Selenium for sepsis

selenase®

• improves selenium status
• eliminates selenium deficiency
• reduces mortality
## High dose for sepsis – so that selenium works

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6h</td>
</tr>
<tr>
<td></td>
<td>2,000&lt;sup&gt;1-3&lt;/sup&gt; µg Se as bolus</td>
</tr>
<tr>
<td></td>
<td>1,600&lt;sup&gt;1-3&lt;/sup&gt; µg Se then as continuous infusion</td>
</tr>
<tr>
<td>at least 7 days</td>
<td>maintenance therapy</td>
</tr>
</tbody>
</table>

### Literature

3. Alhazzani W et al. 2013, Crit Care Med 41:1555–1564

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## selenase<sup>®</sup> for sepsis

- A high dose selenium bolus significantly reduces the death rate for sepsis patients by 27%. [1]
- A high dose of ≥ 1,000 µg selenium as sodium selenite pentahydrate (selenase<sup>®</sup>) per day significantly reduces the mortality by 23%. [1]
- A maintenance therapy of ≥ 7 days significantly improves survival. [1]

---

## Miscibility

### Yes

- 5% glucose solution
- Ringer solution
- Carbohydrate solutions (stability 72 hours (3 days))
- Colloidal volume expander solutions (stability 72 hours (3 days))
- Electrolyte solutions with increased potassium concentration (stability 48 hours (2 days))
- Crystalloid electrolyte solutions (stability 48 hours (2 days))
- Amino acid solutions without cysteine (stability 36 hours (1.5 days))
- Fat emulsions (stability 24 hours (1 day))
- Vitamin solutions (without vitamin C)

### No

- Cytostatic agent solutions [1]
- Amino acid solutions that contain cysteine [2]
- Solutions that contain glutathione (GSH) [3]
- Vitamin solutions that contain vitamin C [4]

---

[1] selenase<sup>®</sup> should generally be administered 1 hour before cytostatic agent application for timely incorporation in the endogenous protective systems.

[2,3] SH groups react to Na-selenite; Na-selenite can no longer satisfy its task as a radical scavenger.

[4] Selenium (Se<sup>IV</sup>) in sodium selenite is reduced by vitamin C to the elementary selenium (Se<sup>0</sup>) and is thereby ineffective.

### Literature:


**Products for injection therapy**

**Prescription only**

<table>
<thead>
<tr>
<th><strong>selenase® 100 µg pro injection</strong></th>
<th><strong>selenase® T pro injection</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100 µg</strong></td>
<td><strong>500 µg</strong></td>
</tr>
<tr>
<td>Selenium / ampoule</td>
<td>Selenium / injection vial</td>
</tr>
</tbody>
</table>

10 (N2) and 50 ampoules with 2 ml solution for injection

---

**selenase® 100 µg / T**

**Active substance:** Sodium selenite pentahydrate, 50 µg selenium per ml.

**Indications:** Clinically proven selenium deficiency that cannot be compensated by nutritional sources. Selenium deficiencies may occur as a result of states of malnutrition and malabsorption, as well as in malnutrition (e.g. due to complete parenteral nutrition).

**Composition:**

- **selenase® 100 µg pro injection:** 1 ampoule of 2 ml solution for injection contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium.
- **selenase® T pro injection:** 1 injection vial of 10 ml / 20 ml solution for injection contains: 1.67 mg / 3.33 mg sodium selenite pentahydrate, corresponding to 500 µg / 1000 µg selenium.
- **selenase® 100 µg peroral:** 1 drinking ampoule of 2 ml oral solution contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg selenium.
- **selenase® T peroral:** 1 ml oral solution contains: 0.167 mg sodium selenite pentahydrate, corresponding to 50 µg selenium.

**Excipients:** Sodium chloride, hydrochloric acid, water for injections.

**Contra-indications:** Selenium poisoning.

**Undesirable effects:** None known to date if the medicinal product is administered according to prescription. After intramuscular administration local pain at the site of administration has been reported. After intravenous administration local pain at the site of administration has been reported. Form of administration, size of packages: **selenase® 100 µg pro injection:** 10 or 50 ampoules of 2 ml solution for injection. **selenase® T pro injection:** 2 or 10 injection vials of 10 ml solution for injection, hospital-size pack 30 (3 x 10) or 50 (5 x 10) injection vials of 10 ml solution for injection, 2 or 10 injection vials of 20 ml solution for injection, hospital-size pack 30 (3 x 10) or 50 (5 x 10) injection vials of 20 ml solution for injection. **selenase® 100 µg peroral:** 20, 50, 90 or 100 ampoules of 2 ml oral solution. **selenase® T peroral:** 10 drinking bottles of 10 ml oral solution plus one measuring cup.

10/14 e
## 8 General facts about sepsis

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- **Which effect does ROS production have on survival?**
- **Why does the selenium status decline in patients with sepsis?**
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## 32 selenase® for sepsis

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<td>Germany registers over 175,000 sepsis patients each year</td>
</tr>
<tr>
<td></td>
<td>Despite medical progress in general, these numbers keep rising</td>
</tr>
<tr>
<td></td>
<td>Diagnosis is encumbered by non-specific symptoms and a lack of generally valid biomarkers</td>
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<tr>
<td></td>
<td>Exorbitant costs for treating sepsis patients</td>
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<td>Organ failure strongly affects ICU mortality rate</td>
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<tr>
<td>selenase® for sepsis</td>
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<tr>
<td>----------------------</td>
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<tr>
<td><strong>Meta analysis</strong></td>
<td></td>
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<tr>
<td>Parenteral sodium selenite treatment significantly reduces total mortality rate by 17% (p = 0.04)</td>
<td></td>
</tr>
<tr>
<td>Higher significant reduction of mortality when a bolus is administered (−27%; p = 0.01), a maintenance therapy ≥ 7 days (−23%; p = 0.01) and a dosing of ≥ 1,000 µg selenium as sodium selenite-pentahydrate (selenase®) per day (−23%; p = 0.04)</td>
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<tr>
<td><strong>Pilot study</strong></td>
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<tr>
<td>Supplementation with selenase® increases the selenium level to values within the normal range</td>
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<tr>
<td>Selenase® supplementation significantly reduces mortality in patients with APACHE III score &gt; 53</td>
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<tr>
<td><strong>SIC trial</strong></td>
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<tr>
<td>Significant reduction in mortality in the selenase®-supplemented group by 14.3% (p = 0.049)</td>
<td></td>
</tr>
<tr>
<td>Significant reduction in mortality in the subgroups (septic shock, APACHE III ≥ 102, &gt; 3 organ failure) in the selenase®-supplemented group by up to 26%</td>
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<tr>
<td><strong>Various trials</strong></td>
<td></td>
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<tr>
<td>Possible correlation between selenium supplementation and procalcitonin</td>
<td></td>
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<tr>
<td>Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity</td>
<td></td>
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<tr>
<td>SIGNET trial: Fewer new infections in patients receiving selenase® supplementation for &gt; 5 days</td>
<td></td>
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<tr>
<td>REDOXS trial: Compared to glutamine, selenium does not have any negative effect on mortality, although the beneficial effect of selenium supplementation is reduced by the lack of selenium deficiency</td>
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<tr>
<td>Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis</td>
<td></td>
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</tbody>
</table>
General facts about sepsis

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</table>

Sepsis: High incidence rate

Sepsis involves a complex systemic inflammatory reaction affecting the entire body and impairs tissue, organs and thereby all vital functions. If sepsis is not diagnosed and treated in a timely manner, it will invariably lead to septic shock, multiple organ failure and death. One third to one half of all patients do not survive sepsis.

Sepsis is the most common infection-related cause of death. Older figures reported 1.5 million sepsis patients annually worldwide. In Germany, the incidence is 154,000 per year (Fig. 1). New publications even reported 175,000 cases. However, the experts meanwhile assume that approx. 18 million people per year become afflicted given that the majority of deaths ascribed to HIV/AIDS, malaria, pneumonia and other infectious diseases are most likely attributable to sepsis.

Despite general progress in medicine, these numbers are rising dramatically. The number of sepsis cases treated in hospital have doubled over the past 10 years and meanwhile exceed the number of hospital admissions due to heart attacks (Fig. 2). Only 20 – 40% of sepsis patients acquired their sepsis outside of the hospital. By contrast, for example, the incidence of postoperative sepsis in the USA tripled from 1997 to 2006.
Fig. 1  Incidence and mortality of sepsis depending on age. [10]

Fig. 2  More hospital admissions due to sepsis than to myocardial infarction. [5, 6]
Sepsis: problematic diagnostics

The diagnosis is frequently confirmed too late because the clinical symptoms and laboratory values (body temperature, heart rate, respiratory rate and white blood cell count) are relatively non-specific and can occur in a large number of other diseases as well. Particularly in children, these symptoms are less meaningful because the onset of sepsis symptoms is usually very subtle, with the clinical picture suddenly worsening dramatically.

The high rate of misdiagnoses or cases diagnosed after it was too late is attributable to deficits still existing in the definition of the condition, insufficient diagnostic criteria and frequently insufficient compliance with clinical guidelines. An additional problem is, that for a diagnosis using blood parameters (“biomarkers”), there are still no generally approved biomarkers, in contrast to other acute diseases. Some national and international guidelines recommend procalcitonin for guiding antibiotic therapy and verifying diagnosis of sepsis.

Sepsis: High costs

Between 1997 and 2008, inflation-corrected costs of hospital treatment for sepsis patients rose annually by an average of 11.9% to approx. $14.6 billion in 2008 [6]. These numbers do not take into account the costs for long-term effects, because they are so far unknown. Sepsis survivors suffer from a large number of severe physical, cognitive and mental problems, which lead to a mortality risk twice as high as that of a population control group even 5 years after surviving sepsis [8].

Over the past 10 years, the mean costs for hospital treatment per sepsis patient increased in the same magnitude to a current level of approx. € 55,000 in Germany as well [9].
## Literature

|---|---|
Details on sepsis

General information

- Correlation between ICU mortality and sepsis incidence in Europe
- Organ failure strongly affects ICU mortality rate
- The number of failed organs increases significantly in severe sepsis
- Increasing number of postoperative sepsis cases

Sepsis in Europe

More exact figures on the topic of sepsis in Europe can be found in the SOPA trial 2006 [1].

Europe-wide, 37% of patients had sepsis during their ICU stay. This number of patients illustrates the high prevalence of sepsis. This combined with the fact, that the sepsis mortality rate in Europe is 27% during an ICU stay and increases to 50% in severe sepsis, shows clearly how important the topic of sepsis is, even in industrialized nations with very good medical care.

A large proportion of sepsis patients display a severe sepsis (79%) and 39% even suffer from septic shock. That means that 15% of all patients admitted to an ICU suffered from septic shock.

ICU mortality in sepsis patients ranges between 10% in Switzerland and 35% in Italy; Germany has 16%, the second lowest ICU mortality rate. The hospital mortality in patients with sepsis in Germany and Switzerland was lowest at 20%, with the Netherlands registering the highest at 47%. A clear correlation between overall ICU mortality and the sepsis rate is evident across the different countries (Fig. 1). Overall, ICU mortality in patients with sepsis was significantly higher than in patients without sepsis (27% vs. 14%; p < 0.001). In patients with severe sepsis and/or septic shock, ICU mortality increased on average to 32.2% and 54.1%, respectively (Fig. 2). In Germany, ICU mortality in severe sepsis was 24%.
Correlation between ICU mortality of all patients and sepsis incidence in Europe. [1]

Comparison of sepsis incidence in ICU patients with ICU mortality in Europe. [1]
Major influence of organ failure on ICU mortality rates

At ICU admission, 81% of patients displayed organ failure. 41% of these patients had sepsis. In 38% of ICU patients without sepsis, no organ failure occurred. Also, ICU mortality in this group was barely 2%. In the remaining 62% of ICU patients without sepsis but with organ failure, ICU mortality increased to 21%. In comparison, all ICU patients with severe sepsis had organ failure, and ICU mortality increased further significantly to 32% (p < 0.01) (Fig. 3).

Independent of an existing sepsis, there was a direct connection between the number of failed organs and ICU mortality (Fig. 4). In patients with no organ failure at ICU admission, the ICU mortality was 6%. In patients with 4 or more failed organs, ICU mortality increased to 65%.
Frequency of organ failure at ICU admission and the corresponding ICU mortality. [1]
ICU mortality rate significantly higher in sepsis patients

Severe sepsis does not impact ICU mortality rate depending on the number of failing organs. But the number of organs that fail in sepsis patients is significantly increased (Fig. 5). Therefore, ICU mortality in ICU patients with severe sepsis is still significantly higher compared to those without sepsis, but with organ failure. If the frequency of multiple organ failure (MOF) could be lowered in patients with sepsis, the high mortality rate in this group of patients would also be markedly reduced.

The number of failing organs is significantly increased in sepsis patients. [1]

![Graph showing the number of failing organs](image)

**Number of organ failures**

<table>
<thead>
<tr>
<th>No sepsis</th>
<th>Severe sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>57%</td>
</tr>
<tr>
<td>3</td>
<td>28%</td>
</tr>
<tr>
<td>≥4</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Literature**


**Diagnostic criteria for sepsis**

According to: Reinhart K, Brunkhorst FM, Bone HG et al. [Prevention, diagnosis, treatment, and follow-up care of sepsis. First revision of the S2k. Guidelines of the German Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI)].* Anaesthesist 2010; 59: 347–370.

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of an infection</td>
<td>Evidence of an infection</td>
<td>Evidence of an infection</td>
</tr>
<tr>
<td>SIRS</td>
<td>SIRS</td>
<td>SIRS</td>
</tr>
<tr>
<td>Acute organ dysfunction</td>
<td>Cardiovascular instability</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence of an infection:**
Diagnosis of infection based on microbiological proof or clinical criteria

**Systemic inflammatory response syndrome (SIRS) – at least 2 of the following criteria:**

- **Fever** (≥ 38°C) or **hypothermia** (≤ 36°C), confirmed through rectal, intravascular or intravesical determination
- **Tachycardia** with a heart rate ≥ 90/min
- **Tachypnea** (respiratory rate ≥ 20/min) or **hyperventilation** (PaCO₂ ≤ 4.3 kPa/ ≤ 33 mmHg)
- **Leukocytosis** (≥ 12,000/mm³) or **leukopenia** (≤ 4,000/mm³) or ≥ 10 % immature neutrophils in the differential blood count

**Acute organ dysfunction – at least 1 of the following criteria:**

- **Acute encephalopathy:** Reduced vigilance, disorientation, agitation, delirium.
- **Relative or absolute thrombocytopenia:** Drop in platelet count >30% within 24 hours or platelet count ≤ 100,000/mm³. Thrombocytopenia due to acute bleeding or immunological causes must be ruled out.
- **Arterial hypoxemia:** PaO₂ ≤ 10 kPa (≤ 75 mmHg) in room air or a PaO₂/FiO₂ ratio ≤ 33 kPa (≤ 250 mmHg) on oxygen. Overt cardiac or pulmonary disease as the cause of the hypoxemia must be ruled out.
- **Renal dysfunction:** Diuresis of ≤ 0.5 ml/kg/h for at least 2 hours despite adequate volume replacement and/or a rise in serum creatinine to more than twice the reference range.
- **Metabolic acidosis:** Base excess ≤ 5 mmol/l or lactate concentration more than 1.5 times the reference range.

**Cardiovascular instability:**
Systolic arterial blood pressure ≤ 90 mmHg and/or mean arterial blood pressure ≤ 65 mmHg lasting for at least 1 hour or use of vasopressor required to stabilize systolic arterial blood pressure ≥ 90 mmHg or arterial mean pressure ≥ 65 mmHg. Hypotension despite adequate volume resuscitation not explained by other causes.
Postoperative sepsis

Sepsis is a major cause of postoperative mortality. A trial conducted in 2010 investigated the development of postoperative sepsis from 1997 – 2006 using the largest patient database in the USA (more than 2 million patients) [2]. During the analysis period, the incidence of postoperative sepsis increased from 0.7% to 1.3% (p < 0.001) and of severe postoperative sepsis from 0.3% to 0.9% (p < 0.001) (Fig. 6). The higher increased rate of severe postoperative sepsis was found in all surgical intervention categories (Fig. 7). A counter trend was observed for hospital mortality rate. The mortality rate declined from 44.4% in 1997 to 34% in 2006 (p < 0.001) (Fig. 8). Even after accounting for potential confounders, a multivariate regression model showed a decline in mortality (OR 0.94; 95% CI, 0.93–0.95 per year increase in the trial period; p < 0.001). Overall, the decline in mortality cannot compensate the increase in postoperative sepsis. Therefore the number of deaths from postoperative stress increases.
Increased number of severe postoperative sepsis is independent of the type of surgical intervention. [2]

10% reduced mortality between 1997 – 2006 in severe postoperative sepsis. [2]
## Selenium and sepsis

<table>
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</tbody>
</table>
Selenium level declines in correlation with sepsis severity

One trial conducted in 2007 compared 45 ICU patients with SIRS (systemic inflammatory response syndrome), mainly after cardiac surgery, with a group of 15 ICU patients without SIRS \(^{[1]}\). The 45 patients were subdivided into the following groups SIRS, severe SIRS and severe sepsis or septic shock: SIRS (n = 15), severe SIRS (n = 15), severe sepsis or septic shock (n = 15). Already at ICU admission, 92% of all patients had a serum selenium value below the German reference range. During their ICU stay, the selenium concentration continued to decline in all groups except for the control group without SIRS. The mean serum selenium levels at ICU admission correlated negatively with sepsis severity (Fig. 1).

![Fig. 1](image-url)

Serum selenium levels in sepsis patients at ICU admission decline depending on sepsis severity. \(^{[1]}\)
Selenium concentration is inversely correlated with APACHE II and SAPS II scores

Minimum serum selenium concentration is inversely correlated with maximum number of leucocytes ($R^2 = 0.22; p < 0.01$), maximum serum C reactive protein (CRP) ($R^2 = 0.28; p < 0.01$), maximum serum procalcitonin (PCT) ($R^2 = 0.3; p < 0.01$) and maximum serum interleukin 6 (IL-6) ($R^2 = 0.42; p < 0.01$).

APACHE II and SAPS II scores, both indicators for inflammation and the degree of organ failure during an ICU stay, correlated inversely with the minimum serum selenium value (APACHE II: $R^2 = 0.31; p < 0.01$; SAPS II: $R^2 = 0.29; p < 0.01$) (Fig. 2). Furthermore the minimum serum selenium concentration is inversely correlated with the maximum degree of organ dysfunction respectively failure during an ICU stay ($R^2 = 0.42; p < 0.01$).

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**Fig. 2** Inverse correlation of serum selenium levels with APACHE II and SAPS II scores. \([1]\)

* SIRS = systemic inflammatory response syndrome
Minimum selenium concentration: independent predictor of ICU mortality

Both the initial serum selenium value as well as the minimum serum selenium concentration were significantly lower in non-surviving compared to surviving patients (Fig. 3). A receiver operating characteristic (ROC) analysis for predicting ICU mortality showed that the SAPS II score (AUC = 0.903; 95% CI: 0.819–0.987, p < 0.01) and minimum serum selenium concentration (AUC = 0.867; 95% CI: 0.753–0.981, p < 0.01) were the most significant predictive factors.

A cut-off value for the minimum serum selenium concentration was set. A cut-off value of 36 µg/l selenium in serum has a sensitivity of 89%, specificity of 71% and positive predictive value of 35%. Most importantly, however, it has a negative predictive value of 95%.

Therefore the probability to die increases below 36 µg/l selenium in serum.

Fig. 3 The serum selenium level in surviving patients is significantly higher. [1]
Cytokines:
- TNFα
- IL-1
- IL-6

Invasion of bacteria and toxins

NF-κB activation

Activation of coagulation

Disseminated intravascular coagulation (DIC)

iNOS

NO

Se

[13]

Signaling processes

Se

[13]

Fever
Tachycardia
Leukocytosis

Neurological abnormalities

 NF-kB activation

Purpura
Petechia

Tissue hypoperfusion
Hypoxia

Tissue damage

Multiple organ dysfunction (MOD)

Multiple organ failure (MOF)

Tissue hypoperfusion
Cardiovascular hyporeactivity

Hypotension

Se

[13]

Tissue damage

Se

[13]

Neurological abnormalities

Fever
Tachycardia
Leukocytosis

Se

[13]

Multiple organ dysfunction (MOD)

Multiple organ failure (MOF)
Invasion of bacteria and toxins

Signaling processes

NF-κB activation

COX-2 5-LO

Adhesion molecules

Neutrophil infiltration + activation

Prostaglandins Leukotrienes Thromboxanes

ROS

Endothelial injury

Capillary leakage

Tissue damage

Death

Where does selenium intervene in the process of sepsis?

Fig. 4

Selenium-Supplementatum [References]

Effect of selenium

References

Se

Se

Se

Se
Which effect does ROS production have on survival?

Huet et al. conducted a trial investigating the extent to which the production of reactive oxygen species (ROS) correlates with the severity of septic shock [2]. For this purpose, naive human umbilical vein endothelial cells (HUVEC) were treated with plasma collected from 21 patients with septic shock and the induced ROS production was quantified. Compared to controls, the plasma-induced ROS production by HUVEC was significantly higher in septic shock and ROS production significantly correlated with the SAPS II score ($p = 0.028$) and the SOFA score ($p = 0.0012$). Moreover, ROS production in non-survivors was significantly higher compared to survivors ($p = 0.0015$) (Fig. 5). These results demonstrate that an early reduction of ROS production, as it can be achieved by application of selenase®, can increase the chance of survival of septic patients.

Why does the selenium status decline in patients with sepsis?

Clinical sepsis is associated with a significant decrease in selenium level [3, 4]. Lipopolysaccharides (LPS) are key players in the development of sepsis. These toxic compounds are produced when attacking bacteria divide, but also when antibiotics actively attack pathogens. An injection of LPS in rats induces an acute-phase response and leads to significantly reduced serum and liver selenium values [4]. Several recent trials have been able to elucidate some of the underlying mechanisms. It was demonstrated that an LPS-induced acute-phase response leads to a reduction in selenoprotein biosynthesis in the liver [5]. The liver is the main location of biosynthesis of selenoprotein P, which is released into the plasma and transports selenium to other tissues. The human selenoprotein P promoter is negatively regulated by pro-inflammatory cytokines in human hepatocytes [6].

In sepsis, a pathogenic cycle may be triggered in which selenoprotein P synthesis in the liver is diminished by sepsis and inflammatory cytokines. This lowers selenium status in other tissues as well, increasing oxidative stress which further amplifies the inflammatory response (Fig. 6). For the immune system, this means that a low selenium status not only diminishes the transport capacity of the lymphocytes and the cells of the innate immune system, but also leads to stress-induced lymphopenia [7].
Fig. 5  Significant difference in ROS production in surviving and non-surviving patients (p = 0.0015). [2]

Fig. 6  Cyclic reduction of selenium level in sepsis and intervention of selenium supplementation in this cycle. [8]
Why is early administration of sodium selenite crucial (within \( \leq 6 \) hours)?

Levy et al. demonstrated that oxidation of cytochrome c by myocardial cytochrome c oxidase is completely inhibited early in sepsis. Myocardial cytochrome c oxidase is the terminal oxidase in the electron transport chain \([9]\). This oxidative stress in mitochondria leads to mitochondrial dysfunction and is irreversible after 48 hours after the onset of tissue hypoxia (Fig. 7). Irreversible inhibition disrupts oxidative phosphorylation, which leads to sepsis-associated cardiac depression. For an effective antioxidant strategy, selenium must be administered as soon as possible after onset of sepsis.

In a phase I dose-escalating clinical trial, it was shown that the glutathione concentration was not decreased by increasing selenium dose in severely ill patients \((p = 0.03)\) \([10]\). Furthermore, an increasing selenium dose decreased the concentrations of thiobarbituric acid reactive substances (TBARS) significantly \((p = 0.03)\) and thus lowered oxidative stress. Motoyama et al. showed that increasing TBARS concentrations in sepsis patients correlated with a higher SOFA score \((p < 0.001)\) \([11]\). Plasma TBARS concentration was significantly higher in sepsis patients with multi organ failure (MOF) than in patients without MOF \((57.1\% \text{ vs. } 15.8\%, p < 0.001)\). Analysis of the ratio of mitochondrial DNA as an indirect marker of mitochondria function showed, that the function of mitochondrias improved with increasing selenium dosage \((p = 0.001)\) (Fig. 8) \([10]\).
Selenium and sepsis

Only a high selenium dosage improves mitochondrial function, reduces oxidative stress and increases antioxidative capacity in sepsis. \(^{[10]}\)

Fig. 8

<table>
<thead>
<tr>
<th>Selenium</th>
<th>GSH level stays stable</th>
<th>antioxidative capacity ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TBARS (thiobarbituric acid reactive substances) ↓</td>
<td>oxidative stress ↓</td>
</tr>
<tr>
<td></td>
<td>mitochondrial DNA ↑</td>
<td>mitochondrial function ↑</td>
</tr>
</tbody>
</table>

Irreversible inhibition of the cytochrome c oxidase after 48 hours in severe sepsis. \(^{[9, 10, x]}\)

Fig. 7

- Competitive inhibition of cytochrome c oxidase
- Antioxidant concentration ↓
- ROS ↑
- Oxidation of mitochondrial DNA
- Non-competitive inhibition of cytochrome c oxidase
- Irreversible mitochondrial damage
- Organ failure

Why inject sodium selenite as bolus?

The effect of a bolus injection of 2,000 µg selenium as sodium selenite pentahydrate was compared to a continuous infusion of 4 µg/kg per hour in an experimental animal model for sepsis in sheep [12]. Only the bolus showed a positive effect on sepsis progression, although the overall dosage was comparable. The likely explanation for this is an early transient pro-oxidative effect of sodium selenite, that can be used as therapeutic strategy to reverse the pro-inflammatory state existing in severe sepsis and septic shock. This excessive pro-inflammatory state is characterized by high levels of circulating cytokines and ROS, phagocytic hyperactivity of leucocytes due to delayed apoptosis, and a prolonged NFkB activation.

A bolus injection in the early phase of septic shock inhibits NF-κB binding to DNA via stabilization of disulfide bonds. This regulates gene expression and synthesis of pro-inflammatory cytokines [13]. Additionally a bolus administration induces apoptosis and cytotoxicity in activated, pro-inflammatory cells along with a direct virucidal or bactericidal effect [14, 15].

---

**High dose for sepsis – so that selenium works**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>as bolus</td>
<td>2,000&lt;sup&gt;1–3&lt;/sup&gt; µg Se</td>
</tr>
<tr>
<td>then as continuous infusion</td>
<td>1,600&lt;sup&gt;1–3&lt;/sup&gt; µg Se</td>
</tr>
</tbody>
</table>

**at least 7 days**

| maintenance therapy | 1,600<sup>1–3</sup> µg Se / Day |

---

**Literature**

1 Manzanares W et al. 2012, Crit Care; 16:R66
2 Huang TS et al. 2013, PLoS One 8:e54431
3 Alhazzani W et al. 2013, Crit Care Med 41:1555–1564
<table>
<thead>
<tr>
<th></th>
<th>Authors</th>
<th>Title</th>
<th>Year</th>
<th>Journal</th>
<th>Page Range</th>
<th>DOI</th>
<th>Notes</th>
</tr>
</thead>
</table>
## General information

- Supplementation with sodium selenite increases the selenium level to values within the normal range
- Significant reduction in mortality in the selenium-supplemented group
- Possible correlation between selenium supplementation and procalcitonin \(^4\)
- Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity
**Meta analysis**

Parenteral sodium selenite treatment significantly reduces total mortality rate by 17% \( (p = 0.04) \)

Higher significant reduction of mortality when a bolus is administered \( (\sim 27\%; \ p = 0.01) \), a maintenance therapy \( \geq 7 \) days \( (\sim 23\%; \ p = 0.01) \) and a dosing of \( \geq 1,000 \) µg selenium as sodium selenite-pentahydrate \( \text{selenase}\) per day \( (\sim 23\%; \ p = 0.04) \)

**Pilot study**

Supplementation with \text{selenase}\ increases the selenium level to values within the normal range

\text{selenase}\ supplementation significantly reduces mortality in patients with APACHE III score > 53

**SIC trial**

Significant reduction in mortality in the \text{selenase}\-supplemented group by 14.3% \( (p = 0.049) \)

Significant reduction in mortality in the subgroups (septic shock, APACHE III \( \geq 102\), > 3 organ failure) in the \text{selenase}\-supplemented group by up to 26%

**Various trials**

Possible correlation between \text{selenase}\ supplementation and procalcitonin

Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity

\text{SIGNET} trial: Fewer new infections in patients receiving \text{selenase}\ supple-mentation for > 5 days

\text{REDOXS} trial: Compared to glutamine, selenium does not have any negative effect on mortality, although the beneficial effect of selenium supplementation is reduced by the lack of selenium deficiency

Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis
**Meta analysis of 9 sepsis trials**

With correct application, sodium selenite significantly reduces mortality.

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A large-bolus injection significantly reduced mortality in sepsis patients by 27%</td>
</tr>
<tr>
<td>• Maintenance therapy lasting ≥ 7 days significantly improved the probability of survival</td>
</tr>
<tr>
<td>• A high dose of ≥ 1,000 µg selenium in the form of sodium selenite pentahydrate (selenase®) per day significantly reduced mortality by 23%</td>
</tr>
</tbody>
</table>

Parenteral sodium selenite treatment significantly reduces total mortality by 17% (p = 0.04).

Twelve trials were included in the meta analysis, whereby the meta analysis was carried out in nine of these (Table 1) [3]. In total, 965 patients took part in the nine studies; 482 participants received a sodium selenite supplementation and 483 a placebo. A total of 148 patients (30.7%) died in the intervention group, while 180 participants (37.3%) died in the placebo group. The mortality varied greatly between the studies, from 24% to 52%. Also the administration scheme differed considerably, both with respect to the duration and dose as well as the strategy. The use of sodium selenite was uniform as the only approved selenium form for the drug product, whereby more than half of the trials were carried out with selenase®. All trials had a low risk of “detection bias”, since mortality was defined as the result. In addition, most trials had a low risk of “attrition bias” e.g. protocol noncompliance.

In total, the meta analysis shows that a parenteral sodium selenite supplementation significantly reduces total mortality (RR 0.83, 95% CI 0.70-0.99; p = 0.04).
<table>
<thead>
<tr>
<th>Tab. 1</th>
<th>Included trials</th>
</tr>
</thead>
</table>

**selenase®**: Studies were carried out with selenase®
Fig. 1 Positive significant impact of selenium as sodium selenite on total mortality in the event of sepsis. [changed according to 1]

At ICU-admission (< 6 h):
Bolus: 2,000 µg Se as sodium selenite
► Mortality rate ↓
(RR 0.73; p = 0.01) [3]

Early death
overwhelming immune response

Bolus
2,000 µg Se
as sodium selenite

1,600 µg Se
as sodium selenite
per day

Minimum 5 days Se as sodium selenite
► New infections ↓
(RR 0.53; p = 0.03) [2]

Meta analysis
(9 studies, n = 965) [3] A sodium selenite supplementation significantly reduces mortality for sepsis patients (RR (relative risk) 0.83 CI (confidence interval) 0.77-0.99; p = 0.04)
Fig. 1 Positive significant impact of selenium as sodium selenite on total mortality in the event of sepsis.

<table>
<thead>
<tr>
<th>Day 16h</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without sodium selenite supplementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum 5 days Se as sodium selenite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▶ Mortality rate ↓ (RR 0.77; p = 0.01) [3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum 7 days Se as sodium selenite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With sodium selenite supplementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Se = selenium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Survival**

Day 5 → Day 6 → Day 7 → Day 10 – 14

- Nosocomial infections
- Viral reactivation
- Late Death

Impaired immunity

Meta-analysis (9 studies, n = 965) [3]
A sodium selenite supplementation significantly reduces mortality for sepsis patients (RR (relative risk) 0.83 CI (confidence interval) 0.77-0.99; p = 0.04)
Meta analysis of 9 sepsis trials
A high-dose bolus significantly reduces mortality in sepsis patients by 27%.

A bolus in the early phase of sepsis has several effects:

1. Down-regulation of the synthesis of pro-inflammatory cytokines
2. Apoptosis and cytotoxicity in activated pro-inflammatory cells
3. Direct virucidal and bactericidal effects

These effects prevent an unchecked immune response (cytokine storm) and thus an early death from sepsis (Fig. 1).

In a comparison of the sodium selenite supplementation with a bolus to a sodium selenite therapy without a bolus, a lower mortality could be shown in the intervention group with bolus (−7%; p = 0.14). A parenteral sodium selenite supplementation with bolus, however, reduced the total mortality with a higher significance (RR 0.73, 95% CI 0.58-0.94; p = 0.01).

A maintenance therapy of ≥ 7 days significantly improves the probability of survival.

The impact of the duration of treatment on mortality was determined by means of uni-variant “random effects meta-regression” analysis. A statistically significant association between the relative risk of mortality and duration of treatment (Fig. 2) was thereby demonstrated. A sodium selenite supplementation of ≥ 7 days reduced total mortality by 23% (RR 0.77, 95% CI 0.63-0.94; p = 0.01).
Fig. 2 | Dependency of the relative risk (RR) on the duration of treatment [3]

Every circle represents one trial, whereby the size of the study correlates with the size of the circle. A negative effect (circle below the regression plot) stands for the reduction of the mortality rate.
**Meta analysis of 9 sepsis trials**

A high dosing of $\geq 1,000$ µg selenium as sodium selenite-pentahydrate per day significantly reduces mortality by 23%.

In their meta analysis, Huang et al. distinguished between sodium selenite supplementation with a high selenium dose ($\geq 1,000$ µg/day) and a low dose (< 1,000 µg/day). A dosing of $\geq 1,000$ µg selenium per day significantly reduced the total mortality (RR 0.77, 95% CI 0.61-0.99; p = 0.04). In a comparison of several sepsis trials, Manzanares et al. could show that only a high sodium selenite supplementation (2,000 µg bolus (day 1) and 1,600 µg/day selenium (day 2 – 10)) suffices to elevate serum selenium concentration into the low reference range or to increase the activity of glutathione peroxidase 3 to a physiological level (Fig. 3) [4]. A low sodium selenite therapy (1,200 µg bolus (day 1) and 800 µg/day (day 2 – 10)) is neither in the position to sufficiently increase the serum selenium concentration nor to sufficiently influence the activity of glutathione peroxidase 3 (Fig. 4).

---

**Fig. 3**

Development of the serum selenium concentration for high and low-dosed sodium selenite supplementation [4]

![Graph showing the development of serum selenium concentration for high and low-dosed sodium selenite supplementation](image-url)
Increase of glutathione peroxidase 3 activity to a physiological level takes place only with a high-dose sodium selenite supplementation \cite{4}.


Pilot study
Supplementation with selenase® increases the selenium level to values within the normal range

A controlled, randomized, prospective, open-label pilot trial analyzed the effects of selenase® supplementation in SIRS patients. The selenase®-supplemented group (n = 21) received descending doses of selenase® of 535 µg selenium per day for 3 days, 285 µg selenium per day for 3 days, 155 µg selenium per day for 3 days, and 35 µg selenium per day thereafter. The control group (n = 21) received 35 µg/day selenium during the entire treatment period.

The serum selenium concentrations were below the defined reference value for selenium in Germany (80 µg/l selenium in serum) at admission to the ICU. Glutathione peroxidase activity was also significantly too low. While the serum selenium levels in the control group did not change over the observation period, the serum selenium concentration increased in the normal range from day 3 in the selenase®-supplemented group (Fig. 5).

The data show that SIRS patients need a selenium dose > 500 µg to reach normal range and that 155 µg selenium per day is not sufficient to maintain a low normal level already achieved.
Fig. 5 Significant increase in serum selenium concentration in the selenase®-supplemented group in the reference range. [6]
Pilot study
Supplementation with selenase® improves clinical outcomes in SIRS patients

In both groups, the baseline APACHE III score was the same and decreased during their ICU stay. However, the APACHE III score in the selenase®-supplemented group improved significantly more pronounced (day 7: p = 0.019; day 14: p = 0.041). Moreover, only 12% of the patients in the selenase®-supplemented group but 42% in the control group had a higher APACHE III score on day 14 compared to ICU admission (p < 0.05).

Mortality at discharge from the hospital was 33.4% in the selenase®-supplemented group and 52.4% in the control group (p = 0.135) (Fig. 6). A comparison of patients with an APACHE III score > 53 highlights the beneficial effect of selenase® on mortality rate. Although the patient population in this subgroup analysis was reduced to 20 (selenase®-supplemented group (n = 11) and control group (n = 9)), there was a significant decrease in mortality in the selenase®-supplemented group (4 of 11 patients (36%)) versus the control group (8 of 9 patients (89%)) (p = 0.0053) (Fig. 7).
Fig. 6  Intention-to-treat analysis of survival time in the selenase®-supplemented group (n = 21) and control group (n = 21). [5]

Fig. 7  Intention-to-treat analysis of survival time in patients with an APACHE III score > 53 (selenase®-supplemented group (n = 11) and control group (n = 9)). [5]
SIC trial (Selenium in Intensive Care)

Phase III trial with selenase®

A prospective, randomized, double-blind, multicenter phase III trial conducted at 11 intensive care units in Germany, analyzed whether the results obtained in the pilot study were reproducible in a phase III trial [2]. Overall, 249 patients with SIRS, sepsis, septic shock and an APACHE III score > 70 were randomized. The selenase® doses administered were increased to a 30-minute bolus infusion of 1,000 µg selenium, followed by 1,000 µg/day selenium as a continuous infusion for 14 days. In the placebo group, a dose of up to 100 µg/day selenium was allowed with the parenteral nutrition.

Eleven of the 249 randomized patients were excluded for various reasons. Thus, the intention-to-treat analysis included 238 patients (Fig. 8). Another 49 of these 238 patients had to be excluded further for the per-protocol analysis either because inclusion criteria were not met (n = 14) or due to severe violations of the trial protocol (n = 35). Therefore, the per-protocol analysis only covered 189 patients, 92 in the selenase®-treated group and 97 in the placebo group.
Study profile of the SIC trial.\(^6\)

Randomized patients
\[N=249\]

- 5 consent withdrawn
- 1 suicide
- 2 lost for follow up
- 1 non-compliant
- 2 termination of treatment

Intention-to-treat analysis
\[N=238\]

- 14 ex/inclusion criteria failure
- 30 trial drug administration failure
- 5 additional selenium substitutions > 100 µg/day

selenase\(^\circledR\)-supplemented group
\[N=116\]

Per-Protocol analysis
\[N=189\]

selenase\(^\circledR\)-supplemented group
\[N=92\]

Placebo group
\[N=122\]

Placebo group
\[N=97\]
**SIC trial**

Significantly increased selenium value in the selenase®-supplemented group only.

The SIC trial also showed that selenium values at ICU admission were very low (Table 2). The selenium concentration increased significantly in the selenase®-supplemented group only (p < 0.001). Despite high-dose daily selenase® supplementation, the median selenium values only increased to 161.9 µg/l selenium in the serum and 144.5 µg/l selenium in whole blood on the last day (day 14) of selenase® supplementation. After completing the intervention, the selenium level decreased markedly within a week (Fig. 9). In the trial, no specific adverse reactions were attributed to supplementation with high-dose selenase®. Overall, there was no significant difference in the adverse reactions in the intervention group (90.2%) and the placebo group (96%).

The positive effect of selenase® supplementation showed in both the selenium concentration in blood and the glutathione peroxidase activity. Both parameters increased from suboptimal baseline values during intervention and decreased again significantly after ending the selenase® supplementation (Fig. 9). The curve characteristics reveals, that an optimal selenium supply during and after sepsis is not sufficient, when a selenium dosage, as is currently used in parenteral nutrition respectively normal nutrition, is applied. Simultaneously the increase in glutathione peroxidase activity during intervention with 1,000 µg selenium as selenase® shows that a daily selenium intake of 100 µg in sepsis patients does not result in a plateau of selenoprotein activity, but increases till ending of intervention. After selenase® supplementation the glutathione peroxidase activity decreased again, though the patients still recieved up to 100 µg selenium with parenteral nutrition.

<table>
<thead>
<tr>
<th>Tab. 2</th>
<th>Comparison of selenium concentration in the selenase®-supplemented versus the placebo group p &lt; 0.001. [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum selenium concentration at ICU admission in all randomized patients (n = 249)</td>
<td>37.9 ± 18.2 µg/l</td>
</tr>
<tr>
<td>Selenium concentration in whole blood at ICU admission in all randomized patients (n = 249)</td>
<td>58.4 ± 17.4 µg/l</td>
</tr>
<tr>
<td>Serum selenium concentration at ICU admission in patients included in the per-protocol analysis (n = 189)</td>
<td>37.9 µg/l</td>
</tr>
<tr>
<td>Serum selenium concentration after 14 days</td>
<td>161.9 µg/l</td>
</tr>
<tr>
<td>Selenium concentration in whole blood after 14 days</td>
<td>144.5 µg/l</td>
</tr>
</tbody>
</table>
Development of selenium concentration and glutathione peroxidase activity during and after selenase® supplementation. [6]

Selenium concentration in whole blood [µg/l]

Glutathione peroxidase activity [U/l]

Reference range

Selenium and glutathione peroxidase reference values in whole blood and plasma of a reference population living in Valencia, Spain.

**SIC trial**

**Significant reduction in mortality in the selenase®-supplemented group**

In the intention-to-treat analysis (n = 238), 46 of 116 patients in the selenase®-supplemented group died and 61 of 122 in the placebo group. Thus, selenase® supplementation reduced mortality non-significantly by 10.3% (p = 0.109; OR, 0.66; 95% CI, 0.39-1.10) (Fig. 10). Mean overall survival increased from 17.6 days in the placebo group to 20.3 days in the intervention group (p = 0.098) (Fig. 11).

As previously mentioned in the SIC trial description, 49 patients were excluded from the per-protocol analysis. Either the inclusion criteria were not met (n = 14) or severe violations of the trial protocol occurred (n = 35). Therefore, the per-protocol analysis only covered 189 patients, 92 in the selenase®-treated group and 97 in the placebo group.

In the per-protocol analysis, 28-days mortality decreased significantly from 56.7% to 42.4% in the selenase®-supplemented group (p = 0.049; OR, 0.56; CI, 0.32-1.00) (Fig. 12). Mean overall survival increased from 16.4 days in the placebo group to 19.7 days in the intervention group (p = 0.048) (Fig. 13).

![Fig. 10](image1.png)  
28-days mortality in the intention-to-treat analysis (n = 238). [6]

![Fig. 12](image2.png)  
28-days mortality in the per-protocol analysis (n = 189). [6]
Survival time in the intention-to-treat analysis. \[^{[6]}\]

![Graph showing survival time in the intention-to-treat analysis.](image)

- Placebo ≤ 100 µg Se/day
- Selenase® ≥ 1,000 µg Se/day
- \( n = 116 \)
- \( n = 122 \)
- \( p = 0.098 \)

Survival time in the per-protocol analysis. \[^{[6]}\]

![Graph showing survival time in the per-protocol analysis.](image)

- Placebo ≤ 100 µg Se/day
- Selenase® ≥ 1,000 µg Se/day
- \( n = 92 \)
- \( n = 97 \)
- \( p = 0.048 \)
**SIC trial**

**Significant reduction in mortality in the subgroups of the selenase®-supplemented group**

The trial plan had already included a subgroup analysis. Patients with an APACHE III score > 102 (n = 27 in each group) benefited even more from a selenase® supplementation (Fig. 14). 28-days mortality decreased in this subgroup by 25.9% from 81.5% to 55.6% (p = 0.04; OR, 0.28; 95% CI, 0.08-0.97). In patients with septic shock, 28-days mortality decreased by 26.2% from 66.7% in the placebo group (30 of 45) to 40.5% in the selenase®-supplemented group (15 of 37 patients) (p = 0.018; OR, 0.34; 95% CI, 0.14-0.84). In patients with more than triple organ failure, 28-days mortality decreased by 22.6% in the comparison between the intervention group (42.5%; 17 of 40 patients) and the placebo group (65.1%; 28 of 43 patients) (p = 0.039; OR, 0.40; 95% CI 0.16-0.96). The subgroup analysis highlights the fact, that the beneficial effect by selenase® supplementation increases with sepsis severity.

**SÉRÉNITÉ trial**

**Comparison of SIC and SÉRÉNITÉ trials**

Like SIC, the SÉRÉNITÉ trial was a prospective, randomized, double-blind, multicenter trial conducted in France. However, this trial only included a total of 60 patients, i.e. a quarter of the number in the SIC trial [7]. The study included only patients with severe septic shock. While the SIC trial enrolled patients within 6 hours after ICU admission and administered a bolus infusion directly after trial enrollment, 90% of the patients in the SÉRÉNITÉ trial were enrolled within 48 hours of ICU admission. Furthermore, a bolus was not given. Instead, 4,000 µg selenium were administered as a continuous infusion. The significance of a bolus

---

**Table: Reduction in mortality**

<table>
<thead>
<tr>
<th>Reduction in mortality</th>
<th>NNT (Number needed to treat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIC trial total</td>
<td>- 14.3 % (p = 0.049)</td>
</tr>
<tr>
<td>defined subgroups:</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>- 26.2 % (p = 0.018)</td>
</tr>
<tr>
<td>APACHE III &gt; 102</td>
<td>- 25.9 % (p = 0.049)</td>
</tr>
<tr>
<td>&gt; 3 organ failure</td>
<td>- 22.6 % (p = 0.039)</td>
</tr>
</tbody>
</table>
consists of improving the selenium status of the sepsis patient as early and as rapidly as possible. This enables the body to fight oxidative stress, and to have an anti-inflammatory effect. The considerably later and slower administration of sodium selenite was not able to compensate the resulting damage even though twice the amount of sodium selenite was used. In the SÉRÉNITÉ trial, the selenium value was not measured at ICU admission nor over the course of the study. Therefore, it is not possible to verify the patients’ selenium concentration at ICU admission. Since many studies have shown that the selenium value at ICU admission is inversely correlated with mortality, the question arises as to whether the patient cohort in the SÉRÉNITÉ trial was more severely ill than in the SIC trial. Another difference was the shorter daily selenium supplementation given for 9 versus 14 days. Here, as well, there is no way to verify which effect the shorter selenium supplementation had on the selenium value; whether the selenium concentration decreased below reference range after the intervention ended, respectively to which degree. In view of these difference, it is no surprise that a reduction in mortality was lacking in the selenium-supplemented group (Fig. 15).

In the SÉRÉNITÉ trial, no adverse reactions were attributed to selenium. This is particularly noteworthy because 4,000 µg selenium were given on day 1, without any adverse effects on the patients.
Valenta et al., 2011
Evidence of a correlation between selenase® supplementation and procalcitonin (PCT)

The trial by Valenta et al. in 2011, produced another interesting result [8]. This prospective, randomized, open-label, single-centre clinical trial enrolled 150 patients with SIRS/sepsis and a SOFA score of >5. 75 patients were supplemented with 1,000 µg selenium (selenase®) on day 1 and 500 µg on days 2 – 14, administered as a 30-minute infusion in the morning. Patients in both, the intervention group and the control group received a standard dose of < 75 µg/day selenium with their parenteral nutrition.

This trial also revealed 3 effects of selenase® supplementation:

- In the intervention group, the selenium value and the glutathione peroxidase activity increased from a very low baseline value in the reference range as compared to the control group (Fig. 16).
- Patients in both groups surviving 28 days showed a trend for a higher serum selenium level compared to non-survivors (59.2 ± 45.7 vs. 56.1 ± 44.2 µg/l; p = 0.068).
- Despite the high-dose selenase® supplementation, no specific adverse reactions or toxic effects occurred. Only 17 of the 799 serum selenium samples taken from 9 patients in the intervention group showed selenium values above the reference range (163.4 ± 14.2 µg/l, reference range 80 – 120 µg/l). All 9 patients survived.

This trial also showed a negative correlation between serum selenium level and several inflammatory markers and sepsis severity at ICU admission (Table 3).
Development of serum selenium concentration during selenase® supplementation compared to the control group. [8]

![Graph showing the development of serum selenium concentration during selenase® supplementation compared to the control group. The graph indicates a significant increase in selenium concentration over time in the selenase® group compared to the control group. The reference range is also shown, with p-values indicating statistical significance at various time points.]

<table>
<thead>
<tr>
<th>Days</th>
<th>Serum selenium concentration [µg/l]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>14</td>
<td>140</td>
</tr>
</tbody>
</table>

Reference range: p < 0.001

Negative correlation between the serum selenium level at ICU admission, inflammatory markers and sepsis severity. [8]

<table>
<thead>
<tr>
<th></th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin (PCT)</td>
<td>-0.172</td>
<td>0.035</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>-0.187</td>
<td>0.022</td>
</tr>
<tr>
<td>SOFA score</td>
<td>-0.277</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The trial showed no significant difference in 28-days mortality between intervention vs. control group (25.3% vs. 32%; \( p = 0.367 \)). A subgroup analysis produced a trend to a lower mortality in the selenase®-supplemented group for patients with APACHE II score > 28 (32.6% vs. 51.6%; \( p = 0.100 \)).

However, Valenta et al. made an interesting discovery in this trial. The comparison of PCT and CRP values between the intervention and the placebo group showed a decrease of both values independently of selenase® supplementation over the course of the 14 days observation period. But the reduction in the intervention group was more pronounced. For PCT, the difference between the selenase®-supplemented group and the control group on day 7 was even significant (Fig. 17). These data suggest a biological interaction between selenium and PCT.
Significantly greater decrease in PCT in the selenase®-supplemented group. There was no significant difference, despite the difference in PCT values between the two groups on day 0 (p = 0.108). \[8\]
Manzanares et al., 2011
Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity

This placebo-controlled, randomized prospective, single-blind phase II trial enrolled 35 patients with SIRS and APACHE II scores of ≥ 15 [9]. The intervention group received a bolus of 2,000 µg selenium and 1,600 µg/day for another 10 days. Both groups received an average of 77 respectively 73 µg/day selenium enterally.

In the sodium selenite-supplemented group, the incidence of early ventilator-associated pneumonia was significantly reduced by 31% (p = 0.04) (Fig. 18). The incidence of nosocomial pneumonia was also reduced in the intervention group by 19% (p = 0.03). The authors attributed this beneficial effect to the administered large bolus, because all three effects of a bolus administration can influence the development of early ventilator-associated pneumonia.

• Reversible inhibition of NF-κB binding to DNA
• Apoptosis and cytotoxicity in activated, pro-inflammatory cells
• Direct virucidal or bactericidal effect

Early ventilator-associated pneumonia in the ICU is a major cause of morbidity, mortality and costs. A reduction in the incidence of early ventilator-associated pneumonia via sodium selenite might make an important contribution.

Furthermore, the SOFA score was reduced in the sodium selenite-supplemented group versus the placebo group on day 10 (p = 0.0001). While the SOFA score in the intervention group continued to significantly decline from day 3 to day 10, the SOFA score in the placebo group remained virtually the same (Fig. 19).
Fig. 18  Sodium selenite reduced the probability for a patient to acquire nosocomial pneumonia. [9]

Fig. 19  Sodium selenite significantly improved sepsis severity based on the SOFA value (p = 0.0001). [9]
SIGNET trial
Fewer new infections in patients receiving selenase® supplementation for > 5 days

The SIGNET trial was a randomized, double-blinded, factorial, controlled multicenter trial with 502 participants [6]. Because of the factorial design, the patients were randomized to the following study arms: Placebo group (n = 125) parenteral nutrition containing standard formulation; selenase® group (n = 127) standard formulation with addition of 500 μg selenium; glutamine group (n = 126) formulation including 20.2 g glutamine; selenase® + glutamine group (n = 125) formulation with addition of 500 μg selenium and 20.2 g glutamine. Only 56% of the patients had sepsis. The selenase®-supplemented group showed a decreased rate of new infections by 5% (p = 0.24) in contrast to glutamine supplementation. selenase® supplementation significantly reduced new infections in patients who received intervention for ≥5 days by 13% (p = 0.03) (Fig. 20).
Fig. 20  At least 5 days selenase® supplementation significantly reduced new infections. \[10\]

![Graph showing infection rates for Placebo and selenase® supplementation (≥ 5 days). The graph illustrates that selenase® supplementation significantly reduced new infections compared to Placebo, with a reduction of 13.4%.](image-url)

- Placebo: 72.3% infections
- selenase® ≥ 5 days: 58.9% infections

\[ p = 0.03 \]
**REDOXS trial**

Compared to glutamine, selenium did not have any negative effect on mortality, although the beneficial effect of selenium supplementation was reduced by the lack of selenium deficiency.

The REDOXS trial was a randomized, controlled, double-blind, 2x2 factorial, multicenter trial with 1,223 severely ill patients with multiple organ failure. Within 24 hours after ICU admission, the patients received either glutamine, antioxidants (including 500 µg selenium as selenase®), both or placebo for a maximum of 28 days (Table 4).

Only in 31% of patients the primary diagnosis was sepsis at ICU admission. Compared to other sepsis trials, the selenium value at ICU admission was not outside the normal range in any of the 66 analyzed trial patients. It is not known whether these patients were sepsis patients. However, the median serum selenium level at 86 µg/l in the antioxidant group and 80 µg/l in the non-antioxidant group was far above the means in sepsis patients at 30 – 40 µg/l selenium in the serum. The aforementioned sepsis trials were exclusively conducted in Europe where the average selenium level in the population is clearly below the reference range of 80 µg/l selenium in the serum.

The REDOXS trial was conducted both in Canada, the USA and Europe. Both in Canada and the USA, the selenium status is markedly above the reference range of 80 µg/l.

In the antioxidant group, the selenium value in the serum increased significantly (p < 0.001), whereas the selenium status in the non-antioxidant group only showed a slight increase (Table 5). Despite the significant increase in selenium concentration, the authors reported that the median selenium level in both groups remained within the normal range at all measurement time points.

Supplementation with antioxidants had no effect on 28-days mortality (30.8% vs. 28.8%; p = 0.48). In addition to the above-mentioned restrictions in the REDOXS trial, the positive effect of selenium might have been negated by the late initiation of supplementation with antioxidants, the too low selenium dose and the interaction of vitamin C with selenium due to its concurrent administration.
### Tab. 4

**Trial arms in the REDOXS trial.** [11]

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Number</th>
<th>Supplementation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Glutamine (Gln)</td>
<td>303</td>
<td>0.5 g Gln/kg body weight</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 g Gln</td>
<td>Enteral</td>
</tr>
<tr>
<td>2 Antioxidants (AOX)</td>
<td>308</td>
<td>500 µg selenium as selenase®</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 µg selenium, 20 mg zinc, 500 mg vitamin E, 10 mg beta-carotene, 1,500 mg vitamin C</td>
<td>Enteral</td>
</tr>
<tr>
<td>3 Gln + AOX</td>
<td>310</td>
<td>1 + 2</td>
<td></td>
</tr>
<tr>
<td>4 Placebo</td>
<td>302</td>
<td>−</td>
<td></td>
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</tbody>
</table>

### Tab. 5

**Increase in serum selenium value in the antioxidant group.** [11]

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<tr>
<th></th>
<th>Antioxidants</th>
<th>No antioxidants</th>
<th>p-value</th>
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<tr>
<td></td>
<td>n</td>
<td>median [Q1, Q3] (µg/l)</td>
<td>n</td>
</tr>
<tr>
<td>ICU day 1</td>
<td>31</td>
<td>86 (71 – 98)</td>
<td>30</td>
</tr>
<tr>
<td>ICU day 4</td>
<td>28</td>
<td>142 (137 – 164)</td>
<td>26</td>
</tr>
<tr>
<td>ICU day 7</td>
<td>25</td>
<td>156 (134 – 174)</td>
<td>19</td>
</tr>
</tbody>
</table>
Sakr et al., 2014
Doctors give selenase® primarily severely ill patients

In a large retrospective study conducted in 2014, Sakr et al. analyzed the effect of a selenium supplementation in 1,047 patients with severe sepsis treated over a period of more than 6 years in a surgical ICU. Due to the retrospective nature of the study, the selenium-supplemented group had only 413 (39%) patients. The control group received 100 µg/day selenium and selenium-supplemented group received a bolus of 1,000 µg selenium (selenase®) and 1,000 µg/day selenium (selenase®) for a maximum of 14 days.

The median duration of adjuvant selenium therapy was 8 days (IQR = 4 – 12). The two groups presented with significantly different patient characteristics. Particularly, the higher SAPS II score (50.8 vs. 47.7, p = 0.001) and the higher proportion of patients with cancer (32.4% vs. 24.6%; p = 0.005) may have affected the study analysis. This is also evident in the parameters measured to test inflammation and organ function (C-reactive protein, PCT, blood lactate) (Table 6).

Do surgical sepsis patients need a different (higher) dosage than medical sepsis patients?

It is known that, among other things, a surgical intervention triggers oxidative stress which significantly heightens the body’s selenium consumption during and after surgery. It can therefore be assumed that, to achieve the same beneficial effect, surgical sepsis patients require higher selenium doses than medical sepsis patients. As trials on selenium supplementation in cardiac surgery have shown, without selenium supplementati-

<table>
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<tr>
<th>Characteristics</th>
<th>Control group</th>
<th>Selenium group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II</td>
<td>47.7 ± 17</td>
<td>50.8 ± 17.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>24.6%</td>
<td>32.4%</td>
<td>0.005</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>78 (13 – 193)</td>
<td>146 (46 – 235)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>2.3 (0.7 – 7.2)</td>
<td>3.7 (0.9 – 12.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blood lactate</td>
<td>2.5 (1.6 – 5.3)</td>
<td>2.9 (1.7 – 5.6)</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>doi</td>
<td>Summary</td>
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Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis

In this retrospective study, overall ICU mortality was 31.3% and hospital mortality 41.8%. Whereas the ICU mortality did not significantly differ in the two groups (29.5% vs. 33.9%; \( p = 0.135 \)), the selenium supplemented group displayed a higher hospital mortality (39.15 vs. 46%; \( p = 0.027 \)). Both the ICU and hospital stays were significantly longer in the intervention group (\( p = 0.01 \) and \( p = 0.001 \), respectively). However, a multivariate analysis showed, that adjuvant selenium therapy was not independently associated with worse hospital mortality (\( OR = 1.19, 95\% \text{ CI} = 0.86-1.65; \ p = 0.288 \)). The multivariate analysis included age, gender, SAPS II score, surgery type, co-morbidities, focus on sepsis, SOFA sub-scores and blood lactate levels.

The authors themselves point out, that the higher hospital mortality and the longer ICU and hospital stays are attributable to the significantly higher number of severely ill patients in the selenium-supplemented group. Furthermore, the authors also point out that unlike early trials, in which the proportion of surgical patients fluctuated between 13% and 40%, their study contained 100% surgical cases (Fig. 21).
Fig. 21 Percentage of medical and surgical sepsis patients in different sepsis trials. [5-8,10]
## Overview of trials

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Number of patients</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Angstwurm et al. (1999) | controlled, randomized, prospective, open-label pilot trial (single center) | N (selenase®) = 21  
N (control) = 21 | Intervention group (selenase®):  
535 µg/day selenium for 3 days,  
285 µg/day selenium for 3 days,  
155 µg/day selenium for 3 days and 35 µg/day selenium thereafter  
Placebo group:  
35 µg/day selenium |
| Angstwurm et al. (2007) | Prospective, randomized, double-blind, multicenter phase III trial | N (selenase®) = 92  
N (placebo) = 97 | Intervention group (selenase®):  
Bolus: 1,000 µg  
1,000 µg/day selenium as selenase® for 14 days  
Placebo group:  
< 100 µg/day selenium |
| Forceville et al. (2007) | prospective, randomized, double-blind, multicenter trial | N (sodium selenite) = 31  
N (placebo) = 29 | Intervention group:  
Bolus: 4,000 µg selenium  
1,000 µg/day selenium for 9 days |
| Valenta et al. (2011) | Prospective, randomized, open-label trial (single center) | N (selenase®) = 75  
N (control) = 75 | Intervention group:  
1,000 µg selenium as selenase® on day 1  
500 µg/day selenium as selenase® for 14 days  
Control group:  
< 75 µg/day selenium |
| Manzanares et al. (2011) | placebo-controlled, randomized, prospective, single-blinded, phase II trial (single center) | N (sodium selenite) = 15  
N (placebo) = 16 | Intervention group:  
Bolus: 2,000 µg selenium  
1,600 µg/day selenium for 10 days  
Placebo group:  
73 ± 16 µg/day selenium |
<table>
<thead>
<tr>
<th>Result</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selenium level at ICU admission markedly below normal</strong>&lt;br&gt;<strong>Intervention group (selenase®):</strong>&lt;br&gt;Selenium level ↑ (p = 0.003)&lt;br&gt;APACHE III score ↓ (p = 0.041)&lt;br&gt;Mortality ↓ (-19%; p = 0.135)&lt;br&gt;<strong>Patients with APACHE III &gt; 53:</strong>&lt;br&gt;Mortality (at hospital discharge) ↓ (-53%; p = 0.0053)&lt;br&gt;No adverse reactions from selenase®&lt;br&gt;No toxic symptoms</td>
<td>• trial size&lt;br&gt;• no placebo group&lt;br&gt;• low selenase® doses</td>
</tr>
<tr>
<td><strong>Selenium level at ICU admission markedly below normal</strong>&lt;br&gt;<strong>Intervention group (selenase®):</strong>&lt;br&gt;Selenium level ↑ (p &gt; 0.001)&lt;br&gt;28-days mortality ↓ (-14%; p = 0.048)&lt;br&gt;<strong>Pat. with septic shock:</strong>&lt;br&gt;28-days mortality ↓ (-26%; p = 0.018)&lt;br&gt;<strong>Pat. with APACHE III &gt; 102:</strong>&lt;br&gt;28-days mortality ↓ (-26%; p = 0.040)&lt;br&gt;<strong>Pat. with &gt; triple organ failure:</strong>&lt;br&gt;28-days mortality ↓ (-23%; p = 0.039)&lt;br&gt;No adverse reactions from selenase®&lt;br&gt;No toxic symptoms</td>
<td>• trial size&lt;br&gt;• Patients enrolled too late (not until after 48h)&lt;br&gt;• baseline selenium value unknown&lt;br&gt;• selenium value not measured</td>
</tr>
<tr>
<td><strong>Selenium level at ICU admission markedly below normal</strong>&lt;br&gt;<strong>Intervention group (selenase®):</strong>&lt;br&gt;Selenium level ↑ (p &gt; 0.001)&lt;br&gt;28-days mortality ↓ (-7%; p = 0.367)&lt;br&gt;<strong>Pat. with APACHE II &lt; 28:</strong>&lt;br&gt;28-days mortality ↓ (-19%; p = 0.100)&lt;br&gt;Significant reduction in PCT vs. control group (p &lt; 0.05)&lt;br&gt;No adverse reactions from selenase®&lt;br&gt;No toxic symptoms</td>
<td>• no bolus</td>
</tr>
<tr>
<td><strong>Intervention group:</strong>&lt;br&gt;Duration of mechanical ventilation = no significant difference&lt;br&gt;Mortality = no significant difference&lt;br&gt;No adverse reactions from sodium selenite&lt;br&gt;No toxic symptoms</td>
<td>• trial size&lt;br&gt;• baseline selenium value unknown&lt;br&gt;• selenium value not measured</td>
</tr>
<tr>
<td>Study</td>
<td>Trial design</td>
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<td>-----------------------</td>
<td>--------------------------------------------------</td>
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</tbody>
</table>
| Andrews et al. (2011) | randomized, controlled, double-blind, factorial, multicenter trial | N (selenase®) = 127 N (glutamine) = 126 N (selenase® + glutamine) = 124 N (placebo) = 125 | Placebo group:  
Standard parenteral nutrition  
Glutamine group:  
+ 20.2 g glutamine  
selenase® group:  
+ 500 µg selenium  
selenase®+ glutamine group:  
+ 500 µg selenium + 20.2 g glutamine |
| Heyland et al. (2013) | Randomized, controlled, blinded, 2-by-2 factorial, multicenter trial | N (antioxidants) = 308 N (glutamine) = 303 N (antioxidants + glutamine) = 310 N (placebo) = 302 | Antioxidant group:  
500 µg/day selenium as selenase® parenteral  
+ 300 µg selenium, 20 mg zinc, 500 mg vitamin E, 10 mg beta-carotene, 1500 mg vitamin C enteral  
Glutamine group:  
0.5 g/kg body weight parenteral + 30 g enteral |
| Sakr et al. (2014)    | Retrospective trial                              | N (selenase®) = 413 N (control) = 634          | Intervention group:  
Bolus: 1,000 µg selenium  
1,000 µg/day selenium for 14 days  
Control group:  
100 µg/day selenium |
<table>
<thead>
<tr>
<th>Result</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| **selenase® group:**  
New infections ↓ (-5%, p = 0.24)  
New infections in patients with ≥ 5 days selenase® supplementation ↓ (-13%, p = 0.03)  
Mortality after 6 months = no significant difference | • Only 56% of participants were sepsis patients  
• baseline selenium value unknown  
• selenium value not measured |

| Limitations |  
Selenium level at ICU admission within reference range  
**Antioxidant group:**  
Selenium level ↑ (p = < 0.001)  
28-days mortality = no significant difference | • only 31% of participants were sepsis patients  
• late initiation of selenium supplementation  
• low selenium dose  
• interaction through concomitant vitamin C |

| Limitations |  
**selenase® group:**  
ICU mortality = no significant difference  
Hospital mortality ↑ (+7%; p = 0.027)  
ICU stay ↑ (p = 0.01)  
Hospital stay ↑ (p = 0.001)  
Selenium supplementation not independently associated with worse outcome (OR = 1.19, p = 0.288)  
Selenium supplementation after a multivariate analysis not associated with hospital mortality | • retrospective trial  
• selenium group contains significantly more severely ill patients  
• no precise criteria for initiation of selenium supplementation  
• All patients were surgical patients with sepsis |
## Selenium in guidelines

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<tr>
<th>Guideline</th>
<th>Adults</th>
<th>Infants with low birth weight</th>
<th>Children (premature and term infants)</th>
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<th>Sepsis patients</th>
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<td>Reinhart K, Bruning FM, AWMF online 2010</td>
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<td>McClave et al., Jpen 33 (2009) 3, 277–316</td>
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<td>Guidelines on Pediatric Parenteral Nutrition</td>
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<td>National Institute for Clinical Excellence Feb 2006, UK</td>
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</table>
Guidelines
biosyn Arzneimittel GmbH

biosyn is the global market leader in high-dose selenium pharmaceuticals

This hidden champion supplies its high-revenue blockbuster selenase® to 22 countries, primarily for oncology and intensive care medicine.

Founded in 1984, biosyn Arzneimittel GmbH was one of the first German biotechnology companies. Now it has around 70 employees in Germany and subsidiaries in Liechtenstein, Austria and the USA.

Its portfolio encompasses some 30 products ranging from biotechnologically engineered medicines through chemotherapeutics to complementary drugs and food supplements for its main fields of intensive care medicine and oncology. The company’s major concern is treating patients as a whole. biosyn, a research-focused pharmaceutical company, puts up to 25 percent of revenues back into its pipeline.

Its mission is to explore, evolve and market highly efficacious drugs with low side effects based on the most up-to-date evidence molecular biology has to offer.

High-quality products from the world’s first GMP-compliant production of sodium selenite

In 2009, biosyn Arzneimittel GmbH was, and presumably still is, the first and only company in the world able to manufacture the active ingredient sodium selenite pentahydrate in internationally prescribed GMP quality – thanks to biosyn’s proprietary and patented production method. Its purification and crystallization technologies allow microbe-free production of high-quality trace element compounds under cleanroom conditions.

This enables the production of injectable liquid pharmaceuticals to meet the particularly stringent demands on quality. biosyn currently manufactures anhydrous sodium selenite and sodium selenite pentahydrate for oral and parenteral formulations.

The biosyn motto “we are research” not only symbolizes our dedication to medical and pharmaceutical progress but also for our drive to develop innovative manufacturing processes.

The company markets its selenium drugs under the brand name selenase® worldwide.
Selenium for sepsis

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Place of performance: Fellbach, Legal venue Stuttgart