selenase®

a chance for your intensive care patients

very well tolerated

↓

modulates inflammatory and coagulation pathways

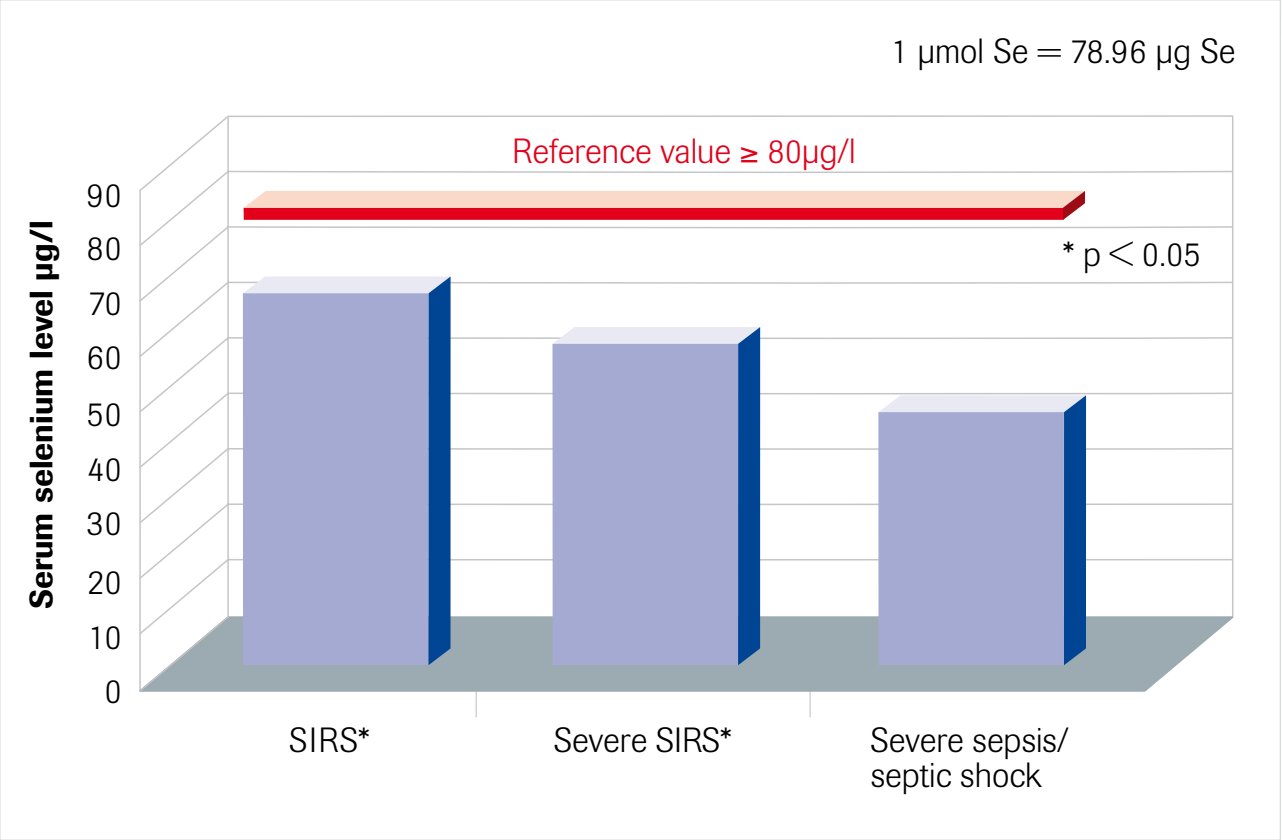
↓

protects from endothelial and organ damage

↓

reduces mortality

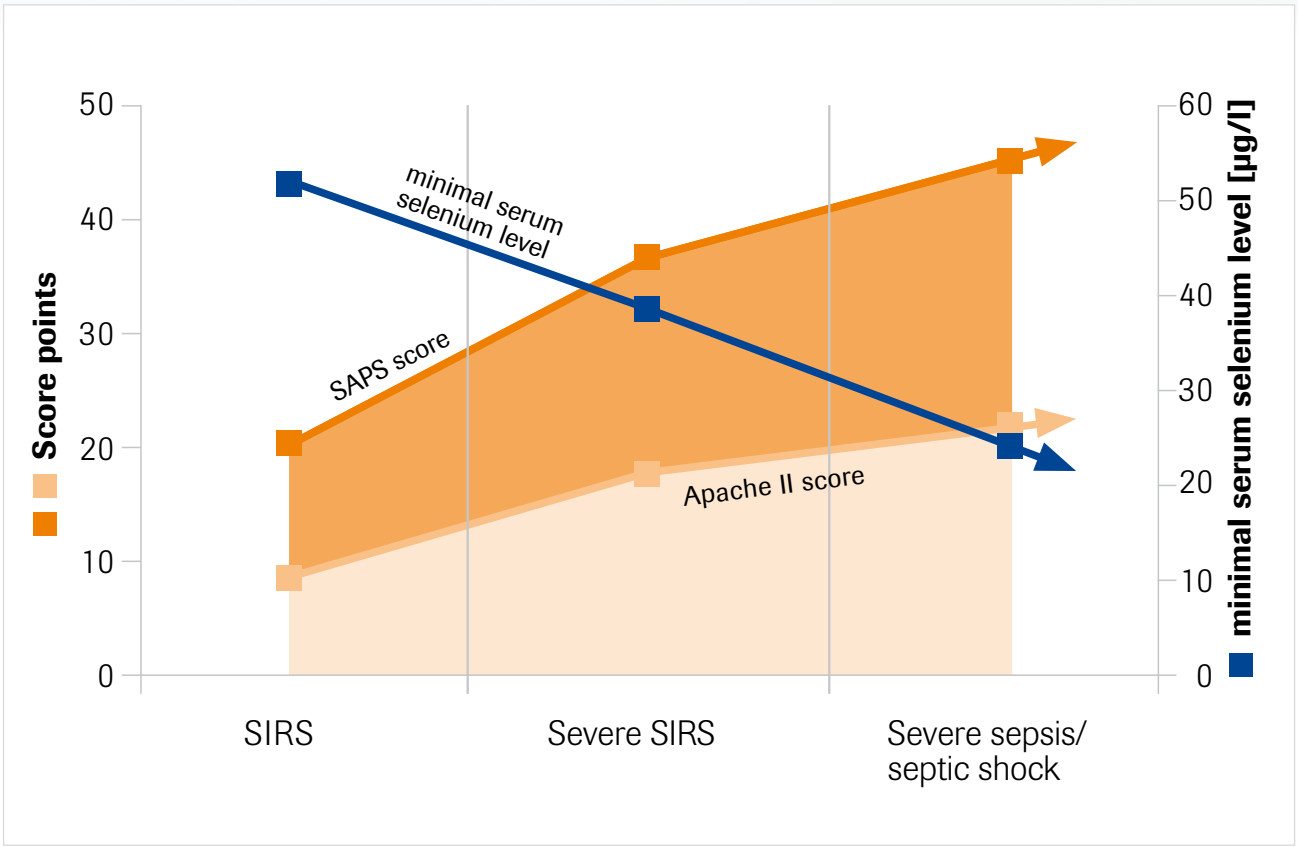
Initial serum selenium levels in sepsis compared to reference values



Patients with SIRS and sepsis have low selenium levels

Sakr et al. 2007

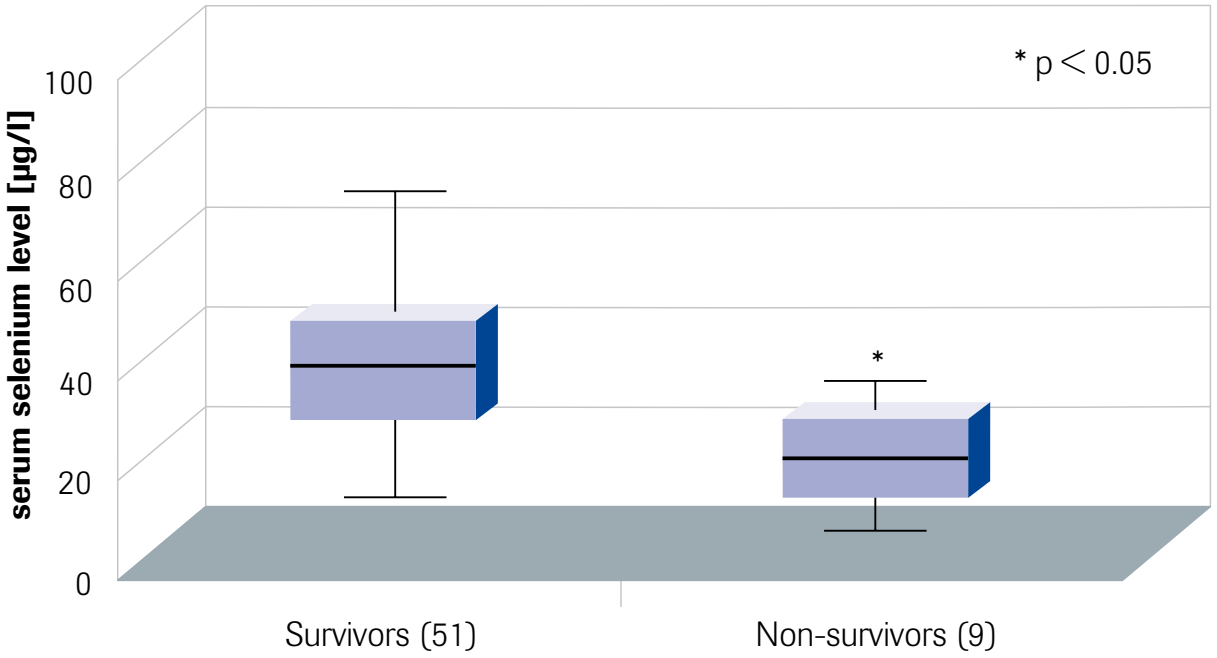
Minimal serum selenium levels in intensive care patients compared to APACHE II and SAPS score



Selenium levels correlate inversely with severity of disease and risk of mortality

Sakr et al. 2007

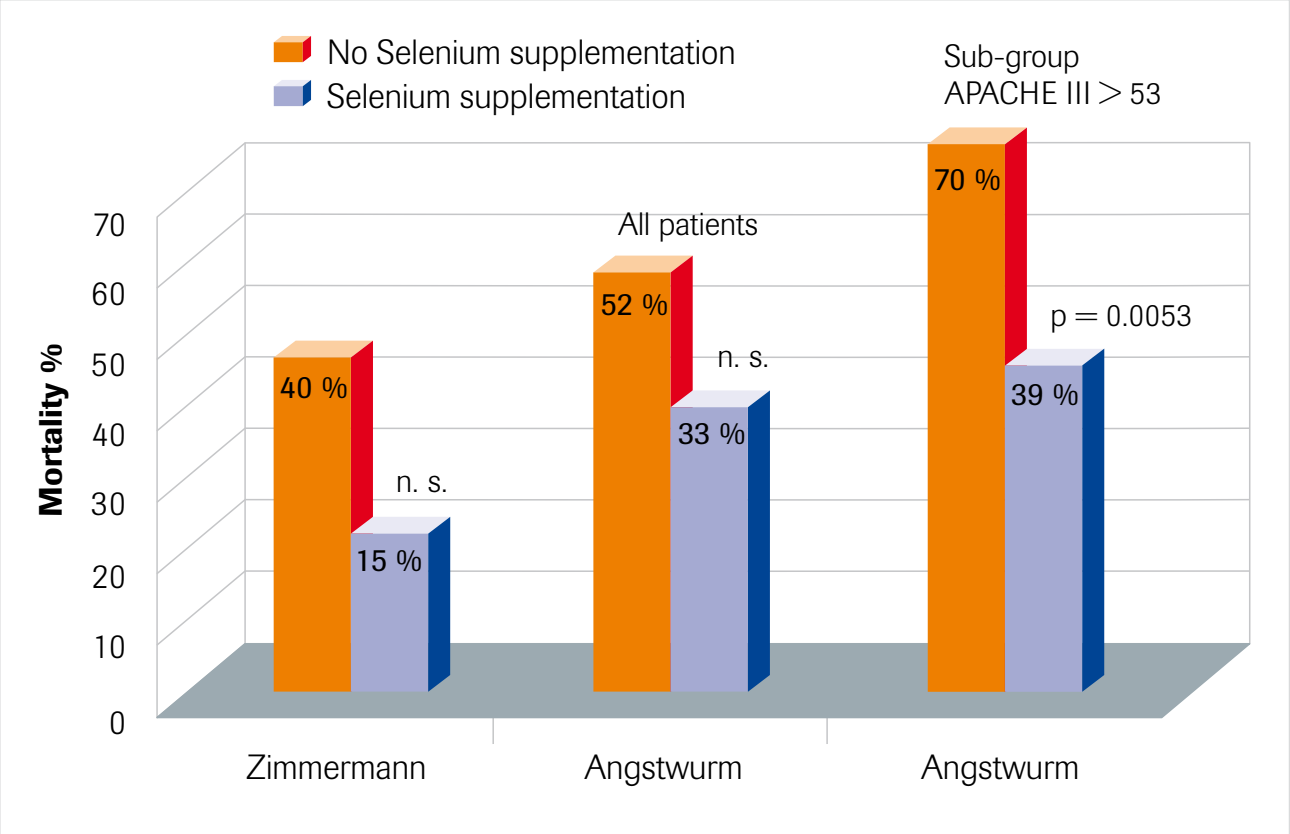
Minimal serum selenium levels in intensive care patients correlate with outcome



Survivors have higher selenium levels

Sakr et al. 2007

Change of mortality during selenase® supplementation



selenase® administration improves prognosis

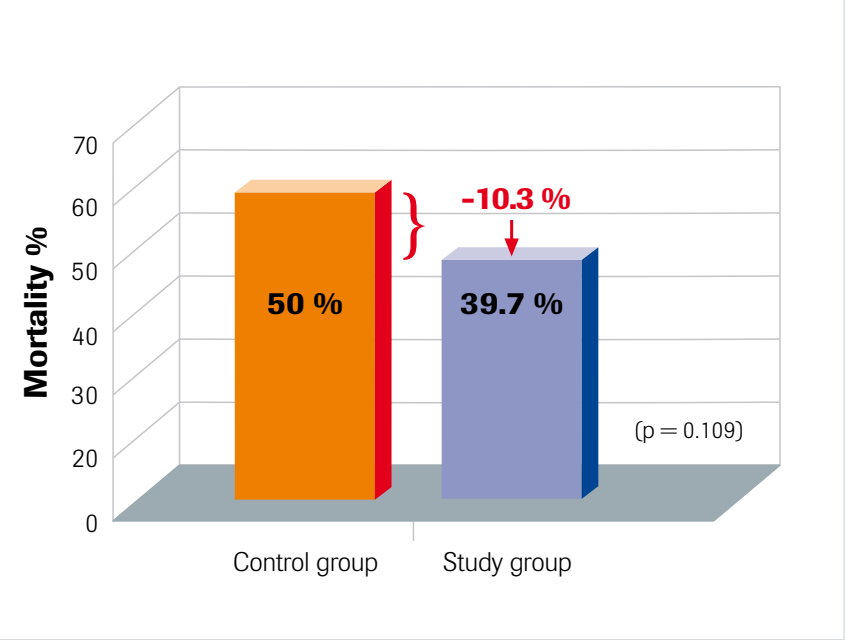
Significant reduction of:

- inflammatory reaction (Zimmermann et al. 1997)
- free radical burden (Zimmermann et al. 1997)
- acute renal failure (Angstwurm et al. 1999)

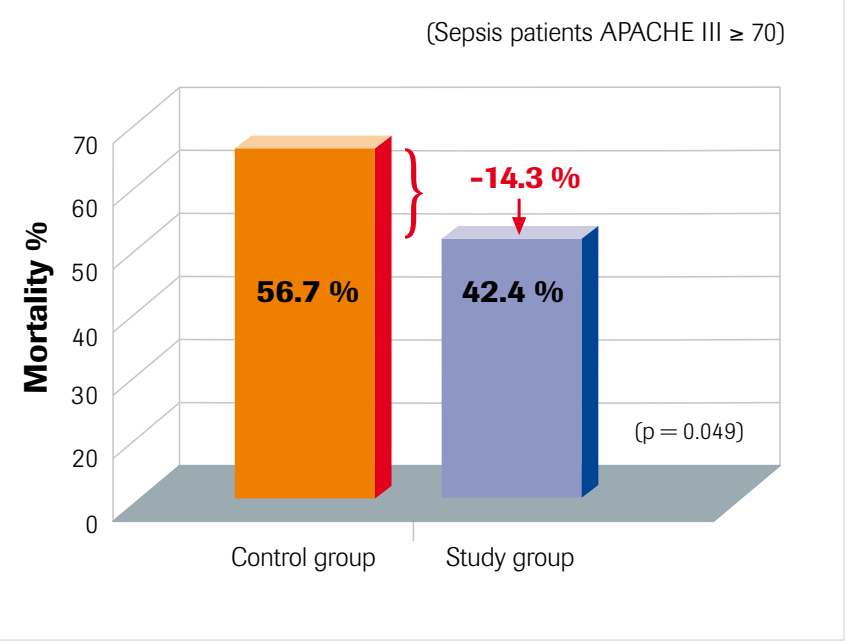
Selenium in Intensive Care (SIC)

Prospective, randomised, double-blind, Phase III multi-centre study in patients with SIRS/Sepsis

28-day mortality
Intention-to-treat analysis
Angstwurm et al. 2007



28-day mortality
Per-protocol group
Angstwurm et al. 2007



selenase® significantly reduces mortality

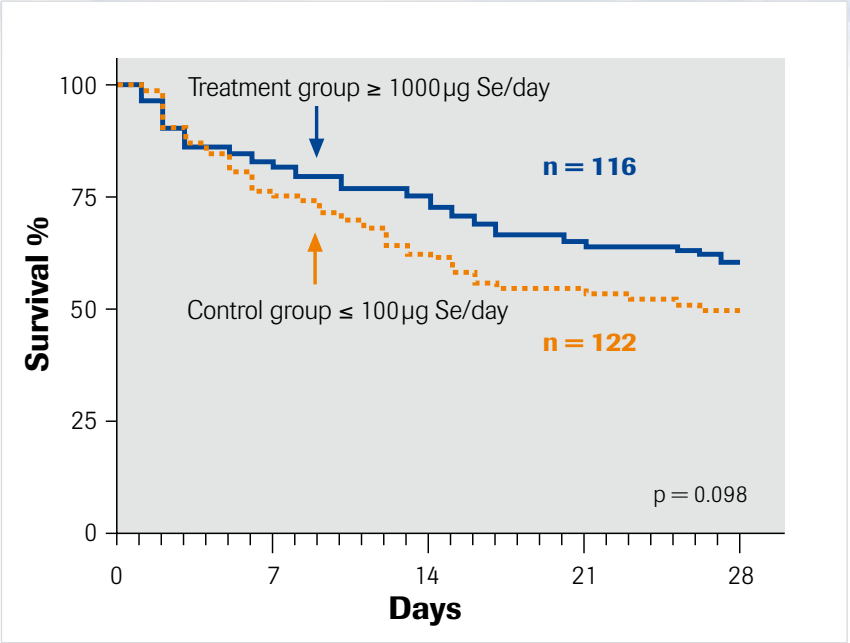
SIC-Study Subgroups

Reduction of mortality:		NNT (Number needed to treat)
SIC in total:	**– 14.3 %** (p = 0.049)	 **= 7**
Defined sub-groups:		
Septic shock:	**– 26.1 %** (p = 0.018)	 **= 4**
APACHE III ≥ 102:	**– 25.9 %** (p = 0.040)	 **= 4**
> 3 Organ failures:	**– 22.6 %** (p = 0.039)	 **= 4–5**

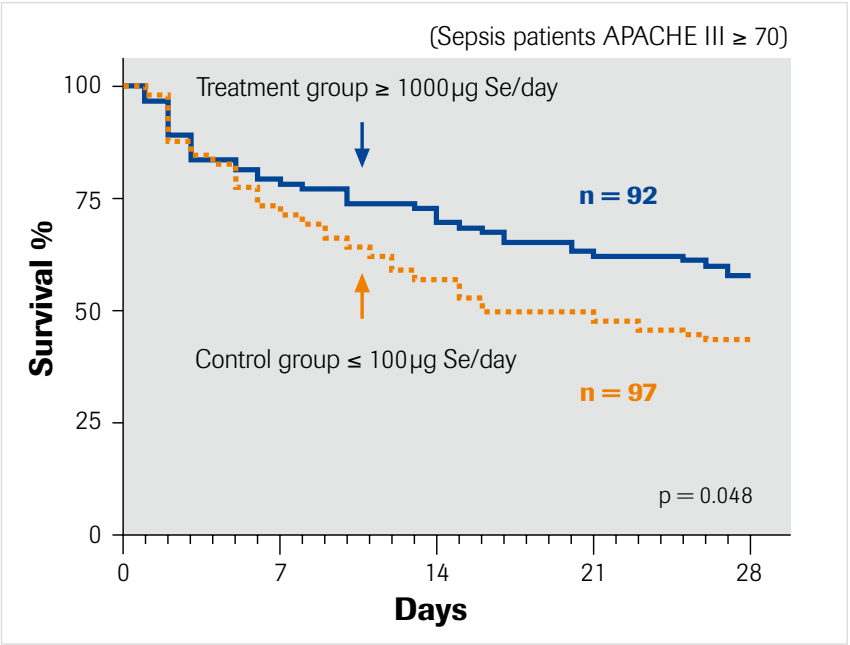
selenase® is efficacious

Duration of survival according to Kaplan-Meier

Intention-to-treat analysis
Angstwurm et al. 2007



Per-protocol group
Angstwurm et al. 2007

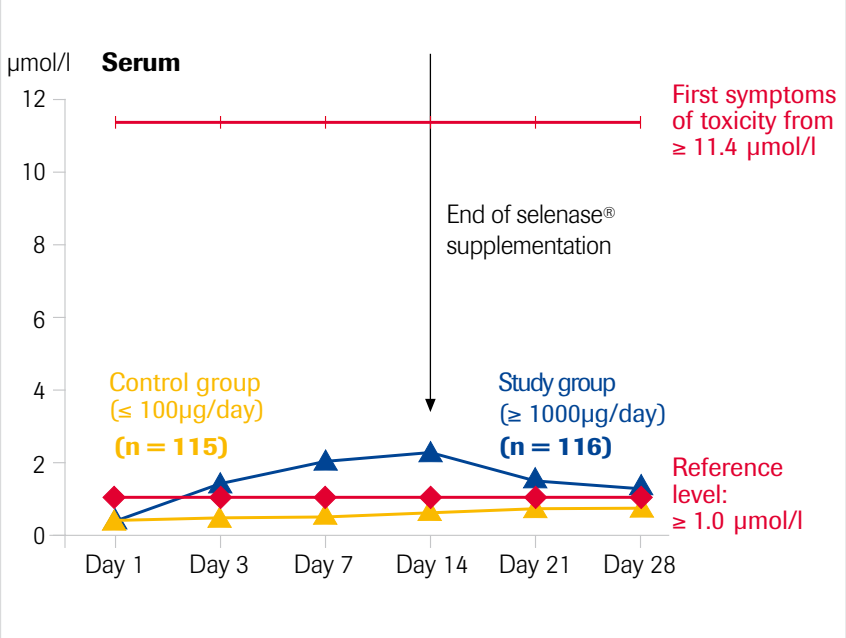


selenase® significantly prolongs survival

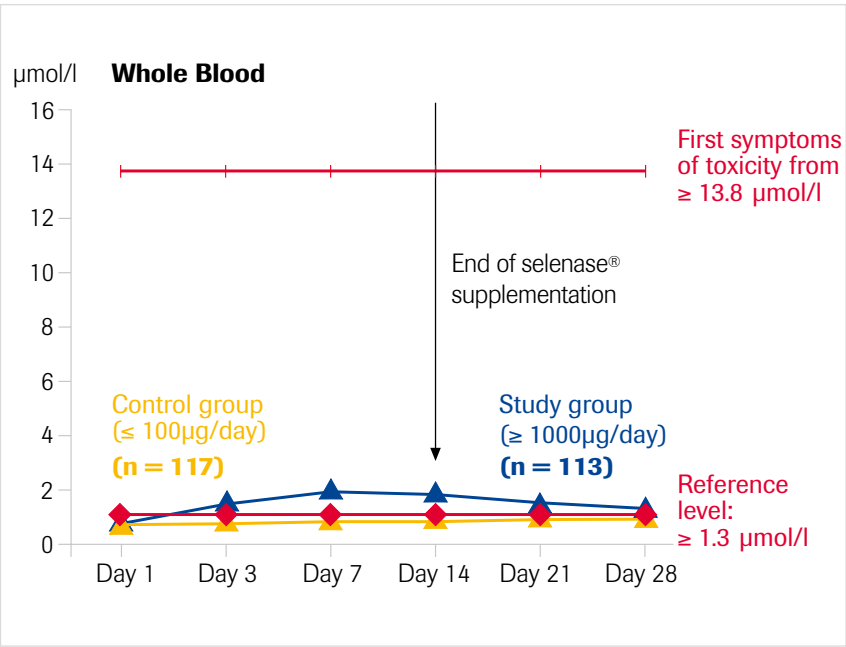
1 µmol Se = 78.96 µg Se

Course of selenium levels

Selenium consumption is particularly high in the acute phase of sepsis/SIRS



Intracellular selenium concentration (whole blood) is the decisive factor for its action

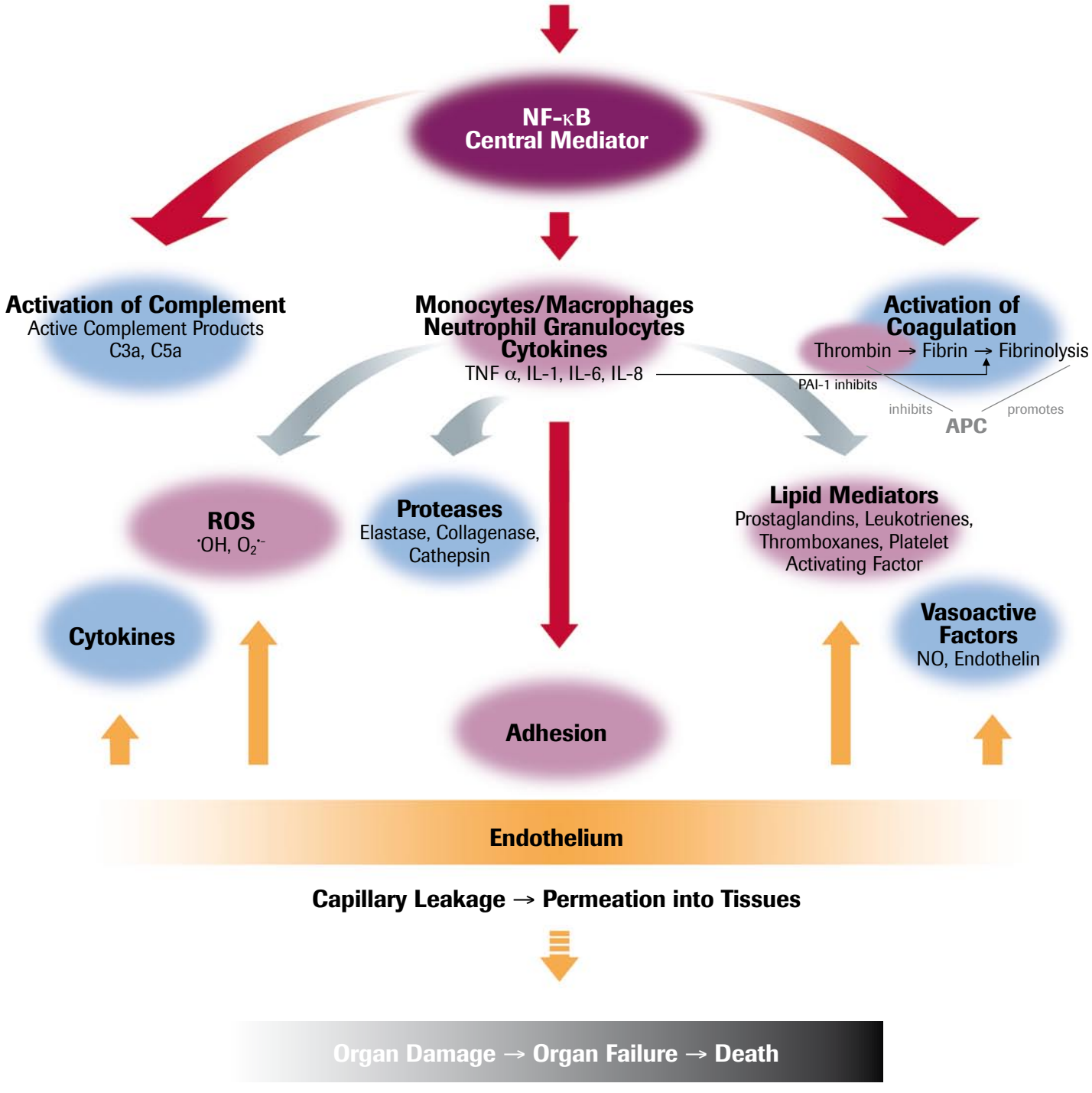


High dose selenase® supplementation is safe

1 µmol Se = 78.96 µg Se

selenase® affects Central Metabolic

Pathophysiology of SIRS/Sepsis



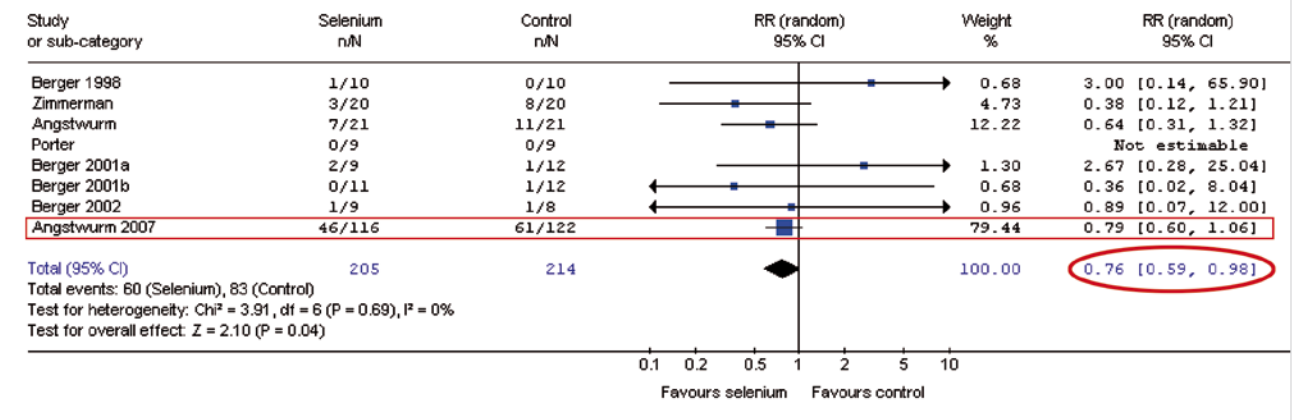
Mediators

NF-κB	As well as increasing GPx-1 and GPx-4 activity selenite reduces NF-κB activation. (Brigelius-Flohé et al. 1997, 2003; Kretz-Remy et al. 1996)
Complement	Selenite reduces complement activation. (Hou 1997)
Cytokines	Selenium is essential for the immune system, acts as an immune modulator (antioxidant and anti-inflammatory). (Ferencik und Ebringer 2003; Rovensky et al. 2002)
ROS (Reactive Oxygen Species)	As well as GPx-1, -2, -3, -4 and TR selenite reduces peroxides and regulate the cellular redox state. Oxidative stress induces the expression of GPx and TR. (McKenzie et al. 2002)
Lipid mediators	The presence of selenium and thus an adequate GPx-3 and GPx-4 activity inhibits thromboxane synthesis in favor of prostacyclin synthesis: vasodilation ↑ coagulation ↓. (Brigelius-Flohé et al. 2003)
Adhesion	Selenite inhibits TNFα induced expression of endothelial adhesion molecules (ICAM-1, VCAM-1, ELAM-1, E-selectin, P-selectin). (Zhang et al. 2002, Horvathova et al. 1999)
Endothelium	**1.** Endothelial cells produce GPx-1, GPx-4 and TR. These regulate vascular tone (maintenance of $O2^{\bullet-}$/$NO^{\bullet}$ balance), cell adhesion (control of expression of cell adhesion molecules), apoptosis (inhibition/promotion of apoptosis-signal-regulating kinase 1), and eicosanoid production (control of activity of cyclooxygenases and lipoxygenases). **2.** An acidic milieu (inflammation) promotes recruiting of SelP into the endothelium (protection against formation of peroxynitrite ($ONOO^-$) from superoxide anion ($O2^{\bullet-}$) and nitric oxide radicals ($NO^{\bullet}$)). (Brigelius-Flohé et al. 2003)
Hydrocortisone	TR stabilizes glucocorticoid receptors → better glucocorticoid response. (Grippo et al. 1985)
Insulin	Selenium stimulates the insulin signaling cascade, it has an insulin-like effect → improved control of glucose levels. (Hei et al. 1998, Pillay u. Makgoba 1992, Stapleton et al. 1997).

Glutathione peroxidases (GPx-): GPx-1: intra cellular, cytosolic, classical; GPx-2: gastrointestinal; GPx-3: plasma, extra cellular; GPx-4: phospholipid-hydroperoxide, membrane bound. Selenoprotein P(SelP): extra cellular, endothelium bound. Thioredoxin-reductases (TR): TR1α/1, TR2β/2, TR3, intra cellular/extra cellular.

Meta-analysis:
selenium in intensive care patients

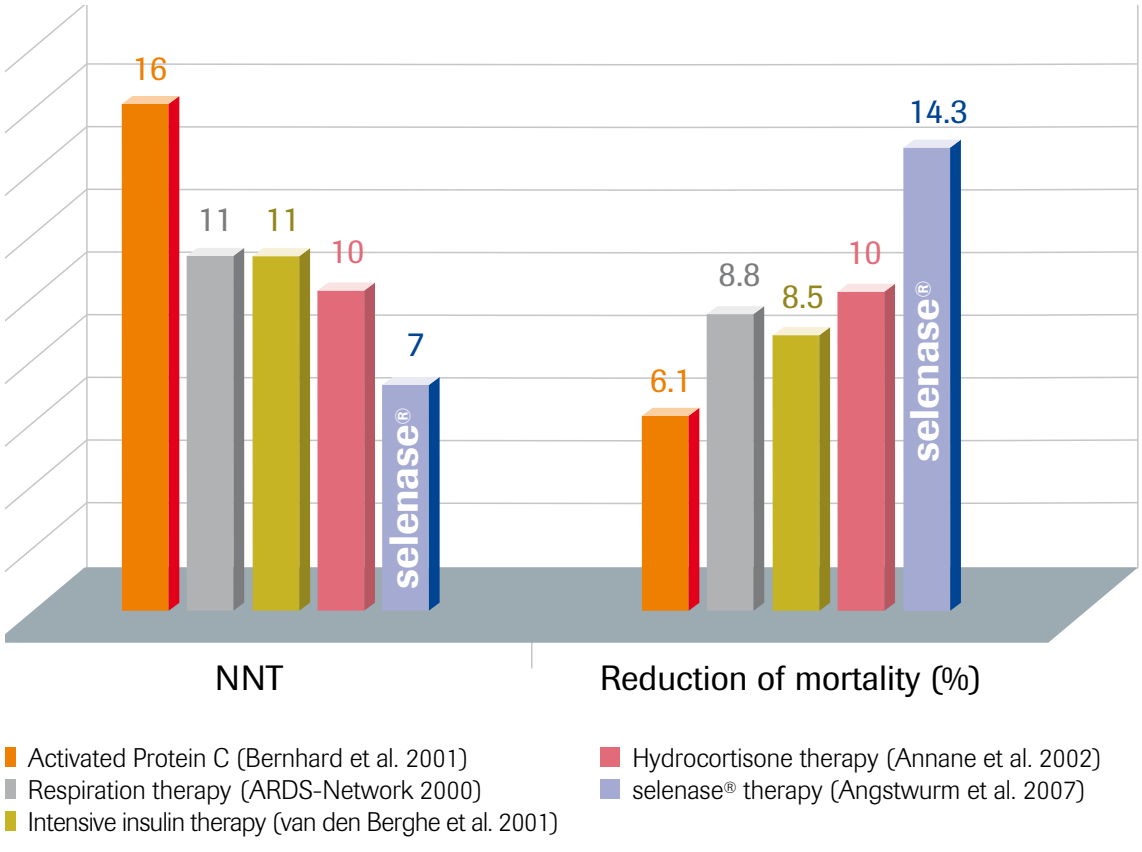
Heyland et al. 2007* (exkl. Kuklinski 1991)



*Daren K Heyland, Kingston, Canada: ISICEM 2007, www.criticalcarenutrition.com

The benefit from selenium is evident

Comparison of therapeutic options



selenase®: progress in sepsis therapy

Guidelines for Selenium

	Adults	Low birth weight neonates	infants (term and pre-term)	Burns patients	Sepsis patients	Intensive care patients in general
Guidelines on Pediatric Parenteral Nutrition Journal of Pediatric Gastroenterology and Nutrition 41: S39-S46 November 2005 ESPGHAN		X				
ESPEN Guidelines on Enteral Nutrition Intensive Care 2006 Clinical Nutrition (2006) 25, 210-223.	X			X		
DGEM* 2007 Guideline for Parenteral Nutrition Biesalski HK et al.: Wasser, Elektrolyte, Vitamine und Spurenelemente. Aktuel Ernaehr Med 2007; 32, Supplement 1:S30-S34.	X	X	X	X	X	
Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients Heyland et al. 2007 www.criticalcarenutrition.com						X
Nutrition Support for Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition National Institute for Clinical Excellence Feb 2006, UK	X					

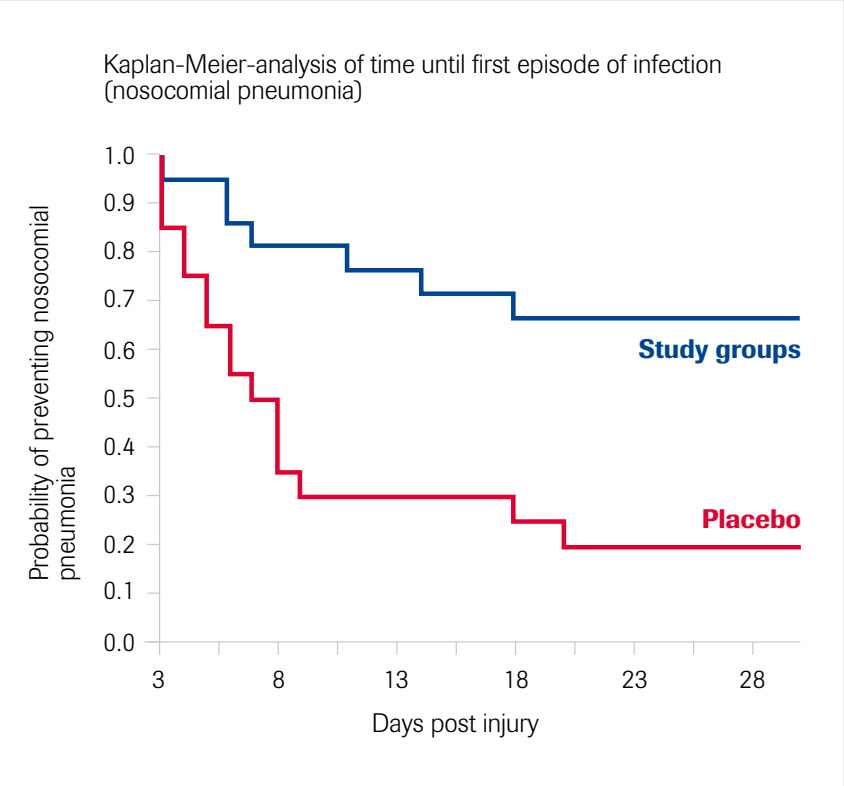
*Deutsche Gesellschaft für Ernährungsmedizin

„Selenium is a must“

(M. Berger, Lausanne 2007, ISICEM)

Selenium in burns patients

- 41 patients with thermal burns (BSA > 20 %)
- Supplementation in the study group 8-21 days
- **Study 1: 315 µg Se/d,** 2.5 mg Cu/d, 26.2 mg Zn/d
- **Study 2: 380 µg Se/d,** 3.1 mg Cu/d, 31.4 mg Zn/d



Berger et al. 2006:
Meta-analysis of 2 studies (1993-1996 and 1998-2003)
Randomised, double-blind, placebo-controlled

Lower incidence of nosocomial pneumonia

1 µmol Se = 78.96 µg Se

Selenium in burns patients

Individual results: significant reduction of

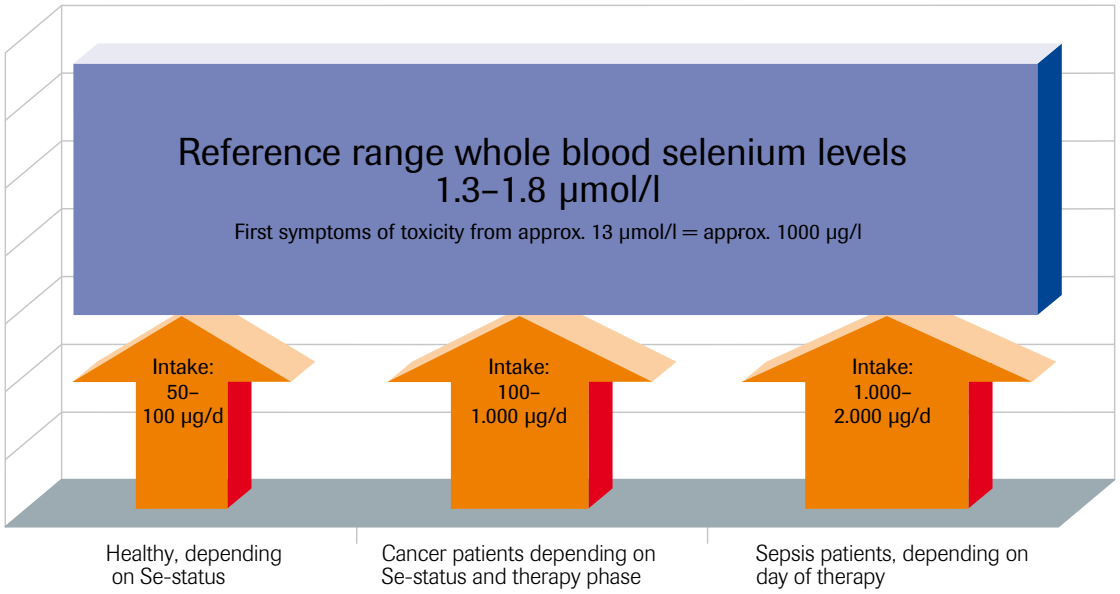
- Number of nosocomial pneumonias
- Number of infectious episodes
- Duration of antibiotic therapy
- Duration of ICU stay

Berger et al. 2006: meta-analysis of 2 studies (1993-1996 and 1998-2003)
Randomised, double-blind, placebo-controlled

Selenium reduces costs

Tolerability of selenium

1 µmol Se = 78.96 µg Se



Literature at biosyn

Information for healthy individuals

Selenium intake

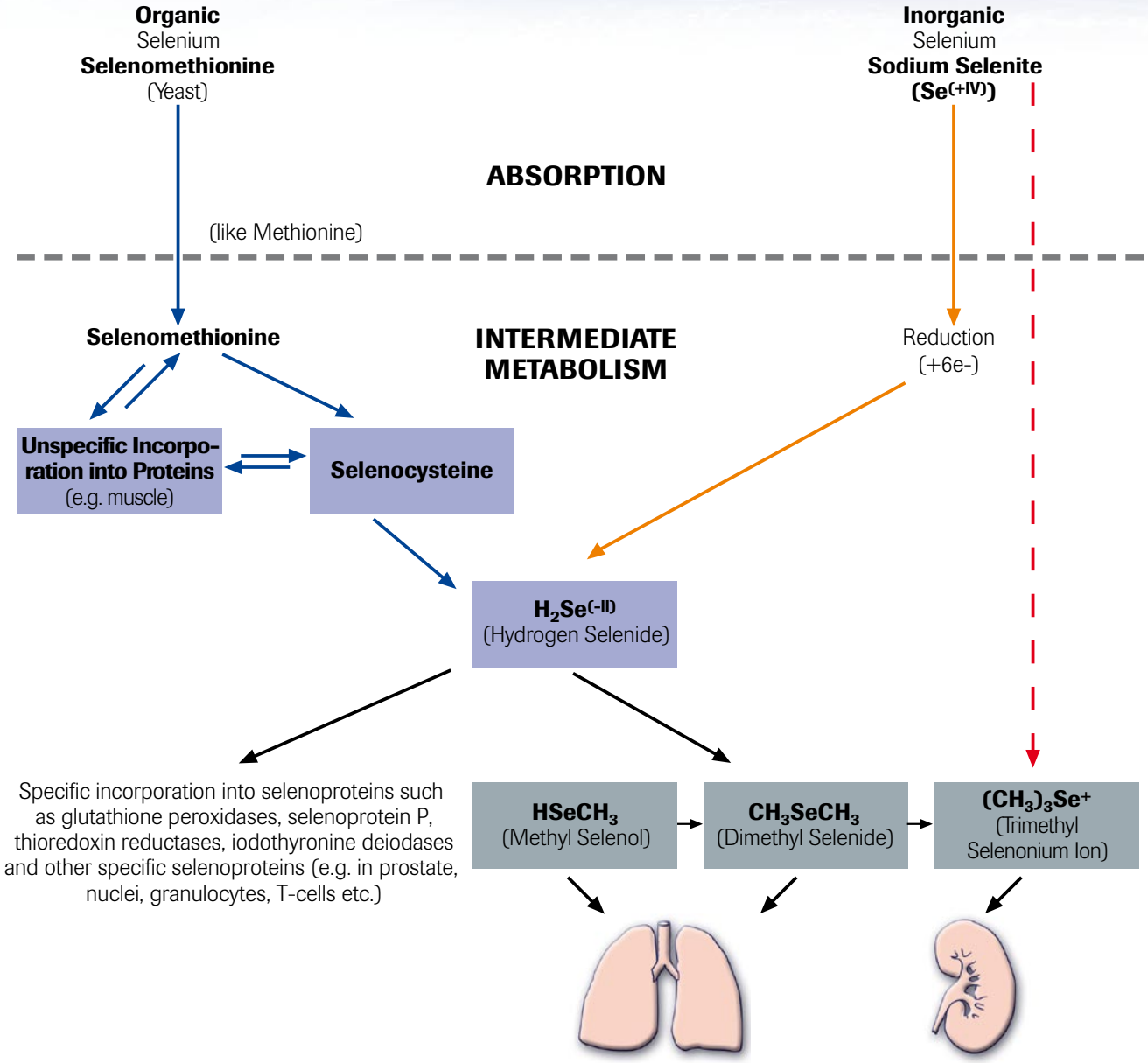
400 – 800 µg/day
= maximum chronic intake (years)

1,000 – 7,000 µg/day
= first reversible symptoms of toxicity with chronic intake

70,000 – 350,000 µg
= lethal as a single dose

Literature at biosyn

Selenium Metabolism (Simplified)



selenase® has optimal bioavailability

Dosage Recommendations*

SIRS/Sepsis

Daily Dose	Adults	Children
Start of Therapy Day 1	**2000 µg selenium =** 4 x selenase® 500 micrograms solution for injection (4 x 10 ml) 	**20 µg selenium/kg bw** as selenase® 100/500 micrograms solution for injection
From Day 2 until Clinical Improvement	**1000 µg selenium =** 2 x selenase® 500 micrograms solution for injection (2 x 10 ml) 	**10 µg selenium/kg bw** as selenase® 100/500 micrograms solution for injection

Literature at biosyn

Multiple Trauma, Cranial Trauma, Burns, Acute Pancreatitis, Acute Myocardial Infarction

Daily dose	Adults	Children
Start of therapy Day 1-5	**1000 µg selenium =** 2 x selenase® 500 micrograms solution for injection (2 x 10 ml) 	**10 µg selenium/kg bw** als selenase®100/T pro injectione solution for injection
From Day 6 until Clinical Improvement	**500 µg selenium =** 1 x selenase® 500 micrograms solution for injection (1 x 10 ml) 	**5 µg selenium/kg bw** as selenase® 100/500 micrograms solution for injection

Literature at biosyn

Total Parenteral Nutrition

Daily Dose	Adults	Children
Continuous Therapy	**200 µg selenium =** 2 x selenase® 100 micrograms solution for injection 	**2 µg selenium/kg bw** as selenase® 100 micrograms solution for injection

Literature at biosyn

Recommendation for the administration of selenase®:
- separately from other infusions, if the pH is lower than 7
- at least 1 hour apart from administration of vitamin C

Reference Values

	Selenium	Decreased	Normal Range in Health	First Symptoms of Toxicity
Whole Blood	µg/l	< 100	100 – 140[1)]	≥ 1087[3)]
	µmol/l	< 1.3	1.3 – 1.8[3)]	≥ 13.8[3)]
Serum	µg/l	< 80	80 – 120[1)]	≥ 900[2)]
	µmol/l	< 1.0	1.0 – 1.5[3)]	≥ 11.4[3)]

[1)] Summary of Product Characteristics (SPC) biosyn, [2)] Yang et al. 1989, [3)] calculated from [1)+2)]

*Further information on dosage and application see national SPC.

selenase® corrects selenium deficiency

selenase®

- protects from endothelial and organ damage
- modulates inflammatory and coagulation pathways
- is very well tolerated

Literature: Angstwurm MWA, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, Strauß R, Meier-Hellmann A, Insel R, Radke J, Schüttler J, Gärtner R: Selenium in intensive care (SIC) study: Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med 35 (2007) 1-9. **Angstwurm MW,** Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, Strauss R, Meier-Hellmann A, Insel R, Radke J, Schuttler J, Gartner R: Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med. 2007 Jan;35(1):118-26. **Angstwurm MWA,** Schottdorf J, Schopohl J, Gaertner R: Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. 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Part II: Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J Trace Elem Electrolytes Health Dis 3 (1989) 123-130. **Zhang F,** Yu W, Hargrove JL, Greenspan P, Dean RG, Taylor EW, Hartle DK: Inhibition of TNF-alpha induced ICAM-1, VCAM-1 and E-selectin expression by selenium. Atherosclerosis. 2002 Apr;161(2):381-6. **Zimmermann T,** Albrecht S, Kühne H Vogelsang U, Grützmann R, Kopprasch S: Selensubstitution bei Sepsispatienten. Eine prospektiv randomisierte Studie. Med. Klin 92 (1997) (Suppl.III) 3-4.

Abbreviated Prescribing Information
selenase® 100 micrograms, solution for injection (50micrograms/ml)
selenase® 500 micrograms, solution for injection (50micrograms/ml)
Active ingredient: sodium selenite pentahydrate. Composition: Each 2ml ampoule/10ml injection vial contains 100micrograms/500 micrograms selenium as 333 micrograms/1.66mg sodium selenite pentahydrate ($Na_2 SeO_3 \times 5H_2O$), corresponding to 50 micrograms/ml. Excipients: Sodium chloride, hydrochloric acid, Water for Injections. Indication: Proven selenium deficiency that cannot be offset from food sources. Posology and Administration: selenase® solution for injection is administered as an intramuscular or intravenous injection at a daily dose of 100 – 200 µg (1.27 – 2.53µmol) selenium. If necessary, this dose can be increased to 500 µg (6.33 µmol) for a typical adult. No dosage adjustment is required for paediatric, renal or hepatic impairment patients. Contraindications: Selenosis. Interactions: Ensure that the pH value does not fall below 7.0 and that the solution is not mixed with reducing substances (e.g. vitamin C). Pregnancy and Lactation: There are no data from the use of selenase in pregnant or lactating women. Undesirable Effects: None known to date when used as directed. Overdose: Counter measures include gastric lavage, forced diuresis, dialysis or administration of high doses of vitamin C. Pharmaceutical Precautions: Store below 25ºC. Legal Category: POM. Presentation: Cartons containing 10 x 2ml ampoules / 10 x10ml glass vials for single use. MA Numbers: PL 20437/0003, PL 20437/0004. MA Holder: biosyn Arzneimittel GmbH, Schorndorfer Str 32, D-70734 Fellbach, Germany. Date of Preparation: November2004

Foreign distributors for selenase®

Great Britain	Oxford Nutrition Ltd.	info@nutrinox.com
Luxembourg	Promopharm S.A.	promopharm@pt.lu
Netherlands	Lamepro B.V.	lamepro@lamepro.nl
Austria	Richter Pharma	office@richter-pharma.at
Russia	Medicana Pharm	irinavitv@yahoo.de; irina_vitv@mtu-net.ru
Switzerland	Robapharm AG	info@robapharm.ch
Slovakia	Vivax Pharmaceuticals s.r.o.	bronislavciko@vivax.sk
South Korea	NMP Korea	smkang@kgbms.org
Turkey	Erkim Ilac	s.oncel@erkim-ilac.com.tr
Czechia	Vivax Pharmaceuticals s.r.o.	bronislavciko@vivax.sk

We research.

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We would be pleased to send you any further information.

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