Does the SISPCT trial provide new insights regarding the use of sodium selenite for sepsis?

Sodium selenite for severe sepsis and septic shock:

- For sodium selenite-treated sepsis patients, the hospital stay is shortened significantly by 3 days
- The question of whether sodium selenite is detrimental for intensive care patients with kidney dysfunction could be clearly negated in the SISPCT trial

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SISPCT – New insights on the use of sodium selenite for sepsis patients?

After publication of the long-awaited SISPCT-trial[1] on the use of sodium selenite on severe sepsis and septic shock, the following points speak in favor of the further use of sodium selenite in such cases:

- Only high-dose sodium selenite is able to remedy massive selenium deficiency in sepsis patients.[1]
- The hospital stay is significantly shortened for sodium selenite-treated sepsis patients.[1]
- There were no negative effects on patients with kidney dysfunction.
- A significant reduction of new infections could be demonstrated in several sepsis trials.[2-4]

Results of the SISPCT trial

Sodium selenite shortened the hospital stay

In total, 1,089 patients with severe sepsis or septic shock were included in the multicenter SISPCT trial.[1] The sepsis patients in both groups treated with sodium selenite received a bolus of 1,000 µg selenium, followed by a continuous infusion of 1,000 µg selenium daily up to discharge from the intensive care unit but no longer than 21 days.
Sodium selenite therapy compared to a placebo group significantly shortened the hospital stay of sepsis patients by three days (26 vs. 29 days; $p = 0.02$).[1]

Only high-dose sodium selenite can remedy massive selenium deficiency

On the average, the participants in the SISPCT trial showed a plasma selenium concentration of 39.4 µg/l.[1] This is a massive selenium deficiency (reference range 80 – 120 µg/l). The indication of the drug product selenase® is: selenium deficiency that cannot be corrected by diet. The recommended daily selenium intake is 70 µg selenium. Up to 100 µg selenium per day were given in the placebo group. This was not sufficient to significantly improve the selenium status. Only treatment with high-dose sodium selenite could significantly increase the selenium status ($p < 0.001$) *(Fig. 1)*.[1]

No negative effect of sodium selenite on patients with kidney dysfunction

A recently published post hoc analysis hypothesized that antioxidants were detrimental for intensive care patients with kidney dysfunction[5]. The SISPCT trial could refute this hypothesis in the case of sodium selenite.[1] Therapy with sodium selenite damaged neither sepsis patients who required renal replacement therapy at the beginning of the trial nor those who required it in the course of the trial *(Tab. 1)*.[1]

No significantly lower mortality

Neither the procalcitonin-controlled administration of antibiotics nor the treatment with sodium selenite could significantly reduce 28-day mortality (25.6 % vs. 28.2 %; $p = 0.34$ or 28.3 % vs. 25.5 %; $p = 0.30$).[1] Also the 90-day mortality showed no difference (sodium selenite vs. placebo 38.3 % vs. 38.1 %; $p = 0.94$; PCT vs. no PCT 37.8 % vs. 38.6 %; $p = 0.80$).

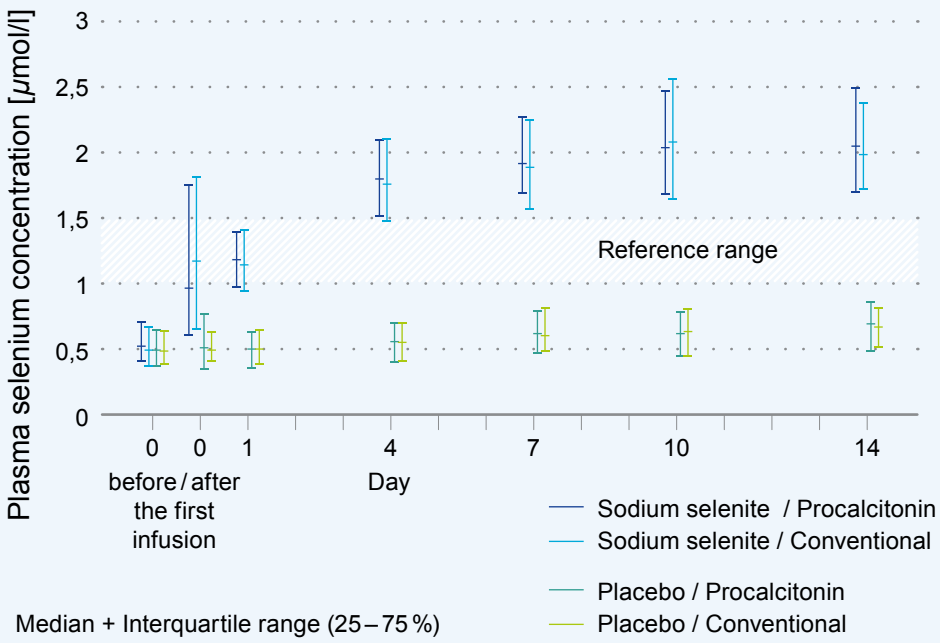
Inexplicably low mortality rate (Statement of the trial authors)

The SISPCT trial consisted of sepsis patients with 87 percent septic shock and 13 percent severe sepsis.[1] According to a trial published in 2016 (based on DRG statistics), the hospital mortality for severe sepsis including septic shock in the time period of the SISPCT trial was between 47.8 % and 43.6 %.[6] The hospital mortality for septic shock alone was 61.0 % to 58.8 %.

When planning the SISPCT trial a 28-day mortality of 40 % was assumed, whereby a reduction of mortality by 10 % could be evaluated as statistically significant. The 28-day mortality of the placebo group of the SISPCT trial (no sodium selenite, no procalcitonin control) was 22.9 % and was thereby 50 % lower than the mortality rate that resulted from the DRG statistics for this time period.

How could the mortality rate in the SISPCT trial be so much lower compared to the Germany-wide numbers over the same time period?

Only high-dose sodium selenite can remedy massive selenium deficiency



Bloos, F. et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern. Med. (2016). doi:10.1001/jamainternmed.2016.2514

Fig. 1

No negative effect of sodium selenite on patients with renal dysfunction

	OR (95 % CI)	p-value
No renal dysfunction	1.3 (0.8 – 2.1)	0.38
Renal dysfunction	1.0 (0.7 – 1.5)	0.93
Sub-groups		
No renal dysfunction, no dialysis	1.3 (0.7 – 2.1)	0.46
No renal dysfunction, dialysis	1.3 (0.4 – 3.9)	0.65
Renal dysfunction, no dialysis	1.3 (0.6 – 2.3)	0.58
Renal dysfunction, dialysis	0.9 (0.5 – 1.5)	0.56

Bloos, F. et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern. Med. (2016). doi:10.1001/jamainternmed.2016.2514

Table 1

Major deficiencies of the SISPCT trial

Inadmissible study design

The SISPCT trial (sodium selenite and procalcitonin-guided antimicrobial therapy in severe sepsis) was conducted as a bifactorial trial *(Fig. 2)*.[1] This is only allowed if there is no interaction between the two factors under investigation. However in the SISPCT trial, there is a statistically significant interaction between sodium selenite and procalcitonin (PCT) (p = 0.03). The authors interpreted this interaction as random, thereby forgetting to mention that several sepsis trials had already been able to demonstrate this interaction.[7,8]

Bifactorial study design of SISPCT

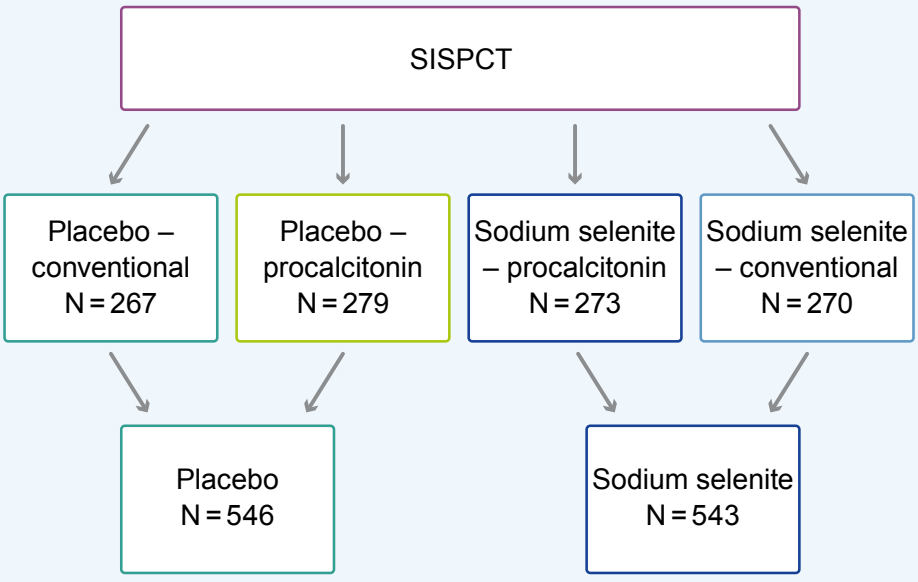


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Fig. 2

Interaction between sodium selenite and PCT

Trial	Measuring point	PCT concentration [ng/ml] median [25–75 %]		p-value
		Sodium selenite	Placebo/control	
Montoya et al.	Baseline	6 (3–9)	5 (3–6)	0.05
	Day 5	2 (1–4)	4 (3–5)	< 0.01
	Day 10	1 (1–2)	2 (1–2)	< 0.01
Valenta et al.	Baseline	1.65 (0.5–4.4)	0.67 (0.4–2.45)	0.108
	Day 7	0.75 (0.25–2.4)	0.5 (0.2–1.1)	
	Day 14	0.5 (0–9.2)	0.36 (0–3)	< 0.05
Bloos et al.	Baseline conventional	8.15 (1.91–30.83)	7.30 (1.69–22.60)	
	Baseline PCT-controlled	6.43 (1.33–21.98)	7.18 (1.48–28.24)	

Bloos, F. et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern. Med. (2016). doi:10.1001/jamainternmed.2016.2514.

Valenta, J., Brodska, H., Drabek, T., Hendl, J. & Kazda, A. High-dose selenium substitution in sepsis: a prospective randomized clinical trial. Intensive Care Med. 37, 808–815 (2011).

Montoya GC HL, Villalobos SJA, Olvera GC, Aguirre SJ & Franco GJ. Anti-inflammatory effect of selenium in septic patients. Rev Asoc Mex Med Crit Ter Int 23, 199–205 (2009).

Table 2

Proven interaction in two additional sepsis trials

Already in 2011 the prospective, randomized open-label study by Valenta et al. showed an interaction between sodium selenite and PCT *(Tab. 2)*. The comparison of 75 sepsis patients treated with selenase® with an equally large control group displayed a significantly greater decrease in the PCT level in the intervention group after 7 days ($p < 0.05$). [7] In an additional prospective, randomized, double-blind trial with in total 68 sepsis patients, the PCT value in the intervention group decreased significantly more on day 5 and 10 ($p < 0.01$). [8]

Ineffective randomization

The second major problem of the SISPCT trial is the unequal distribution of the trial participants into four groups. The trial group that was treated with sodium selenite and received no procalcitonin control contained significantly more sepsis patients who had required renal replacement therapy prior to trial start (22.2 % vs. 16.1 % vs. 14.0 % vs. 13.2 %). A renal replacement therapy significantly increases the risk of 28-day mortality by 62 % (OR 1.62; 95 % CI 1.06–2.47; $p = 0.03$). At the same time, the participants in this trial group showed significantly higher pro-adrenomedullin plasma concentrations. Higher pro-adrenomedullin values also increase the 28-day mortality (OR 1.11; 95 % CI 1.07–1.15; $p < 0.001$). [1]

Expected and actual 28-day mortality in the SISPCT trial

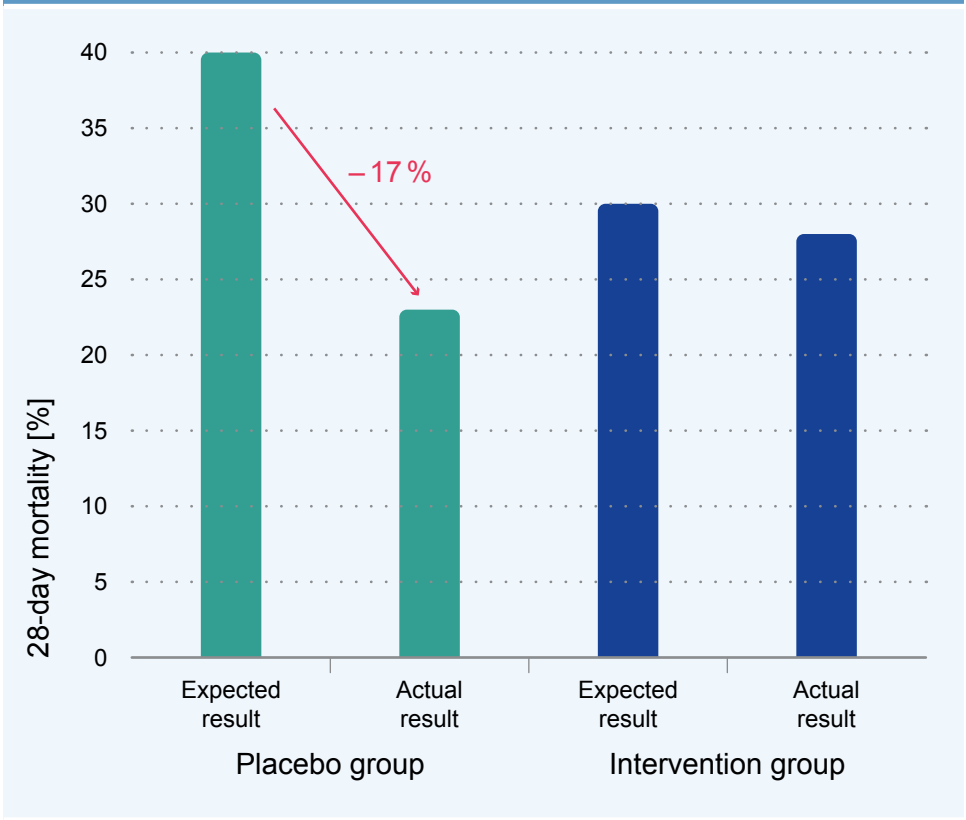

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Fig. 3

Incorrect basic assumptions

When planning a trial based on a selected primary endpoint, the necessary number of participants that would be necessary to obtain a significant result is statistically calculated. In the case of the SISPCT trial, the 28-day mortality was chosen. A 28-day mortality of 40 % was assumed, whereby a reduction of mortality by 10 % was estimated as statistically significant.

The 28-day mortality of the double placebo group in the SISPCT trial (no sodium selenite, no pro-calcitonin control) was 22.9 % and thus the lowest of all four groups *(Fig. 3)*. The basic assumption of the SISPCT trial was wrong.

Does the SISPCT trial nonetheless provide clinically significant results on the use of sodium selenite?

Numerous reasons continue to support the use of sodium selenite:

1. Only high-dose sodium selenite could compensate the massive selenium deficiency in sepsis patients (average 39.4 µg/l selenium in the serum).[1] Low-dosed selenium in the parenteral diet was not sufficient for this purpose.

2. Significant shortening of the hospital stay by three days with a sodium selenite therapy (26 vs. 29 days; $p = 0.02$).[1]

3. In several sepsis trials, a significant reduction of nosocomial infections and ventilator-associated pneumonia with a sodium selenite therapy was demonstrated.[2–4]

4. No increased mortality of sepsis patients treated with sodium selenite who required renal replacement therapy at the start or in the course of the trial.[1]

Summary

Based on the numerous shortcomings of the SISPCT trial, the authors' statement that a treatment with high-dose sodium selenite for patients with severe sepsis and septic shock cannot be supported should be critically questioned and should not obfuscate the positive experiences made to date.

Sepsis incidence and mortality in Germany (2007 – 2013)

In a recently published survey, sepsis cases treated in the hospital were analyzed using the Germany wide payment-per-case applied hospital statistics (DRG statistics) from 2007 to 2013.[6] The previous surveys were limited to intensive care units and patients with severe sepsis. Sepsis cases without organ dysfunction, which are usually not treated in the intensive care unit, were only estimated. The outcome of the survey for 2003 were 154,000 sepsis cases and about 60,000 deaths.[9]

Significantly increasing numbers of sepsis cases

The result of this new survey for 2007 were 200,535 sepsis cases and 54,169 deaths.[9] This corresponds to a rate of 256 sepsis cases per 100,000 inhabitants with a hospital mortality of 27.0 %. Until 2013, the sepsis cases had increased by almost 40 % to 279,530. The number of deaths was 67,849. The hospital mortality thereby dropped to 24.3 %, but the sepsis incidence increased to 335 per 100,000 inhabitants *(Fig. 4)*.

High hospital mortality with severe sepsis and septic shock

Also for severe sepsis including septic shock, the number of cases increased significantly (+ 54 %; 53,772 [2007] vs. 115,421 [2013]).[9] The hospital mortality declined from 49.5 % to 43.6 %. Since 2010 severe sepsis and septic shock have been reported separately. Also here, the number of cases increased from 22,326 to 33,815 (+ 34 %). In 2010, the hospital mortality for septic shock was 61.0 %, in 2013 it was 58.8 %.

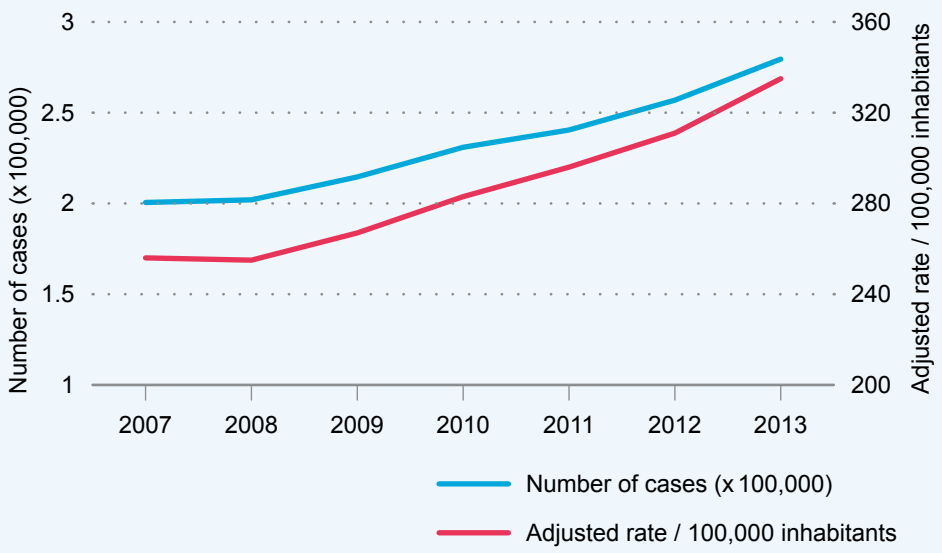
Inexplicably low mortality rate in the SISPCT trial

Especially interesting are the numbers in this new survey compared to the results of the SISPCT trial. The SISPCT trial was carried out between 2009 and 2013.[1] Of the 1,089 sepsis patients included, 87 % showed septic shock and the residual 13 % severe sepsis. The 28-day mortality was 22.9 % in the placebo group.

28-day mortality is not necessarily directly comparable to hospital mortality. However, the average hospital stay in the SISPCT trial was 28 days and thus corresponded exactly to the number of days of the 28-day mortality. If one compares the 28-day mortality rate of the SISPCT trial with the hospital mortality rate from severe sepsis and septic shock in 2013 (22.9 % vs. 43.6 %), the mortality rate in the SISPCT trial was almost halved *(Fig. 5)*. If one considers that 87 % of the participants in the study showed septic shock, the difference is even more extensive (22.9 % vs. 58.8 %).

The authors of the trial can provide no explanation for the low mortality rate; originally 40 % was assumed. Since the SISPCT trial is a large multicenter trial with 33 intensive care units, the question is how these low mortality rates came about.

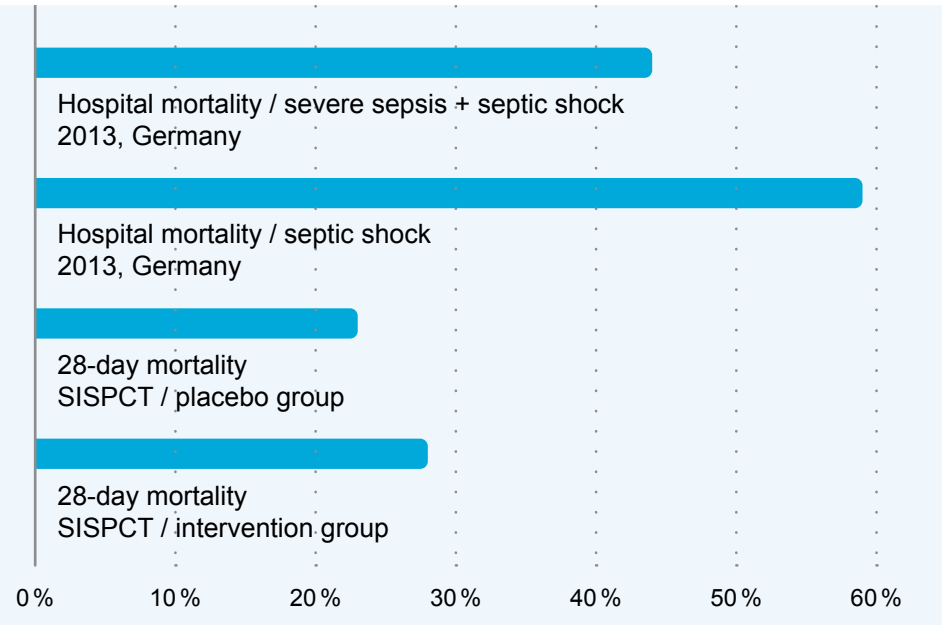
Significantly increased number of sepsis cases



Fleischmann, C. et al. Hospital incidence and mortality rates of sepsis. Dtsch. Aerzteblatt Online 113, 159–166 (2016)

Fig. 4

Inexplicably low mortality rate in the SISPCT trial



Average hospital stay SISPCT = 28 days

Bloos, F. et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern. Med. (2016). doi:10.1001/jamainternmed.2016.2514.

Fleischmann, C. et al. Hospital incidence and mortality rates of sepsis. Dtsch. Aerzteblatt Online 113, 159–166 (2016).

Fig. 5

Sodium selenite reduces the incidence of nosocomial infections

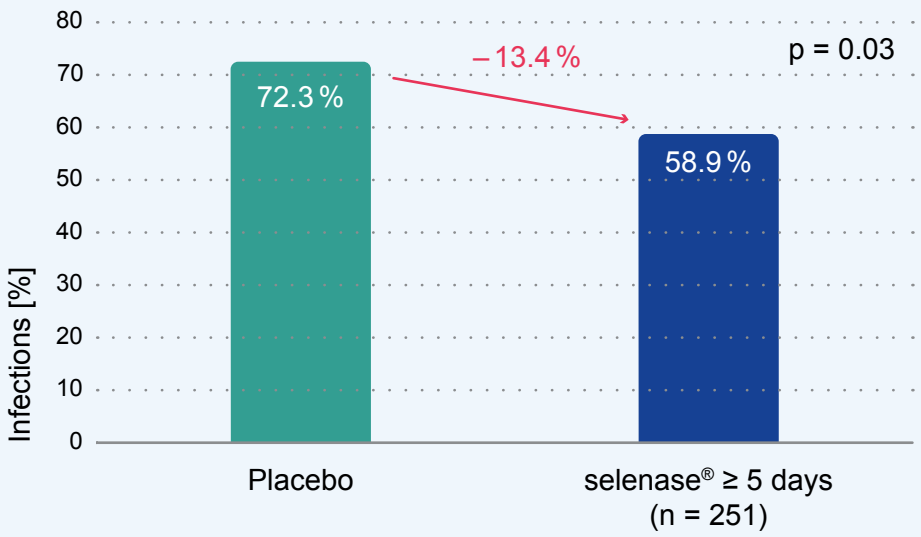
Meanwhile, a reduction of nosocomial infections in intensive-care patients has been demonstrated in several trials with high-dose sodium selenite. This includes the so-called SIGNET trial, a randomized, controlled, double-blind, bifactorial, multicenter trial with 502 participants.[2] Apart from sodium selenite, the supplementation with glutamine was investigated. The daily selenium dose was 500 µg. In the sodium selenite-treated group, the nosocomial infections were significantly reduced by 13 % ($p = 0.03$), however only if the participants in the study received sodium selenite for five days or longer *(Fig. 6)*.

Reduction of ventilator-associated pneumonia with sodium selenite

In a placebo-controlled, randomized, prospective, single-blind phase II trial, 35 patients with SIRS and APACHE II values of ≥ 15 were included.[3] The intervention group received one bolus of 2,000 µg selenium as well as 1,600 µg/day for additional 10 days in the form of sodium selenite. In the group treated with sodium selenite, ventilator-associated pneumonia was reduced significantly by 31 % ($p = 0.04$). Also hospital-acquired pneumonia was reduced by 19 % ($p = 0.03$).

This finding was confirmed in an additional trial. In the prospective, randomized, blinded trial with 54 sepsis patients, a bolus of 2,000 µg selenium as well as 1,500 µg/day for additional 14 days was administered in the form of sodium selenite.[4] Ventilator-associated pneumonia was significantly reduced in the group treated with sodium selenite by 30 % ($p = 0.023$) *(Fig. 7)*.

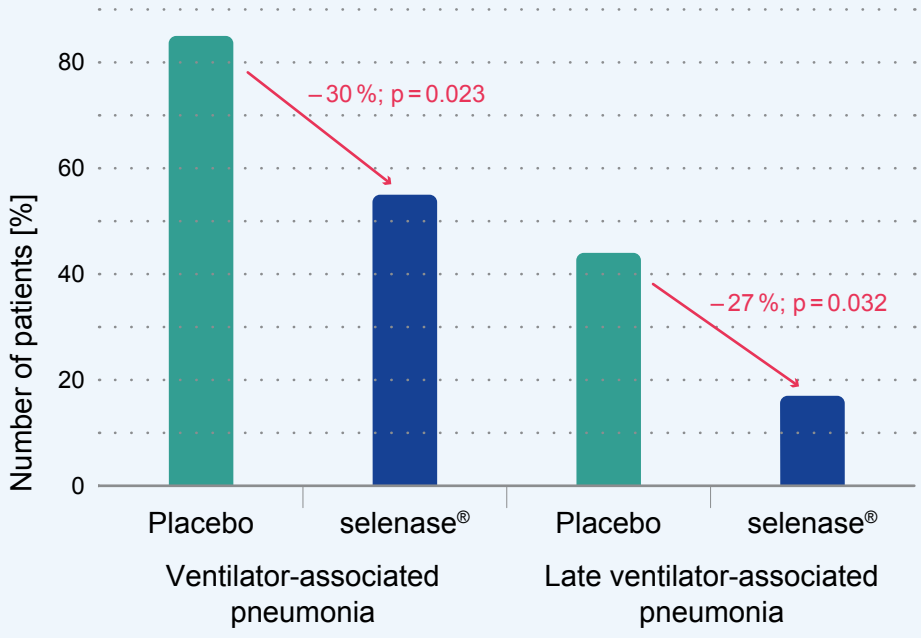
selenase® therapy significantly reduced new infections



Andrews, P. J. D. et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ 342, d1542–d1542 (2011)

Fig. 6

Reduction of ventilator-associated pneumonia with selenase®



Chelkeba, L. et al. The effect of parenteral selenium on outcomes of mechanically ventilated patients following sepsis: a prospective randomized clinical trial. Ann. Intensive Care 5 (2015)

Fig. 7

Upgrading of the Canadian guidelines due to the positive impact on infections

A reduction of infections (RR = 0.88; 95 % CI 0.78 – 0.99; p = 0.04) by sodium selenite was pointed out in the Canadian guideline for intensive care patients.[10] On this basis, the treatment with high-dosed selenium has been upgraded to “should be considered”.

Sodium selenite in patients with kidney dysfunction?

A post-hoc analysis of a large-scale trial (REDOXS trial) with intensive care patients had raised the question of whether antioxidants are detrimental for patients with kidney dysfunction and increase their mortality.[5] This bifactorial trial, which investigated the administration of glutamine and/or antioxidants, showed that patients in the glutamine group and the group treated with antioxidants, who suffered from kidney dysfunction at the beginning of the study but who did not undergo dialysis during the trial, showed an increased mortality, whereas the group treated with glutamine + antioxidants did not. However, among trial participants with kidney dysfunction and dialysis during the trial, only the glutamine + antioxidants group displayed increased mortality *(Fig. 8)*. The authors could not provide an explanation for these results.

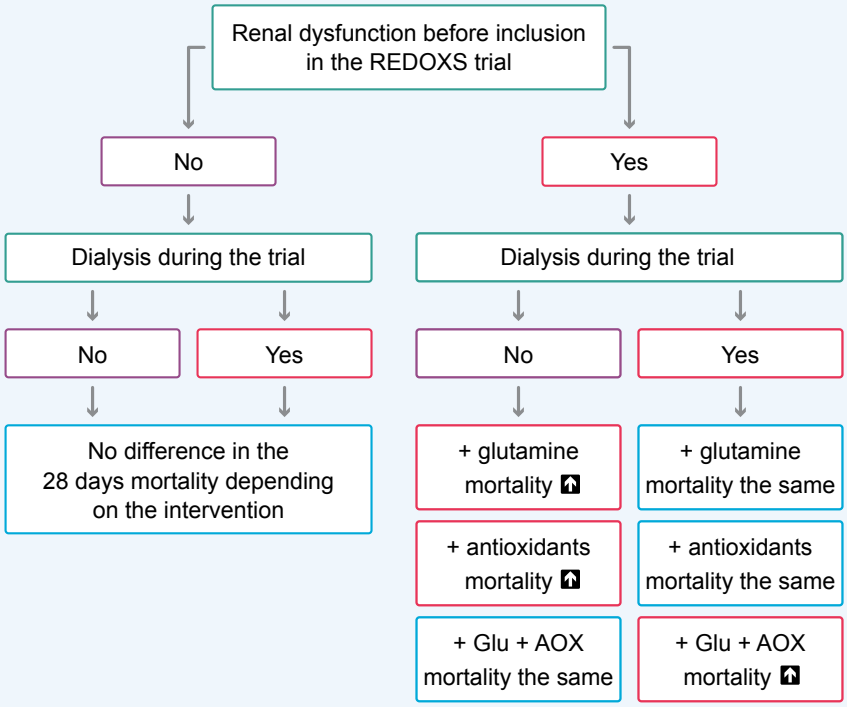
Sodium selenite is nephroprotective

Based on this publication, treatment with sodium selenite for intensive patients with kidney dysfunction was not recommended, since sodium selenite was also contained in the antioxidant cocktail. But this recommendation ignored numerous trials in which a nephroprotective effect of sodium selenite and other forms of selenium was demonstrated. Among other things, selenium significantly reduced the nephrotoxicity of cisplatin in cancer patients.[11] Furthermore, numerous trials were published in which dialysis patients were treated with selenium, since these patients frequently show a selenium deficiency. The selenium status of the dialysis patients could be improved by the supplementation (if the selected selenium dose was not too low).[12–14] No negative effects were determined.

SISPCT trial: sodium selenite does not increase mortality in patients with kidney dysfunction

In the SISPCT trial, a large sepsis trial with over 1,000 trial participants, no impact of sodium selenite on the mortality of patients with kidney dysfunction could be detected, independent of whether the renal dysfunctions were already present at the beginning of the study, developed during the trial, or whether dialysis was performed *(Tab. 3)*.[1]

Result of the post-hoc analysis of the REDOXS trial



Heyland, D. K. et al. Glutamine and antioxidants in the critically ill patient: a post hoc analysis of a large-scale randomized trial. JPEN J. Parenter. Enteral Nutr. 39, 401–409 (2015)

Fig. 8

No negative effect of sodium selenite in patients with renal dysfunction

	OR (95% CI)	p-value
No renal dysfunction	1.3 (0.8–2.1)	0.38
Renal dysfunction	1.0 (0.7–1.5)	0.93
Sub-groups		
No renal dysfunction, no dialysis	1.3 (0.7–2.1)	0.46
No renal dysfunction, dialysis	1.3 (0.4–3.9)	0.65
Renal dysfunction, no dialysis	1.3 (0.6–2.3)	0.58
Renal dysfunction, dialysis	0.9 (0.5–1.5)	0.56

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Table 3

Clinical trials in intensive care

Randomized, controlled trials, so-called RCTs, are considered the non plus ultra of clinical progress. The result of a large Phase III trial influences guidelines and thereby country-wide therapeutic decisions. But what happens if most of the conducted trials are negative, such as in the case of intensive care? Does this mean that intensive-care patients cannot be helped? Or do additional factors play a role in the significance of clinical trials?

Primary endpoint mortality: Only 10 percent of the trials are positive

The results of the clinical trials in the intensive-care field are sobering.[15] Of 146 RCTs, only 54 (37 %) were positive. The most frequent primary endpoint was mortality (n = 40). In these clinical trials only 10 % of the cases showed a positive outcome. Better results can be attained with clinical endpoints connected with infections. 58 % of such trials resulted in a positive outcome.

The number of study centers influence the result

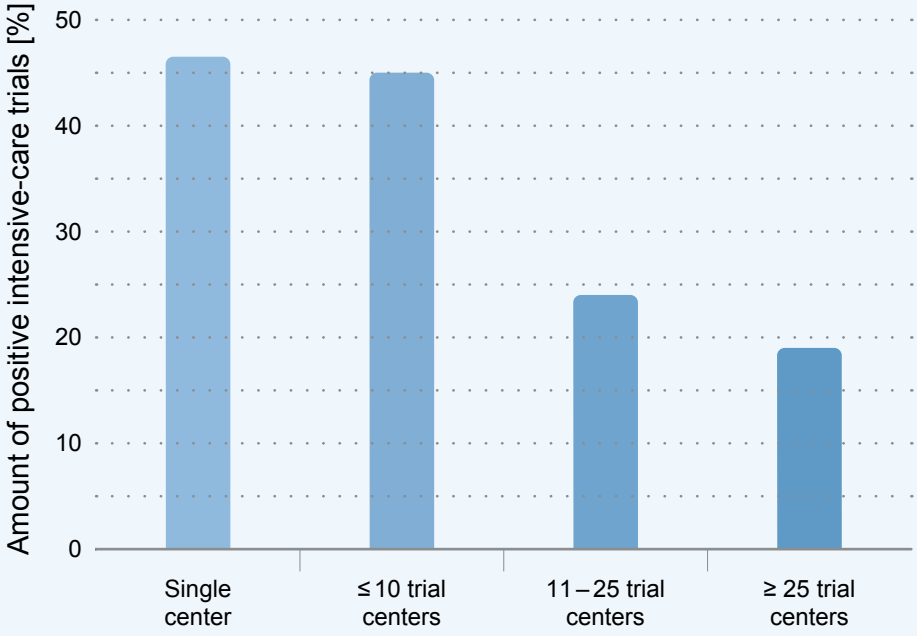
With regard to explanatory power and practical relevance, results from multicenter trials are more highly valuated compared to single-center trials. The larger number of participants can reduce a possible bias. It is therefore not surprising that the results in an single-center trial are positive to 46 % and multicenter trials only to 32 %.[15]

If the multicenter intensive-care medical trials are more precisely subdivided, the results are once again different.[15] Multicenter trials with ≤ 10 ICUs show with 45 % almost the same number of positive clinical trials as single-center trials. If the ICU number increases to 11 – 25 centers, only about 24 % of the trials are positive. At > 25 ICUs the value decreases to only 19 % *(Fig. 9)*. With a large number of involved centers, additional factors appear to have an impact on the result of clinical trials.

What is the significance of mortality as endpoint?

Can an intervention significantly reduce mortality? This is usually the first question of an intensive-care physician. Mortality is a meaningful endpoint when there is a high risk of death. But mortality must also be defined more closely. The 28-day mortality benchmark is used in many intensive-care medical trials. In order for this short-term survival to be meaningful, the 28-day mortality should predict long-term survival with an acceptable quality of life. For sepsis cases, the first criterion (high mortality rate) applies, but it fails on the other ones.[16] The 90-day mortality is already significantly higher for sepsis patients and remains significantly increased over the years.

Number of trial centers influences the outcome



Harhay, M. O. et al. Outcomes and Statistical Power in Adult Critical Care Randomized Trials. Am. J. Respir. Crit. Care Med. 189, 1469–1478 (2014)

Fig. 9

How exaggerated assumptions of outcome negatively influence clinical trials

The diet of intensive care patients or the interventions associated with it (selenium, glutamine, hypocaloric diet, omega-3 fatty acids, etc.) have been investigated in numerous clinical trials. The results usually do not comply with the expectations of the intensive-care physician. Do the respective interventions have no positive benefit at all or do additional factors possibly play a role in this research area?

What is important for a significant trial?

A recently published systematic review analyzed randomized, controlled trials (RCT) on this topic conducted between 2005 and 2015.[17] Four variables are necessary for an informative trial: significance level (usually p = 0.05), power (usually lies between 80 % and 90 %), event rate (e. g. mortality in the control group) and the delta value (e. g. mortality in the control group minus mortality in the intervention group). While significance level and power are specified, the event rate and the delta value must be estimated. If these two values are forecast wrongly, it leads to the lower significance of the trial and to an increased risk of a false-negative result. Especially the overestimation of the delta value has a severe impact *(Tab. 4)*.

Frequent overestimation of the delta value (possible risk reduction)

For ten RCTs with a mortality endpoint, the authors described how they calculated the significance of the clinical trial.[17] The median of the participants in the study was 1,139 (120 – 4,640). The difference between the predicted and the actual event rate was between – 3.9 and + 23.7 % (∅ 2.6 %). For the delta value, the difference was on average 7.5 % (3.2 % – 25.2 %).

For all RCTs, the possible risk reduction was overestimated at the planning stage and thereby the number of participants necessary for the trial was set too low in order to demonstrate a statistically significant effect *(Tab. 5)*. Trials with a lower number of participants are more easily conducted due to lower costs.

Increased risk of a false-positive result based on the overestimation of the delta value	
Trial 1 / prediction	Trial 1 / outcome
Event rate = 20 %	Event rate = 20 %
α (two-tailed) = 0.05	α (two-tailed) = 0.05
β = 0.02	β = 0.02
δ = 7.5 (reduction of mortality from 20 % to 12.5 %)	δ = 5.0 (reduction of mortality from 20 % to 15 %) → no significant outcome
Necessary number of participants: 810	Necessary number of participants: 1,890
Is the intervention actually ineffective (reduction of mortality by 7.5 % [prediction] vs. 5 % [result]), or is a false-negative result due to the overestimation of the delta value?	

Table 4

Impact of the overestimation of the delta value on the size of the trial	
Trial 1	Trial 2
Event rate = 20 %	Event rate = 20 %
α (two-tailed) = 0.05	α (two-tailed) = 0.05
β = 0.02	β = 0.02
δ = 7.5 (reduction the mortality from 20 % to 12.5 %)	δ = 1.0 (reduction the mortality from 20 % to 19 %)
Necessary number of participants: 810	Necessary number of participants: 50,000
Both trials have the same significance	

Table 5

Are large trials worthwhile for diet-associated interventions?

One can now assess diet-associated interventions as irrelevant for the patients. But the authors of the review demonstrate with simple examples how small reductions in risk can prevent a large number of deaths.

Diet-associated interventions can be used for a large number of intensive-care patients. If a mortality of 20 percent in the control group is assumed and a statistically-significant reduction of only one percent should be demonstrated, a trial with 50,000 participants would be necessary. At first the number appears to be vast in order to prove such a slight risk reduction. In 2013, Germany recorded 115,421 cases of severe sepsis including septic shock. It can be assumed that these patients obtained a diet therapy in some form or other. A reduction of mortality by one percent corresponds to more than 1,150 additional survivors.

These numbers show that such a large trial of diet-associated interventions would be worthwhile for the patients, primarily because these trials usually involve low costs for the interventions. Therefore larger efforts should be undertaken to conduct such trials.

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selenase® 100 µg pro injectione	**selenase®** T pro injectione
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10 (N2) and 50 ampoules with 2 ml solution for injection	2, 10 (N2), 30 (3 × 10) and 50 (5 × 10) glass vials with 10 ml solution for injection

selenase® corrects selenium deficiency

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 maldigestion and malabsorption, as well as in malnutrition (e.g. due to complete parenteral nutrition). **Composition: selenase® 100 µg pro injectione:** 1 ampoule of 2 ml solution for injection contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium. **selenase® T pro injectione:** 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. **selenase® 100 µg / T pro injectione: General disorders and administration site conditions:** Frequency not known (cannot be estimated from the available data): After intramuscular administration local pain at the site of administration has been reported. **Form of administration, size of packages: selenase® 100 µg pro injectione:** 10 or 50 ampoules of 2 ml solution for injection. **selenase® T pro injectione:** 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, 60, 90 or 100 ampoules of 2 ml oral solution. **selenase® T peroral:** 10 drinking bottles of 10 ml oral solution plus one measuring cup. Subject to prescription
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