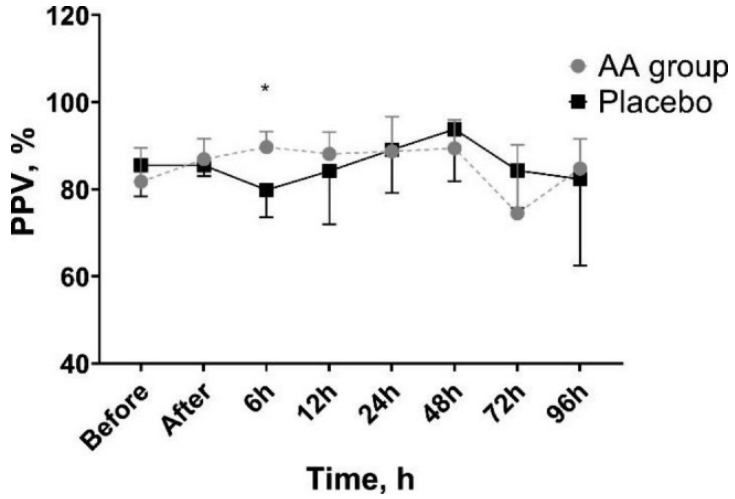
	N	Duration	Dose	Adjuvants	ΔSOFA	Mortality	Time of pressors
Phase I safety trial 2014	24	96 h	50mg/kg/d 200mg/kg/d		Improved	Not reported	Not reported
CITRIS-ALI 2019	167	96 h	200mg/kg		Improved	Improved	Not reported
ATESS 2020	111	48 h	100mgkg	Thiamine Hydrocortisone	No difference	No difference	Not reported

Research | Open Access | Published: 12 September 2023

Effect of high-dose intravenous ascorbic acid on microcirculation and endothelial glycocalyx during sepsis and septic shock: a double-blind, randomized, placebo-controlled study

Egle Belousoviene, Zivile Pranskuniene, Egle Vaitkaitiene, Vidas Pilvinis & Andrius Pranskunas

BMC Anesthesiology **23**, Article number: 309 (2023) | Cite this article

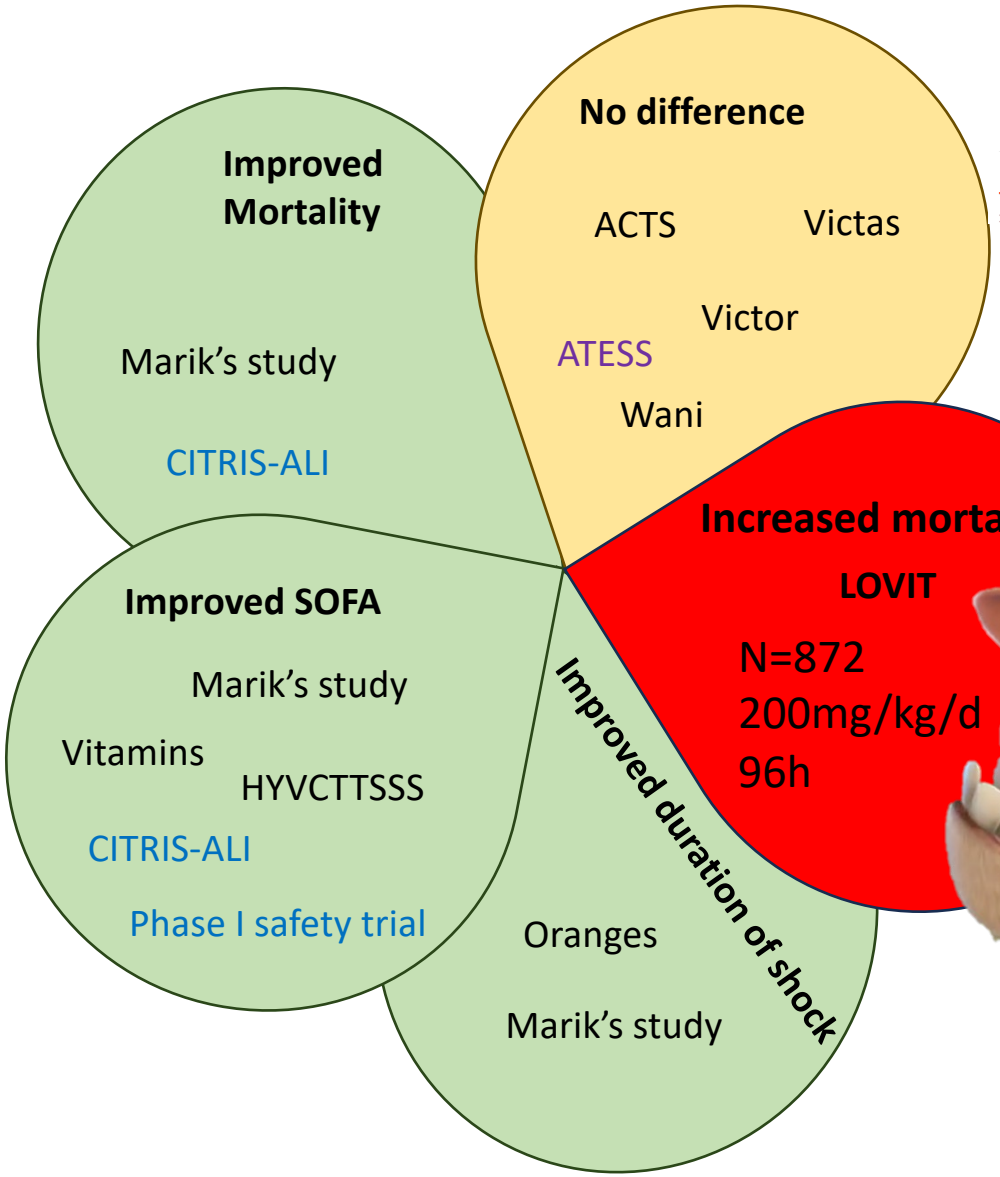


N=23

Dose 200mg/kg/d divided in 4 doses for 96 hours

Conclusion:

High-dose parenteral ascorbic acid tends to increase the proportion of perfused microvessels in the early period of sepsis and septic shock.



ORIGINAL ARTICLE

Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

François Lamontagne, M.D., Marie-Hélène Masse, M.Sc., Julie Menard, Ph.D., Sheila Sprague, Ph.D., Ruxandra Pinto, Ph.D., Daren K. Heyland, M.D., Deborah J Cook, M.D., Marie-Claude Battista, Ph.D., Andrew G. Day, M.Sc., Gordon H. Guyatt, M.D., Salmaan Kanji, Pharm.D., Rachael Parke, R.N., M.H.Sc., Ph.D., et al., for the LOVIT Investigators and the Canadian Critical Care Trials Group*

Article Figures/Media Metrics

32 References 86 Citing Articles

June 23, 2022
N Engl J Med 2022; 386:2387-2398
DOI: 10.1056/NEJMoa2200644


hulu

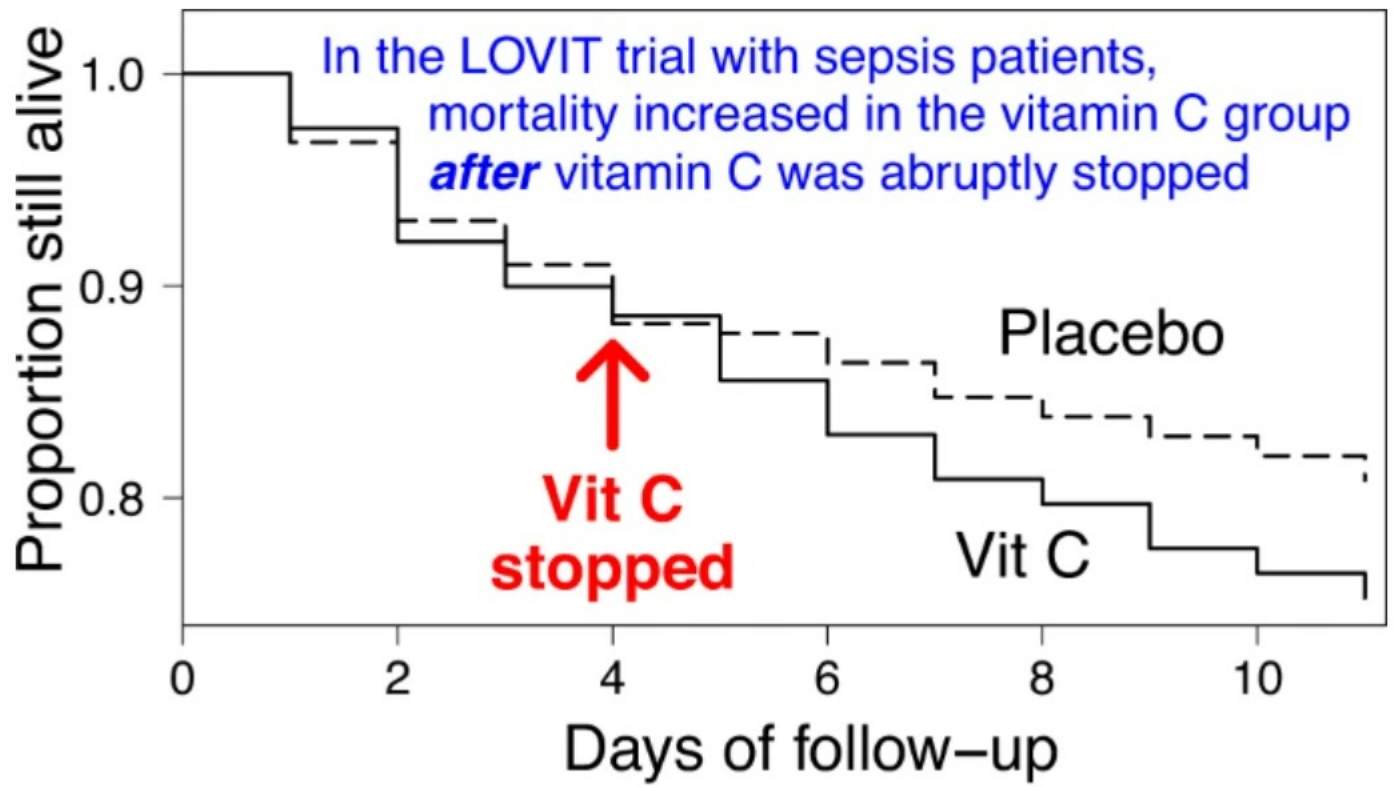
Article | Open Access | Published: 20 December 2022

Nutrition in acute and chronic diseases

Abrupt termination of vitamin C from ICU patients may increase mortality: secondary analysis of the LOVIT trial

Harri Hemilä & Elizabeth Chalker

European Journal of Clinical Nutrition **77**, 490–494 (2023) | Cite this article



IV Vitamin C in Critically Ill Patients: A Systematic Review and Meta-Analysis

Jayshil J. Patel, MD[1] Alfonso Ortiz-Reyes, MSc[2] Rupinder Dhaliwal, RD[2]

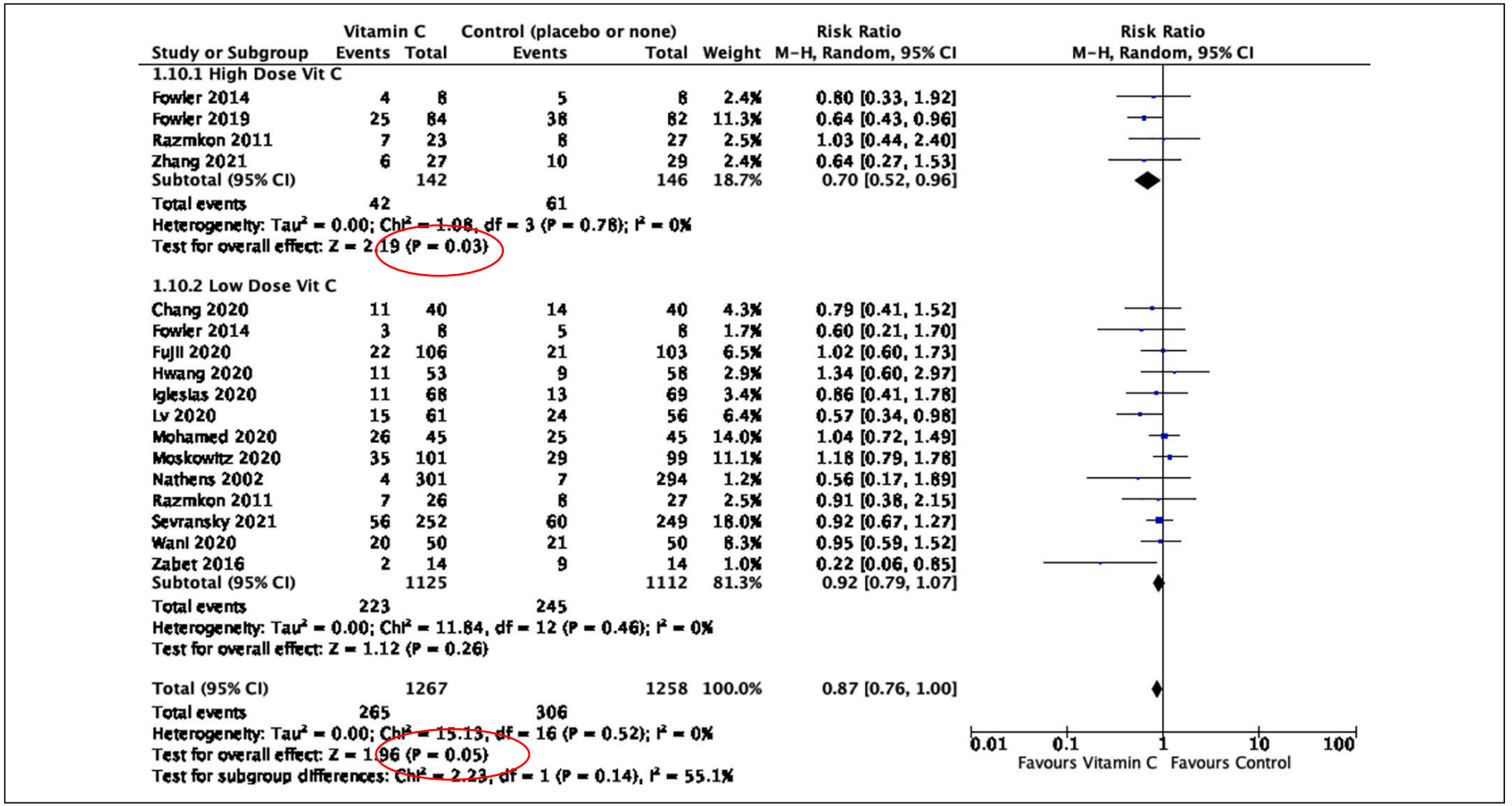


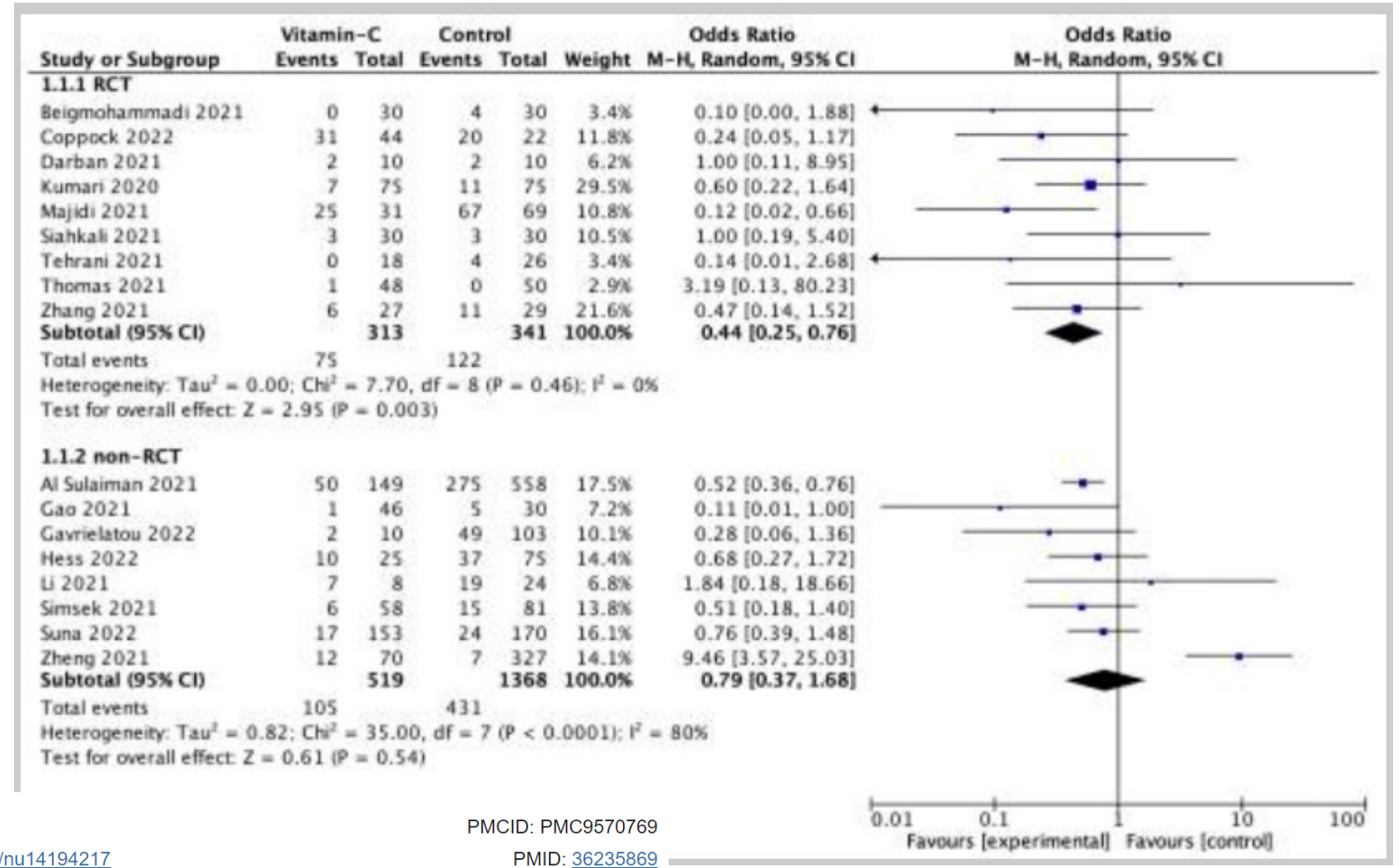
Figure 4. Meta-analysis and forest plot of overall mortality: high-dose IV vitamin C (IVVC) (≥ 10,000 mg/d) versus low-dose vitamin C (< 10,000 mg/d). *df* = degrees of freedom, M-H = Mantel-Haenszel.

March 2022 • Volume 50 • Number 3

- 21 RCT
- N=2490

Result

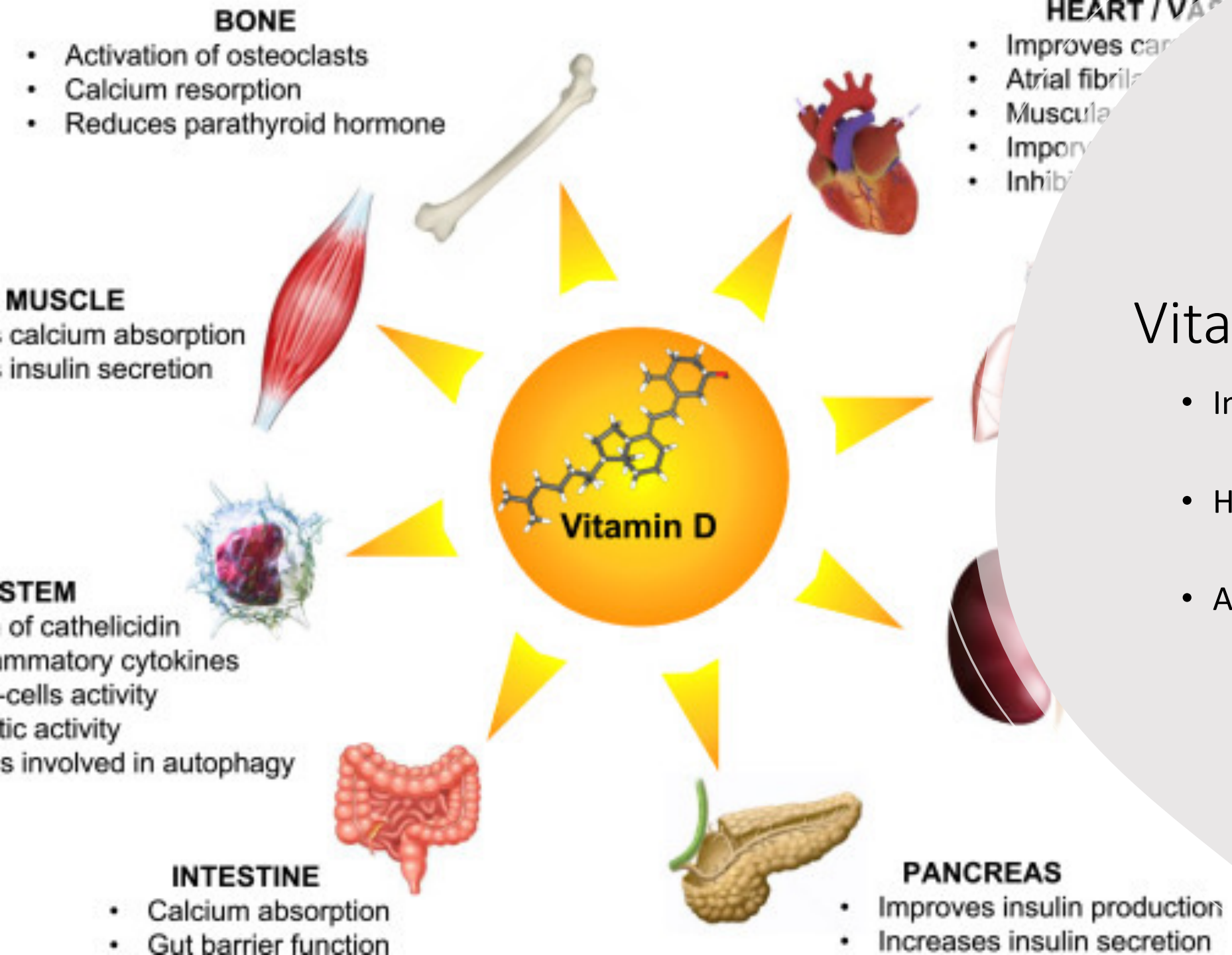
- High dose (>10g/d) of vit C decreased mortality



Nutrients. 2022 Oct; 14(19): 4217.
Published online 2022 Oct 10. doi: 10.3390/nu14194217
PMCID: PMC9570769
PMID: 36235869

Vitamin C Supplementation for the Treatment of COVID-19: A Systematic Review and Meta-Analysis

Monika Olczak-Pruc,[1] Damian Swieczkowski,[2] Jerzy R. Ladny,[3,4] Michal Pruc,[4] Raul Juarez-Vela,[5] Zubaid Rafique,[6] Frank W. Peacock,[6] and Lukasz Szarpak[6,7,*]



Vitamin D

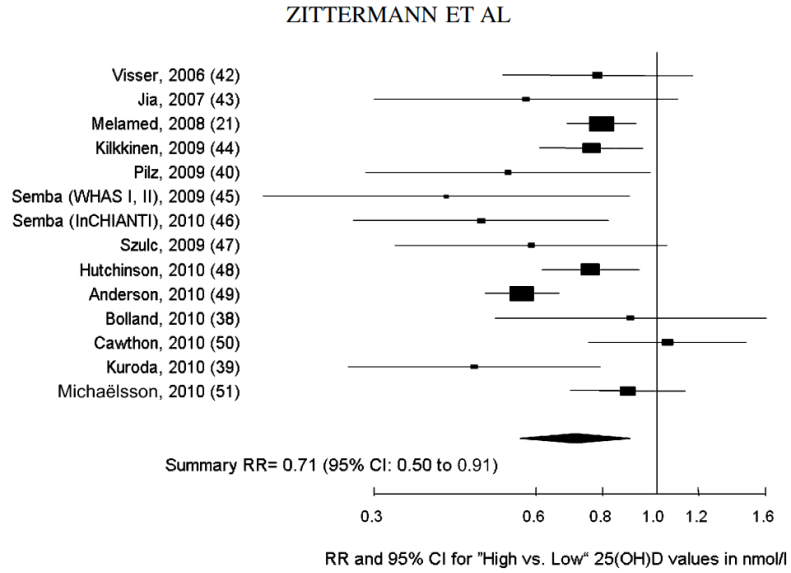
- Imunomodulator
- Hormone precursor
- Antioxidant

A paper in the Christmas edition of the *Medical Journal of Australia* posits a new theory of why, in fantasy novels, the bad guys tend to lose: Vitamin D deficiency. The authors write, "Systematic textual analysis of *The Hobbit* supports our initial hypothesis that the triumph of good over evil may be assisted to some extent by the poor diet and lack of sunlight experienced by the evil characters." In other words, a Gollumesque "aversion to sunlight ... may lead to vitamin D deficiency and hence reduced martial prowess."

Meta-Analysis > Am J Clin Nutr. 2012 Jan;95(1):91-100. doi: 10.3945/ajcn.111.014779.
Epub 2011 Dec 14.

Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies

Armin Zittermann [1], Simona Iodice, Stefan Pilz, William B Grant, Vincenzo Bagnardi, Sara Gandini



Observational Study > Crit Care Med. 2014 Jan;42(1):97-107.
doi: 10.1097/CCM.0b013e31829eb7af.

Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill

Takuhiro Moromizato [1], Augusto A Litonjua, Andrea B Braun, Fiona K Gibbons, Edward Giovannucci, Kenneth B Christopher

TABLE 2. Patient Characteristics Stratified by Serum Vitamin D

Variable	Preadmission 25-Hydroxyvitamin D			
	≤ 15 ng/mL	15–30 ng/mL	≥ 30 ng/mL	*p*
n	566	1,305	1,515	
Age, mean (SD)	61.9 (16.5)	64.9 (16.4)	68.4 (15.2)	< 0.0001[a]
Gender, *n* (%)				0.07
Male	254 (44.9)	598 (45.8)	631 (41.7)	
Female	312 (55.1)	707 (54.2)	884 (58.3)	
Race, *n* (%)				< 0.0001
Non-White	152 (26.9)	271 (20.8)	219 (14.5)	
White	414 (73.1)	1,034 (79.2)	1,296 (85.5)	
Patient type, *n* (%)				0.2
Medical	399 (70.5)	863 (66.1)	1,007 (66.5)	
Surgical	167 (29.5)	442 (33.9)	508 (33.5)	
Season 25-hydroxyvitamin D drawn, *n* (%)				0.009
Summer	128 (22.6)	331 (25.4)	421 (27.8)	
Winter	123 (21.7)	285 (21.8)	284 (18.8)	
Fall	128 (22.6)	311 (23.8)	401 (26.5)	
Spring	187 (33.0)	378 (29.0)	409 (27.0)	
Sepsis, *n* (%)	123 (21.7)	224 (17.2)	221 (14.6)	< 0.0001
Vasopressors/inotropes, *n* (%)	168 (29.7)	417 (32.0)	420 (27.7)	0.05
Mechanical ventilation, *n* (%)	98 (17.3)	217 (16.6)	152 (10.0)	< 0.0001
Deyo-Charlson index, *n* (%)				0.01
0	28 (5.0)	105 (8.1)	96 (6.3)	
1–3	115 (20.3)	253 (19.4)	260 (17.2)	
4–6	172 (30.4)	446 (34.2)	506 (33.4)	
≥ 6	251 (44.4)	501 (38.4)	653 (43.1)	
Acute Physiology and Chronic Health Evaluation II,[b] mean (SD)	23.7 (8.0)	25.7 (8.5)	23.6 (9.6)	0.06[a]

Menger et al. Critical Care (2022) 26:268
https://doi.org/10.1186/s13054-022-04139-1

REVIEW Open Access

Administration of vitamin D and its metabolites in critically ill adult patients: an updated systematic review with meta-analysis of randomized controlled trials

Johannes Menger[1], Zheng-Yii Lee[2], Quirin Notz[1], Julia Wallqvist[3], M. Shahnaz Hasan[2], Gunnar Elke[4], Martin Dworschak[5], Patrick Meybohm[1], Daren K. Heyland[6] and Christian Stoppe[1,6*]

- 16 RCT's
- N=1449
- Result:
  - ↓ mortality
  - ↓ ICU length of stay
  - ↓ Days on mechanical ventilation

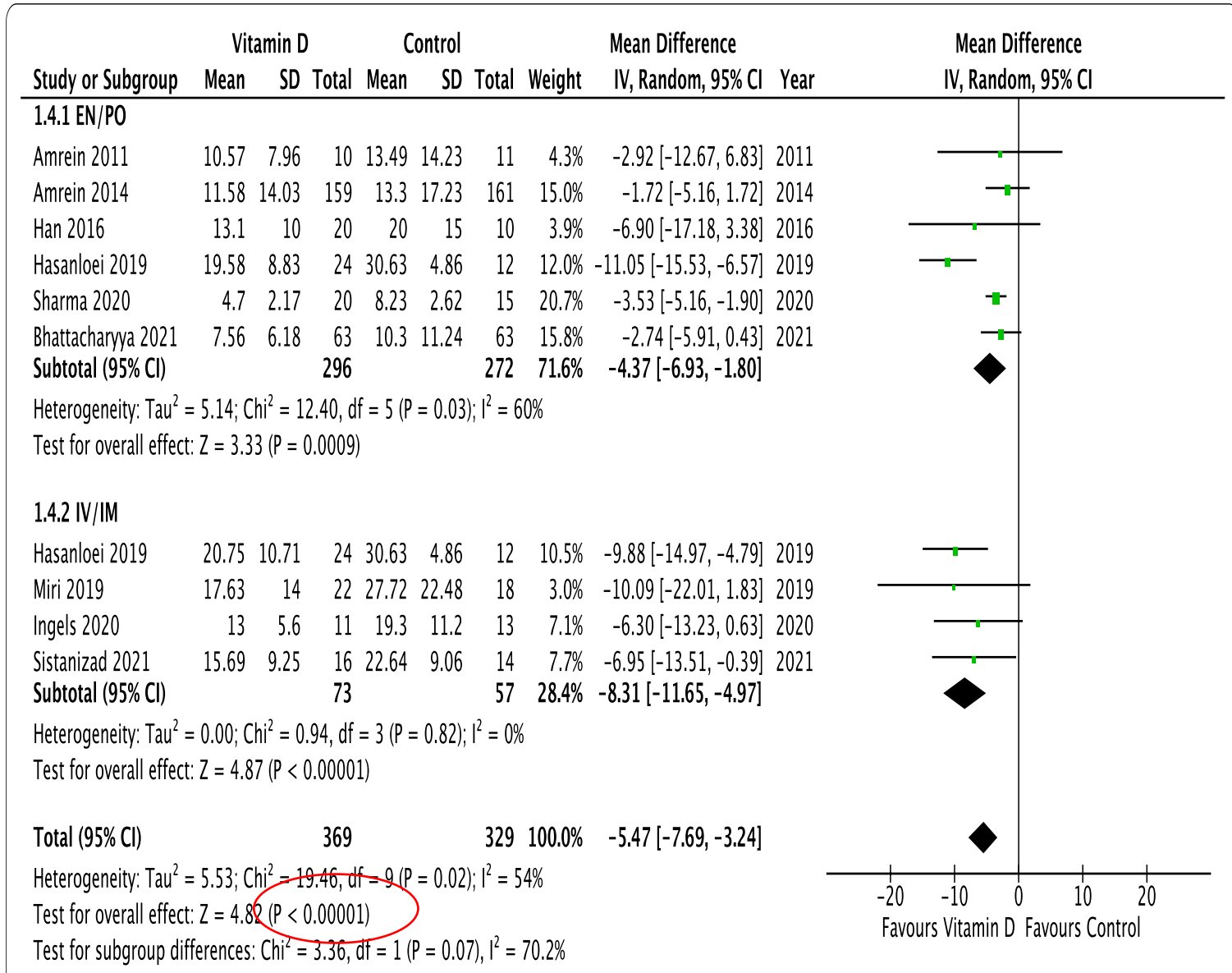


Fig. 4 Duration of mechanical ventilation in critically ill patients: vitamin D compared to placebo (or standard of care) including subgroup analysis of route of administration

- Target level of 30–40 ng/ml and a repeat 25OHD measurement after a few weeks.
- Loading dose to improve 25(OH)D levels within a few days
- Daily or weekly maintenance dose
- Usually higher doses than healthy individuals are needed.

frontiers in Medicine

Front Med (Lausanne). 2022; 9: 1083760. PMCID: PMC9885715
Published online 2023 Jan 11. doi: 10.3389/fmed.2022.1083760 PMID: 36726354

An update of the effects of vitamins D and C in critical illness

Aileen Hill,[1,2,*] Christina Starchl,[3] Ellen Dresen,[4] Christian Stoppe,[4,5] and Karin Amrein[3,*]

Alpha-tocopherol

- Essential component of the cell membrane
- Free radical scavenger
- Antiinflammatory potential
- Improves immune response
- Inhibits cell proliferation
- Regulates gene expression

Front Nutr. 2021; 8: 648442.
Published online 2021 Jun 16. doi: 10.3389/fnut.2021.648442
PMCID: PMC8241937
PMID: 34222298

The Association Between Vitamin E Deficiency and Critically Ill Children With Sepsis and Septic Shock

Hongxing Dang,[1,2,3,*] Jing Li,[1,2,3] Chengjun Liu,[1,2,3] and Feng Xu[1,2,3,*]

Crit Care Med. 1995 Apr;23(4):646-51. doi: 10.1097/00003246-199504000-00011.

Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction

H F Goode [1], H C Cowley, B E Walker, P D Howdle, N R Webster

Comparative Study > Int J Microcirc Clin Exp. 1997;17 Suppl 1:18-20. doi: 10.1159/000179262.

Oxidant-induced increase in vascular permeability is inhibited by oral administration of S-5682 (Daflon 500 mg) and alpha-tocopherol

E Bouskela [1], E Svensjö, F Z Cyrino, L Lerond

Affiliations + expand

PMID: 9477040 DOI: 10.1159/000179262

Antioxidants (Basel). 2020 Mar; 9(3): 195.
Published online 2020 Feb 26. doi: 10.3390/antiox9030195
PMCID: PMC7139367
PMID: 32110961

Differential Effects of MitoVitE, α-Tocopherol and Trolox on Oxidative Stress, Mitochondrial Function and Inflammatory Signalling Pathways in Endothelial Cells Cultured under Conditions Mimicking Sepsis

Beverley E. Minter, Damon A. Lowes,† Nigel R. Webster, and Helen F. Galley*

PLoS One. 2015; 10(8): e0134740.
Published online 2015 Aug 5. doi: 10.1371/journal.pone.0134740
PMCID: PMC4526657
PMID: 26244369

α-Tocopherol Improves Microcirculatory Dysfunction on Fructose Fed Hamsters

Beatriz C. S. Boa,* Carlos M. M. R. Barros, Maria das Graças C. Souza, Raquel C. Castiglione, Fátima Z. G. A. Cyrino, and Eliete Bouskela

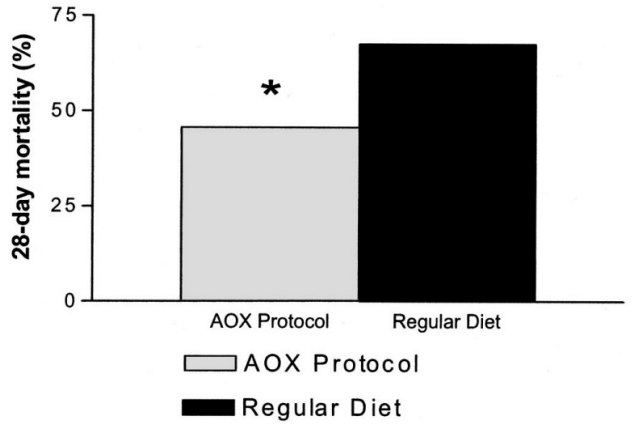


Figure 1. The 28-day mortality between groups of critically ill patients. *$P < 0.05$. AOX = antioxidant.

Table 2. Clinical Events Recorded in the Study Population

Variable	AOX protocol (n = 105)	Regular diet (n = 111)	P value
ARDS	18 (17.1%)	21 (18.9%)	NS
Multiple organ failure	22 (20.9%)	25 (22.5%)	NS
Patients requiring mechanical ventilation	79	84	
Duration of mechanical ventilation, (days) (mean ± SD)	6.2 ± 2.3	8.9 ± 1.8	0.05
Ventilator-free days (mean)	15.7	11.2	0.01
Hospital length of stay (days)	23.2	27.5	NS (0.092)

ARDS = acute respiratory distress syndrome; AOX = Antioxidant; NS = not significant.

Clinical Trial › Anesth Analg. 2004 Sep;99(3):857-863. doi: 10.1213/01.ANE.0000133144.60584.F6.

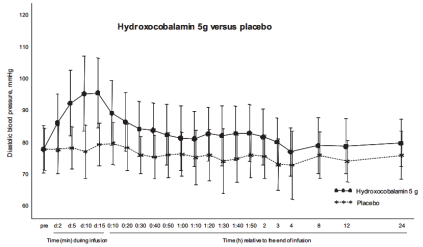
The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial

Ettore Crimi [1], Antonio Liguori, Mario Condorelli, Michele Cioffi, Marinella Astuto, Paola Bontempo, Orlando Pignalosa, Maria Teresa Vietri, Anna Maria Molinari, Vincenzo Sica, Francesco Della Corte, Claudio Napoli

- N=216 (ICU population)
- Enteral 500mg/d of ascorbic acid+400IU/d of alpha-tocopherol

Did you know ?

Rain contains vitamin B12



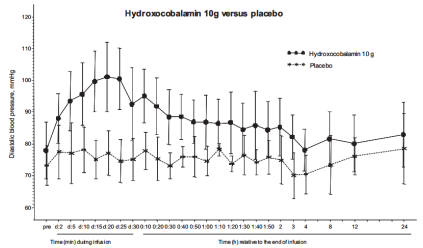
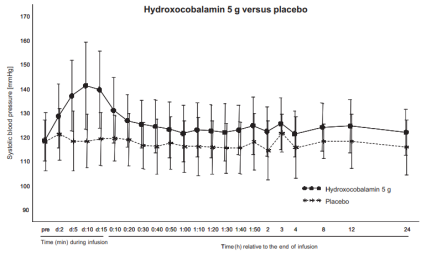


FIG. 3. Mean diastolic blood pressure in volunteers administered hydroxocobalamin (5 g or 10 g) or placebo. The predose value ("pre") is the median of 3 predose measurements obtained 20, 40, and 60 minutes before start of infusion.



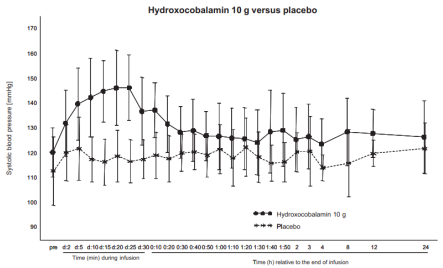


FIG. 2. Mean (SD) systolic blood pressure in volunteers administered hydroxocobalamin (5 g or 10 g) or placebo. The predose value ("pre") is the median of 3 predose measurements obtained 20, 40, and 60 minutes before start of infusion.

Randomized Controlled Trial > Clin Toxicol (Phila). 2006;44 Suppl 1:17-28.
doi: 10.1080/15563650600811755.

Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study

Wolfgang Uhl [1], Arno Nolting, Georg Golor, Karl Ludwig Rost, Andreas Kovar

- N=136,
- 2.5g/7.5g/10g over 7.5-30min

Single dose 5g i/v
N=20

Clinical Trial > Chest. 2023 Feb;163(2):303-312. doi: 10.1016/j.chest.2022.09.021. Epub 2022 Sep 26.

High-Dose IV Hydroxocobalamin (Vitamin B12) in Septic Shock: A Double-Blind, Allocation-Concealed, Placebo-Controlled Single-Center Pilot Randomized Controlled Trial (The Intravenous Hydroxocobalamin in Septic Shock Trial)

Table 2 Summary of Vasopressor Dose and Change in Dose at T0, T1, T2, and T3

Characteristic	Hydroxocobalamin (n = 10)	Placebo (n = 10)	*P* Value
Total norepinephrine dose, μg/kg/min			
T0[a]	0.29 (0.20-0.36)	0.34 (0.24-0.51)	.4
T1	0.25 (0.20-0.38)	0.31 (0.20-0.54)	.7
T2	0.14 (0.10-0.21)	0.30 (0.20-0.72)	.01
T3	0.13 (0.10-0.21)	0.26 (0.17-0.90)	.06
% Change			
T1 to T2	–36 (–48 to –31)	4 (–5 to 13)	< .001
T1 to T3	–28 (–67 to –12)	10 (–14 to 49)	.01

Data are presented as median (interquartile range), unless otherwise indicated. T0 = at randomization; T1 = 1 min before start of hydroxocobalamin or placebo infusion; T2 = 30 min after infusion; T3 = 3 h after infusion.

melatonin

SOD

metallothionein

GPx

glutathione

CAT

Ferritin

Vit A

ubiquinone

Vit C

Coenzyme Q10

Phenolic compounds

A-lipoic acid

Zn

L-carnitine

Albumin

Vit E

BH4

Se

Uric acid

Bilirubin

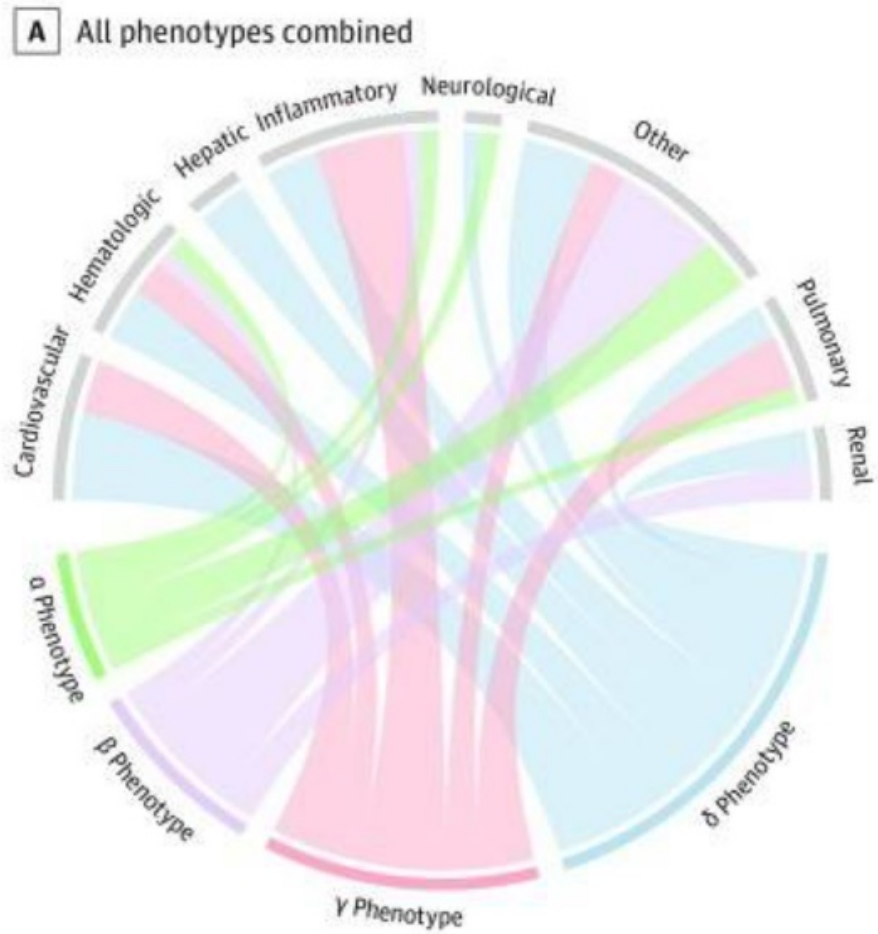
JAMA
View Article

JAMA. 2019 May 28; 321(20): 2003–2017.
Published online 2019 May 19. doi: 10.1001/jama.2019.5791

PMCID: PMC6537818
PMID: 31104070

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc,[1,2,3] Jason N. Kennedy, MS,[1,3] Shu Wang, MS,[4] Chung-Chou H. Chang, PhD,[3,4,5] Corrine F. Elliott, MS,[6] Zhongying Xu, MS,[4] Scott Berry, PhD,[6] Gilles Clermont, MD, MSc,[1,3] Gregory Cooper, MD, PhD,[7] Hernando Gomez, MD, MPH,[1,2,3] David T. Huang, MD, MPH,[1,2,3] John A. Kellum, MD, FACP, MCCM,[1,3] Qi Mi, PhD,[8] Steven M. Opal, MD,[9] Victor Talisa, MS,[4] Tom van der Poll, MD, PhD,[10] Shyam Visweswaran, MD, PhD,[7] Yoram Vodovotz, PhD,[11] Jeremy C. Weiss, MD, PhD,[12] Donald M. Yealy, MD, FACEP,[2] Sachin Yende, MD, MS,[1,3,13] and Derek C. Angus, MD, MPH[1,3,5]



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Vitamin C for ≥ 5 days is associated with decreased hospital mortality in sepsis subgroups: a nationwide cohort study

Sun-Young Jung,[#1,2] Min-Taek Lee,[#2] Moon Seong Baek,[3] and Won-Young Kim[✉3]

N=72654

AA reduced mortality in:

- Older than 70 years
- Multiple comorbidities
- Pneumonia and urinary tract as source of infection
- Septic shock
- Need of mechanical ventilation
- Patients with more pronounced inflammatory response

AA did not reduce mortality in:

- Abdominal sepsis
- Renal replacement therapy

Conclusions

- Measurement of a single compound or enzyme probably does not reflect the real antioxidant capacity
- Supplementation with one compound does not cure critical illness
- Adjuvant treatment might be useful in selected patients
- So many antioxidants so many future research

Thank you for your attention!