

Vitamine und mehr – supportive Therapien beim kritisch Kranken

Sebastian Rehberg

**Klinik für Anästhesiologie, Intensiv-, Notfallmedizin,
Transfusionsmedizin und Schmerztherapie
Universitätsklinikum OWL der Universität Bielefeld
Campus Bielefeld-Bethel**

Vitamine sind gesund !



www.pinterest.de

Mangelzustände: (Vor-)Erkrankungen

Disease-specific risks of depletion or deficiency in trace elements and vitamins. Note: the below list of diseases associated with known alterations of MNs is non-exhaustive (alphabetic order) and may in some cases be less fully supported by the evidence. These and other diseases may have further or still unknown associations with various MN inadequacies.

Disease	Deficiency favouring disease development	Inadequacy or deficit worsening the condition	Deficiency as a result of disease	References
Alcoholism		B1, Fe	A, D, E, K, B1, B2, B6, B7, B9, B12, C, Zn	[4, 44]
Alcoholic hepatitis	B6, Zn	Se, Zn		[45]
Anaemia	B1, B6, B9, B12, Fe, Cu, Co			[4]
Cancer cachexia	D, Zn			[46, 47]
Cardiomyopathies/ Heart failure	B1, B6, D, Se, Fe	Se		[4, 48, 49]
Chronic obstructive pulmonary disease	D, Cu, Se, Mn, Zn			[50, 51]
Chronic intestinal failure			B2, B7, B9, B12, A, D, E, K, Cu, Fe, Zn	[52–54]
Chronic (atrophic) gastritis			B9, B12, C, D, Fe	[55, 56]
Diabetes mellitus	B9, Cr			[57–61]
Inflammatory bowel diseases		Zn	B1, B6, B12, A, D, E, K, Fe, Se, Zn	[4, 62]
Non-alcoholic fatty liver disease	Cu			[63]
Liver diseases		Zn	B12, A, D, E, Se, Zn	[4, 64, 65]
Multiple Sclerosis	B7			[66]
Obesity	β-carotene, E, Se, Zn	B1, B9, D, Fe, Se, Zn		[55, 67–69]
Obesity Post Bariatric surgery			A, D, E, K, B1, B9, B12, C, Cu, Fe, Zn	[69–71]
Osteoporosis	B12, D, K, Cu, Fe, Zn, Mn, F, Bo			[72, 73]
Renal failure (chronic)			B1, B6, B9, K, D, Cu, Se, Zn	[74, 75]
Sarcopenia	B1, B12, D, carnitine, Zn	D, Se, Zn		[55, 76]
Critical illness		B1, C, D, Cu, Fe, Se, Zn	B1, B12, C, D, Fe, Se, Zn	[76–79]

Mangelzustände: Interventionen

Treatment associated specific risks of depletion, deficiency, or excess in MNs.

Therapy	MN deficit due to treatment	
Renal replacement therapy	all water-soluble vitamins, Carnitine	[80]
Diuretic therapy	Cu, Fe, Se,	
	Thiamine (B1)	[81,82]
Proton Pump Inhibitors	Se	[49]
	B12	[83]
Metformin	B12	[84–87]
Isoniazid treatment	B6	[88]
		[89,90]
Antiretroviral HIV therapy	D	[91]
Antiepileptic drugs	B9, B12, D	[92]
Thymoglobulin (immunosuppression)	B6	[93]

Editorial > Chest. 2020 Jul;158(1):13-14. doi: 10.1016/j.chest.2020.03.030. Epub 2020 Jul 2.

Additional Trials of Vitamin C in Septic Shock: A Bag of Mixed Fruit

Tomoko Fujii ¹, Andrew A Udy ²

Comment > Chest. 2021 Jan;159(1):452-453. doi: 10.1016/j.chest.2020.07.056.

Would You Withhold Fruit From the Critically Ill?

Jose I Iglesias ¹;

Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis (ORANGES) investigators* ²



COMMENT


Open Access

Intravenous vitamin C in adults with sepsis in the intensive care unit: still LOV'IT?



Stoppe et al. Crit Care 2022;26:230

Evidenz-basierte Medizin

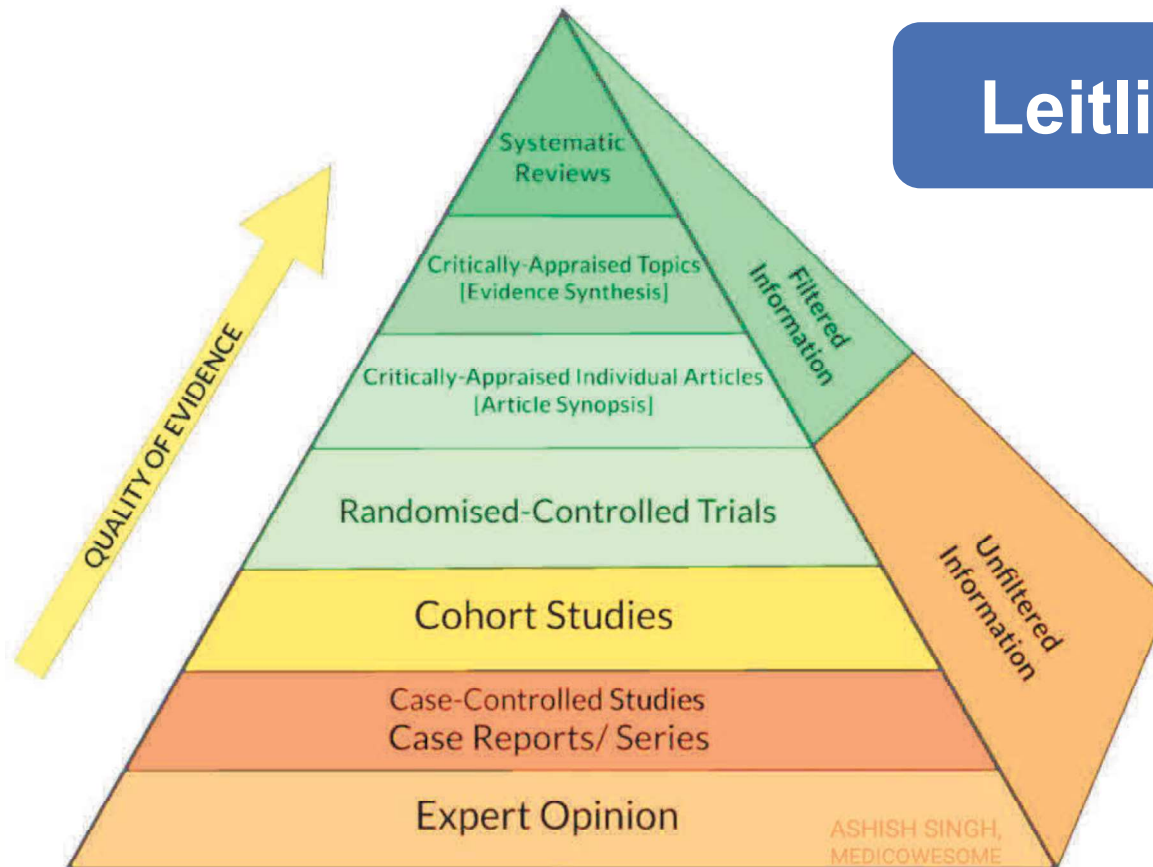


“Evidence-based care is not about the evidence, but about responding to patient problems with evidence”

Victor Montori
#CochraneForAll

Qualität der Evidenz

Leitlinien

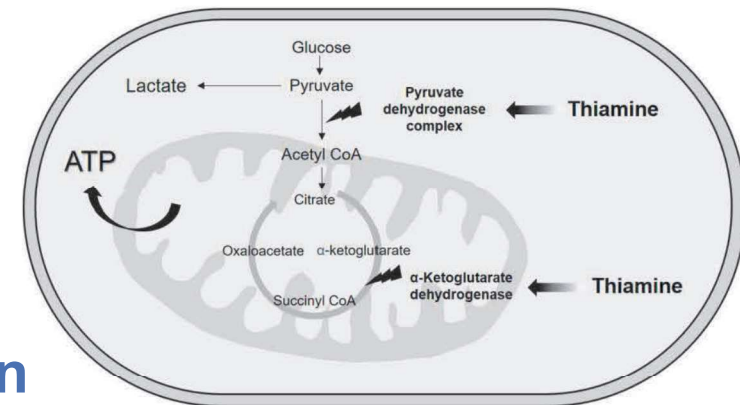


Überblick

- **Thiamin (Vitamin B1)**
- **Vitamin D**
- **Vitamin C**
- **N-Acetylcystein**
- **Glutamin**
- **Selen**

Thiamin (Vitamin B1)

- essentielles wasserlösliches Vitamin
- Mangel bei 20-60% der Patienten*innen im septischen Schock (Nierenersatztherapie!)
- essentielles Coenzym im Pyruvatdehydrogenasekomplex, Krebs-Zyklus, für ATP-Produktion und Glukosestoffwechsel !



Amrein et al. Intensive Care Med 2018;44:1940-44
Costa et al. Front Med 2022; 8:805119

Thiamin (Vitamin B1)

- **Monotherapie:**
- **3 RCTs: 210 Patienten*innen im septischen Schock**
- **3 retrospektive Studien: 69.673 Patienten*innen im septischen Schock**
- **1 Sekundäranalyse: 70 Patienten*innen im septischen Schock**

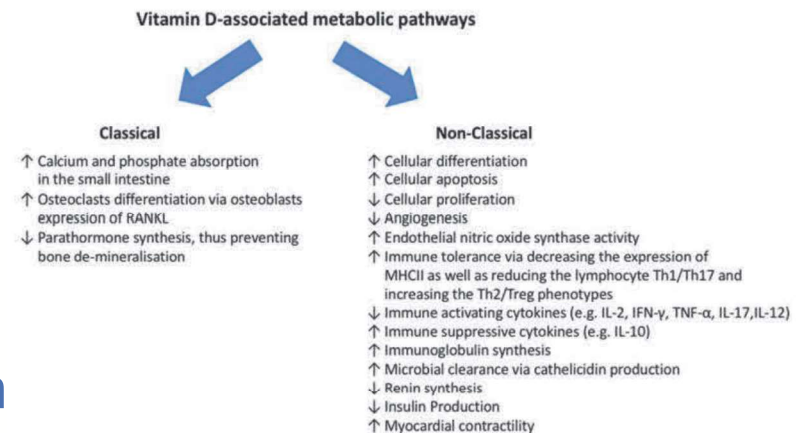
Thiamin (Vitamin B1)

- Monotherapie:

“Despite the excellent safety profile, good biologic rationale and promising clinical studies, no robust results support routine thiamine supplementation to improve outcomes.”

Vitamin D

- endogene Synthese unter ausreichend UV-B Strahlung
- Mangel bei 30-60% der Intensivpatienten*innen
- Regulation der enteralen Kalziumaufnahme
- Glutamat-Stoffwechsel
- Redoxregulation und Immunmodulation
- Cave: Überdosierung möglich



- Assoziation zwischen niedrigem Vit D-Spiegel und schlechtem Outcome ...
- ... aber bisher keine Kausalität

Table 2. Large-scale randomized clinical trials on vitamin D supplementation in critically ill patients.

Authors, Year of Publication	Study Sites	Study Duration	Number of Patients	Inclusion Criteria	Intervention	Primary Outcome	Patients Characteristics	Main Result
Amrein et al. (the VITdAL-ICU trial), 2014 [12]	Single centre, Austria	2012–2015	475	Adult white critically ill patients, expected length of ICU stay ≥ 48 h and with 25-hydroxyvitamin D blood level of ≤ 20 ng/mL	Enteral vitamin D3 protocol administration: 540,000 IUs followed by monthly 90,000 IU for 5 months vs. Placebo	Length of hospital stay	Surgical patients were prevalent Mean body mass index about 27 kg/m ² Mean eGRF slightly above 60 mL/min/1.73 m ²	No difference for the primary outcome
Ginde et al. (the VIOLET trial), 2019 [13]	44 centres, USA	2017–2018	1078	Adult patients with with >1 risk factors for death or lung injury, deemed to be managed in the ICU and with 25-hydroxyvitamin D blood level ≤ 20 ng/mL	Enteral vitamin D3 protocol administration: 540,000 Ius vs. Placebo	90-day mortality rate	Medical patients were prevalent Black patients about 20% Mean body mass index about 30 kg/m ² Mean eGRF slightly about 60 mL/min/1.73 m ²	No difference for the primary outcome

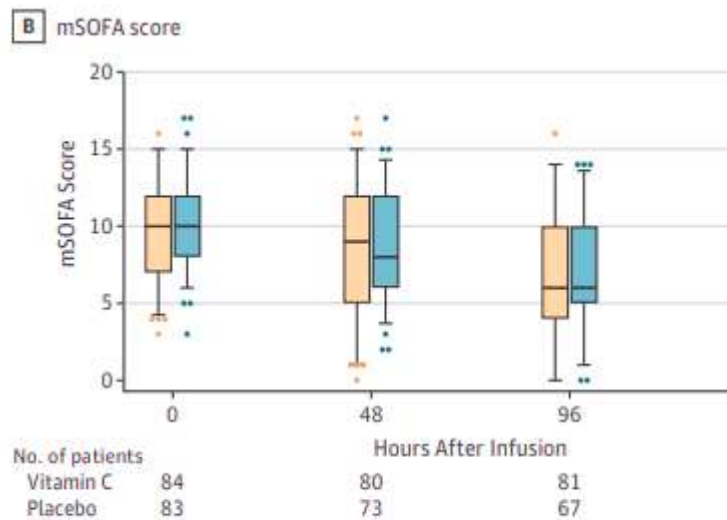
eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

Vitamin C

- **essentielles Vitamin**
- **akuter Mangel bei kritisch Kranken**
- **stärkstes wasserlösliches Antioxydans**
- **Cofaktor der Biosynthese u.a. von Neurotransmittern, Peptidhormonen, Kollagen**
- **Anti-inflammatorisch, Förderung der Wundheilung, Reduktion von Ischämie-Reperfusionsschäden**

Vitamin C

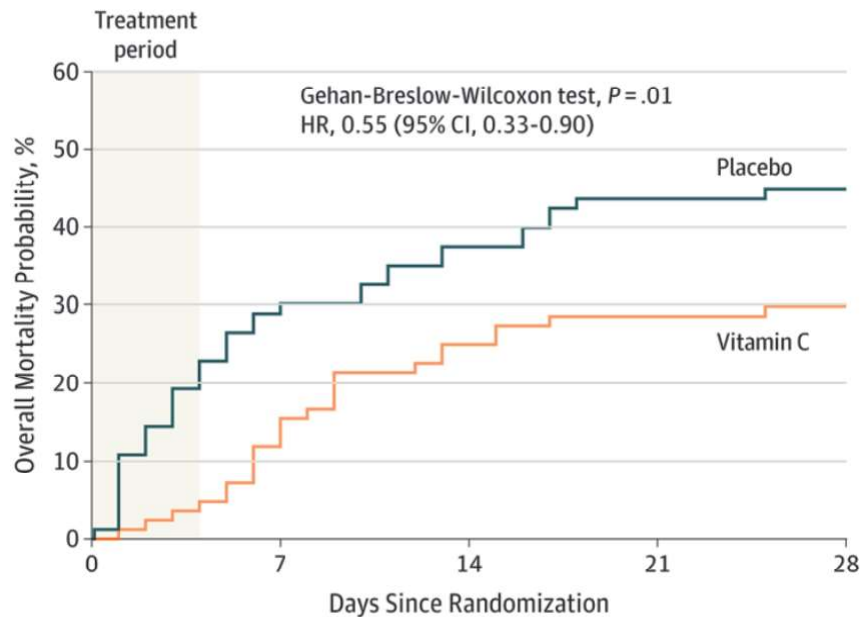
Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure The CITRIS-ALI Randomized Clinical Trial



„Among patients with sepsis and ARDS, high-dose vitamin C infusion compared with placebo did not significantly reduce organ failure scores at 96 hours or improve biomarker levels at 168 hours.“

Vitamin C

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure The CITRIS-ALI Randomized Clinical Trial

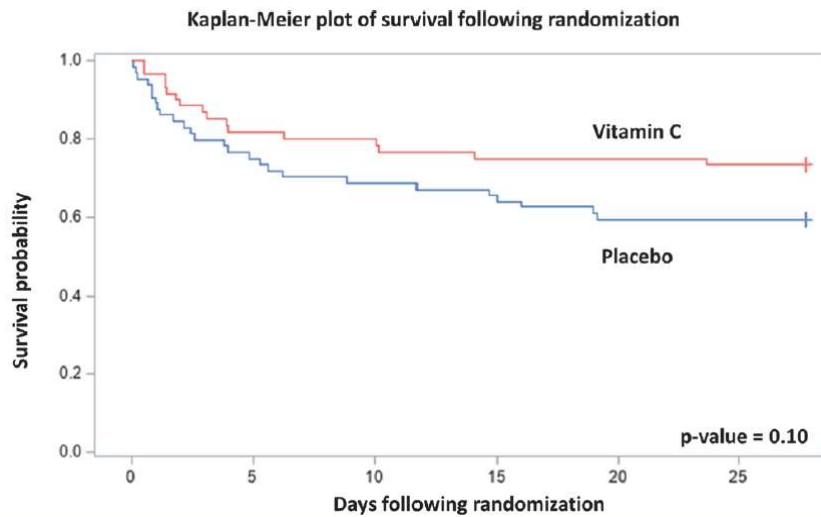


“Vitamin C–infused patients exhibited a significant reduction in 28-day all-cause mortality, although the P value was not adjusted for multiple comparisons. The median observation time was 28 days.”

Fowler et al. JAMA 2019;322:1261-70

Vitamin C

Evaluating Vitamin C in Septic Shock: A Randomized Controlled Trial of Vitamin C Monotherapy*



“Vitamin C monotherapy failed to significantly reduce mortality in septic shock patients as hypothesized. Our findings do not support its routine clinical use for this purpose.“

Kombinationstherapie

JAMA | Original Investigation

Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock

The ACTS Randomized Clinical Trial

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone and Thiamine on Time Alive and Free of Vasopressor Support in Patients With Septic Shock

The VITAMINS Randomized Clinical Trial

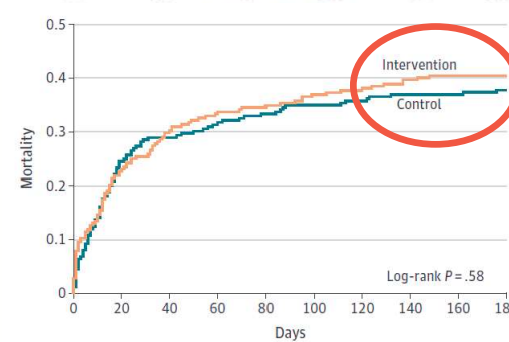
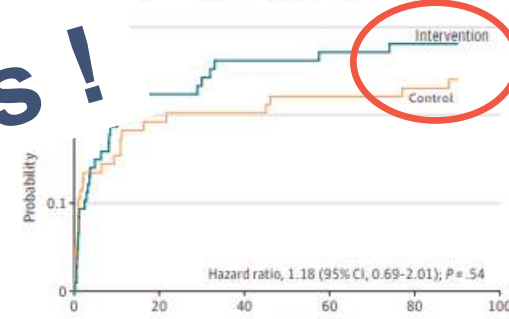
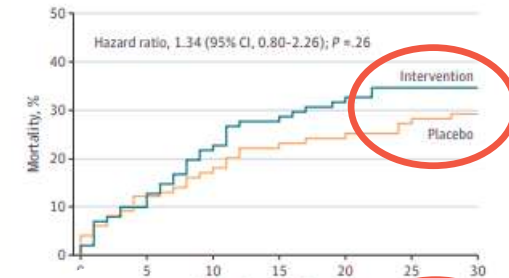
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis

The VICTAS Randomized Clinical Trial

Keine Evidenz in RCTs!

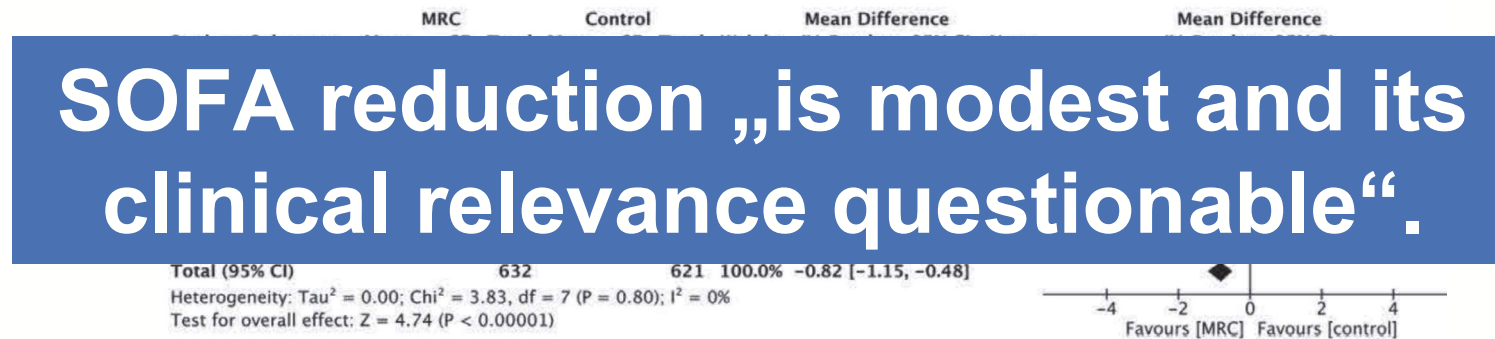
Fujii et al. JAMA 2020;323:423-31
Moskowitz et al. JAMA 2020;324:642-50
Sevransky et al. JAMA 2021;325:742-50



Metaanalyse Kombination

- **8 randomisierte, kontrollierte Studien**
- **1335 Patienten*innen mit Sepsis oder septischem Schock**
- **Primäres Ziel: SOFA-Score Reduktion nach 72h**
- **Sekundäre Ziele:**
 - **Dauer der Vasopressortherapie**
 - **Nierenfunktion**
 - **ITS-Sterblichkeit**

- **SOFA-Score Reduktion nach 72h**



- **Dauer der Vasopressortherapie: Reduktion**
- **Nierenfunktion: kein Unterschied**
- **ITS-Sterblichkeit: kein Unterschied**

SYSTEMATIC REVIEW

Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis



- **“Metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not proven to decrease longer term mortality.”**

Das bekannte Problem mit den Studien...

... aber schaden kann es nicht.



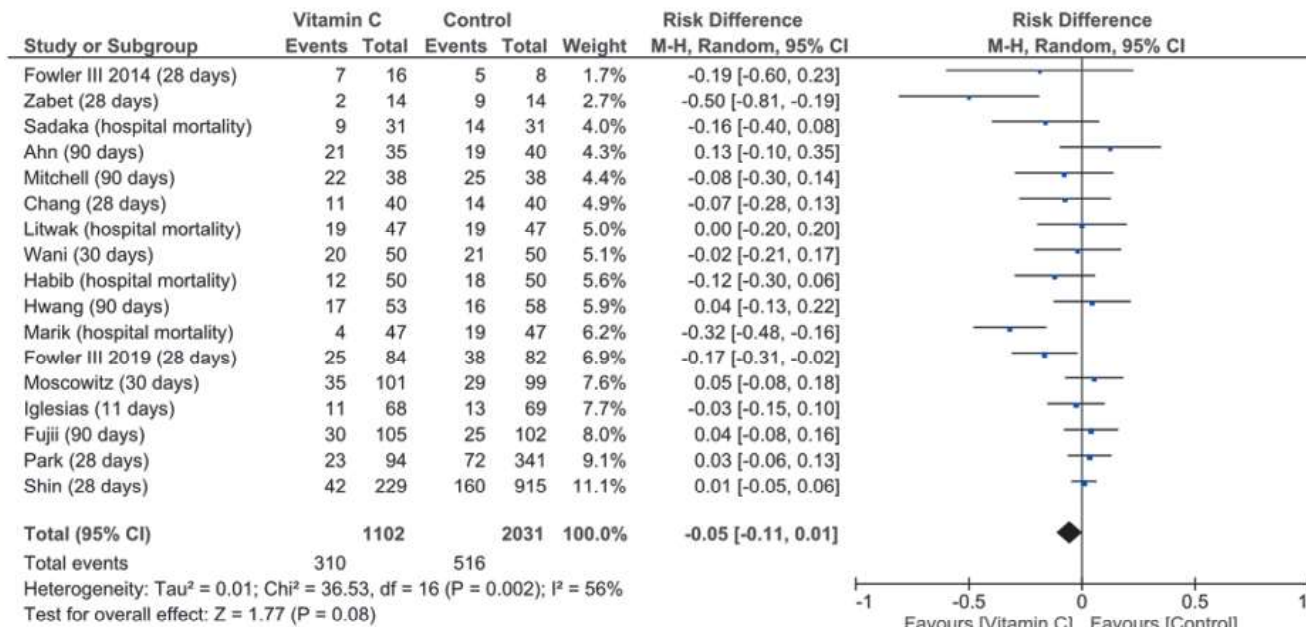
www.depositphotos.com

RESEARCH

Open Access



Mortality in septic patients treated with vitamin C: a systematic meta-analysis

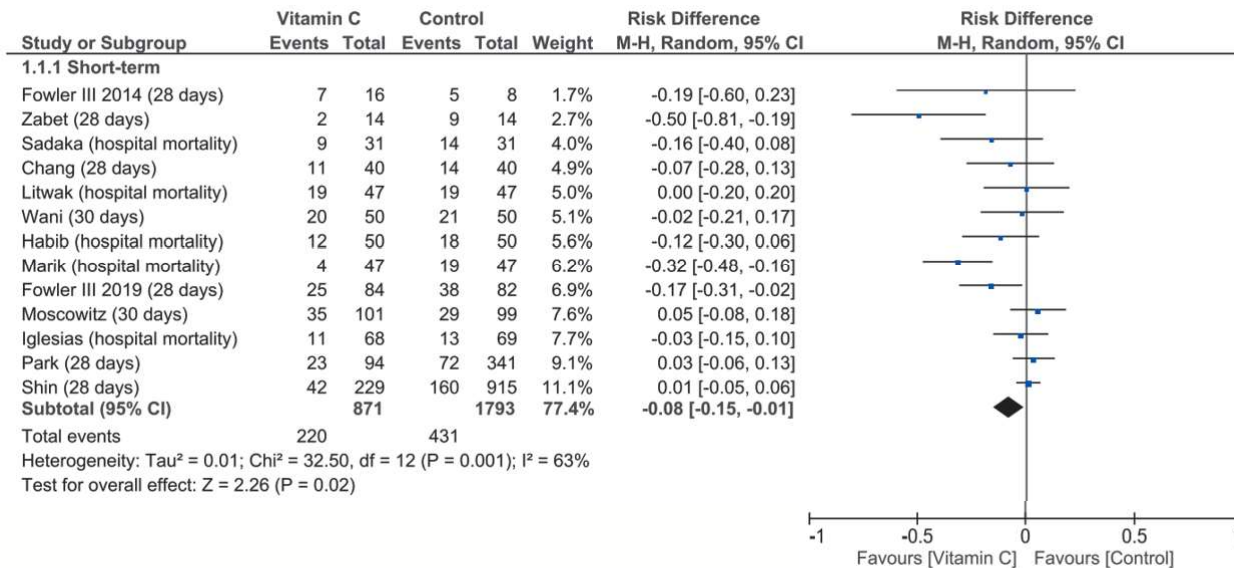


RESEARCH

Open Access



Mortality in septic patients treated with vitamin C: a systematic meta-analysis



RESEARCH

Open Access



Mortality in septic patients treated with vitamin C: a systematic meta-analysis

1.1.2 Long-term

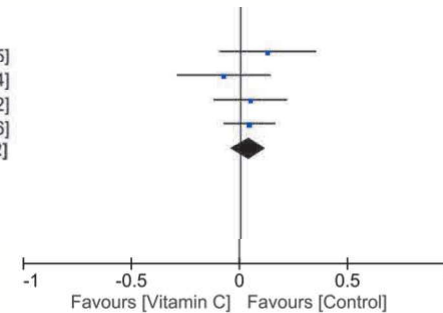
Ahn (90 days)	21	35	19	40	4.3%	0.13 [-0.10, 0.35]
Mitchell (60 days)	22	38	25	38	4.4%	-0.08 [-0.30, 0.14]
Hwang (90 days)	17	53	16	58	5.9%	0.04 [-0.13, 0.22]
Fujii (90 days)	30	105	25	102	8.0%	0.04 [-0.08, 0.16]
Subtotal (95% CI)		231		238	22.6%	0.04 [-0.05, 0.12]

Total events

90 85

Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 1.69$, $\text{df} = 3$ ($P = 0.64$); $I^2 = 0\%$

Test for overall effect: $Z = 0.84$ ($P = 0.40$)

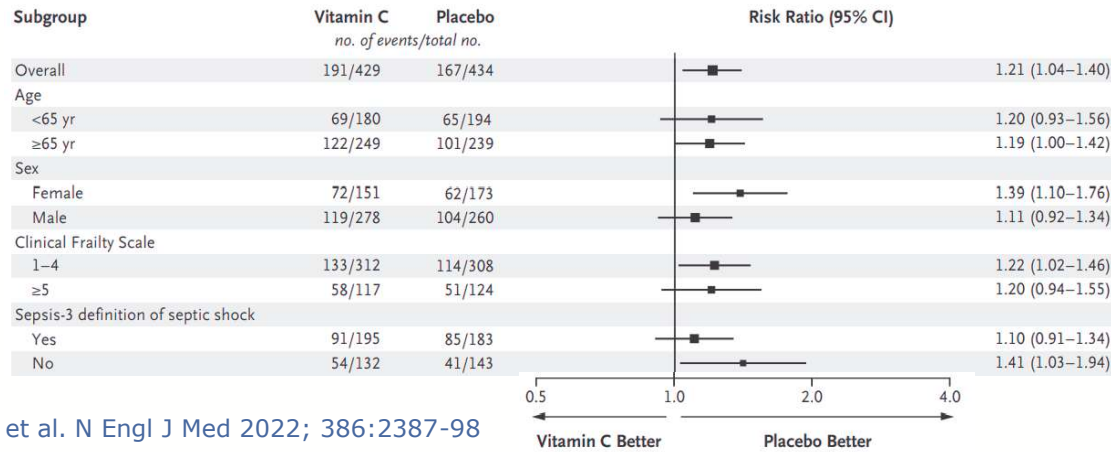
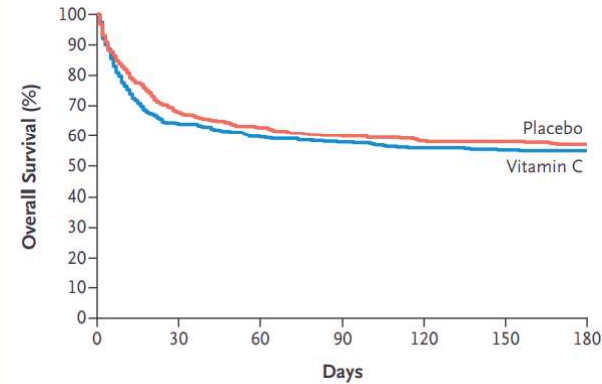
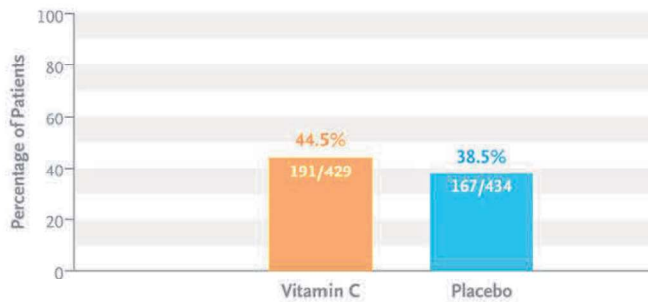


Verdacht auf negativen Langzeiteffekt!

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

Death or Persistent Organ Dysfunction at 28 Days

Risk ratio, 1.21; 95% CI, 1.04 to 1.40; P = 0.01



Lamontagne et al. N Engl J Med 2022; 386:2387-98

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

Vitamin C in Sepsis — No Longer a Benign Intervention?

Lamontagne et al. *N Engl J Med* 2022; 386:2387-98
Goodwin et al. *NEJM Evid* 2022;1:[e2200163](#)

Parenteral Vitamin C in Patients with Severe Infection: A Systematic Review

Table 2. Evidence Profile for Mortality in Trials of Parenteral Vitamin C Limited to Published Blinded Full-Text Trials and at Low Risk-of-Bias.*

Meta-analysis	Absolute Effect Estimates, No. per 1000 (95% CI)			
---------------	--	--	--	--

„For 90-day mortality, all trials had low risk-of-bias; moderate-certainty evidence suggested harm.“

(combined in-hospital and 30-day mortality)	based on data from 2214 participants in 11 trials			fewer to 19 more)	serious imprecision† and some concerns regarding inconsistency‡	may reduce risk of early mortality
90-day mortality	1.07 (0.94 to 1.21) based on data from 1722 participants in 5 trials	356	381	25 more (21 fewer to 75 more)	Moderate, due to serious imprecision†	Parenteral vitamin C probably increases risk of 90-day mortality

* Risk ratio is expressed as vitamin C compared with the control. CI denotes confidence interval.

† Imprecision was assessed as serious due to the 95% CI crossing the null.

‡ Inconsistency was assessed as serious due to dissimilarities in point estimates, lack of overlap in CIs, and statistical evidence of heterogeneity.

„Metabolic Resuscitation“

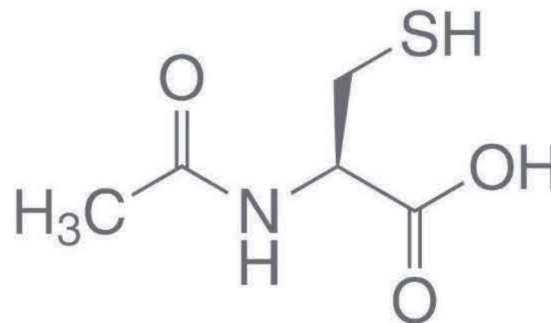
- **Keine Evidenz in allen aktuellen RCTs: weder für Mono- noch für Kombinationstherapien**
- **Risiko für langfristig erhöhte Sterblichkeit (90d) beim Vit C**



www.emoji.co.uk

N-Acetylcystein

- **Synthetisch hergestellter Abkömmling von Cystein**
- **Einsatz als „Hustenlöser“**
- **Antidot bei Paracetamolintoxikation**



N-Acetylcystein



Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

N-acetylcysteine for sepsis and systemic inflammatory response in adults

- 41 Studien
- 2768 Patienten/innen

N-Acetylcystein



Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

N-acetylcysteine for sepsis and systemic inflammatory response in adults

- This meta-analysis puts doubt on the safety and utility of intravenous N-acetylcysteine as an adjuvant therapy in SIRS and sepsis.

N-Acetylcystein



Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

N-acetylcysteine for sepsis and systemic inflammatory response in adults

- This meta-analysis puts doubt on the safety and utility of intravenous N-acetylcysteine as an adjuvant therapy in SIRS and sepsis.
- At best, N-acetylcysteine is ineffective in reducing mortality and complications in this patient population.

N-Acetylcystein



Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

N-acetylcysteine for sepsis and systemic inflammatory response in adults

- This meta-analysis puts doubt on the safety and utility of intravenous N-acetylcysteine as an adjuvant therapy in SIRS and sepsis.
- At best, N-acetylcysteine is ineffective in reducing mortality and complications in this patient population.
- At worst, it can be harmful, especially when administered later than 24 hours after the onset of symptoms, by causing cardiovascular depression.

Glutamin

Glutamine and Antioxidants in the Critically Ill Patient: A Post Hoc Analysis of a Large-Scale Randomized Trial

- **1223 Patienten/innen mit Multiorganversagen und mechanischer Beatmung**
- **Gruppen:**
 - Placebo
 - Glutamin
 - Antioxidantien (Vit C + E, Zink, Selen)
 - Glutamin und Antioxidantien

Glutamin

Glutamine and Antioxidants in the Critically Ill Patient: A Post Hoc Analysis of a Large-Scale Randomized Trial

Schlussfolgerungen:

- keine positiven Effekte auf die Sterblichkeit
- Hinweise auf erhöhte Sterblichkeit
- negative Effekte insbesondere bei bestehender renaler Funktionseinschränkung

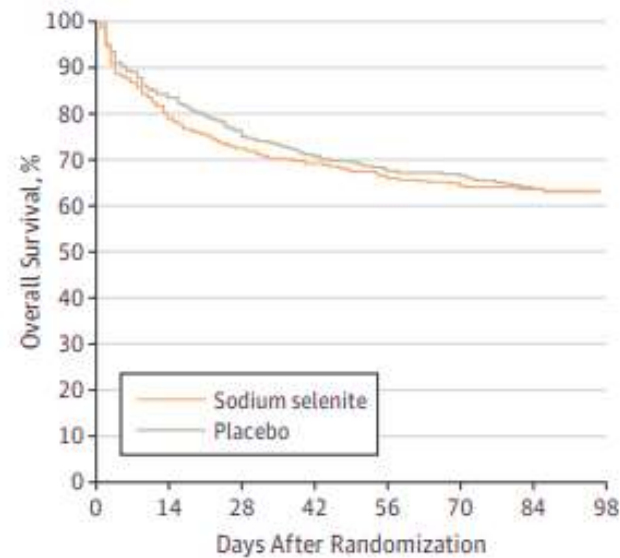
Selen

Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock A Randomized Clinical Trial

- **1089 Patienten/innen mit schwerer Sepsis oder septischem Schock**
- **1000 µg Bolus, anschließend 1000 µg/d kontinuierlich**

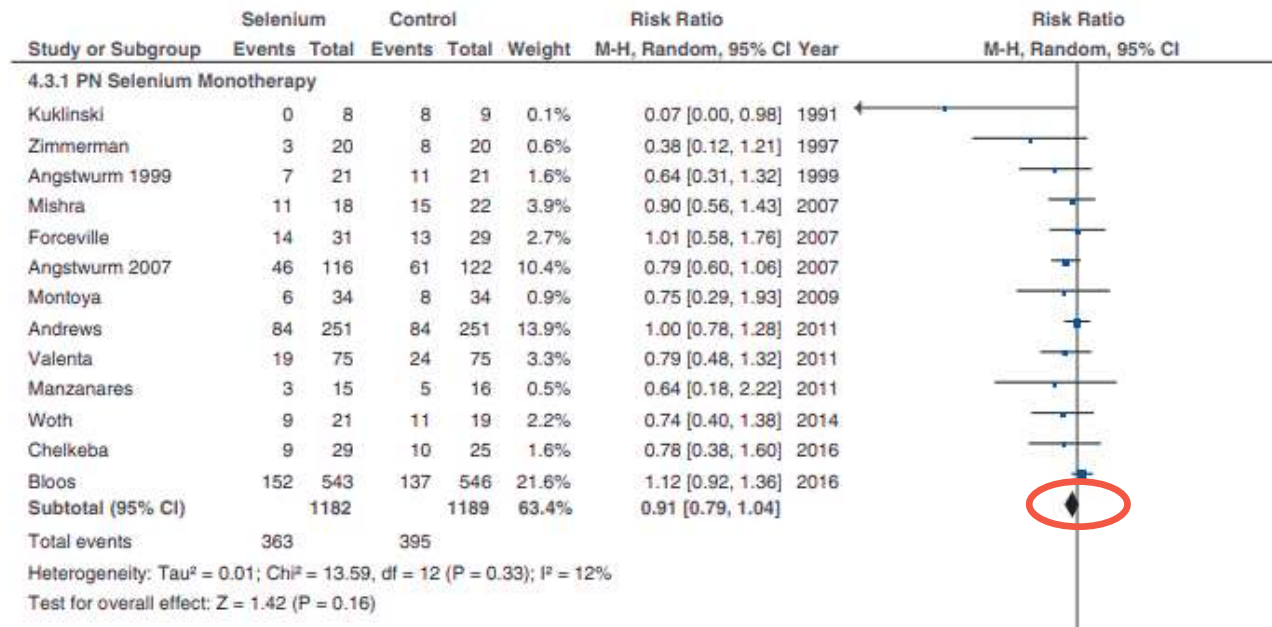
Selen

Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock A Randomized Clinical Trial



Bloos et al. JAMA Intern Med 2016;176:1266-76

High-dose intravenous selenium does not improve clinical outcomes in the critically ill: a systematic review and meta-analysis



Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

We recommend against the use of **IV selenium** to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).

. We recommend against the use of **glutamine** to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).

We suggest against the use of **arginine** to treat sepsis and septic shock (weak recommendation, low quality of evidence).

Leitlinien

S3-Leitlinie Sepsis – Prävention, Diagnose, Therapie und Nachsorge

AWMF-Registernummer: 079 – 001

Langversion 3.1 – 2018

Wir empfehlen, dass von der Verwendung von **intravenösem Selen** bei der Behandlung von Patienten mit Sepsis und septischem Schock abgesehen wird.

Empfehlungsgrad

stark

Wir empfehlen, dass von der Verwendung von **Glutamin** bei der Behandlung von Patienten mit Sepsis oder septischem Schock abgesehen wird.

Evidenzgrad

moderat

Wir empfehlen, dass von der Verwendung von **Omega-3-Fettsäuren** als Immunsupplement bei kritisch kranken Patienten mit Sepsis oder septischen Schock abgesehen wird. Dies betrifft nicht den Einsatz Omega-3-fetthaltiger Lipidemulsionen im Rahmen der parenteralen Ernährung.

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021



Vitamin C

Recommendation

70. For adults with sepsis, we suggest against using IV vitamin C. (Low quality of evidence)

! Negativ-Empfehlung !

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021



Andere Substanzen ???

Keine Erwähnung

Review

Nutrition in Sepsis: A Bench-to-Bedside Review

Elisabeth De Waele ^{1,2,3,*}, Manu L.N.G. Malbrain ^{1,3} and Herbert Spapen ^{1,3}

- „take home messages“:

Glutamine administration has no benefit and may even be harmful in septic patients.

Lack of firm evidence argues against **arginine** supplementation in sepsis and septic shock.

The scientific evidence to justify **fish oil supplementation** in patients with sepsis or septic shock is weak.

Selenium alone or in combination with other antioxidants is not recommended in sepsis.

At present, insufficient evidence supports routine **vitamin C** administration in sepsis.

Review

Nutrition in Sepsis: A Bench-to-Bedside Review

Elisabeth De Waele ^{1,2,3,*}, Manu L.N.G. Malbrain ^{1,3} and Herbert Spapen ^{1,3}

- **Schlussfolgerung:**

„The theoretical benefit of adjuvant pharmaco-nutrition does not translate into better outcome in patients with sepsis or septic shock.“

! Schlusswort !

Case presentation and panel discussion: Micronutrient therapy in critical illness

Jose M. Pimiento MD¹  | Todd W. Rice MD²  | Daren K. Heyland MD^{3,4} |
Christian Stoppe MD⁵  | Jennifer Katz MD⁶ | Chet Morrison MD⁷  |
Jeffrey I. Mechanick MD^{8,9} | Jayshil J. Patel MD¹⁰ 

„... data from randomized controlled trials do not support the use of supraphysiologic doses of micronutrients (vitamin C, vitamin D, selenium, or zinc) in critically ill patients.“

„Metabolic Resuscitation“

... oder reicht evtl. doch die
reguläre Zufuhr ?



www.myloview.de

Vielen Dank !

