Metabolic resuscitation in sepsis

Metabolická resuscitácia sepsy

Roman Záhorec

II. KAIM LFUK a onkologický ústav
svätej Alžbety v Bratislave

Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic?

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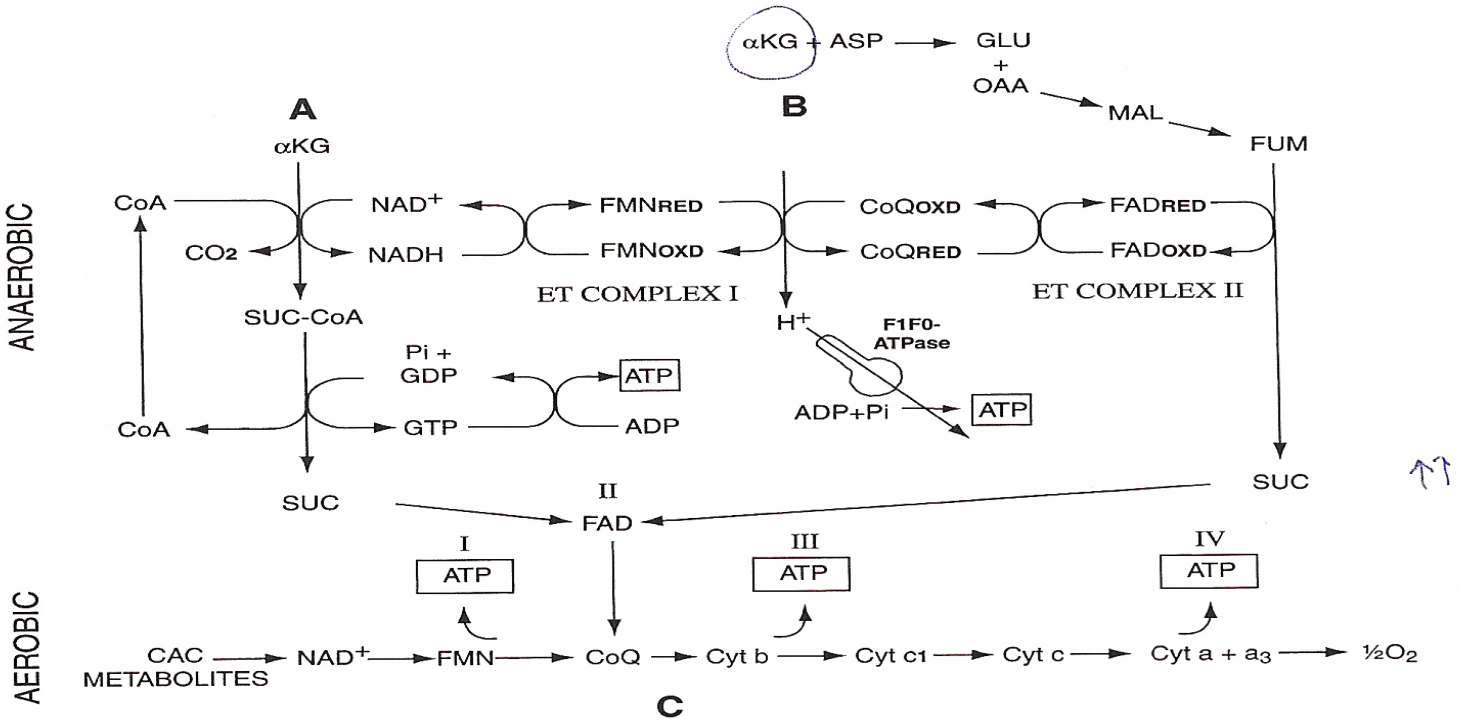
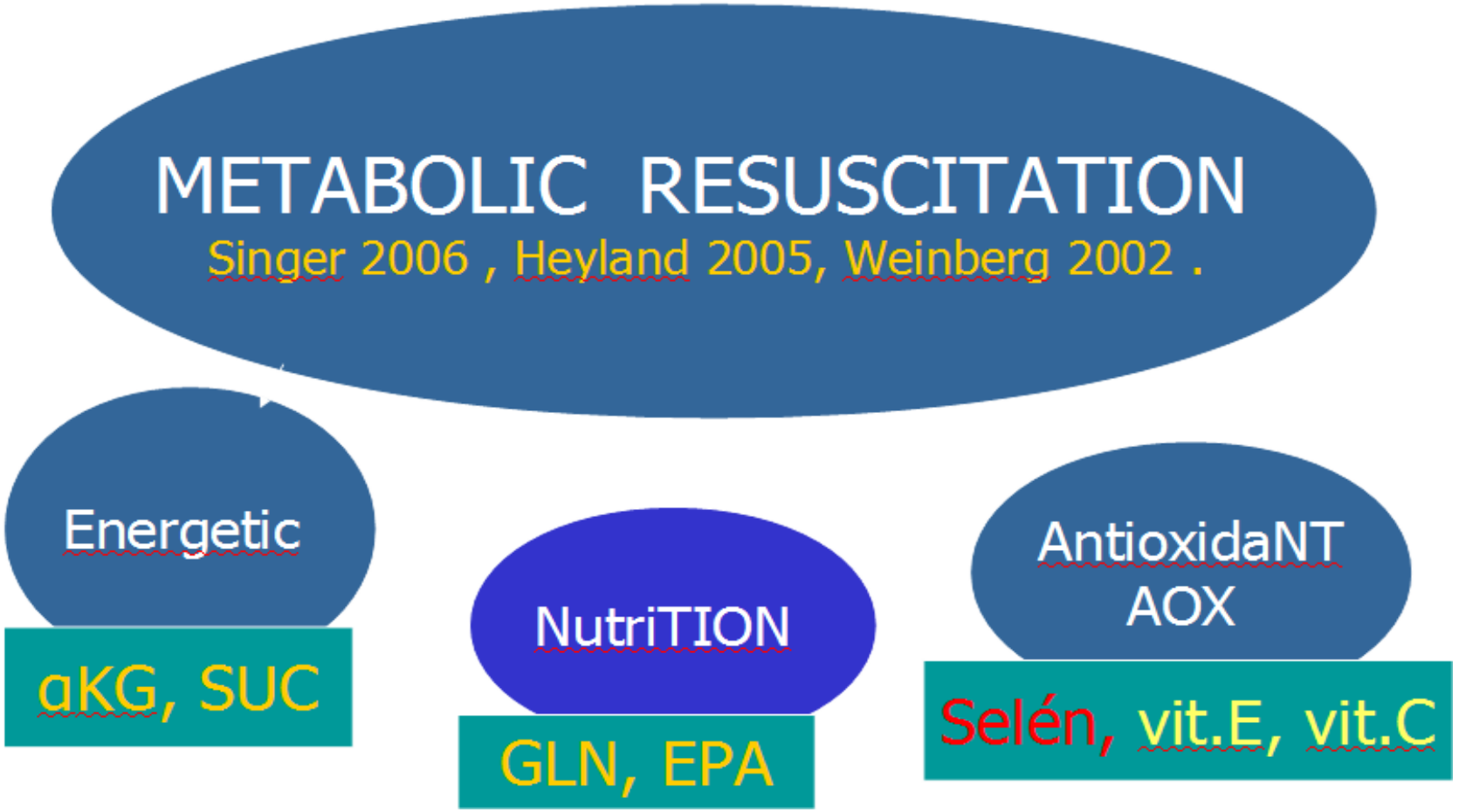


Fig. 5A–C. Metabolic pathways for protective effects of citric acid cycle intermediates. A Sub-

Crit Care Med. 2007 ,35, suppl. Sept No.9

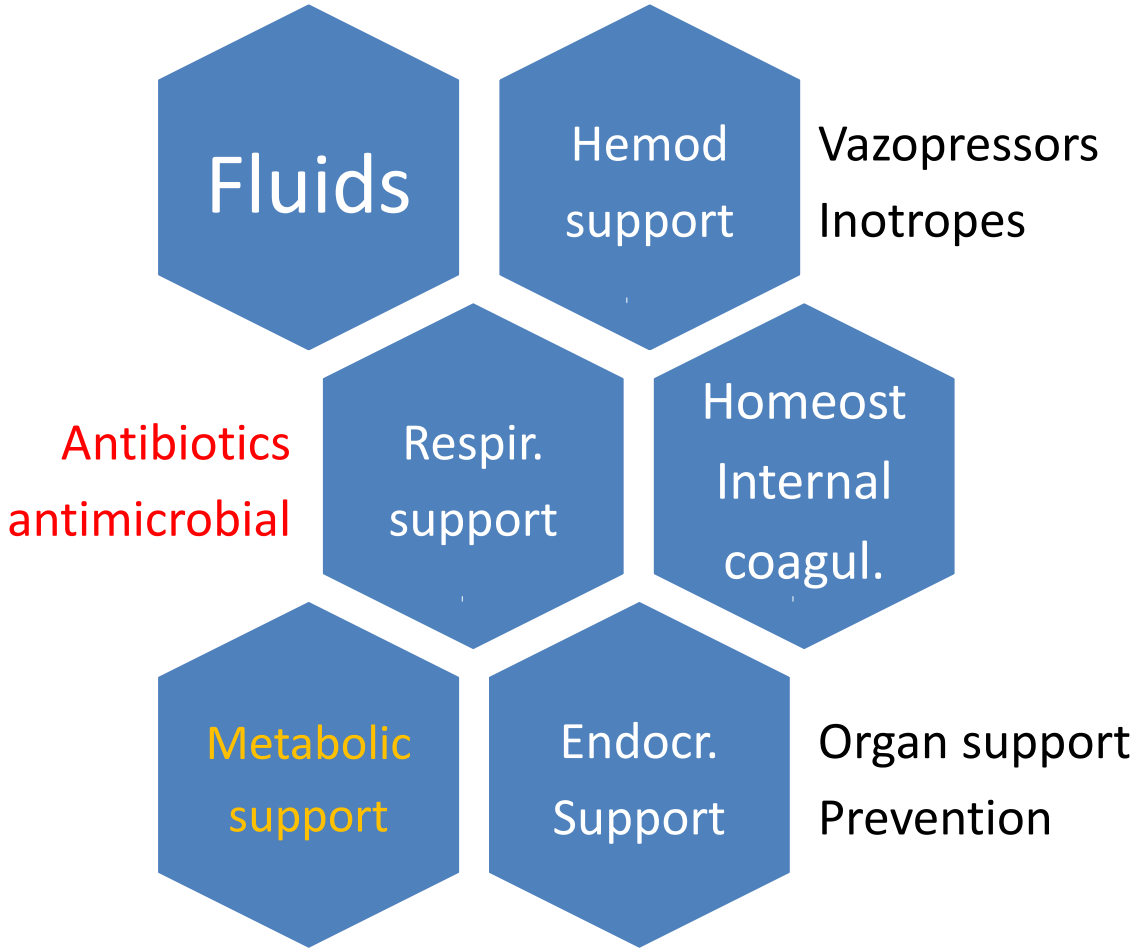
Critical ill pts : SIRS + MODS

(Hypoxémia, hypotension, tachypnoe, tachycardia, metabolic acidosis, cells stress – mitochondrial dysfunction)



Principles of therapy for sepsis

SSC Guidelines 2012 , Dellinger et al. CCM 2013.



Metabolic resuscitation in sepsis

Vitamins : **B1, B6,**

C vit, E vit,

25OH-D3 vita

Cholesterol - rich

Thiol – rich Nutrition ,

L-carnitin,

phosphate CrP,

Mitochondria

,

Krebs cycle,
RC, AOX,

Micronutrients :

Selenium, Zinc

Endocrinne support:

Insulin, T3-trijodtyronin, GH, oxandrolone, melatonin

Effects of vitamin B1 – Thiamin in intermediary metabolism , Donnino M.W. et al., CCM 2016, 44: 360-67.

- THIAMINE B1 key co-factor for pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase and transketolase , *Frank et.al. Thiamine –dependent enzymes, 2007*
- ***PDH* enzyme** gate-keeper for entry to Krebs cycle, synthesis of acetyl-coenzyme A (in dysfunction : pyruvate –to - lactate)
- Alpha-ketoglutarate dehydr. – normal function of Krebs cycle,
- Transketolase is a key enzyme for the pentose phosphate pathway –production of NADPH and pentose m. for DNA/RNA.
- *Thiamine* necessary fo all three steps of intermediary metabolism
- *Untreated* thiamin deficiency (<7 ng/ml) inadequate functioning of aerobic metabolism !!! Donnino 2016 ,

Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study

Michael W. Donnino, M.D.[1,2]; Lars W. Andersen, M.D.[1,3]; Maureen Chase, M.D. M.P.H.[1]; Katherine M. Berg, M.D.[2]; Mark Tidswell, M.D.[4]; Tyler Giberson, B.S.[1]; Richard Wolfe, M.D.[1]; Ari Moskowitz, M.D.[5]; Howard Smithline, M.D.[6]; Long Ngo, Ph.D.[5]; Michael N. Cocchi, M.D.[1,7]
for the Center

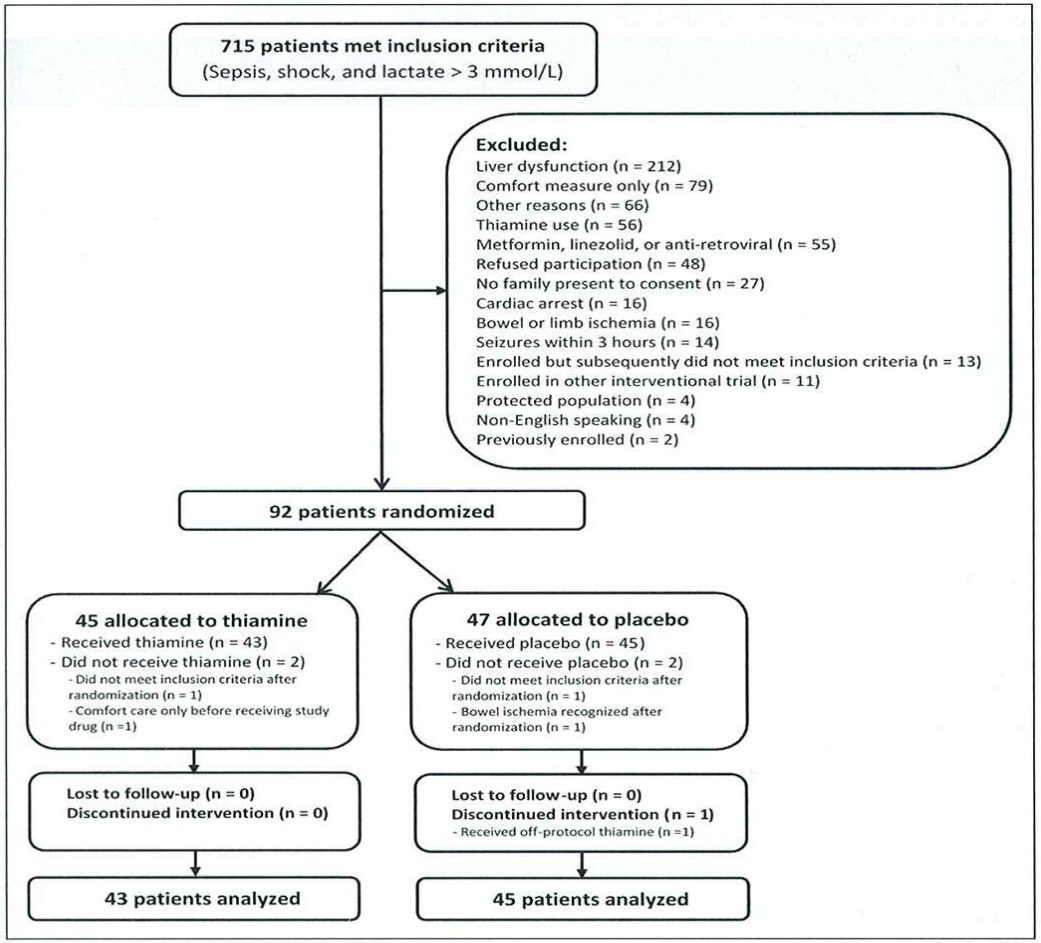


Figure 1. CONSORT flow diagram. Out of 715 patients with septic shock and elevated lactate, 88 were included in the analysis.

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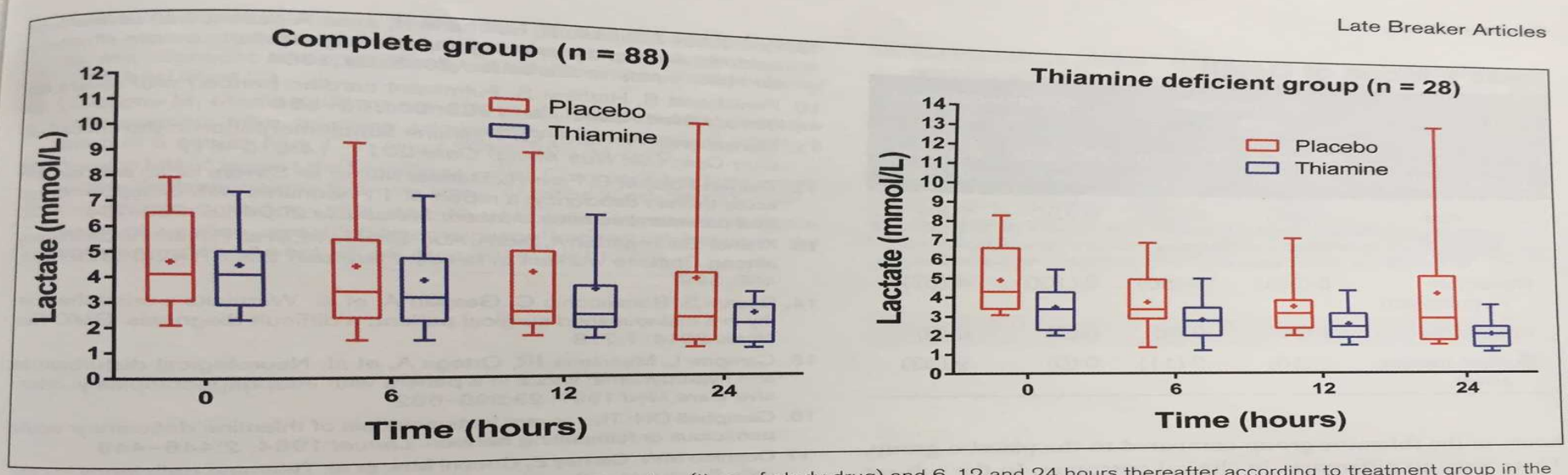

Figure 2. Lactate levels over time. Lactate levels at baseline (time of study drug) and 6, 12 and 24 hours thereafter according to treatment group in the full study group (left) and in the thiamine deficient cohort (right). The boxplots represent the 1st quartiles, median, and 3rd quartile. The whiskers represent the 10th and 90th percentile and the "+" is the mean.

was small, and future studies will be necessary to validate these findings. That thiamine would decrease lactate in deficiency states is consistent with the expected pathophysiology and suggests that a sub-clinical form of beriberi may exist in patients with septic shock. Septic shock can have manifestations of cardiac beriberi (hypotension, hyperdynamic [illegible] and thiamine levels lactate (i.e. the inclusion criteria in this study) were similar to the current trial (41).

The current trial has several limitations. Enrollments were predominately from one site and generalizability may be limited. The sample size for the thiamine deficient group was small (n = 28) and therefore the results for this population need to be reproduced. Our inclusion and exclusion criteria

Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study

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reported studies in septic shock (38–40), but this is likely reflective of differences in the inclusion/exclusion criteria. A recent, large study from the Surviving Sepsis database reveals that mortality rates among those with hypotension and elevated

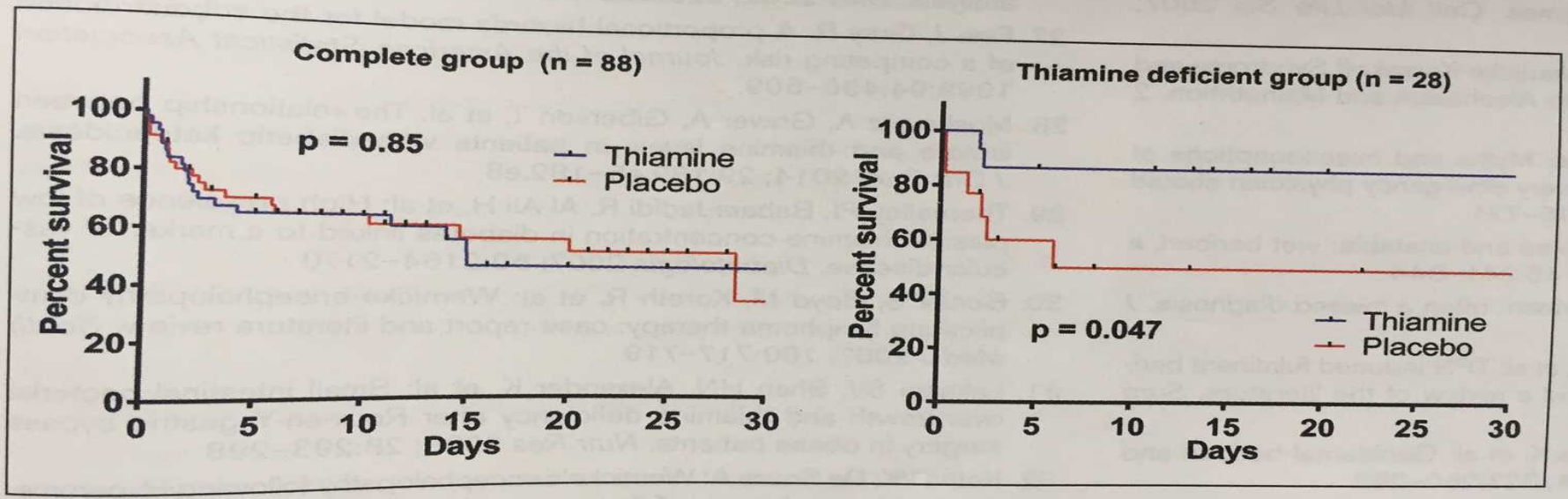


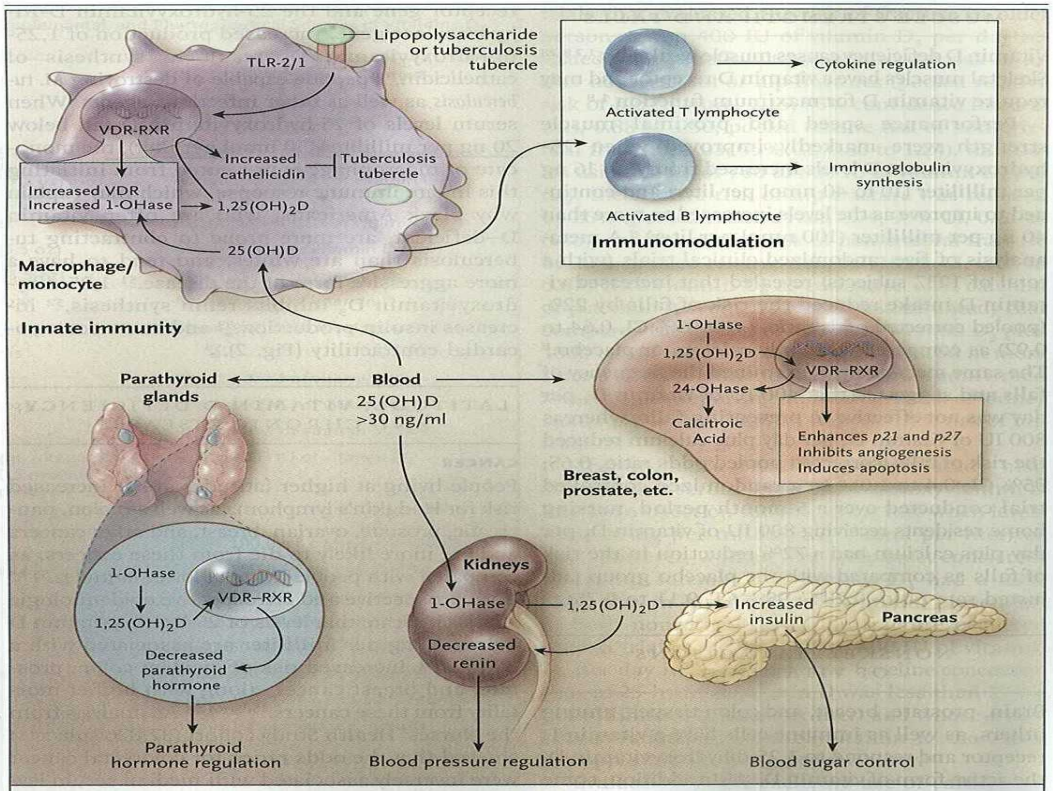
Figure 3. Kaplan Meier survival curves. Survival curves for the thiamine and placebo groups in the full study group (left) and the thiamine deficient group (right). Patients were censored at hospital discharge. The graph is truncated at 30 days for illustrative purposes. Vertical lines represents censored patients and the p-value is from the log-rank test.

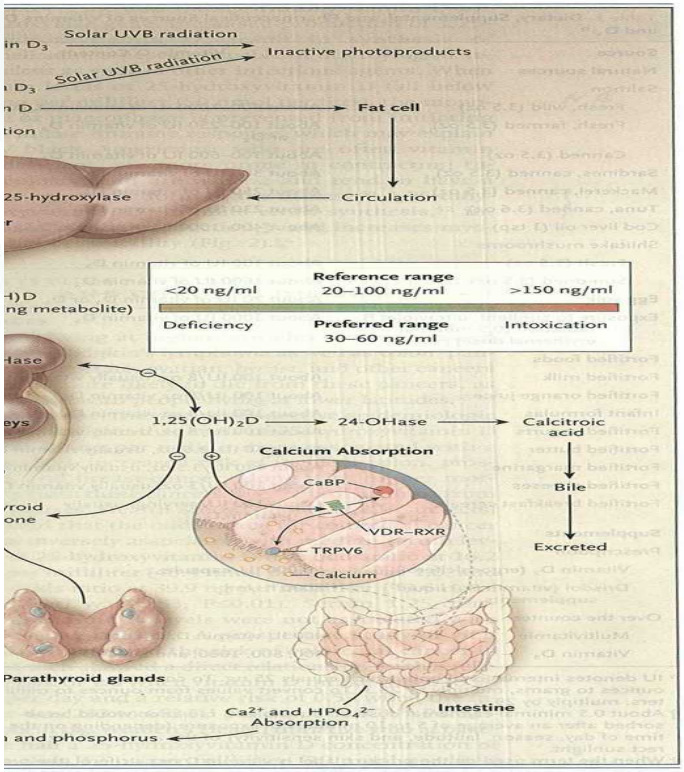
REVIEW ARTICLE

MEDICAL PROGRESS

Vitamin D Deficiency

Michael F. Holick, M.D., Ph.D.





Vitamin D Deficiency in Critically Ill Patients

Lee P. NEJM 2009, Apr 30th, vol.360:1912-13

Table 1. Characteristics of 42 Critically Ill Patients Referred for Endocrinologic Evaluation.

Characteristic	No. of Patients (%)
Sex	
Male	20 (48)
Female	22 (52)
Diagnosis	
Cardiac disease	3 (7)
Neurologic disease	3 (7)
Metabolic disease	3 (7)
Trauma	5 (12)
Sepsis	13 (31)
Respiratory disease	15 (36)
Condition identified as reason for referral*	
Hyperglycemia	27 (64)
Abnormal thyroid function	15 (36)
Hyponatremia	12 (29)
Hypocortisolemia	8 (19)
Hypocalcemia	2 (5)†
Medications	
Corticosteroids	28 (67)
Calcium supplement	12 (29)
Vitamin D supplement	10 (24)
Level of 25-hydroxyvitamin D	
Sufficient, >60 nmol/liter	3 (7)
Insufficient, >30 to ≤60 nmol/liter	23 (55)
Deficient, >15 to ≤30 nmol/liter	16 (38)
Undetectable, ≤15 nmol/liter	7 (17)

* Referrals could specify more than one condition.
† Only one of the two patients had an undetectable level of 25-hydroxyvitamin D.

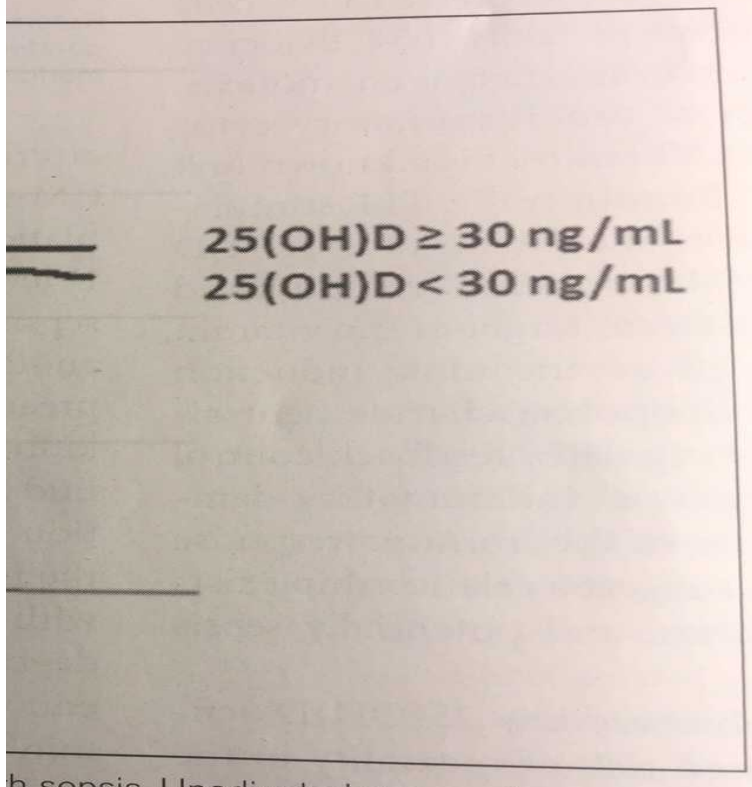
Association of Low Serum 25-Hydroxyvitamin D Levels and Sepsis in the Critically Ill

Takuhiro Moromizato, MD[1]; Augusto A. Litonjua, MD, MPH[2]; Andrea B. Braun, MD[3]; Fiona K. Gibbons, MD[4]; Edward Giovannucci, MD, ScD[5]; Kenneth B. Christopher, MD[1]

TABLE 6. Analysis of Mortality in Patients With *International Classification of Diseases*, 9th Edition, Clinical Modification–Defined Sepsis ($n = 568$)

Variable	OR	95% CI	p
Unadjusted			
In-hospital mortality			
25(OH)D < 30 ng/mL	1.43	0.96–2.14	0.08
25(OH)D ≥ 30 ng/mL	1.00	Reference	
30-d mortality			
25(OH)D < 30 ng/mL	1.38	0.92–2.05	0.1
25(OH)D ≥ 30 ng/mL	1.00	Reference	
90-d mortality			
25(OH)D < 30 ng/mL	1.41	0.98–2.03	0.07
25(OH)D ≥ 30 ng/mL	1.00	Reference	
Adjusted			
In-hospital mortality			
25(OH)D < 30 ng/mL	1.62	1.07–2.46	0.02
25(OH)D ≥ 30 ng/mL	1.00	Reference	
30-d mortality			
25(OH)D < 30 ng/mL	1.55	1.02–2.34	0.04
25(OH)D ≥ 30 ng/mL	1.00	Reference	
90-d mortality			
25(OH)D < 30 ng/mL	1.63	1.11–2.39	0.01
25(OH)D ≥ 30 ng/mL	1.00	Reference	

OR = odds ratio, 25(OH)D = 25-hydroxyvitamin D.
Reference in each case is 25(OH)D ≥ 30 ng/mL. Estimates adjusted for age, gender, race (White, non-White), Deyo-Charlson index, and type (surgical vs medical).



h sepsis. Unadjusted event rates
ared with the use of the log-rank test.
ry analyses. Observations are truncated at

Hypocholesterolemia in SIRS and Sepsis

Lipoproteins : HDL-chol., LDL-chol. during SIRS have a function like negative Acute Phase proteins . Intesity of systemic inflammatory response correlates with plasmatic leves of HDL-chol. , and total cholesterol

HUDGINS L.,et al, J.LIPID RES 2003.-

HDL-cholesterol bind and inactivate endotoxin (LPS)

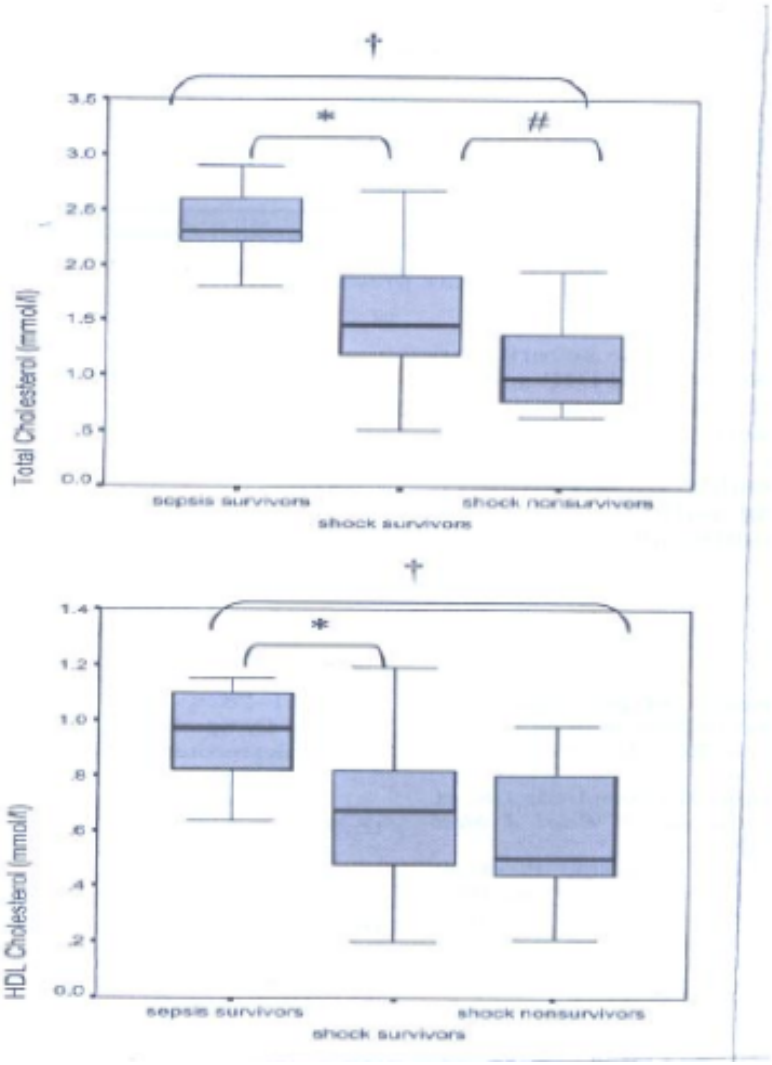
LEVINE 1993

SIRS after trauma, severe burns, after major surgery, or sepsis signific decrease in blood plasma total cholesterol, HDL-chol, LDL-chol, apo-A1, PC – fosfatidyl cholín.

Serum lipids in children with severe meningococceal sepsis.

Vermont C et al, CCM 2005, 33: 1610-1615

- Meningococc. Sepsis and men. Septic shock is associated with decline of total cholesterol, HDL-c, LDL-c.
- Total cholest. in plasma is significantly lower in nonsurvivors than in survivors
- Hypocholesterolemia is associated with hypokortisolism
- Surviving children after 24 hours are able to increase plasm. concentration of total cholesterolu and HDL-c, LDL-c.



Low Preoperative Cholesterol Level Is a Risk Factor of Sepsis and Poor Clinical Outcome in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass*

Laurent Lagrost, PhD[1,2]; Claude Girard, MD, PhD[1,2]; Sandrine Grosjean, MD, PhD[1,2]; David Masson, PharmD, PhD[1,2]; Valérie Deckert, PhD[1]; Thomas Gautier, PhD[1]; Frédérique Debomy, MS[2]; Sandrine Vinault, BSc[3]; Aline Jeannin, MS[1]; Jérôme Labbé, MS[1]; Claire Bonithon-Kopp, MD, PhD[1,3]

patients with sepsis than in those without sepsis (**Fig. 2**). As shown in **Figure 3**, the ROC analysis revealed that the discriminative power of baseline cholesterol with regard to sepsis was fairly good as assessed by an AUC of 0.78 (95% CI, 0.72–0.84). Finally, and in addition to the higher propensity to develop sepsis, a low plasma cholesterol level at baseline was found to be associated with more complications and the greater use of aggressive therapeutic strategies. This is underlined by the multivariable analysis, baseline cholesterol, along with CPB time, was found to be an independent and significant determinant of PCT and IL-8 [illegible] addition to female gender for IL-8. In contrast, [illegible]-8, baseline cholesterol was not an independent factor of IL-6 elevation, which was only related to CPB time, and to a lesser extent to atrial fibrillation (**Table 5**). Further adjustment for statin use did not alter these results.

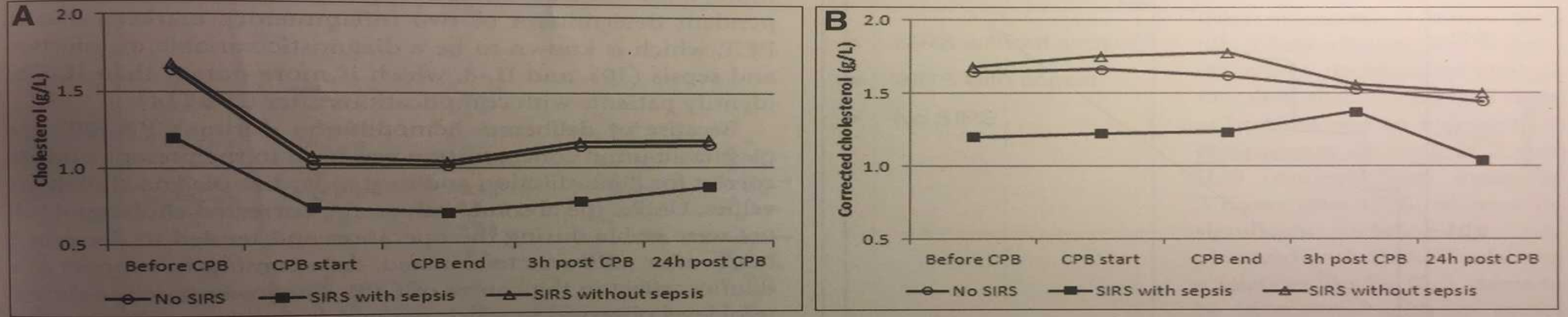


Figure 1. Time-course curves of cholesterol concentrations in patient subgroups. Plasma cholesterol concentrations in patients without systemic inflammatory response syndrome (SIRS), with SIRS without sepsis, and with SIRS with sepsis were expressed as absolute values (**A**) or as corrected for hemodilution using albuminemia (**B**) (see *Materials and Methods* section). In all patient subgroups, changes in absolute cholesterol concentration from baseline values and during the course of operation were statistically significant ($p < 0.009$ in all cases—a). When values were corrected for hemodilution, plasma cholesterol was stable during cardiopulmonary bypass (CPB) in all subgroups and it decreased significantly 24 hr after CPB in sepsis patients, and 3 hr and 24 hr after CPB in non-SIRS patients and in SIRS patients without sepsis ($p < 0.01$ in all cases—b). At any time point, and whether values were corrected or not for hemodilution, plasma cholesterol concentration was constantly and significantly lower in sepsis patients than in patients without sepsis ($p < 0.001$), with the exception of the 3-hr post-CPB time point when there was no significant difference between the three subgroups.

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TABLE 4. Main Complications and Therapeutic Strategies After Cardiopulmonary Bypass Surgery by Quintiles of Baseline Cholesterol Levels

Follow-Up Variables	Q1 Cholesterol < 1.23 g/L (*n* = 43)	Q2 Cholesterol (1.23–1.55 g/L) (*n* = 43)	Q3 Cholesterol (1.55–1.74 g/L) (*n* = 44)	Q4 Cholesterol (1.74–2.03 g/L) (*n* = 43)	Q5 Cholesterol ≥ 2.03 g/L (*n* = 44)	*p*
Median intubation duration, hr	12.6 (9.2–25.5)	12.4 (9.3–19.9)	10.3 (8.5–16.1)	10.6 (8.7–13.6)	9.8 (8.1–13.6)	0.049
Intubation duration > 24 hr (%)	28.6	14.6	13.6	4.7	9.1	0.022
Noradrenaline use (%)	60.7	53.5	59.1	48.8	29.6	0.028
Intra-aortic balloon counterpulsation (%)	9.3	7.0	6.8	2.3	0	0.22
Dialysis (%)	4.7	7.0	0	0	0	0.048
Blood transfusion (%)	51.2	46.5	47.7	41.9	18.2	0.013
Atrial fibrillation[a] (%)	20.9	18.6	22.7	18.6	18.2	0.98
Renal failure[a] (%)	23.3	27.9	29.6	25.6	22.7	0.94
Sepsis (%)	18.6	9.3	4.6	2.3	0	0.005

[a]New occurrence of atrial fibrillation or renal failure after cardiopulmonary bypass surgery.

Antioxidant supplementation in sepsis and systemic inflammatory response syndrome.

Berger M, Chioléro R., CCM 2

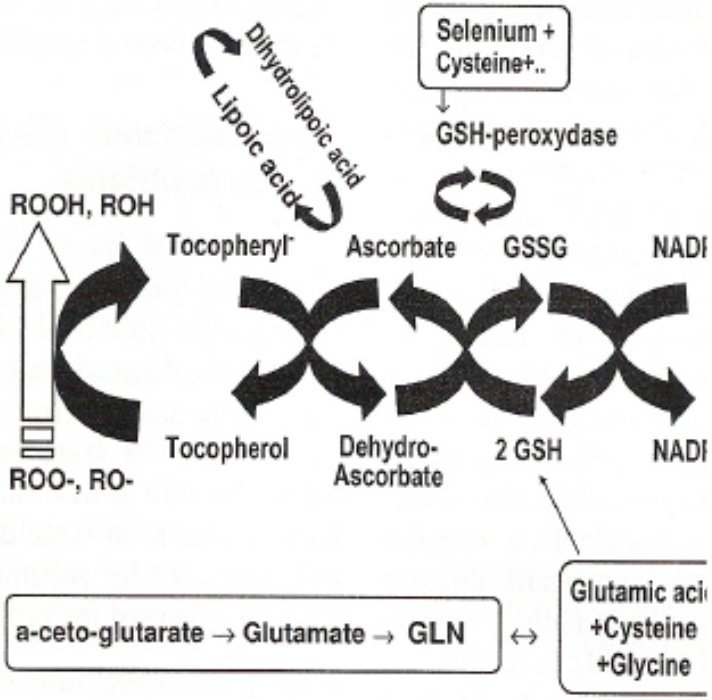


Figure 1. Conceptual description of interactions between selected antioxidants, s
tions in the antioxidant spiral of the various endogenous antioxidants. *GSH*,
hydroperoxides; *ROH*, hydroxy derivatives of hydroperoxides; *ROO*, cumene
radical; *GSSG*, oxidized glutathione; *NADPH*, nicotinamide adenine dinucleotide p
state; *NADP*, nicotinamide adenine dinucleotide phosphate in oxidized state.

Characteristics of trace element supplementation studies.

Trial	Critical Illness	No. of Patients	Micronutrients	End point
Kuklinski 1991[24]	Pancreatitis	17	Selenium	Mortality
Young 1996[25]	Head injury	68	Zinc	Neurological outcome Mortality
Zimmerman 1997[26]	SIRS	40	Selenium	Mortality
Berger 1998[27]	Burns	20	Selenium, Copper, Zinc	Infection Length of Stay
Angstwurm 1999[28]	Sepsis/SIRS	42	Selenium	Blood antioxidant status Mortality
Porter 1999[29]	Trauma	18	Selenium	Infection Length of Stay
Berger 2001[30,31]	Trauma	32	Selenium, Copper, Zinc	Blood antioxidant status Thyroid hormone metabolism
Berger 2004[32]	Burns	21	Selenium, Copper, Zinc	Blood antioxidant status Skin protein turnover
Berger 2006*[33]	Burns	41	Selenium, Copper, Zinc	Blood antioxidant function Infections (pneumonia)
Mishra 2007[34]	Sepsis/SIRS	40	Selenium	SOFA score, Mortality Antioxidant function
Angstwurm 2007[35]	Sepsis/SIRS	249	Selenium	Mortality
Forceville 2007[36]	Septic shock	60	Selenium	Time to vasopressor withdrawal Mortality
Berger 2008[37]	Cardiac surgery, major trauma, SAH	200	Selenium, Zinc,	Organ dysfunction
Beale 2008[38]	Sepsis	55	Selenium, Zinc	Organ dysfunction (SOFA)

Mortality in TCR SIC 2005... Angstwurm 2007

Table 1. Mortality rate of per-protocol population

	Se1 (n = 92)		Se0 (n = 97)		Comparison of Treatment Groups				
Visit, Days	No.	%	No.	%	χ^2 Test	*p* Value	Odds Ratio	Lower CI	Upper CI
7	20	21.7	28	28.9	1.27	.261	0.68	0.35	1.33
14	28	30.4	42	43.3	3.35	.067	0.57	0.31	1.04
21	35	38.0	51	52.6	4.02	.045	0.55	0.31	0.99
28	39	42.4	55	56.7	3.87	.049	0.56	0.32	1.00

Se1, treatment group; Se2, placebo group; CI, confidence interval.

28-day mortality
Intention-to-treat
238 pac. (39% vs 50%
Absolute reduction mortality o 10.3%
P= 0.109
Per - protokol
Absolute reduction in mortality o 14.3 %.
P = 0.049 !

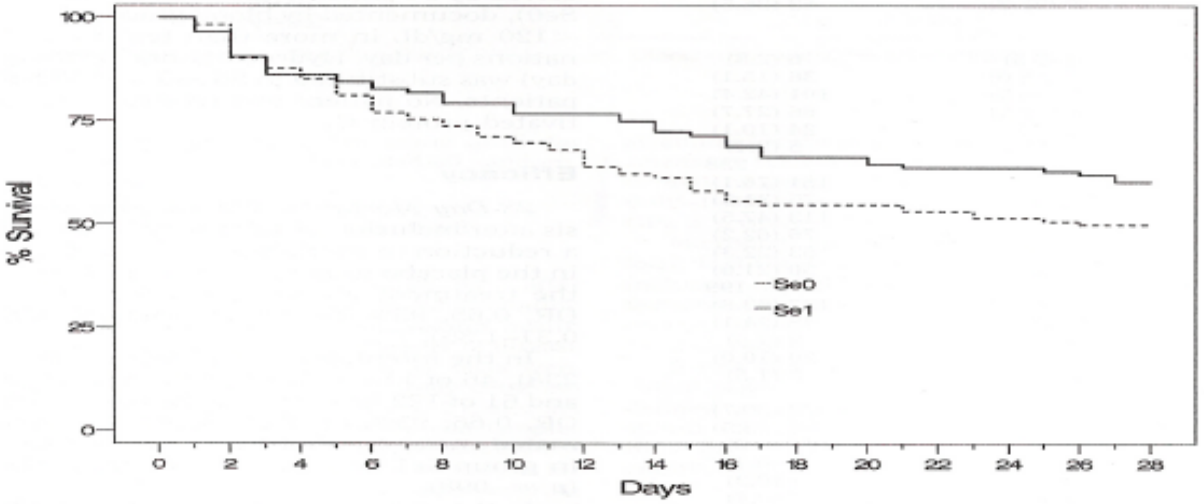


Figure 2. Survival time. Survival curves in patients of the intention-to-treat analysis were generated by the Kaplan-Meier curve. Difference between groups was calculated by the log rank test. The estimated mean survival time was 20.3 days in treated patients (*solid line*) compared with 17.6 days in the placebo group (*dotted line*) ($p = .098$). *Se1*, treatment group; *Se0*, placebo group.

Selenium supplementation in critically ill pts: a systematic review and meta-analysis. Landucci F et al. J. Crit Care 2014, 29: 150-56

- 9 RCT met inclusion criteria. Selenium supplementation was associated with a reduction in 28-day mortality of borderline statistical significance p=0,04 and RR = 0, 84
- Significant effects regarding the supplementation with doses of **selenium =< 500 ug/day** in adults , or 5-7 ug/kg IBW /day.
- The use of high-dose selenium might be associated with beneficial effects on 28-day mortality in critically ill patients

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

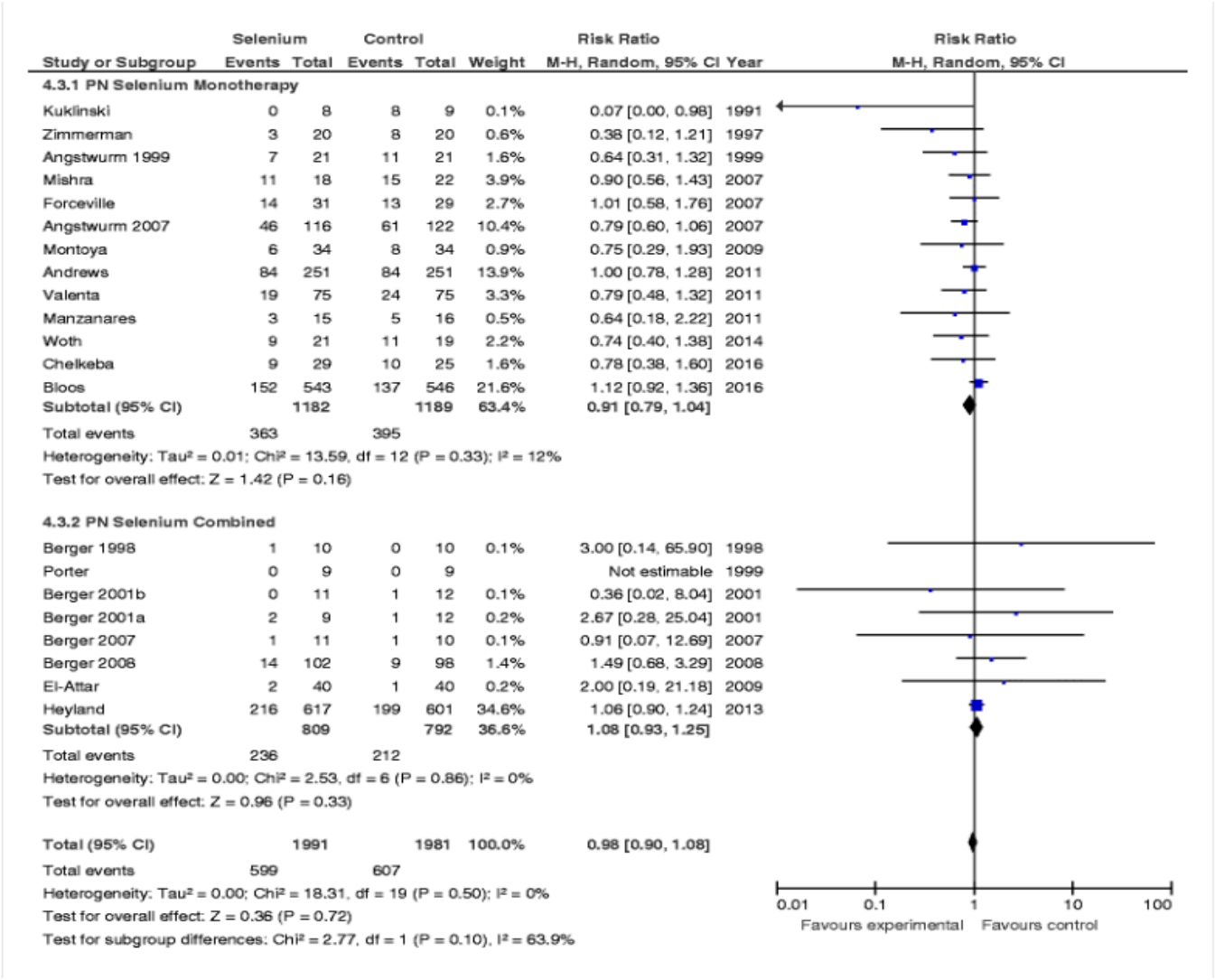
Manzanares W. et al, Crit Care 2016

exploring 21 RCT (1991-2016)

- Recently, in the largest trial on IV Se monotherapy (SISPCT), investigators **were unable to find any clinical benefit of high-dose sodium selenite in patients with sepsis and septic** shock. (*Bloos et al, JAMA 2016).*
- According to our findings, there is no evidence for a beneficial effect on mortality, infections, and other relevant clinical outcomes of high-dose IV Se as single or combined therapy (antioxidant cocktails) in critically ill patients.
- IV Se may be able to significantly reduce infections in those studies performed with nonseptic patients and when **high-dose Se as an initial IV bolus is not administered**

High-dose intravenous selenium does not improve clinical outcomes in the critically ill: a systematic review and meta-analysis. 21 RCTs on high-dose selenium...

Manzanares W. et al, Crit Care 2016 , vol.20,R



Conclusions

- Metabolic resuscitation in sepsis is an important part of complex multimodal therapy of sepsis /SIRS and MODS
- In sepsis and critical illness is significant decrease of vitamins, and micronutrients in blood plasma|tissues
- Altered „stressed“ metabolism, hypermetabolism, and functional deterioration of metabolic pathway need
- Strong metabolic support with metabolic „resuscitators“
- Supplementation with high–dose vitamines (B1, C, E, D) micronutrients (Se, Zn), thiol-rich (taurin, cystein) and cholesterol-rich substances (eg.FFP) at least few days

Lipid-soluble vitamins in CIP

Vitalipid – účinné látky (10 ml)

- A: Retinolipalmitas 1941 µg (3300 IU)
- D: Ergocalciferolum 5 µg (200 IU)
- E: Tocoferolum alfa 9,1 µg (10 IU)
- K1: Phytomenadionum 150 µg (150 IU)

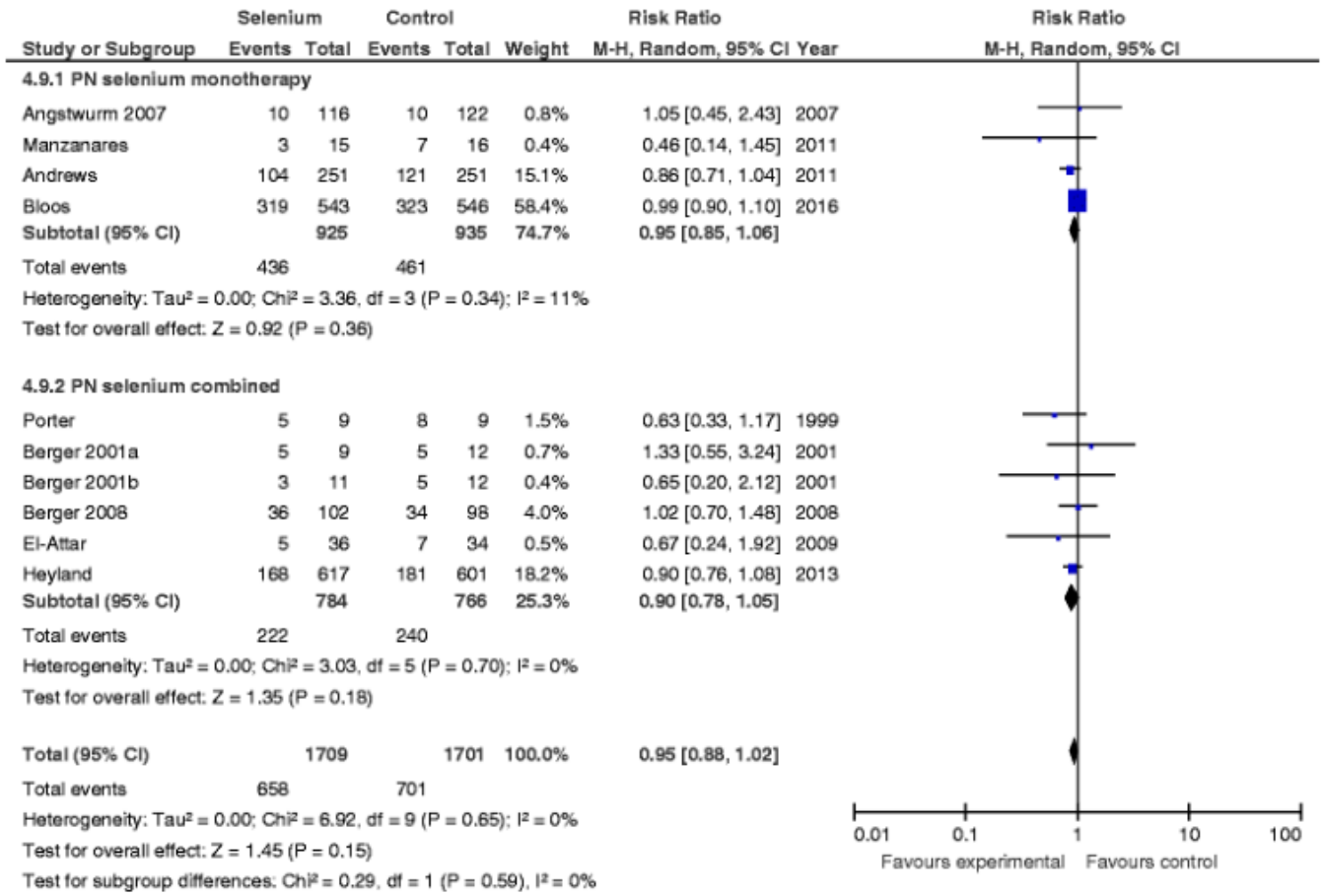

Selenium
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
4.9.1 PN selenium monotherapy
Angstwurm 2007 10 116 10 122 0.8% 1.05 [0.45, 2.43] 2007
Manzanares 3 15 7 16 0.4% 0.46 [0.14, 1.45] 2011
Andrews 104 251 121 251 15.1% 0.86 [0.71, 1.04] 2011
Bloos 319 543 323 546 58.4% 0.99 [0.90, 1.10] 2016
Subtotal (95% CI) 925 935 74.7% 0.95 [0.85, 1.06]
Total events 436 461
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.92 (P = 0.36)
4.9.2 PN selenium combined
Porter 5 9 8 9 1.5% 0.63 [0.33, 1.17] 1999
Berger 2001a 5 9 5 12 0.7% 1.33 [0.55, 3.24] 2001
Berger 2001b 3 11 5 12 0.4% 0.65 [0.20, 2.12] 2001
Berger 2008 36 102 34 98 4.0% 1.02 [0.70, 1.48] 2008
El-Attar 5 36 7 34 0.5% 0.67 [0.24, 1.92] 2009
Heyland 168 617 181 601 18.2% 0.90 [0.76, 1.08] 2013
Subtotal (95% CI) 784 766 25.3% 0.90 [0.78, 1.05]
Total events 222 240
Heterogeneity: Tau² = 0.00; Chi² = 3.03, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Total (95% CI) 1709 1701 100.0% 0.95 [0.88, 1.02]
Total events 658 701
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 9 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%
0.01
0.1
1
10
100
Favours experimental
Favours control

Fig. 2

Recommended doses of micronutrients in critically patients , dose of selenium up to 500 ug/5 days

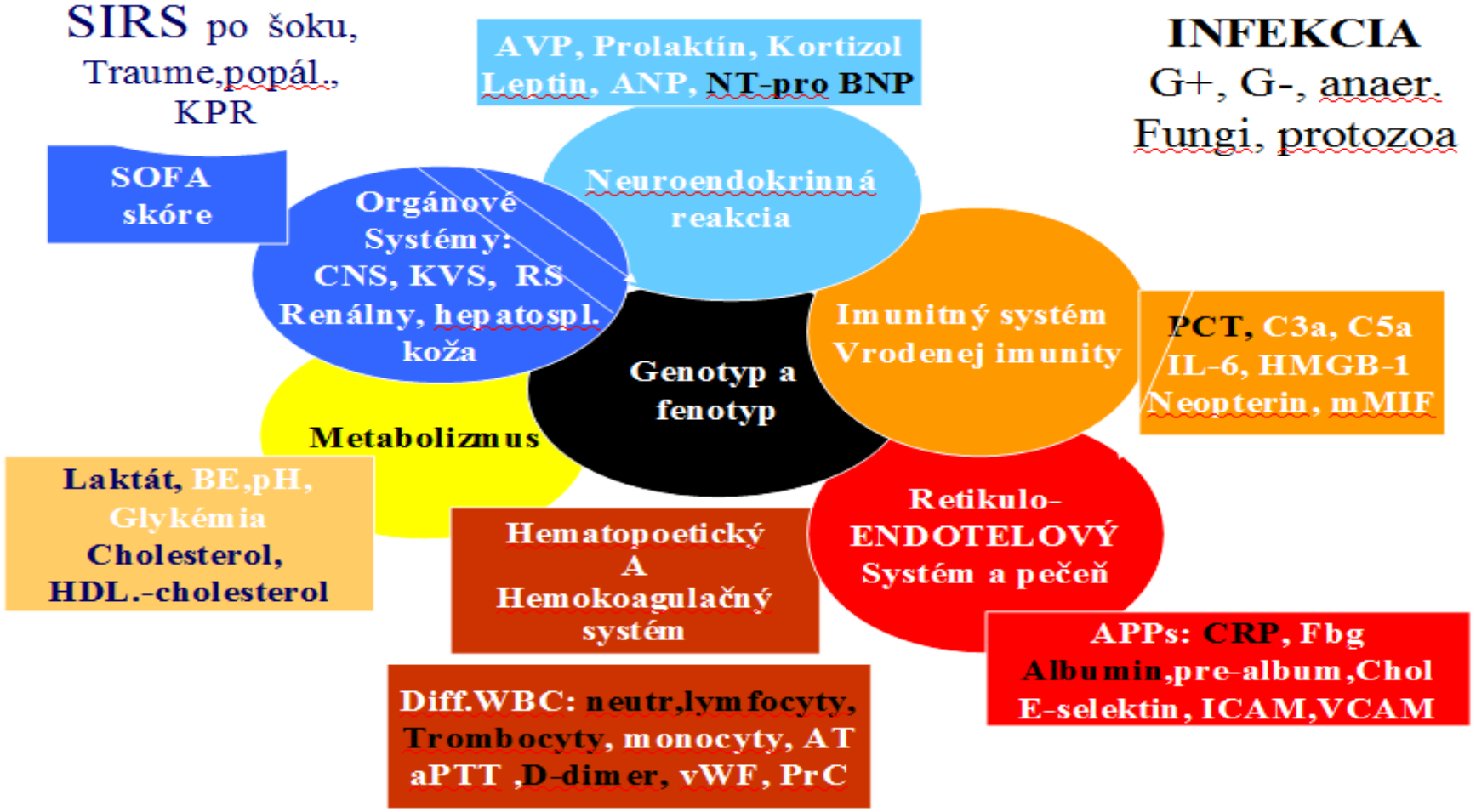
Odporučené denné d. v PEN

chromium	10–20 µg (= 0.05–0.10 µmol)
copper	0.3–1.2 mg (= 4.7–18.8 µmol)
iodine	70–140 µg (= 0.54–1.08 µmol)
iron	1–1.5 mg (= 18–27 µmol)
manganese	0.2–0.8 mg (= 3.6–14.6 µmol)
selenium	20–80 µg (= 0.25–1.0 µmol)
zinc	2.5–4 mg (= 38–61 µmol)

Biesalski HK.et al.,: Water, electrolytes, vitamins and trace elements –
Guidelines on Parenteral Nutrition, GMS 2009

Seven systems and organs responsible for pathobiology and develpoment of Sepsis

Kliknúť na vloženie nadpisu



Metabolic resuscitation of energetic metabolism in Mitochondria afer ischemia/ hypoxia Weinberg JM, 2002

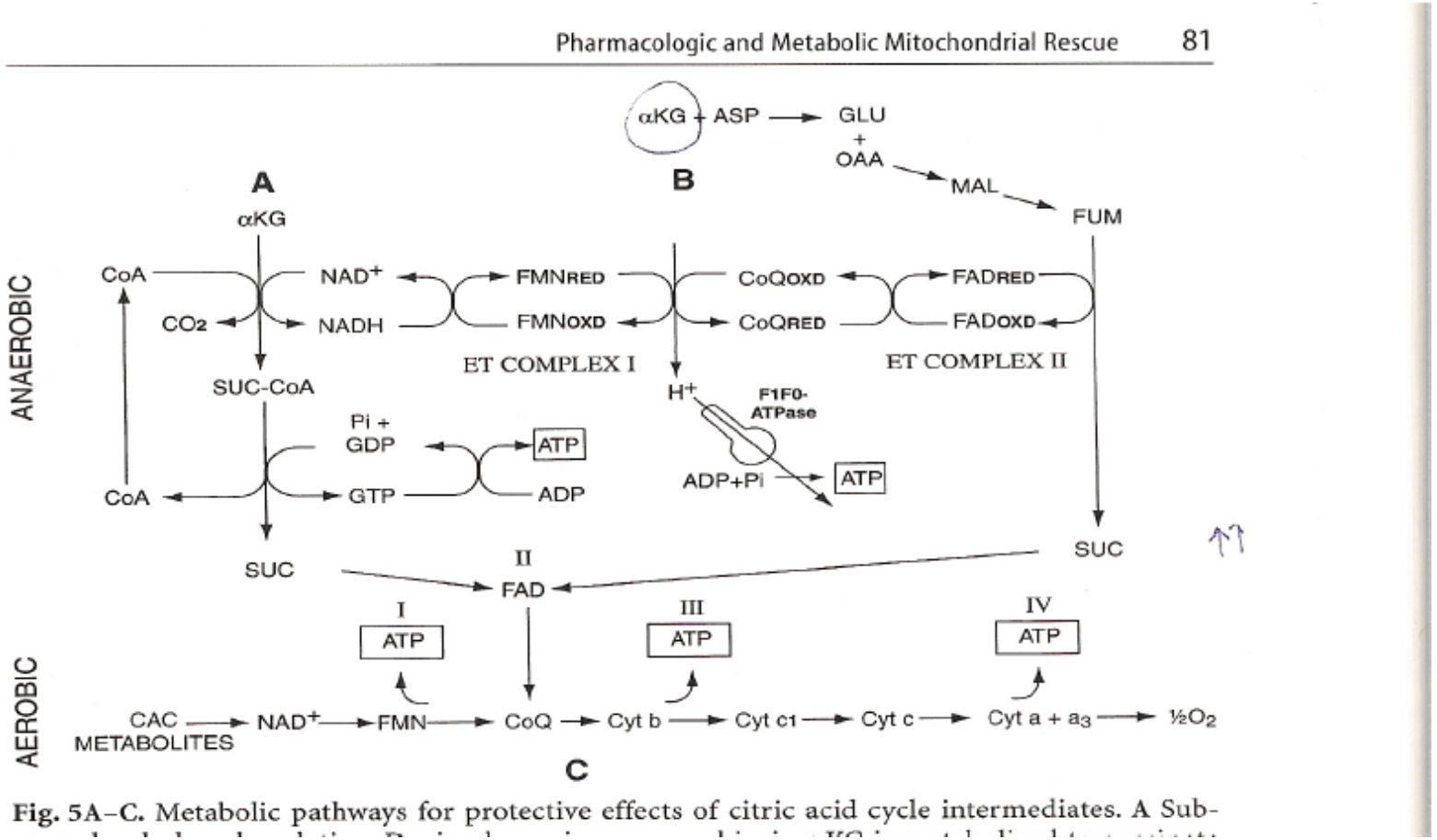


Fig. 5A–C. Metabolic pathways for protective effects of citric acid cycle intermediates. A Sub-

Referenčné hodnoty selénu u zdravej populácie Angstwurm, CCM 2007, 35:118-

Látka	Fyziologické Hodnoty µmol/l	Fyziologické hodnoty µg/l
Selén v plazme	0.72 – 1.33	74 – 140
Selén v plnej krvi	0.96 – 1.78	89 – 168
Aktivita GPx-3	96 -150 IU/L	
Selén v moči	0.02 – 0.79	0.16 - 80

SIRS after abdominal surgery – cholesterol levels.

Uhliarikova et al. 2008

CHOLESTEROL LEVELS in CANCER pts
After abdominal colorectal surgery – 41 pts

New clinical criteria for septic shock: serum lactate level as new emerging vital sign

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Email: anws@dau.ac.kr.