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Standardisierung der Ernährung in der Intensivmedizin

Standardized supply of micronutrients

Friday 18 June 2001, 4.30

Prof Mette M Berger
Service de Médecine Intensive Adulte & Brûlés
CHUV – Lausanne

CHUV

Essential Micronutrients

AOX

Trace elements (11)		Vitamins (13)	
Cu	Copper	A	Retinol
Se	Selenium	D	Cholecalciferol*
Zn	Zinc	E	Alpha-tocopherol
Fe	Iron	K	Phyloquinone
Mn	Manganese	B1	Thiamin
Mo	Molybdenum	B2	Riboflavin
Cr	Chromium	B3	Niacin(PP)*
F	Fluoride	B5	Pantothenic acid
I	Iodide	B6	Pyridoxine
Co	Cobalt	B8	Biotine(H)
V	Vanadium	B9	Folic acid
		B12	Cobalamin
+	Ni, Si, Sn,	C	Ascorbic acid

* Synthetized by the body

Micronutrient Functions

Nutrition + Anabolism	Prevention of deficiencies: enzyme cofactors of carbohydrate, lipid and protein metabolism
Immunity	Humoral: immunoglobulin production Cellular: macrophages, neutrophil, lymphocytes
Regulation	Gene expression, transcription factors
AOX defence	Confine free radicals in defined spaces and [ ] Modulation of the extension of acute diseases Prevention of chronic diseases

Selenium & Selenoproteins (Reeves-Hoffman, Cell Molec Life, 2009)

Glutathione peroxidases

GPx1: cellular GPx – most abundant, ubiquitous; one of the most sensitive to changes in Se status

GPx2: gastrointestinal tract (max crypts)

GPx3: plasma – regulates bioavailability of NO in platelets and endothelial cells

GPX4: lipid peroxidation - cytosol + nucleus, ubiquitous

GPX5: epididymal androgen-related

GPx6: embrio life, olfactory epithelium

Thioredoxin reductases

Txnrd1 (=TrxR1): cytoplasmic / nuclear

Txnrd2: mitochondrial

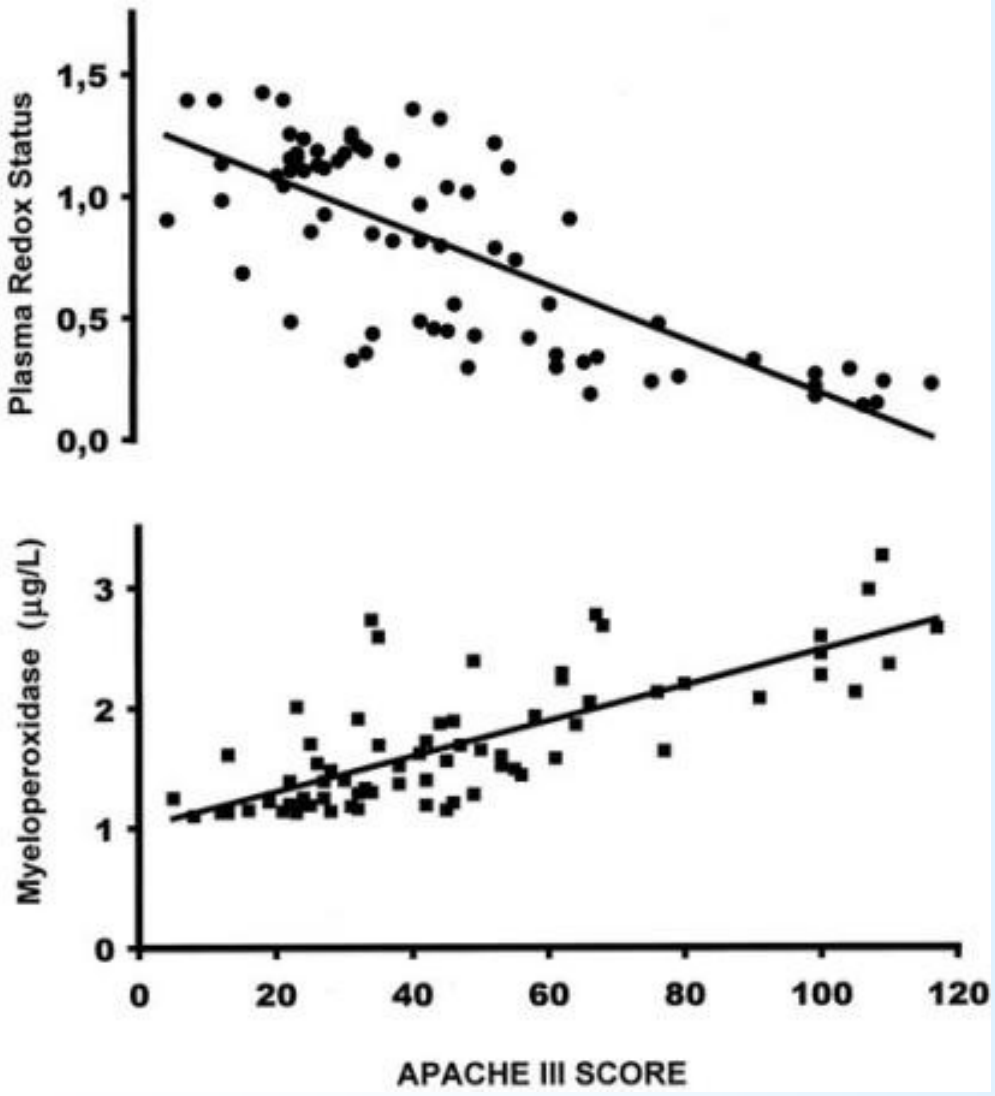
Txnrd3: testes-specific

Deidodinases: D1, **D2**, D3 – membrane anchored enzymes

Selenoproteins: H, I, K, M, N, O, **P**, R, S, V, W

Plasma redox status relates to severity in critically ill patients

Alonso de Vega J et al, CCM 28:1812, 2000

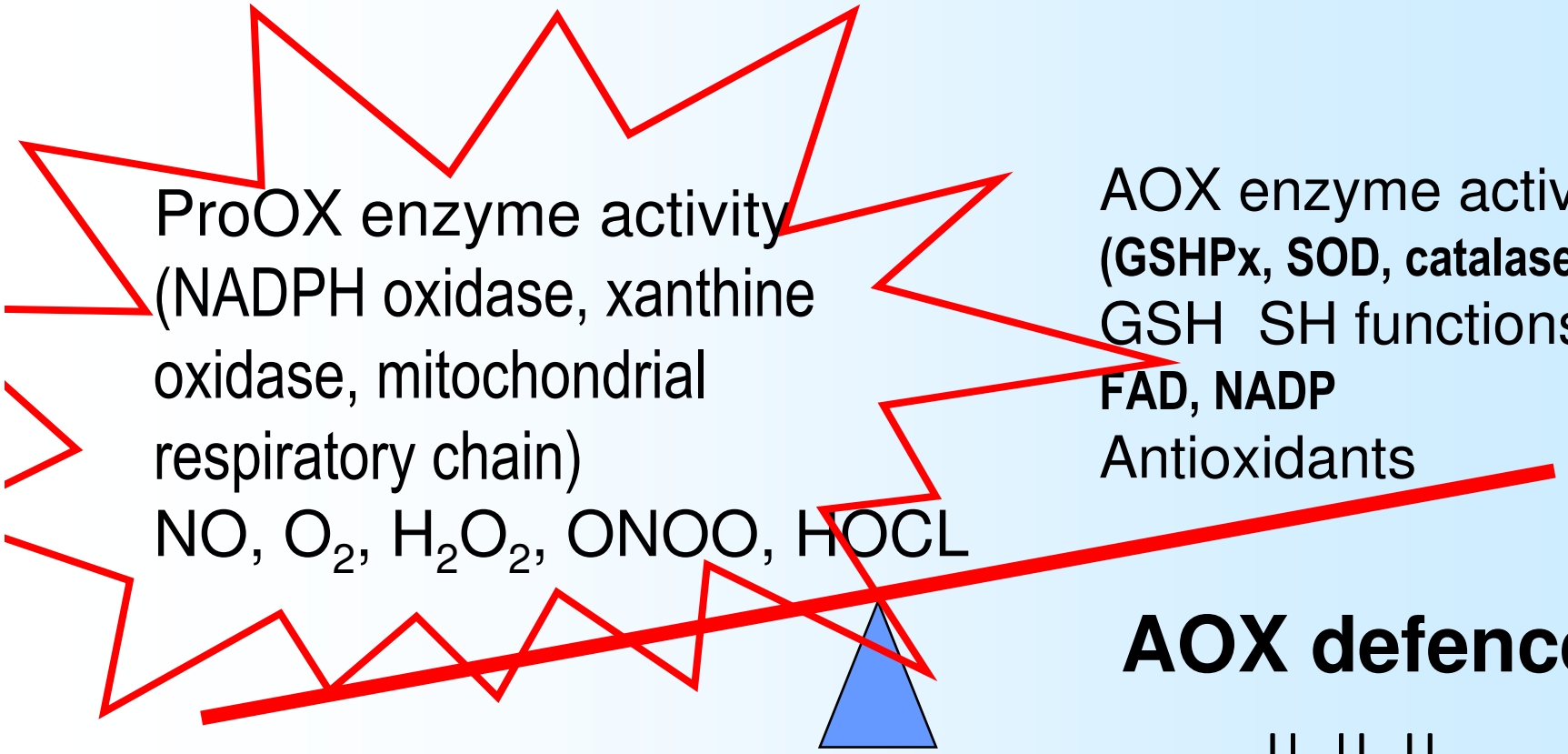


APACHE III scores and plasma redox status ($r^2 = 0.56$; $p < .001$) as defined by the ratio total antioxidant capacity (mM) / lipoperoxides (uM)

APACHE III scores and plasma myeloperoxidase concentrations ($r^2 = 058$; $p < .001$)

73 patients at admission to a mixed ICU: 8 deaths

Redox balance during critical illness



AOX defences

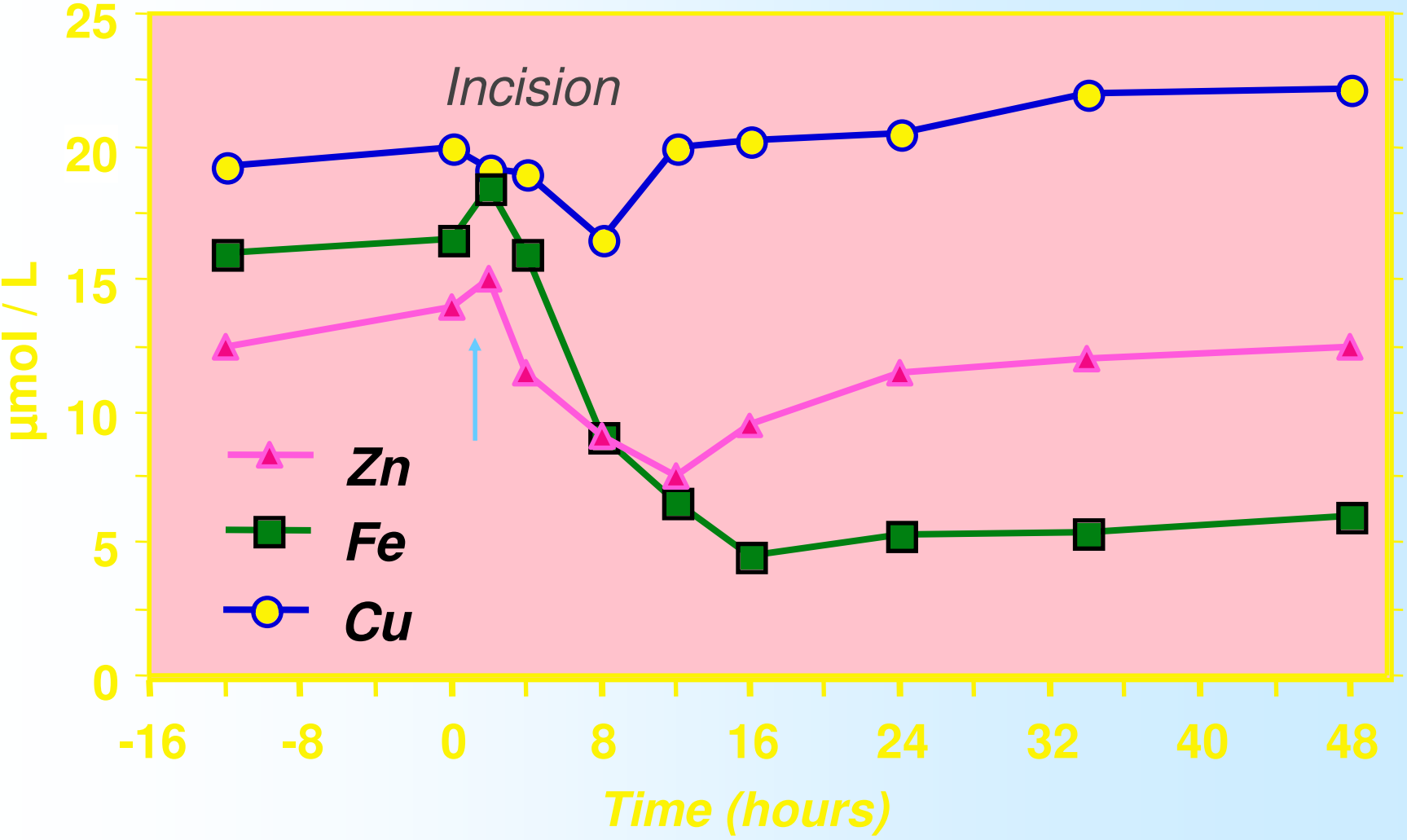
⇓ ⇓ ⇓

Oxidative stress

ICU patients ⇑ ⇑ ⇑

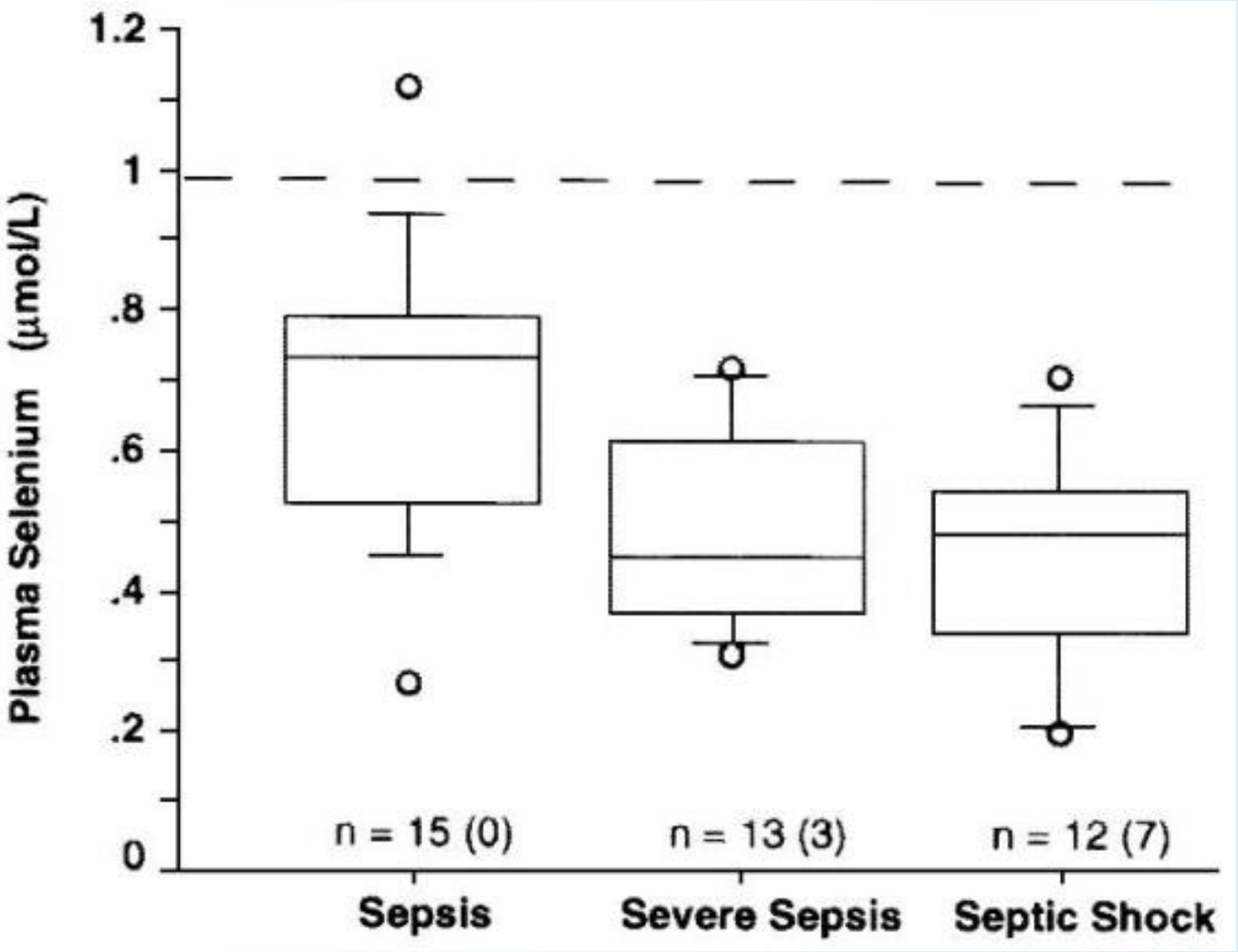
Trace elements
Acute phase response

Shenkin, Nutrition 11:100, 1995



Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients

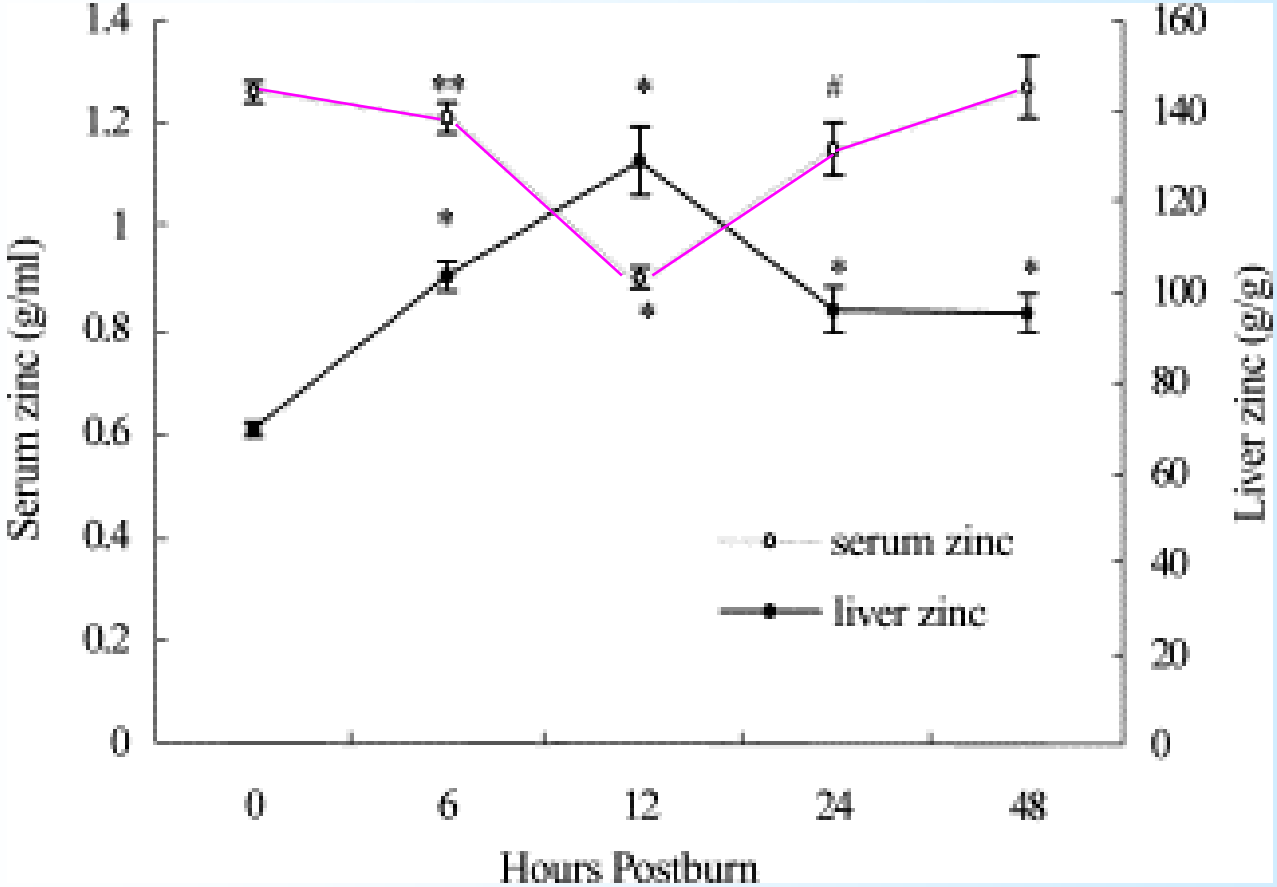
Forceville X et al, CCM 26:1536, 1998



Admission plasma [Se] related to severity of sepsis

Oxidative stress and metallothionein expression - liver of rats with severe thermal injury

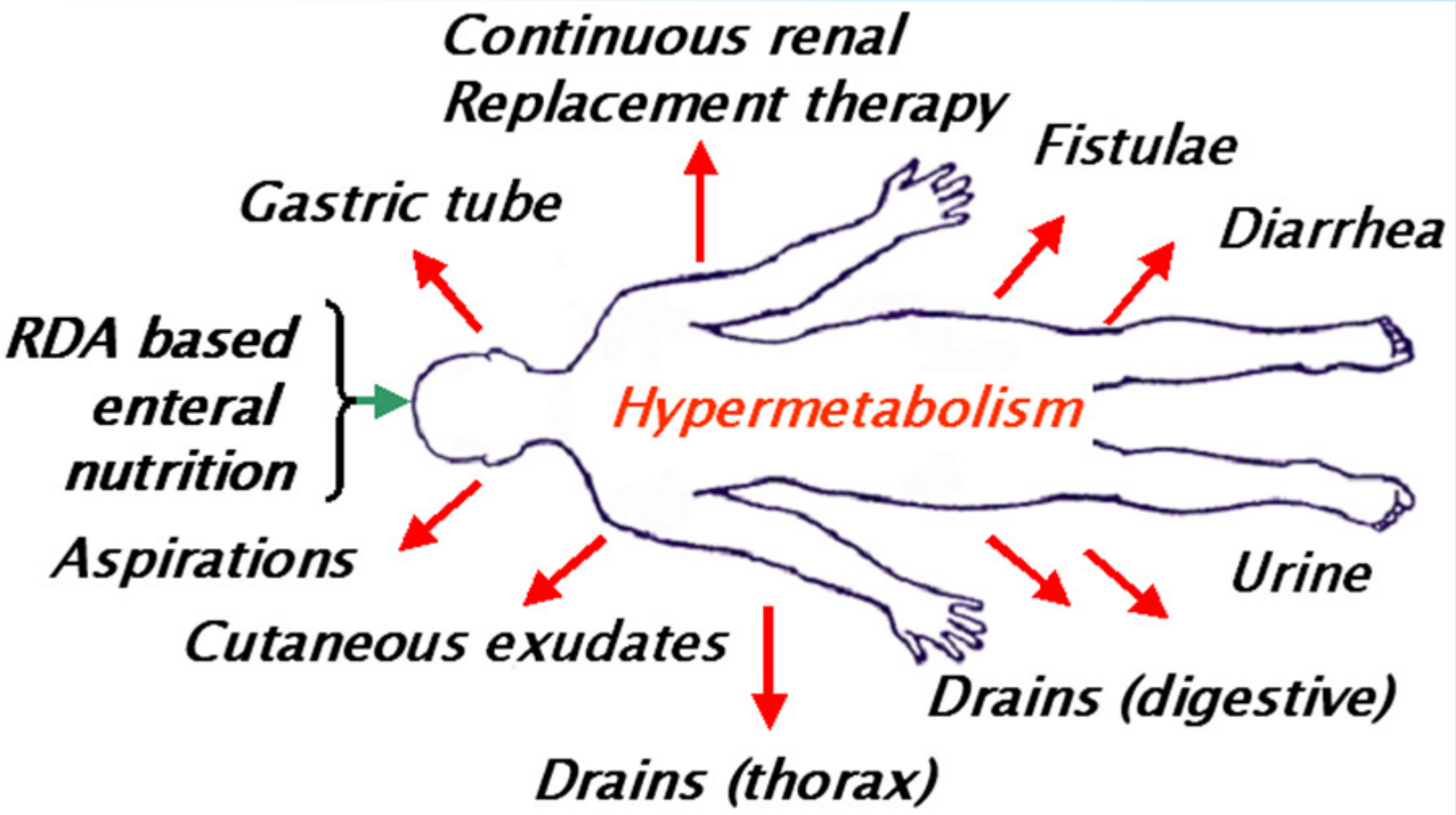
Ding et al Burns, 28:215, 2002



Effects of severe thermal injury on the zinc concentrations both in the serum and in the liver. mean±sem, n=5. $^{*}P<0.001$, $^{**}P<0.01$ and $^{\#}P<0.05$ vs. the corresponding normal control

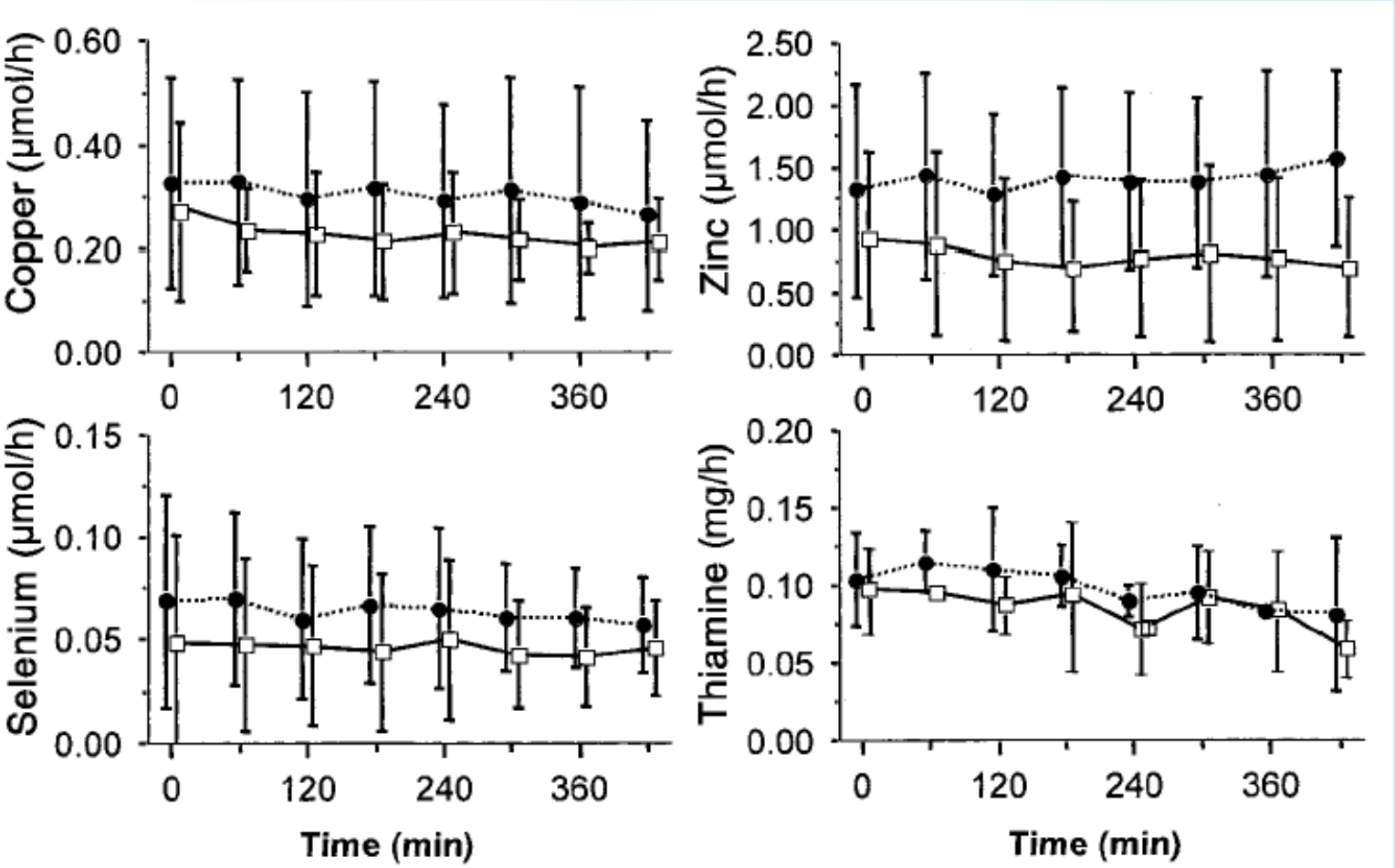
Negative balances – the causes in critically ill

Berger, NCP 21:438, 2006



Micronutrient losses during CVVH

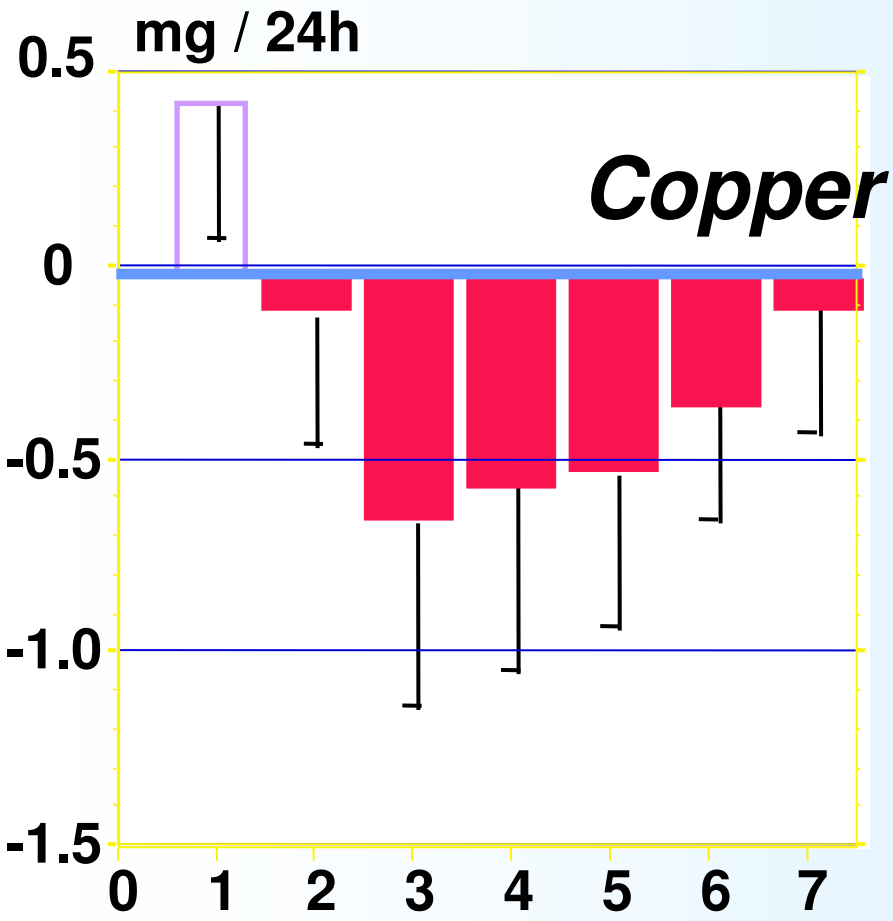
Berger MM et al, Amer J Clin Nutr, 410, 2004



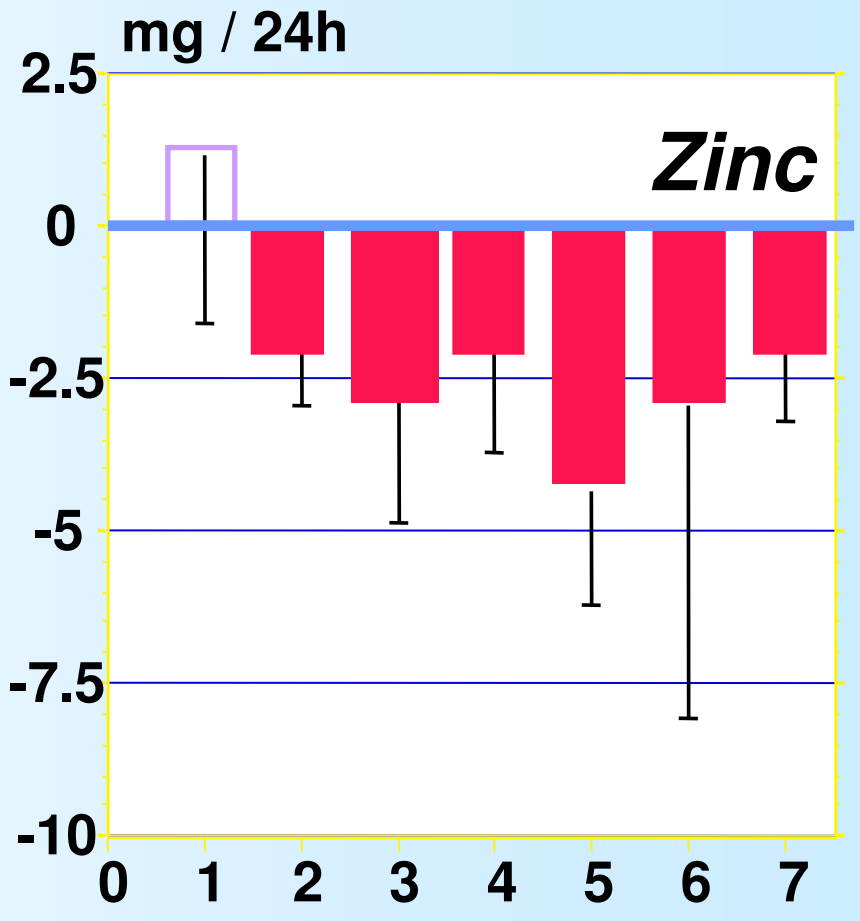
Plasma Cu, Se, Zn, and thiamine in effluents from patients with acute renal failure under CRRT with either Na-bicarbonate (Bic group; Full) or Na- lactate (Lac group;)

Cu, Se & Zn balances after major trauma

Berger MM et al, J Trauma, 40:103, 1996



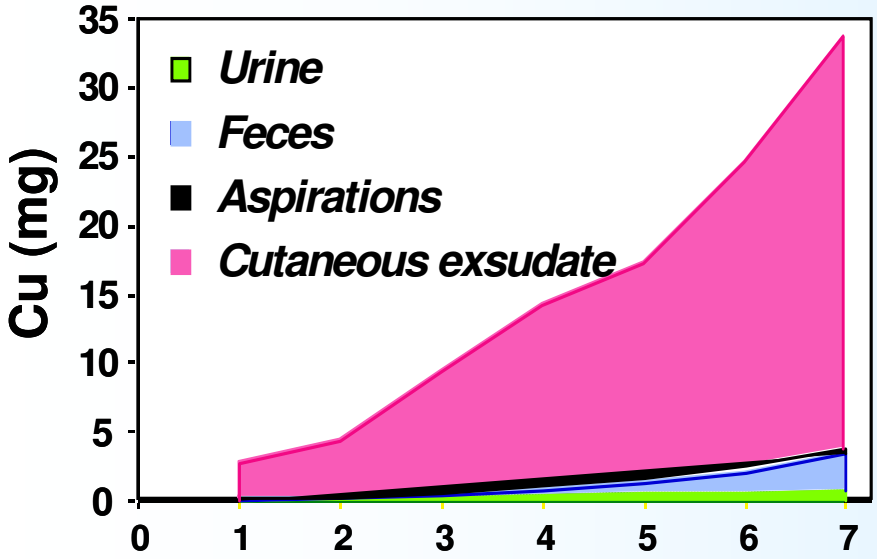
n = 11
x ± sd

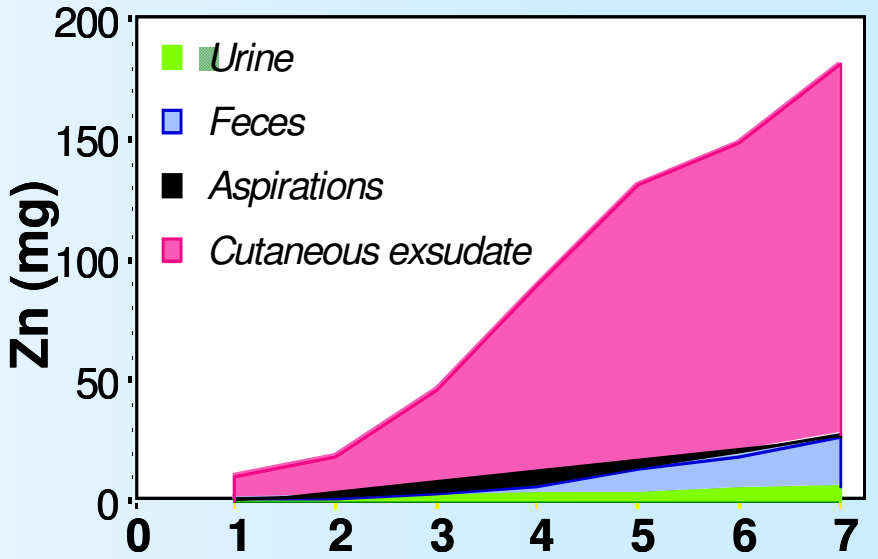


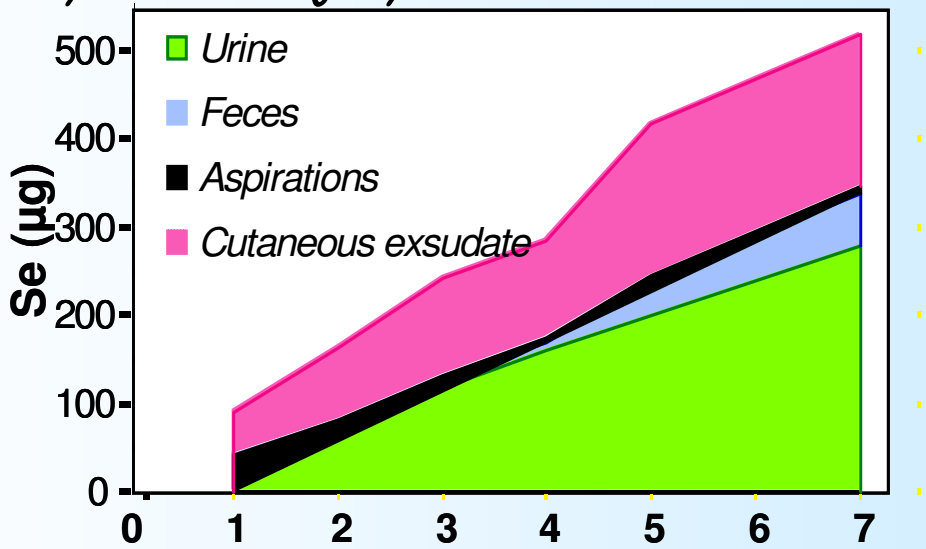
N=10, 33% BSA

Major burns – trace element losses

Berger et al, Burns, 1992,18:373, Clin Nutr 1992,11:75, AJCN 1997,65:1473

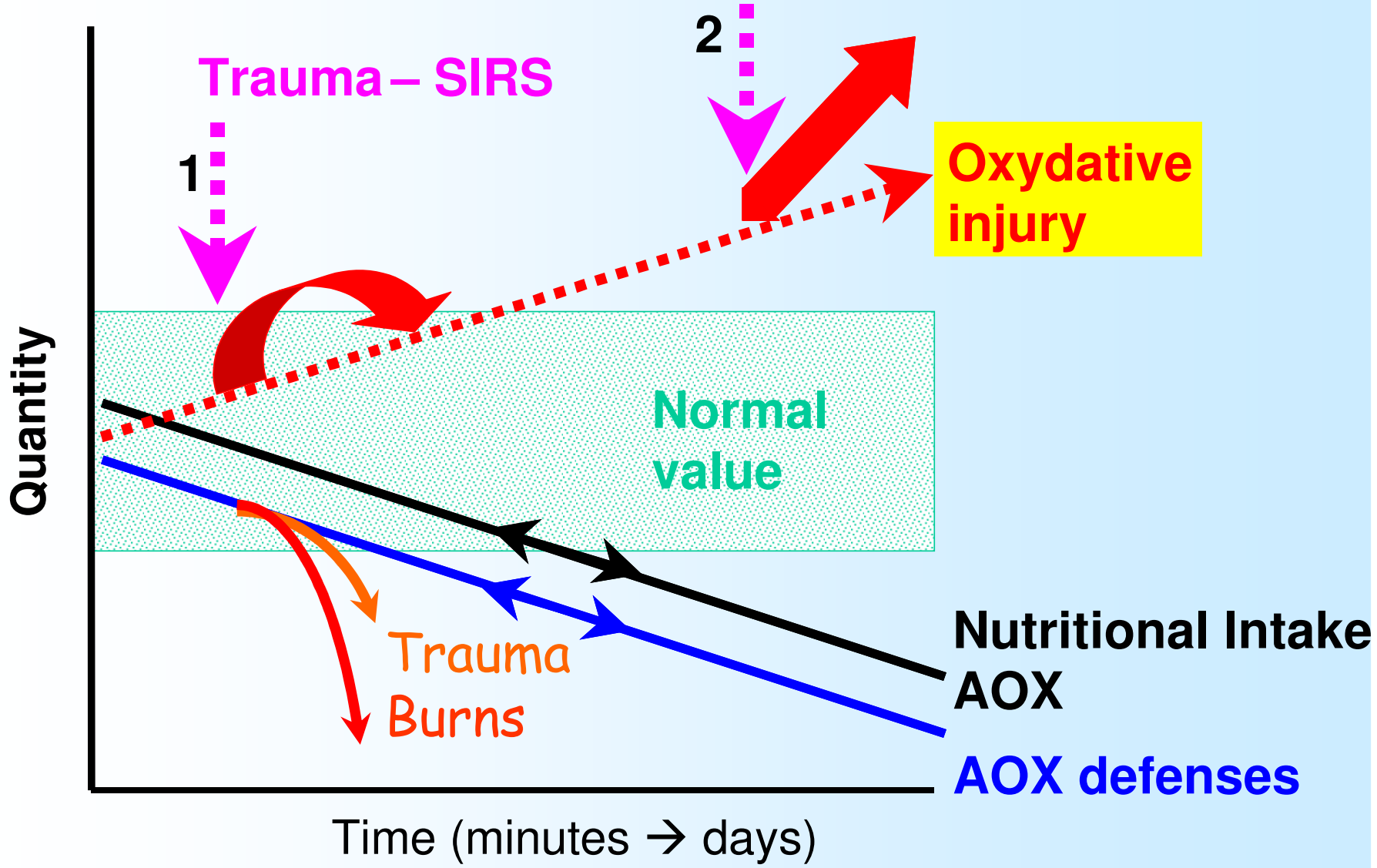






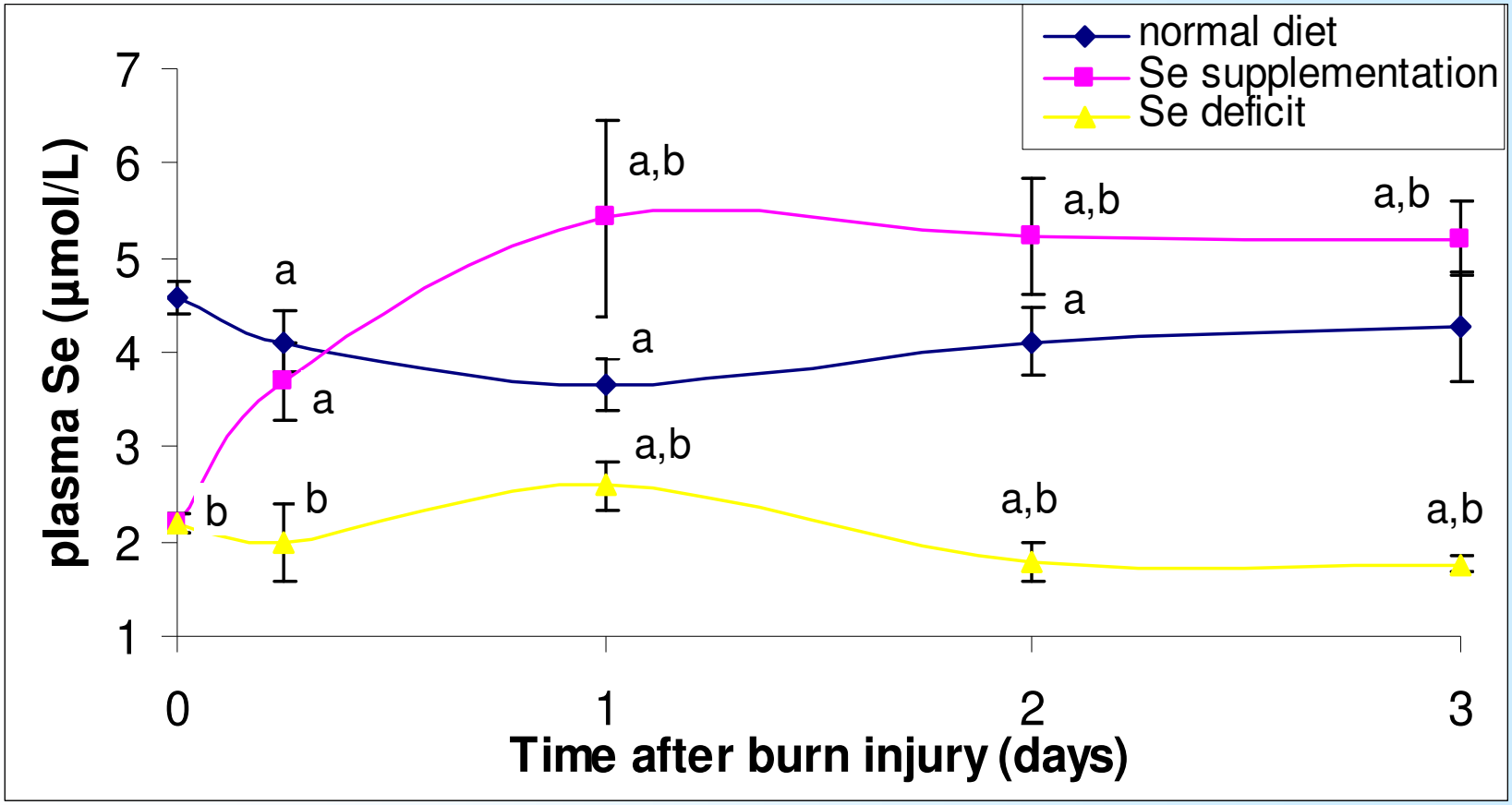
Can oxidative damage be treated nutritionally?

Berger MM Clin Nutr, 2005



Kinetic Changes of Oxidative Stress & Se Status after Burn in Se-Deficient and Se-Supplemented Rats

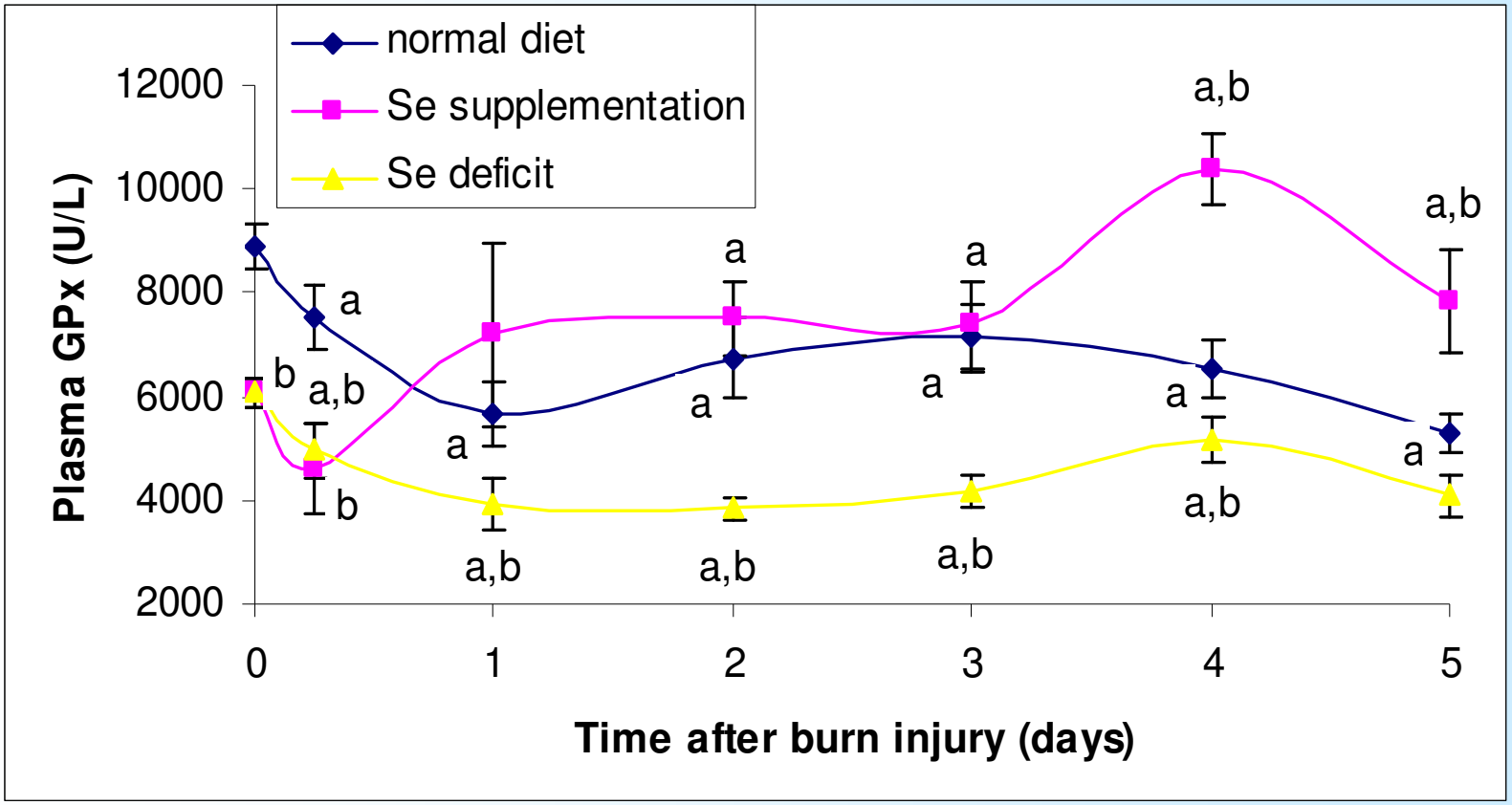
Sandre C et al, J Trauma 2006, 60:627



Time-dependent changes in plasma selenium levels after burn injury **selenium-adequate diet or a selenium-depleted diet for 5 weeks, before burn injury**

Kinetic Changes of Oxidative Stress & Se Status after Burn in Se-Deficient and Se-Supplemented Rats

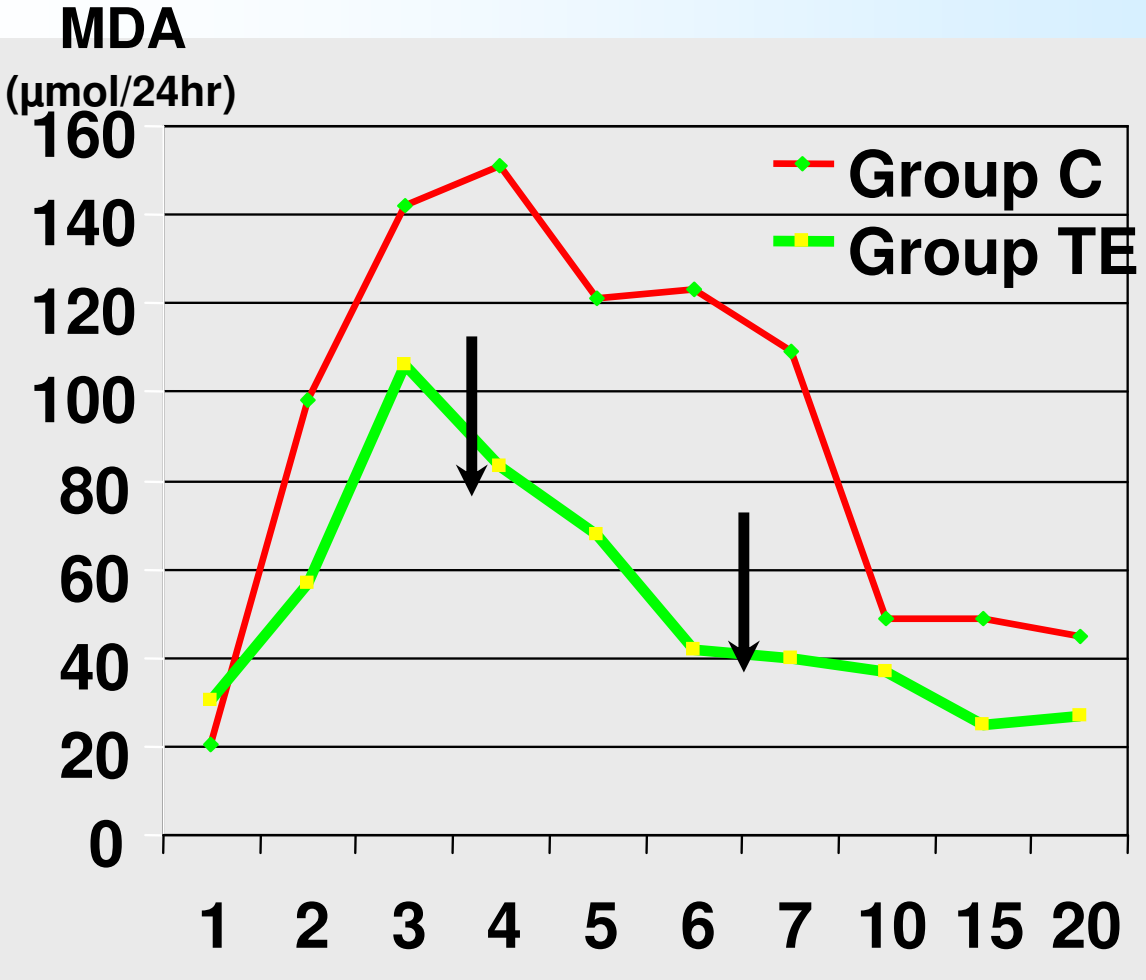
Sandre C et al, J Trauma 2006, 60:627



Plasma Glutathione Peroxidase (GPx) activity

Accelerated MDA decay with trace elements

Berger & Chiolero, Burns, 21: 507, 1995



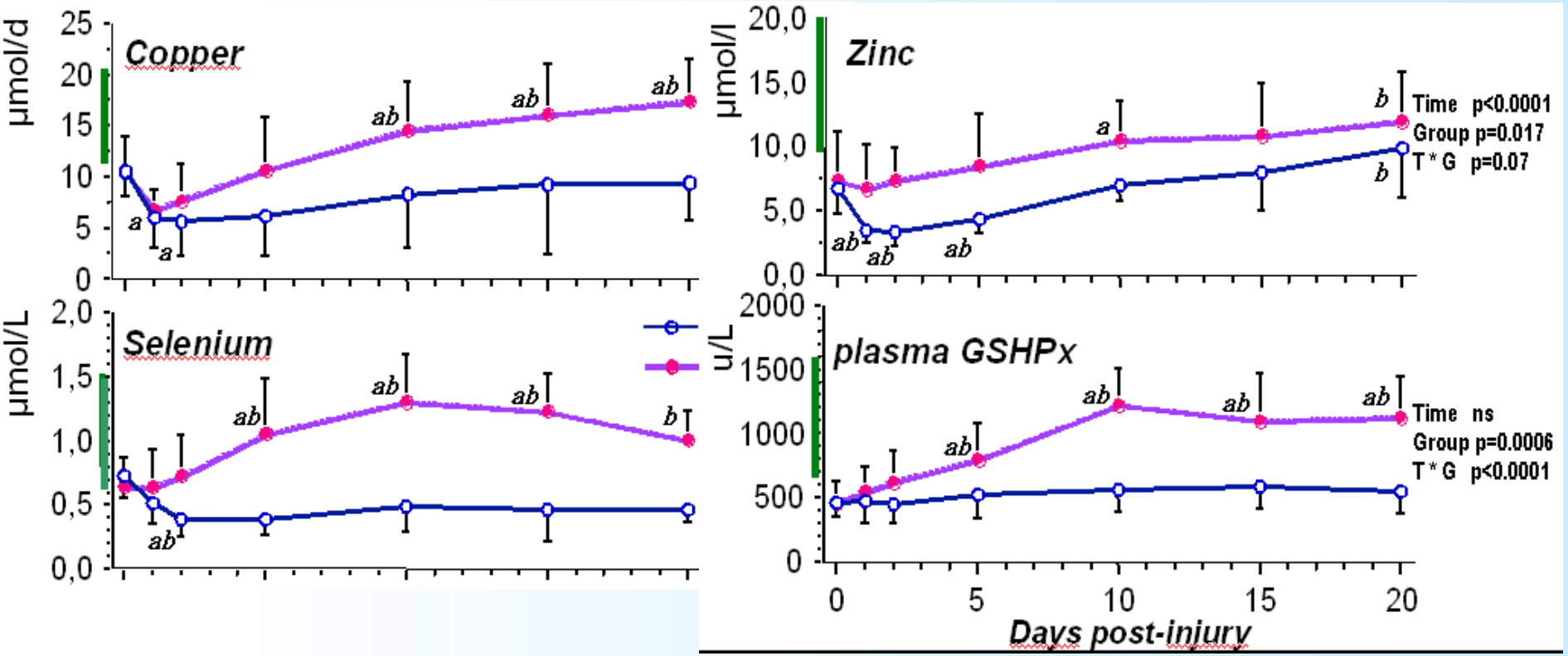
Design: PCT
11 patients (5 / 6)
BSA 42 / 43 %
Group control: ø
Group TE:
Cu,Se,Zn
Urine: 24 hr coll.
$p<0.03$

Substitution

Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations[1–3]

Mette M Berger, Malcolm Baines, Wassim Raffoul, Messod Benathan, René L Chiolero, Chris Reeves, Jean-Pierre Revelly, Marie-Christine Cayeux, Isabelle Sénéchaud, and Alan Shenkin

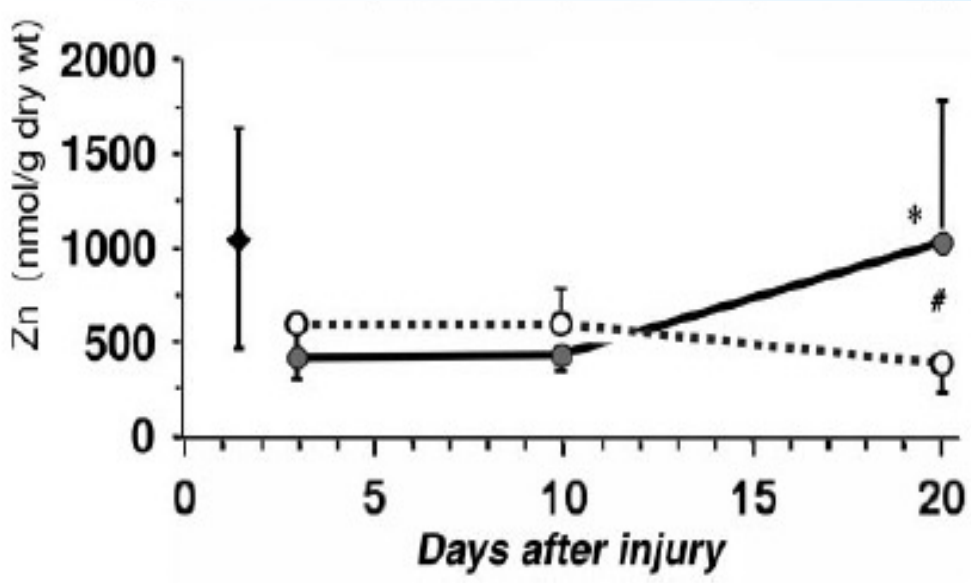
Mean plasma TE over time

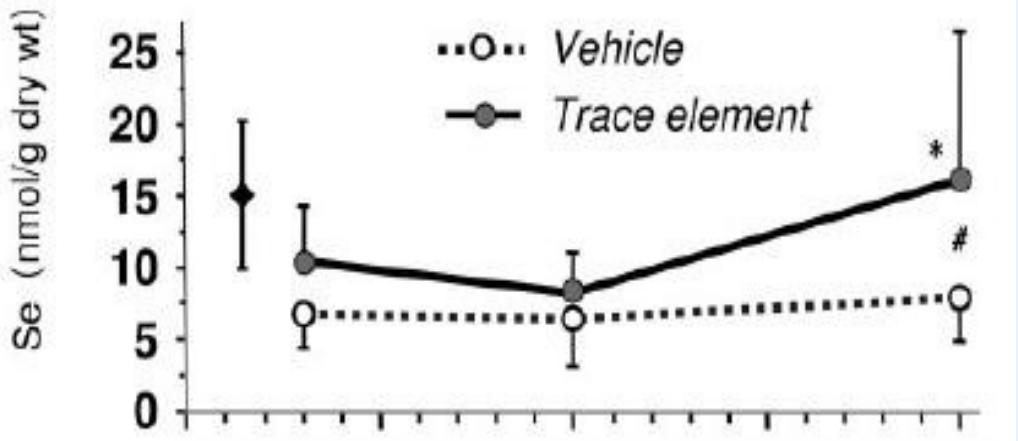


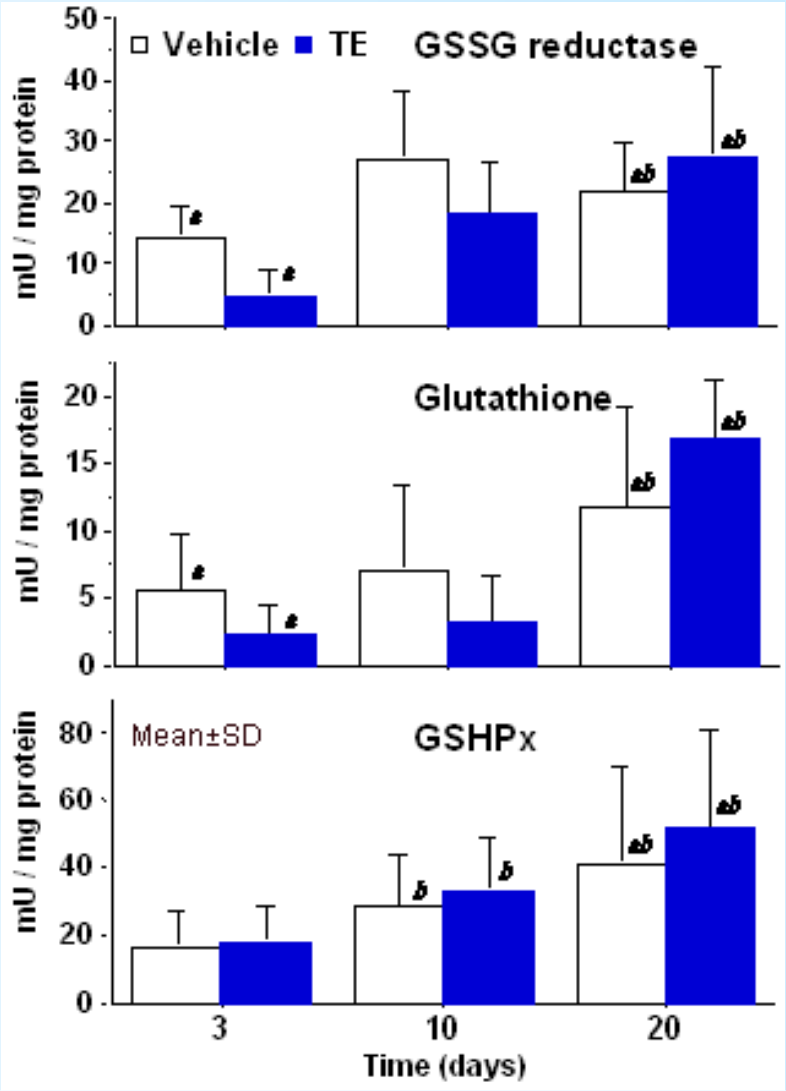
Am J Clin Nutr 2007; 85: 1293

TE after major burns increase [burned skin] and modulate local protein metabolism

Berger et al, Am J Clin Nutr 2007; 85: 1301







Trace elements and skin protein catabolism

Berger et al AJCN, 2007;85:1301- 6

	V group	TE group
n	10	11
Patients with skin biopsies (*n*)	—	—
Sex (F/M)	4/6	2/9
Age (y)	38 ± 16[2]	46 ± 15
Burned skin amount (% BSA)	44 ± 20 [41][3]	45 ± 22 [40]
Surgical burns (% BSA)	34 ± 16 [29]	31 ± 30 [22]
Regrafting index (%)	18 ± 7 [8]	2 ± 7 [1][4]

p=0.0

	V group, isotopes	TE group, isotopes
n	5/10	5/11
Patients with skin biopsies (*n*)	7/10	5/11
Sex (F/M)	3/2	1/4
Age (y)	32 ± 9 [26]	46 ± 19 [51]
Burned skin amount (% BSA)	45 ± 26 [36]	62 ± 21 [65]
Surgical burns (% BSA)	38 ± 19 [30]	56 ± 24 [60]
Regrafting index (%)	27 ± 41 [10]	3 ± 19 [2]

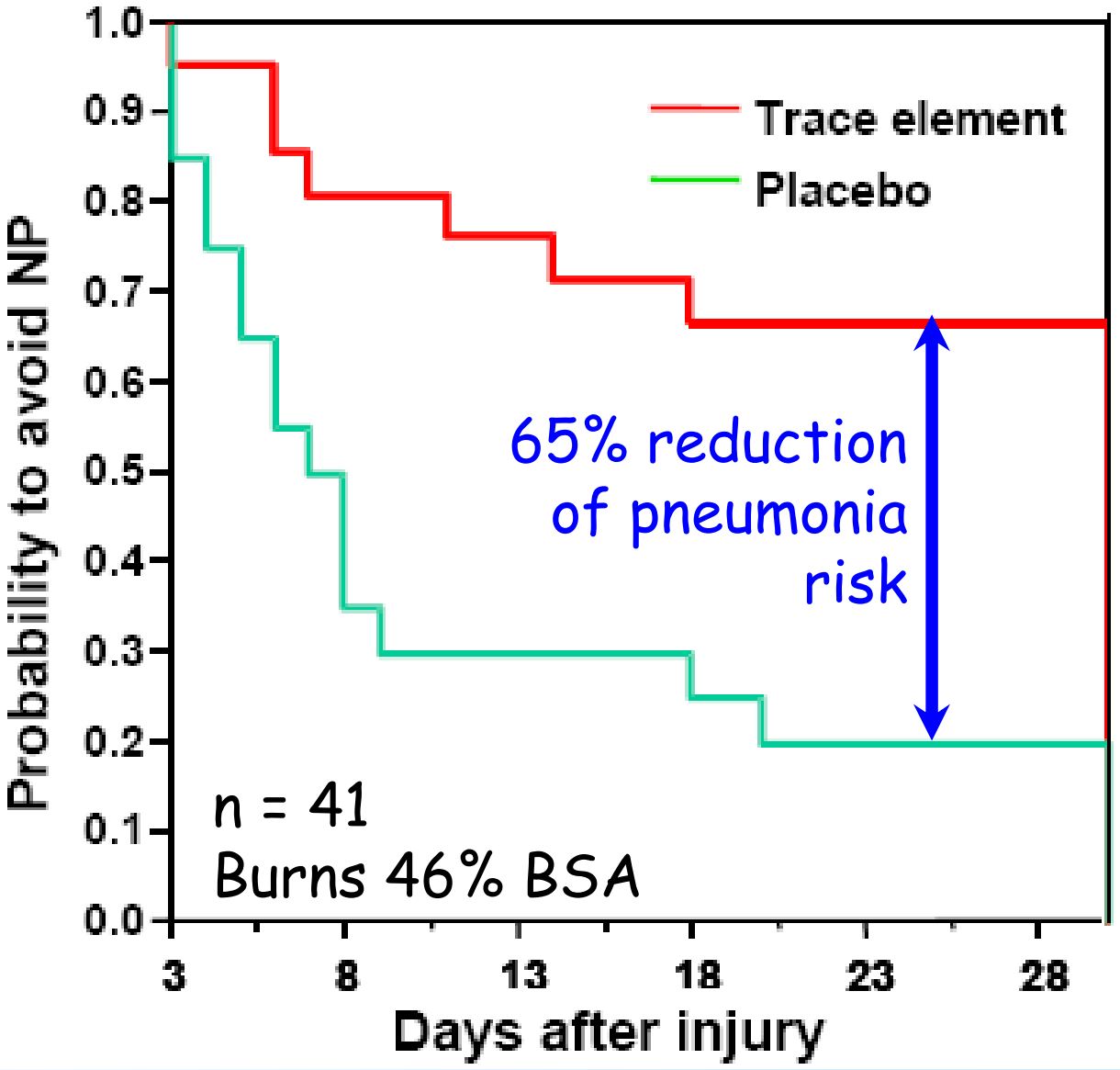
Trace element (Cu,Se,Zn) substitution in Burns - Nosocomial pneumonia

Berger et al, 2006, Crit Care 10:R153

Aggregation of 2 consecutive Randomized Trials → IV

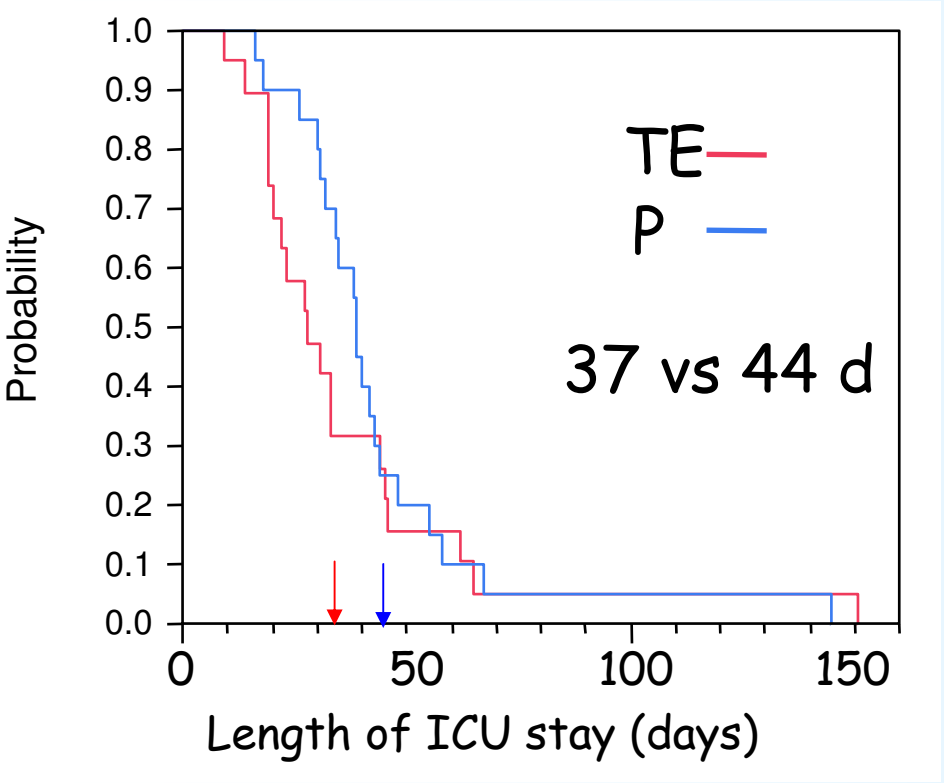
- **Cu 3 mg**
- **Se 300 mcg**
- **Zn 30 mg**

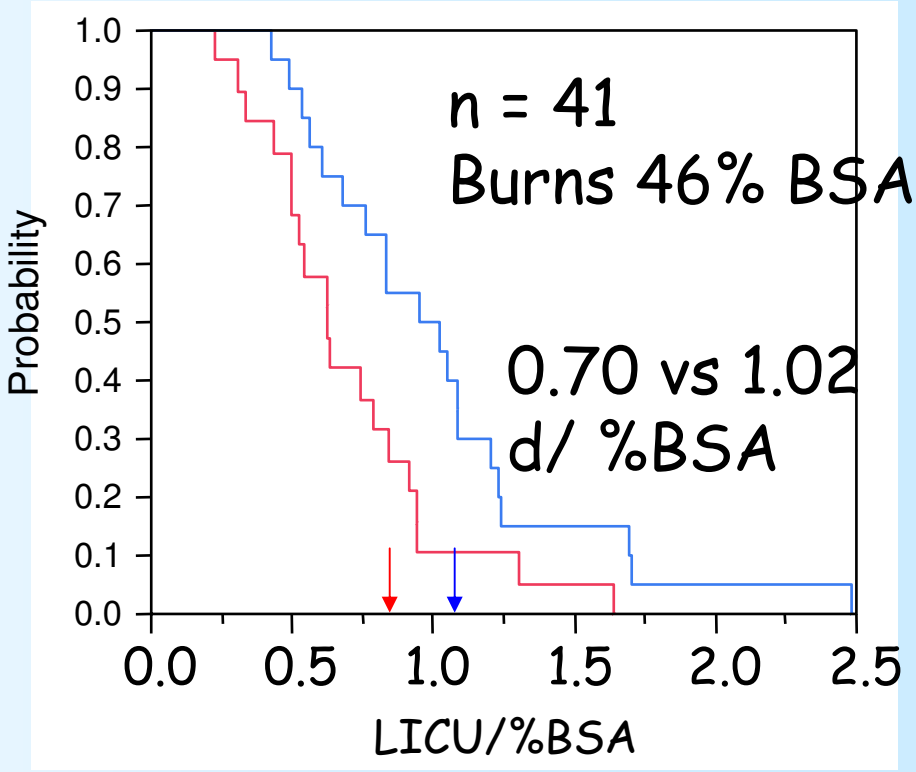
Log Rank
p=0.0014
Wilcoxon
p=0.0019



Length of stay: PRCT TE/placebo

Berger et al, Crit Care 2006, 10:R143





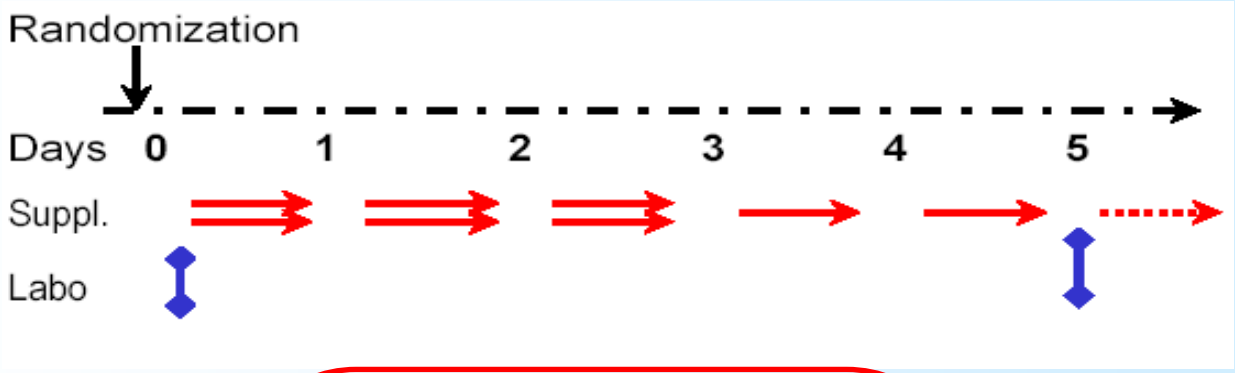
Test	Chi2	DF	Prob>Chi2
Log-Rank	0.4406	1	0.5068
Wilcoxon	2.4457	1	**0.1179**

Tests Between Groups

Test	Chi2	DF	Prob>Chi
Log-Rank	5.3770	1	**0.0204**
Wilcoxon	5.5177	1	**0.0188**

5 days AOX supplements in 200 ICU patients

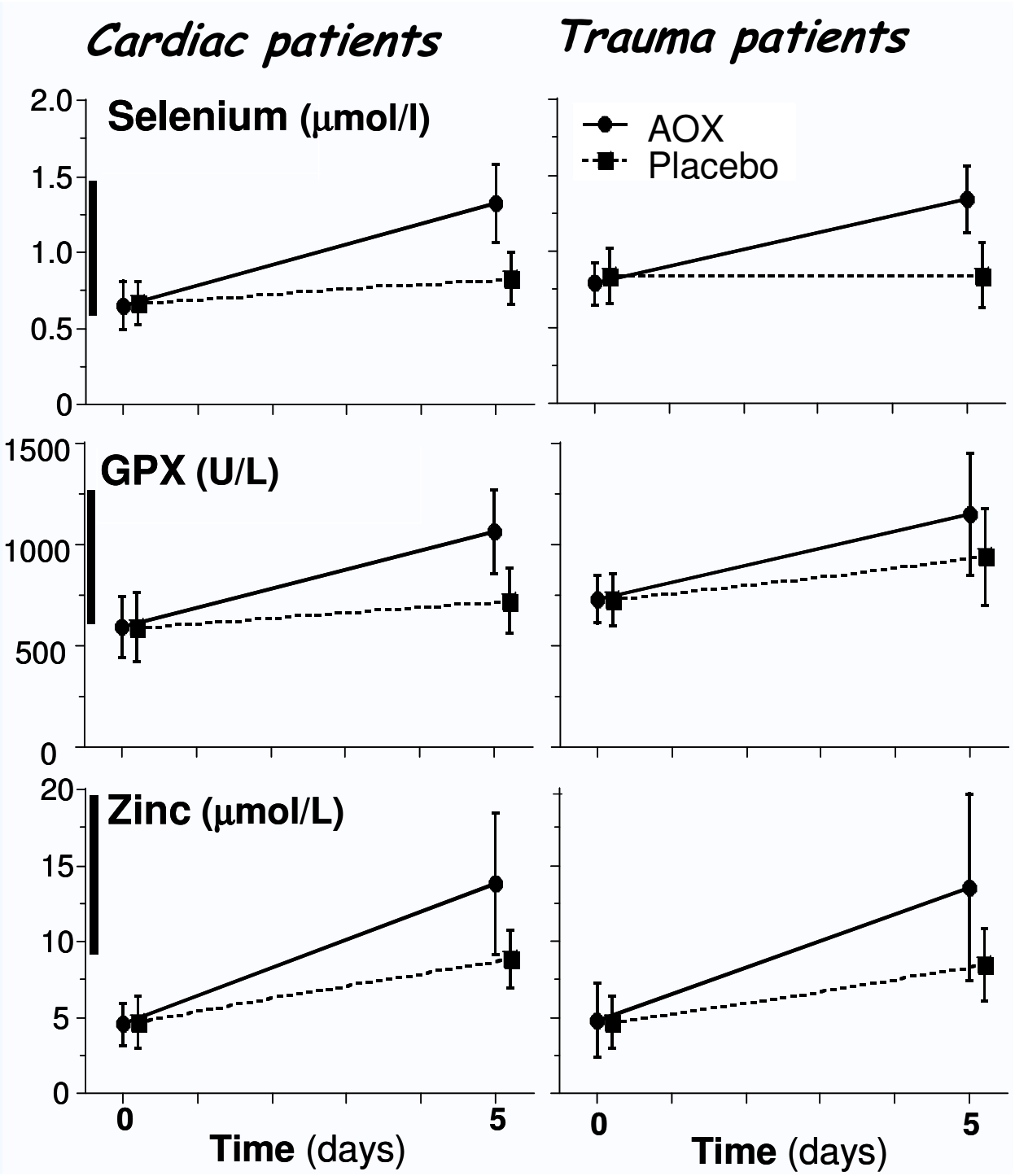
Berger et al Crit Care 2008; 12:R101



	Daily dose D1+D2 Double dose	Daily dose D3-D4-D5 Single dose	Comparison TPN dose D1-2/ D3…
Selenium	540 µg	270 µg	**12x / 6x**
Zinc	60 mg	30 mg	**12x / 6x**
Vitamin C	2,7 g	1,6 mg	**34x / 20x**
Vitamin B1	300 mg	100 mg	**120x / 40x**
Vitamin E	600 mg NG + 12.8* mg iv	300 mg NG + 6.4* mg iv	**40x / 20x** **2x / 1x**

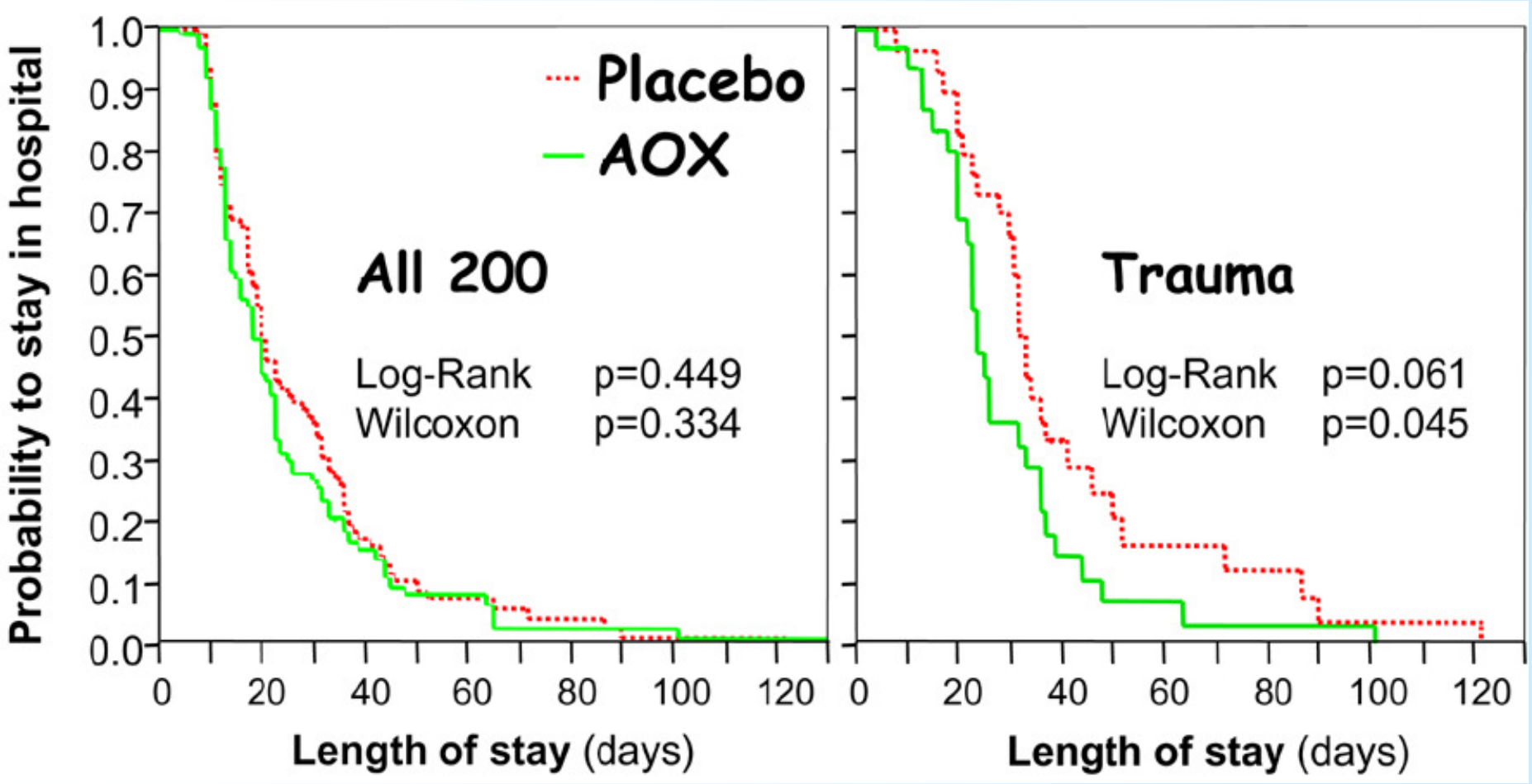
5 days iv AOX supplements in 200 ICU patients

Berger et al Crit Care 2008; 12:R101



AOX trial - 205 critically ill: trauma-cardiac-SAH
Se, Zn, Vit E, Vit C, Vit B1

Berger et al Crit Care 2008



- 11 days in hospital

Impact of high-dose antioxidants on outcomes in acutely injured patients

Collier and al, JPEN 2008

Retrospective study, before / after

TTT: vitamin C 1g, E 1000 ui, selenium 200 mcg

Results: 4,294 patients (AOX+, n= 2,272; AOX-, n= 2022).

Hospital (4 vs 3 days, P < .001) and ICU stay (3 vs 2 days, p= .001) median length of stays were significantly shorter in the AO+ group. Mortality significantly lower in the AO+ group (6.1% vs 8.5%, p = .001), translating into a 28% RR reduction for mortality with AOX

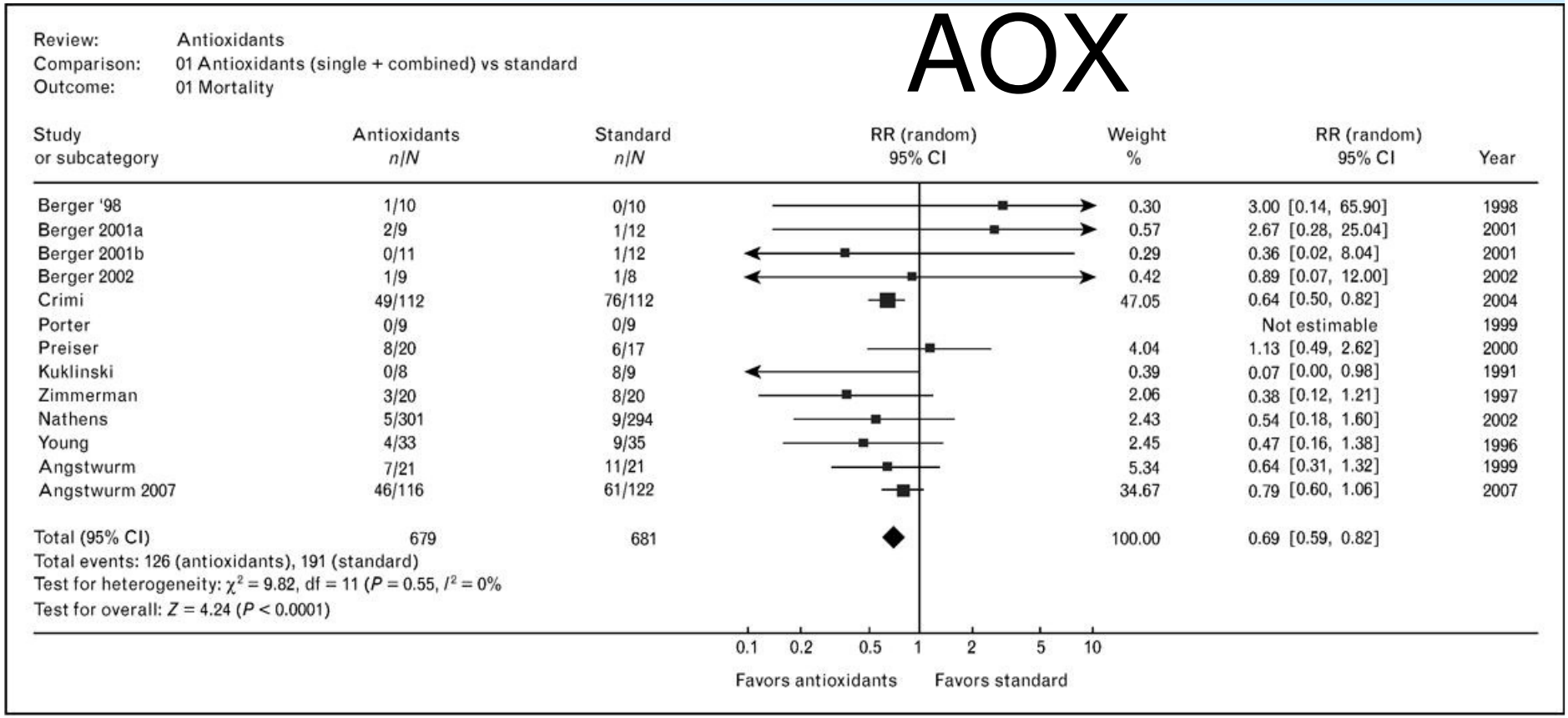
After adjusting for age, gender, and probability of survival, AOX exposure was associated with even lower mortality (OR 0.32, 95% CI 0.22-0.46). Patients with an expected survival <50% benefited most

A high-dose AOX protocol resulted in a 28% RR reduction in mortality and a significant reduction in both hospital and ICU length of stay.

Inexpensive intervention to reduce mortality/morbidity in the trauma patient.

Risk ratio (RR) and associated 95% CIs for the effect of AOX supplementation on mortality in critically ill patients

Jones & Heyland, Curr Opin Gatroenteral 2008 24:215

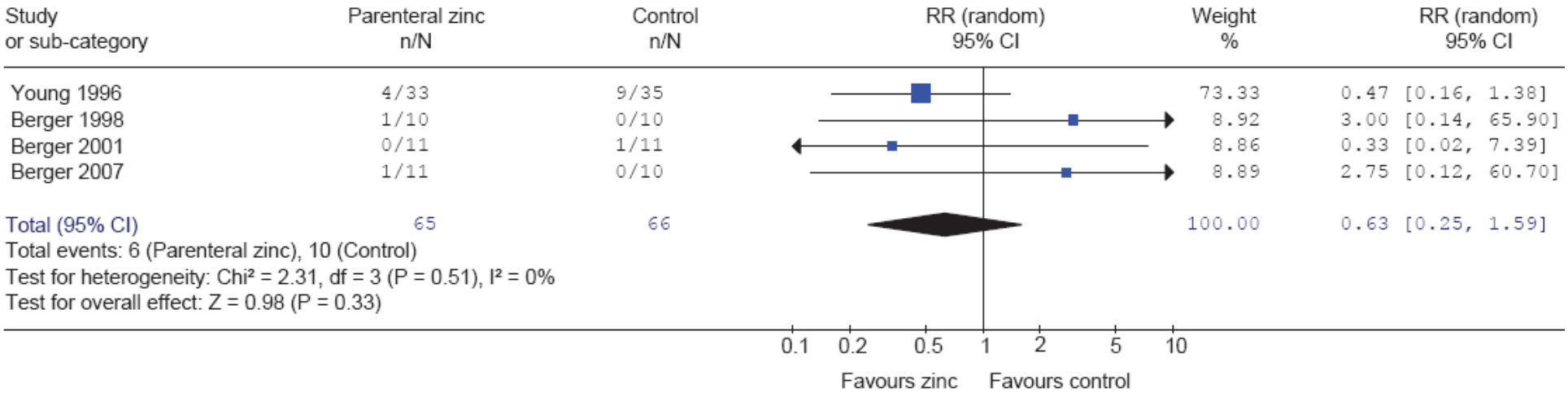


n/*N*, number of patients that die/total number of patients in group.

RR and associated 95% CI for the effect of Zn supplementation on mortality of ICU patients

Heyland et al, *JPEN* 2008;32:509

Review: Parenteral Zinc
Comparison: 01 Parenteral Zinc vs control
Outcome: 01 Mortality

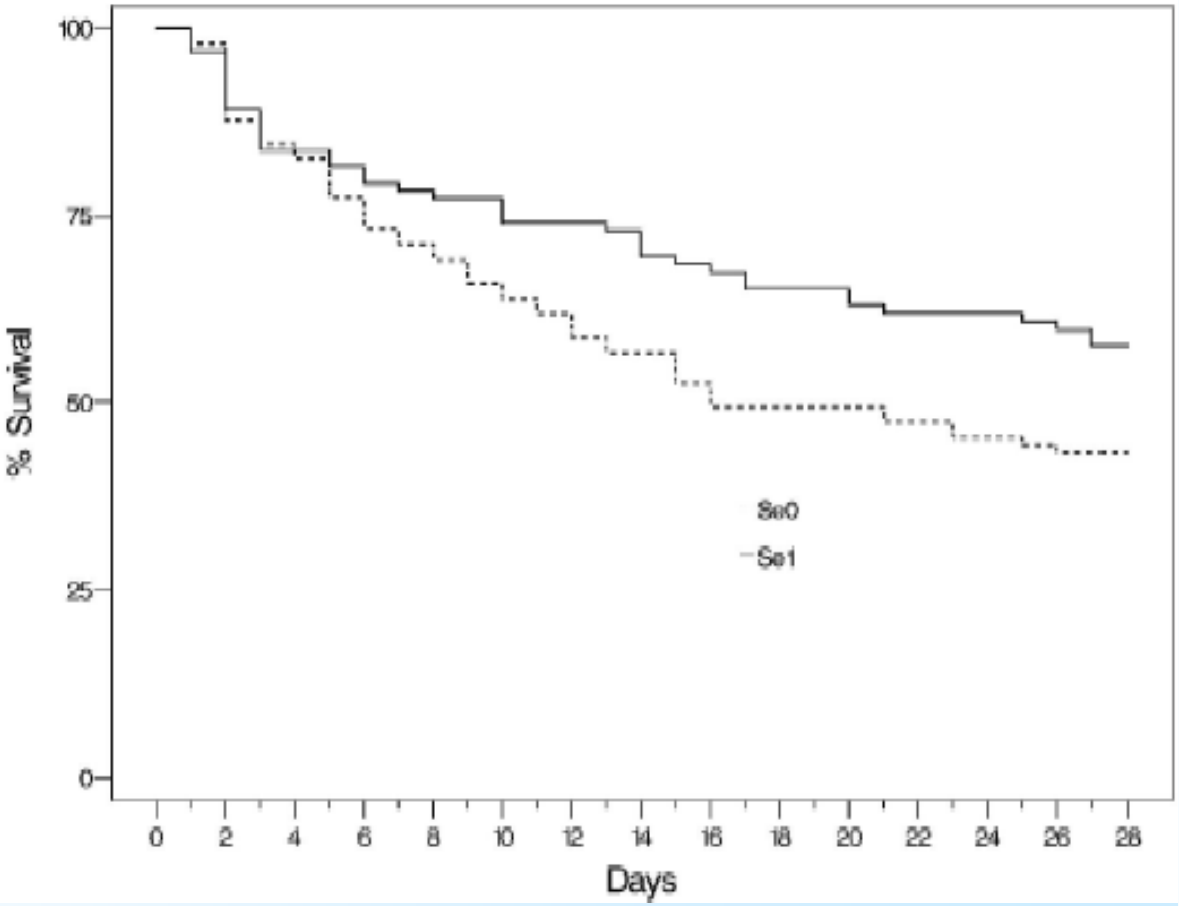


Selenium in ICU septic patients – PRCT

Angstwurm et al- CCM 35:118,2007

249 patients - severe sepsis or septic shock: 1000 mcg Se or placebo daily for 2 weeks after a loading dose

Kaplan -Meier survival curves in patients by intention to treat analysis. Difference between groups by log rank test.

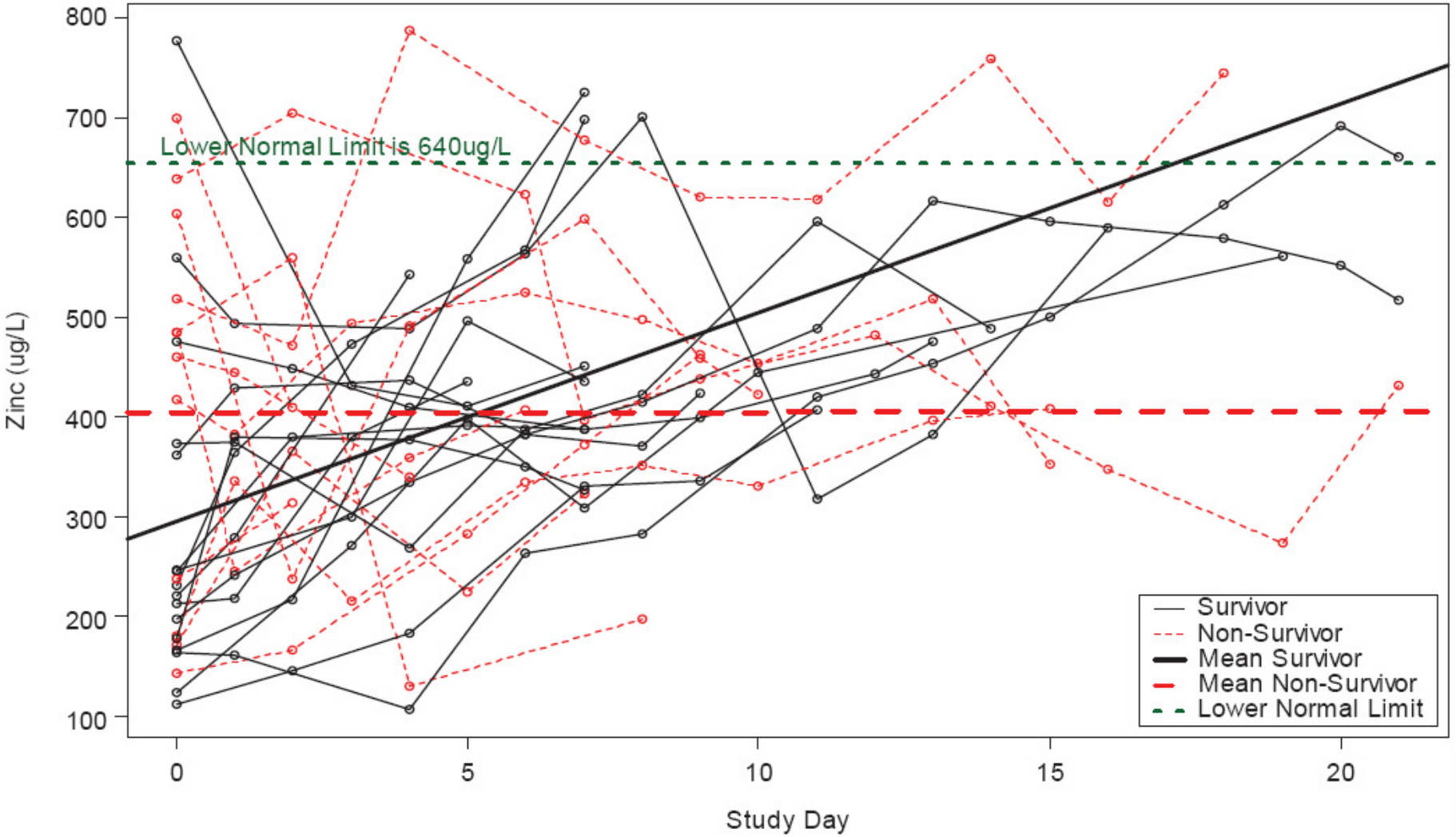


The estimated mean survival time was 19.7 days in Se1 patients (bold line) versus 16.4 days in the Se0 group (dotted line) (p = 0.0476).

Beware !!!
More is not necessarily good

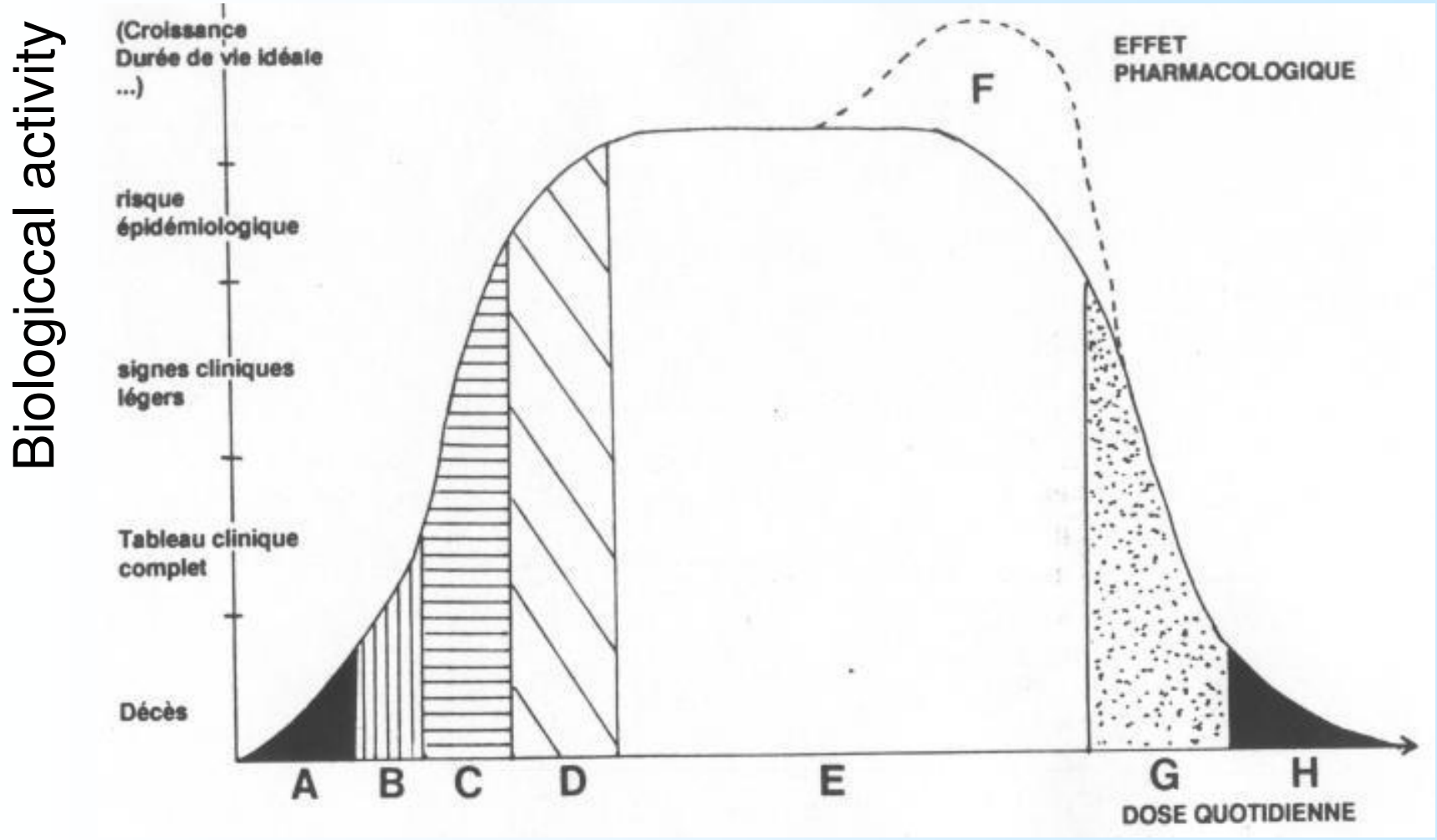
+
GI Absorption
totally uncertain

REDOXS dose finding results
Heyland et al, *JPEN* 2008;32:509



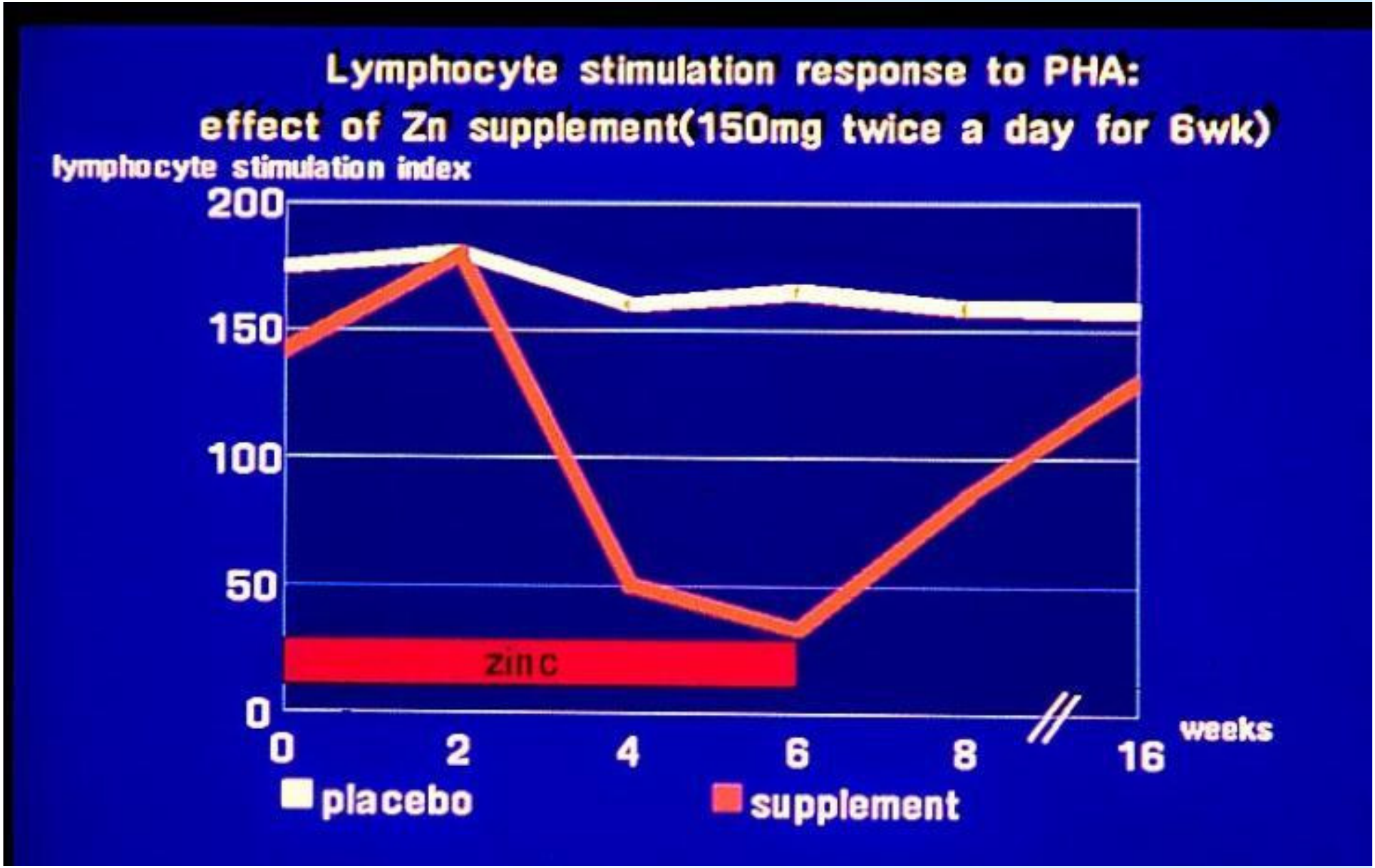
Individual plasma zinc profiles over time by 31-day survival status

Dose response curve



A+B+C deficieny, D suboptimal, E optimal, G toxicity, H lethal

Zinc supplementation in healthy subjects



Prasad et al

Effects of high doses of selenium in septic shock: PRCT, double-blind, phase II study

Forceville X et al, Crit Care 2007,11:R73

At least one serious adverse event in 18 (62%) in placebo vs. 25 (81%) in Se groups (p=0.111)

Adverse event did not differ between groups :

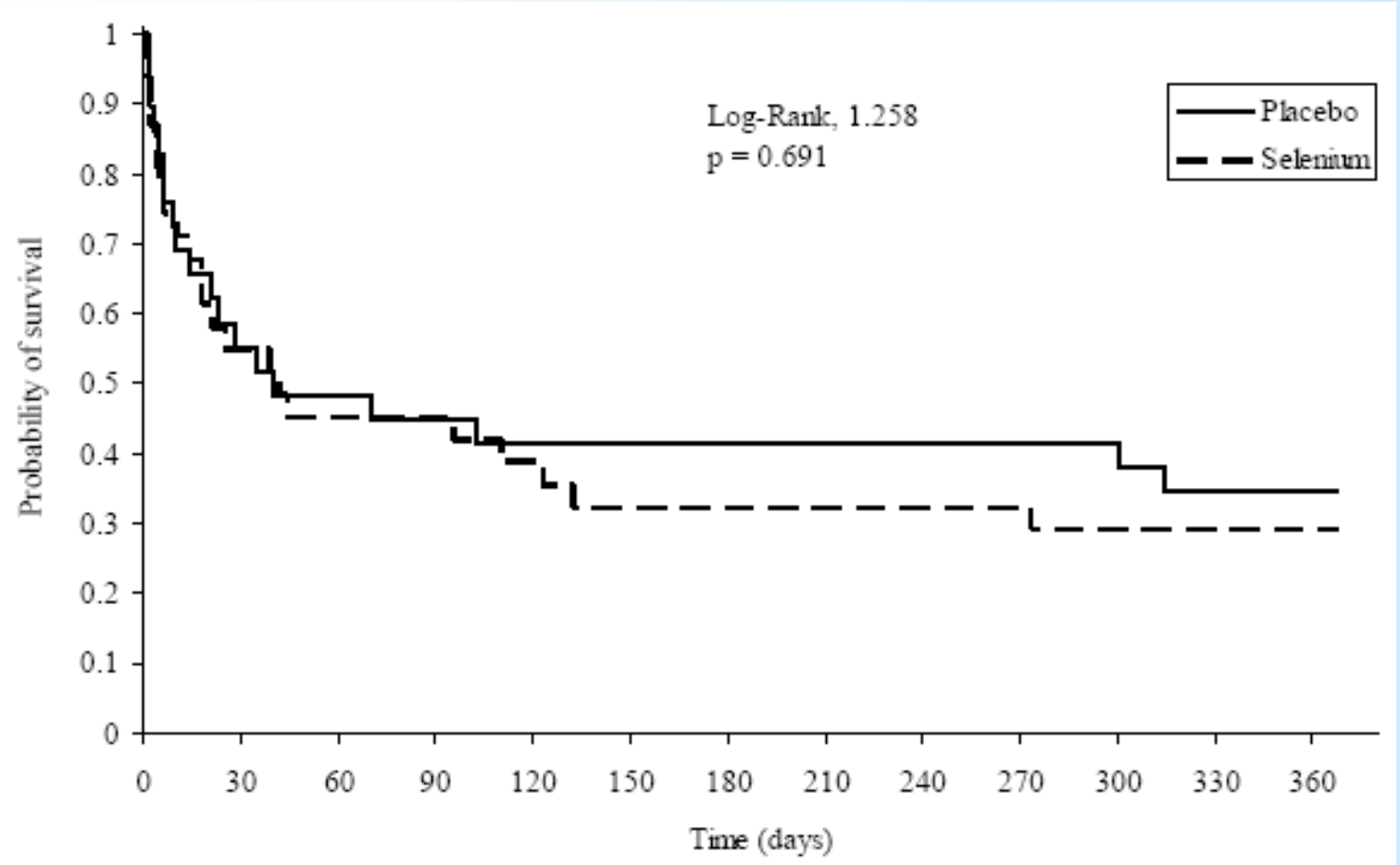
- Cardiac failure
- Renal failure
- Ischemic event
- Intracranial hemorrhage
- Refractory shock
- Multi organ failure
- Super infection
- Others

But

Duration of mechanical ventilation (days) was **25**±43 in placebo and **34**±54 in Se

Effects of high doses of selenium in septic shock: PRCT, double-blind, phase II study

Forceville X et al, Crit Care 2008



One year survival distribution

Effects of high doses of selenium in septic shock: PRCT, double-blind, phase II study

Forceville X et al, Crit Care 2008

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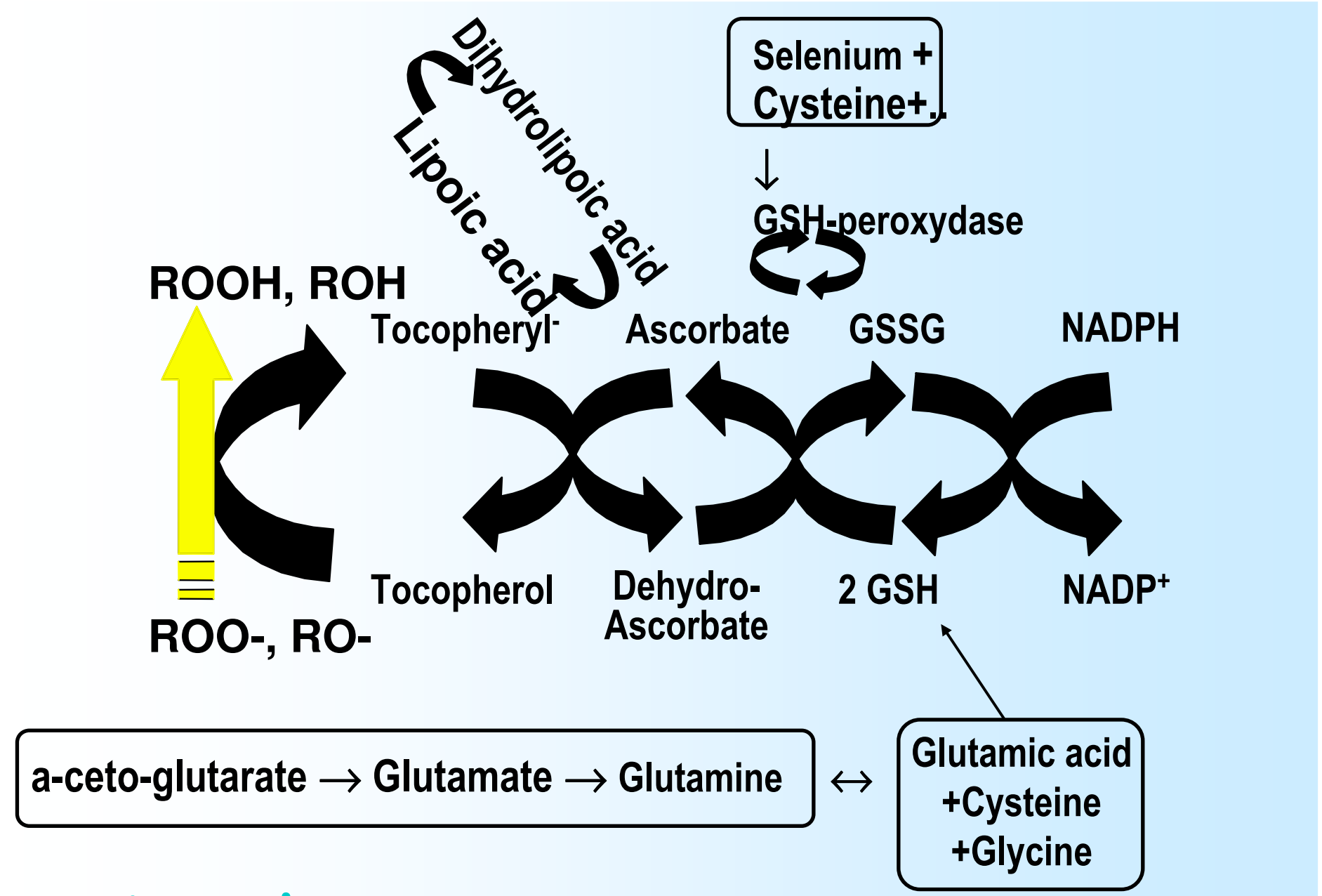
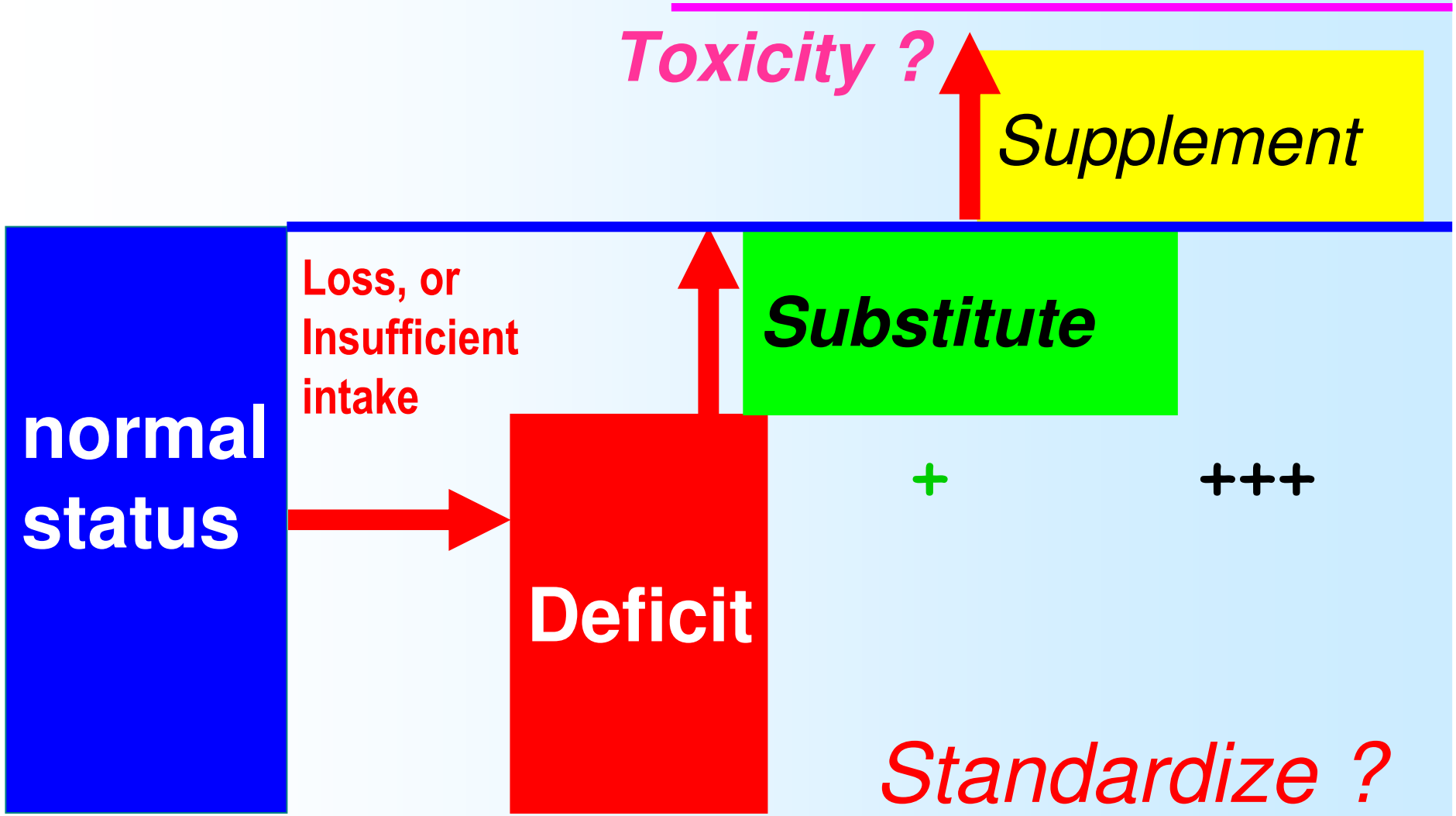


Antioxydant synergy

Berger & Chiolero, CCM, 2007, 35(suppl) S584

Substitute or supplement?
2 different conditions and aims



STANDARDIZE ? Yes!

Recognize different patient categories with different requirements:

- With acute deficit
  - Major burns, major trauma, CVVH
- With SIRS
  - ARDS, septic shock, pancreatitis, organ TX
- Near normal:
  - eg “simple postoperative”

Micronutrient standard policy – CHUV ICU

Type de patient / Type de Nutrition	**Patient agressé et/ou dénutri** (Niveau C) Polytrauma, TCC sévère, Hépatopathie fulminante, sepsis sévère, ARDS, MODS, Transplantation hépatique et pulmonaire, Choc cardiogène, mucoviscidose, BPCO sévère, maladies inflammatoires du tube digestif
Nutrition entérale	Profil agressé-NP : J1 à J6 Profil standard dès J7 **Polytraumatisé, avec ou sans TCC :** +500 ml Intestamine de J1 à J10
Nutrition parentérale	Profil agressé-NP dès début nutrition IV
Alimentation per os	Profil agressé-NP : J1 à J6 Profil standard dès J7

Profil standard : 1 cp multi-vitaminé et multi-minéraux (Supradyn®) : per os ou entéral

Profil agressé-NP: **ET** : 1 fiole solution ET (Décan®) + 100 µg Sélénium + 5 mg Zinc : injecter le Zinc et le Sélénium dans la fiole de Décan. Overs central venous line 6h.

Vit. :1 amp. solution multi-vitaminée (Cernévit®) + 500 mg vit. C (vitamine C Streuli®) + 100 mg vit. B1 (Benerva®). vvc dans 100 ml de Glucose 5% en 6h (0h-6h), after ET.

Vit. :Vit. K (Konakion®) : 10 mg 1x par semaine (le lundi).

Profil Brûlé : **ET** :1 Flex ET-Plus Pharmacie CHUV (3.75 mg cuivre, 375 µg sélénium, 37.5 mg zinc, 1200 mg phosphate). Flex de 250 ml dans NaCl 0,9%. Central line in18h

ET :1 EO - ET (Décan®) : en 6h (18h-0h).

Vit. :1 amp. solution multi-vitaminée (Cernévit®) + 500 mg vit. C (vitamine C Streuli®) + 100 mg vit. B1 (Benerva®). vvc dans 100 ml de Glu 5% en 6h (0h-6h), à la suite des ET,

Vit. :100 mg vitamine E (Vitamine E Streuli ®) : per os ou entéral

Standardize Trace element treatment
Conclusions

Se = an ubiquitous « generalist antioxidant »

Zn : essential immune and anabolic functions

Depletion and deficit have been repeatedly shown to be harmful and to increase mortality

Substitution is beneficial in major burns & other pre-illness or acute deficit conditions

Supplementation using doses 3-10 times the nutritional doses for 5-14 days → clinical benefit in patients with intense SIRS

Standardize Trace element treatment
Conclusions ’

Rational for substitution is obvious

Recognition of

- Specific TE functions
- Safe levels and durations
- High “proxidant doses” have not proven safe

Standardized supplementation in SIRS requires respect of “primum non nocere”

which means using doses proven safe

34 Selenium & Selenocysteine