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How to Prevent Deaths from Sepsis

by Max Langen and Dr. med. Petra Wiechel

OMNS (June 23, 2023) Sepsis is one of the leading causes of mortality worldwide and also one of the leading causes of death in intensive care units. It is an overreaction of the immune system to any viral, bacterial or fungal infection acquired in the community or in the hospital and is a common pathway to death from many different infectious diseases. Respiratory infections, (including severe colds, influenza or covid-19), pneumonia, ventilator-associated pneumonia, infections of the digestive system (including diarrhoeal diseases), urinary system or bloodstream and wound infections are among the leading causes of this life-threatening syndrome. Symptoms include feeling light headed, shivering, fast shallow breathing, change in mental status and symptoms specific to the infection (like worsening of fever and cough during pneumonia). [1-3]

Annually, sepsis affects almost 50 million people and contributes to or causes more than 11 million deaths. [4] This number of deaths corresponds to 1.3 times the entire population of New York, the most populous city in the US. While many of these deaths occur in low income countries, sepsis is also a leading cause of death in wealthier countries. In the US alone, it claims 260,000 lives per year. A comprehensive analysis estimated that sepsis was involved in 20% (1 in 5) of all global deaths in 2017. [4] It constitutes a global emergency.

However, as many studies show, orthomolecular or natural medicine can solve or at least greatly improve this situation. This existing knowledge from the peer-reviewed literature only needs to be adopted. If healthcare practitioners world-wide could learn from these results and utilize them, this could save millions of lives every year.

Many of the following treatments are not only effective for therapy of acute septic shock, but also help prevent infections and reduce the risk of developing serious infectious disease complications like

pneumonia or sepsis. Especially people at higher risk of getting sepsis, which includes older people, pregnant women, neonates, hospitalized patients or especially patients in the intensive care unit (ICU), people who received antibiotics recently and people with comorbidities like autoimmune diseases, overweight, diabetes, cancer, HIV, liver cirrhosis etc. should receive preventative care with high dose nutrients and herbal medicine to reduce the risk of community- or hospital-acquired infections and the development of sepsis.

Sepsis is characterized by increased inflammatory processes, oxidative stress, mitochondrial dysfunction and coagulation (risk of thrombi development). The following treatments have significant anti-infective, antiviral, antibacterial, anti-oxidative, anti-inflammatory, immunomodulatory, mitochondria-modulating, antithrombotic/anticoagulant effects. The earlier the treatment starts (in early stages of sepsis), the higher the chance of success. In the studies presented in this article, the investigated treatment was usually added to the standard treatment.

Coenzyme Q10

Patients with septic shock are deficient in coenzyme Q10 and have much lower Q10 levels than healthy controls. [5-6] This deficiency may contribute to the increased risk of developing serious complications (like pneumonia or sepsis) from different infectious diseases. The body's own Q10 synthesis declines continuously with increasing age and patients with chronic diseases also have lower Q10 levels. A recent study showed that supplementation of 200 mg of Q10 reduces inflammation in early phase septic ICU patients and can strongly reduce the mortality rate. While of those in the control group, 65% died, the Q10 group only had a 20% death rate (a 70% lower risk of death). [7] Of course, the earlier the treatment starts, the higher the chance of success. If the therapy is started very late (when the patients already progressed to a severe sepsis or septic shock), it is less likely to help. [8]

Q10 supplementation is also an effective therapy for pneumonia. Hospitalized pneumonia patients who received 200 mg of Q10 per day recovered significantly faster, had a lower risk of treatment failure and were able to leave the hospital earlier than the control group. [9] In a recent study, Q10 supplementation was also

associated with a significantly lower risk of requiring hospitalization due to Covid-19. [10]

Omega-3 fatty acids

Omega-3 fatty acids also have an essential role in the regulation of the immune system. An omega-3 index (fraction of omega-3 fatty acids in red blood cells) of 8 to 11% in the blood is considered ideal and protects from many cardiovascular, neurological, inflammatory conditions etc. In many individuals blood index levels of omega-3 fatty acids (EPA and DHA) are insufficient (4 - 8%) and far from optimal ranges. [11] A recent meta-analysis of 49 RCTs showed that omega-3 supplementation in the hospital (added to the parenteral nutrition) reduced the risk of an infection by 40%, and the risk of developing sepsis was reduced by 56%. [12] Another study showed that in septic patients, omega-3 supplementation (for example 1000 mg three times daily) can reduce mortality, especially in those with both sepsis and gastrointestinal dysfunction. In those patients, the risk of death was reduced by 50% due to treatment with omega-3 fatty acids. [13] In ICU patients, omega-3-supplementation significantly accelerated the recovery time. Compared to standard parenteral nutrition, the additional administration of omega-3 reduced the costs per case by approximately $10,000, suggesting that orthomolecular medicine can also lead to significant cost-savings. [14] In some studies Covid-19 patients with a higher omega-3 index (> 5.7%) had a 75% lower risk of mortality, [15] and this also improved and accelerated the recovery of their clinical symptoms. [16]

Melatonin

Melatonin is one of the most powerful anti-oxidative and anti-inflammatory biomolecules. It is a hormone involved in controlling the day-night cycle of vertebrates, but it also regulates the immune system and prevents severe infectious disease outcomes. Yet the body's own nocturnal melatonin synthesis declines proportionally with increasing age. [17] Older people often suffer from both a severe deficiency of vitamin D and melatonin, which causes a state of increased oxidative stress, silent inflammation and mitochondrial dysfunction. All of these factors greatly increase the risk of developing sepsis. [18]

A recent study showed that melatonin treatment was associated with a 34% lower risk of mortality. [19] Both oral or intravenous melatonin (50 to 60 mg/d) are effective treatments. Septic patients who received melatonin required less vasopressors and less ventilator support, recovered faster and stayed fewer days in the ICU and the hospital, and had about 40% lower mortality. [20,21]

On the assumption that adequate melatonin may reduce the risk of sepsis mortality by 40%, 4 million lives per year could be saved. This number corresponds to the entire population of Los Angeles. However, active prevention of sepsis with melatonin could lead to even more lives saved. An RCT with Covid-19 patients showed that those who received melatonin (10mg/d) had a 70% lower risk of developing sepsis. [22] Several studies showed that early melatonin treatment (10 mg/d) can cut the recovery time of Covid-19 patients in half [23-25] and massively reduce mortality, especially when given early enough. Therefore, it is likely that many cases of sepsis could be prevented if hospitalized patients who are vulnerable to the development of sepsis, would receive melatonin early during an infection to prevent the progression to more severe outcomes like sepsis.

Neonates are susceptible to sepsis, and they do not produce melatonin during the first months after birth. [17] While breast milk contains melatonin, many neonates receive only infant formula, which lacks melatonin. [26] And neonates given formula are especially susceptible to severe infections and sepsis. Early administration of breast milk in neonates protects from critical illness and sepsis. [27,28] Of course, breast milk contains many protective ingredients besides melatonin. But its melatonin content may be one of the most important protective factors. A recent study showed that melatonin is an effective treatment for neonatal sepsis, significantly improving the clinical condition. [29]

Many viral and bacterial infections can likely be treated by melatonin, including influenza and even Ebola. [30-32] And it may also prevent viral (or vaccine-induced) myocarditis. However, in malaria high dose melatonin may be contraindicated (at least unless it is administered in combination with a melatonin antagonist). [33-34]

Vitamin C

According to cardiologist Dr. Thomas Levy, an expert on the use of vitamin C, sepsis is due in large part to vitamin C depletion. Sepsis is essentially a rapid-and- acute-onset scurvy, and very high dose vitamin C can prevent sepsis mortality. Several studies and meta-analyses indicate that intravenous vitamin C can significantly reduce sepsis mortality. [35-40]

However, some studies have found no effect of vitamin C upon sepsis, and these results have been cited widely as "evidence" against intravenous vitamin C therapy in sepsis. [35,40] However, a problem with many studies that tested vitamin C against sepsis is that they administered an inadequate dose. For example, in some studies, sepsis patients received IV doses between 6 and 16 g/day. Although this has been described as "high dose" treatment, it may be insufficient in many cases.

Yet there is also clear evidence that the therapeutic effect of vitamin C is dose-dependent. Severely sick patients may require much higher doses of vitamin C than the doses administered in many of the failed "high dose" sepsis trials. Vitamin C has been used successfully for the treatment of infectious diseases, cancer and burn patients in much higher doses (often above 50 to 200 grams per day). [40-42]

Dr. Robert Cathcart, who treated thousands of patients with very high dose vitamin C, described that if vitamin C is given orally, it should be administered according to the individual bowel tolerance level. [42] Each individual has a different requirement that depends upon the stage of illness and many other factors. Cathcart described that a severe cold or influenza may require treatment with 60 to 150 g of vitamin C per day. Viral pneumonia may require 150 to 200+ g/day. [42] Cathcart described that lower doses were much less effective. [42]

Oral intake is possible if no intravenous administration is available. Dr. Andrew Saul wrote:

"Robert F. Cathcart, MD, successfully treated pneumonia with up to 200,000 milligrams of vitamin C daily. One can, to a significant extent, simulate an IV of vitamin C by taking it by mouth very, very often. When I had pneumonia, it took 2,000 mg of vitamin C every six minutes to get me to saturation (bowel tolerance). In three hours,

fever was reduced several degrees and coughing virtually stopped. At an oral daily dose of just over 100,000 mg, recovery took just a few days." [43]

However, intravenous administration can be more effective, as Cathcart explained:

"Symptoms from acute viral diseases can most frequently be more permanently eliminated with intravenous sodium ascorbate. While it is true that tolerance doses of oral ascorbate will usually eliminate complications of acute viral diseases; at times, such as with certain cases of influenza, the large amount of oral ascorbate necessary to suppress symptoms over a period of a week or more, sometimes makes intravenous ascorbate desirable. Clinically large amounts of ascorbate used intravenously are virucidal (...) Ascorbate is more efficient intravenously than orally probably because chemical processes in the gut destroy a percentage of that orally administered. Doses of 400 to 700 mg/kg of body weight per 24 hours usually suffice." [44]

So, if severely sick septic patients receive a dose of 6 to 16 g in a given study, this dose might be 10 to 20 times too low. In fact, a recent review suggests investigating the effect of much higher doses. [40] Also, published reports about covid-19 indicate that a dose of 50 g or more may be necessary to prevent mortality. For example, in a study with 50 Covid-19 patients, treatment with 10 to 20 g of vitamin C led to an improvement, and faster recovery and there was no mortality. However, one patient deteriorated rapidly, so a bolus dose of 50 g was administered over 4 hours. The patient's pulmonary status stabilized and improved immediately. Had this patient not received this truly high dose that he required in this moment, he would have likely died. [45,46] Similarly, another report about another critically ill Covid-19 patient with low blood pressure, acute respiratory distress syndrome and acute kidney injury showed that an IV vitamin C dose of 60 g led to immediate improvements. The patient survived and was discharged from the hospital several days later. [40]

In another case, a retired physician who got severely sick with Covid-19 only experienced a small temporary improvement following an intravenous infusion of 25 g of vitamin C. The disease progression could not be stopped, his condition kept deteriorating,

and his oxygen levels decreased. However, a subsequent infusion of 50 g resulted in a greater improvement of his clinical condition -- and then the physician recalled that severe viral disease may require 200 g of vitamin C. So he prepared his treatment with 4 intravenous bags containing 5% dextrose, 50 g of vitamin C and 4 ml magnesium sulfate. They were administered one after another over several hours, which led to a dramatic improvement, the oxygen level increased, and the cough became much less severe. In the following days he continued high dose vitamin C (50 g/d) and got progressively better and was finally cured. [47]

The implication of these reports is that even 25 g of vitamin C (which is sometimes considered "high dose") would not have saved him from dying. He needed much more. However, modern clinical trials which claim use of "high dose" vitamin C rarely even give 25 g per day. The abstracts of all such clinical trials should be corrected. No matter what the result of the study was, the abstract should contain the sentence that "the dose was likely too low."

The fact that some of the sepsis trials and meta analyses only found a small positive effect or no effect can likely be explained by: The chosen dose was too low, strong treatment delay, dangerous treatments which might increase sepsis mortality were given in combination with vitamin C, and the administration time was too short.

Therefore, the suggested approach for septic patients is to:

- Receive a dose that is truly high enough. This dose is likely individual (some may require, for example, 20 g, others may require 200 g per day). Leading vitamin C experts recommend that if no improvement occurs with the chosen dose, the dose should be increased further and further, until improvement is seen.
- Receive treatment as early as possible. Do not wait for the occurrence of septic shock before administering vitamin C.
- Receive vitamin C in combination with other treatments which have shown to be effective for sepsis. For example, hydrocortisone, ascorbate, and thiamine (HAT) therapy is considered to be helpful in sepsis. [48]
- Receive vitamin C for a long enough duration, until recovery is achieved -- and not only for 4 days, as has strangely been

> done in some studies. This is also important to prevent a rebound effect. Recently a study was published that administered vitamin C (16 g/d) for a short time (4 days) misleadingly concluded that vitamin C had a negative effect on clinical outcomes. A secondary analysis of this study showed that the negative effect did not occur during the treatment episode but thereafter, which indicates that the short administration time caused a rebound effect. The rationale for a rebound effect is that vitamin C levels decrease to an even lower level than pre treatment because administration leads to a higher activity of enzymes that metabolize vitamin C. Thus, by administering it only for a short time, the level may drop to an even lower level following treatment cessation, which can be detrimental if the patient is still severely sick. [49]

From this we can learn that it is of vital importance to administer vitamin C for a sufficient time, until recovery is achieved. And it might be reasonable to keep administering vitamin C following recovery, intravenously or at home in high oral doses, based on the bowel tolerance level [42] and only reduce the dose slightly over the following weeks, to make sure the body and the enzyme activity can adapt accordingly to the decreasing dose, so that the vitamin C level won't decline too strongly or too rapidly which might otherwise increase the risk of developing a new infection or other conditions.

"Start giving sepsis patients 25 grams of vitamin C every six hours, and all will be saved unless they were literally on death's doorstep when the vitamin C was started." - (Thomas E. Levy, MD, JD)

A review that investigated risk of adverse effects of very high dose vitamin C (50 to 100 g/d) therapy found no consistent evidence that this therapy is more harmful than a placebo. [35,50] However, adverse events can not be excluded completely and in some rare cases, events like oxalate nephropathy or glucometer error are possible. Although the body metabolizes vitamin C to produce small quantities of oxalate, for individuals with normal kidney function IV vitamin C does not contribute to calcium oxalate kidney stones. More important sources of oxalate for most individuals are the amount of cruciferous vegetables, tea, and other sources in the diet. These oxalates bind with the excess calcium that is in our dairy, fortified foods, and supplements. To prevent oxalate stones, in

general, and when taking oral vitamin C, it is important to drink adequate amounts of fluid and avoid excessive calcium levels in the diet. In addition, magnesium supplements (300-500 mg/day, in malate, citrate, or chloride form) can prevent calcium from precipitating with oxalate to form stones. [51] Elevated urine oxalate is a risk factor for stone disease in patients with preexisting kidney disease only. [52] In patients with kidney disease or kidney injury (due to severe illness) it is recommendable to monitor the kidneys in association with the administration of vitamin C. Early treatment with high dose vitamin C during the initial stages of sepsis will be much less likely to cause problems like oxalate nephropathy compared with a situation when treatment starts late while organs like kidneys have already been harmed significantly. Therefore, kidney monitoring is important during high dose IV vitamin C treatment.

In patients with the enzyme deficiency G6PD (glucose-6-phosphate dehydrogenase deficiency) high dose vitamin C could lead to hemolysis. [50] However, this deficiency is not necessarily a contraindication against moderately high doses of vitamin C. "The G6PD level should be assessed before beginning intravenous vitamin C (IVC). (At the Riordan Clinic, G6PD readings have yielded five cases of abnormally low levels. Subsequent IVC at 25 grams [25,000 mg] or less showed no hemolysis or adverse effects.)" [53] Therefore, while IV-C is usually not recommended for patients with G6PD deficiency, IV-C appears to be safe for patients with G6PD deficiency at moderate infusion dosages of 25g. The Riordan Clinic recommends checking red blood cell G6PD levels prior to onset of IV-C therapy. In patients with severe iron overload, high dose vitamin C might also be contraindicated.

Vitamin D

Vitamin D is important for the activation of the immune defense and many studies show that a sufficient level is associated with a much lower risk of infections. Worldwide, 75% of adults have an insufficient vitamin D level, below 30 ng/ml, [54] which is an important risk factor for infectious diseases. Individuals with a level >38 ng/ml had a 50% lower risk of a community-acquired respiratory infection. [55] A sufficient level can also protect from hospital-acquired infections. [56]

Supplementation of vitamin D (cholecalciferol), daily or weekly, can reduce the risk of viral, and specific bacterial and fungal infections, and consequently can reduce the need for antibiotics. [56,57] A recent meta-analysis showed that vitamin D supplementation can reduce the risk of influenza by 22%. [58] Daily supplementation of 5000 IU. drastically reduced the risk of an influenza-like illness in healthcare workers. [59] Prophylactic vitamin D supplementation has shown to be associated with a reduced risk of SARS-Cov-2 infection, severe cases and Covid-19 mortality in several studies, especially when a level well above 30 ng/ml is achieved with supplementation. [60,61]

Recent studies showed that daily vitamin D supplementation can reduce the risk of a SARS-CoV-2 infection, [62] and those who received two bolus doses of vitamin D, followed by daily supplementation of 5000 IU for several months had a much lower risk of developing a symptomatic Covid-19 Infection than those who received no bolus doses and took only 2000 IU daily.

A recent study showed that individuals with low baseline levels of vitamin D are at greatest risk of upper respiratory infection, but also achieve the strongest risk reduction (70% lower) from supplementation. [63] The risk of urinary tract infections can be reduced by half from weekly vitamin D supplementation. [64] By reducing the risk of infections, a more healthy level of vitamin D can help prevent many sepsis cases.

For patients who are already suffering from a severe infection, treatment with a high dose of vitamin D (200,000 IU for 5 days) may promote recovery and reduce the risk of progression to sepsis. [65] In patients with ventilator-associated pneumonia, high dose vitamin D administration reduced the risk of death by 58%, [66] and vitamin D supplementation can reduce the risk of a repeat episode of pneumonia by 30%. [67]

In hospitalized patients with a severe viral infection, early administration of vitamin D as calcifediol reduced the risk of admission to the intensive care unit and mortality by 80% [68,69] -- suggesting that early administration of calcifediol may also be a great solution to prevent sepsis. Calcifediol has the advantage that it increases the vitamin D level (25(OH)D) much faster than cholecalciferol -- and especially in acutely ill patients, every second

counts. Therefore, calcifediol (administered in repeated doses over several days and weeks) is the preferred form for use with an acute illness.

Vitamin D supplementation (parenteral administration) as cholecalciferol significantly reduced mortality in critically ill patients as well as improved and accelerated the recovery of neonatal sepsis and urosepsis. [70-72] However, cholecalciferol is not always effective in acute sepsis [73] which may be due to the delay in conversion. In acute sepsis, calcifediol may be preferable.

If calcifediol is not available, cholecalciferol can be administered to treat and improve the recovery of severe infectious diseases in order to reduce the incidence of sepsis. But a very important factor to consider is that whenever calcifediol or cholecalciferol is administered, it is of vital importance to provide repeated doses over several days or weeks rather than a single high dose. Even though some studies indicate that single high doses can also have positive effects, the results have not always been consistent. For example, in severely sick covid-patients, a single high dose administration of cholecalciferol (like 200,000 or 500,000 IU during one day) has often been ineffective. [74,75]

On the other hand, the administration of repeated and somewhat lower doses of cholecalciferol or calcifediol led much more reliably to positive outcomes in hospitalized patients with severe covid-19, including faster recovery, and lower risk of disease progression, ICU admission and mortality. [68,76-78] This is because single high doses (very infrequent bolus doses) may sometimes even have an inhibitory effect on the immune system. They can trigger countervailing factors that turn off hormonal activation processes and result in a downregulation of active vitamin D (1,25(OH)2D). So, although high bolus doses can increase the vitamin D level (25(OH)D), the activation of vitamin D may be downregulated by such infrequent single high doses, which can inhibit immune regulation. On the other hand, a more moderate dosing in shorter intervals (daily or weekly) does not trigger such countervailing factors. Also, cholecalciferol, which has a 20 hour half life, has intracellular activity and even greater cellular effects than either the storage form 25(OH)D or the active/hormonal form 1,25(OH)2D of vitamin D. [79]

Therefore, frequent intake of moderate doses is biochemically reasonable and very infrequent dosing of very high doses is unnatural and biochemically inappropriate. Unfortunately, studies that administered single high doses of cholecalciferol and which therefore did not show high efficacy, have been cited widely as "evidence against vitamin D" for preventing or treating infectious diseases like covid-19. For the reasons explained above, such news reports are severely misleading. The studies referenced above [54-78] clearly showed that cholecalciferol or especially calcifediol, given in repeated doses, greatly improved Covid-19 outcomes.

Of note, even though a combination of both high dose vitamin C and vitamin D can have positive synergistic effects and help save lives of severely sick patients, no clinical trials have tested this combination. Since vitamin D may increase calcium levels, including calcium levels in urine, when attempting this approach in patients with kidney disease or kidney injury it may be wise to monitor the kidneys and to make sure sufficient liquid is administered. Hydration with fresh lemon and water will help dilute the urine and greatly lower the risk of oxalate stone formation. And as suggested above, magnesium (as citrate, malate or chloride) also prevents calcium from precipitating with oxalate to form stones, so to further reduce the risk of stone formation, vitamin C or vitamin D can be taken in combination with magnesium. A recent study also suggested that intravenous magnesium sulfate may help improve and shorten the recovery of septic patients in the ICU. [80]

Note: This article does not provide or replace medical advice, as it is for educational purposes only. Before taking any supplements or drugs or before making any lifestyle changes, consult a qualified practitioner who can provide personalized advice and details of risks and benefits based on your medical history and situation. Both (prescription-free) supplements and drugs can have side effects that are not listed in this article. Interactions between drugs and supplements can be possible in some cases. This article does not claim to list all potential benefits and risks (including side effects) of the described treatments. Also, some of the treatments described here should not be used before a surgery due to their strong anti-thrombotic efficacy.

Editor's note: Part two of this paper will also be published by the *Orthomolecular Medicine News Service*. It will include discussion of zinc, N-Acetylcysteine (NAC) and glycine, probiotics, curcumin, black cumin, safflower yellow, xuebijing, acupuncture, nutrition, fasting, intestinal health, and psychological stress relief.

(Max Langen has found that his own health problems were greatly alleviated by orthomolecular medicine. He is currently working on a book about it, and has plans to qualify as a therapist. Dr. Petra Wiechel is chief physician of the Swiss Mountain Clinic in Switzerland [https;//www.swissmountainclinic.com]. She is expert in biological and orthomolecular medicine, and treats her patients holistically.)

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