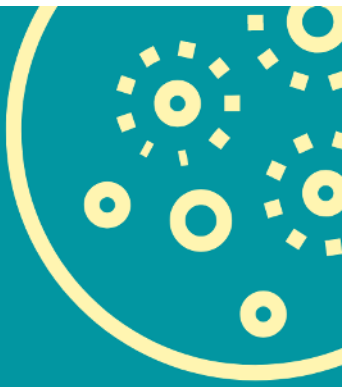

SEPSIS CARE

A GUIDE TO INPATIENT AND OUTPATIENT TREATMENT

September 2023

FLCCC®
ALLIANCE

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DISCLAIMER

The information in this document is our recommended approach to treating sepsis in hospital and outpatient settings. It is provided as guidance to healthcare providers worldwide and should only be used by medical professionals in formulating their approach to sepsis. Patients should always consult with their providers before starting any medical treatment.
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INTRODUCTION

Sepsis is a life-threatening medical condition that occurs when an infection triggers an extreme response in the body. If not treated in time, sepsis can rapidly lead to organ failure, tissue damage, or death. In most cases, sepsis, or the infection that leads to sepsis, starts before a patient goes to the hospital. (1)

The CDC estimates that in a typical year: (2)

- At least **1.7 million** American adults develop sepsis.
- At least **350,000** adults who develop sepsis die during hospitalization or are discharged to hospice.
- **30% of patients who die in hospital** had sepsis during their hospital stay.

In some cases, sepsis progresses to septic shock, which is a severe drop in blood pressure. The risk of death greatly increases if this happens. Symptoms of septic shock can include not being able to stand up, having a hard time staying awake, extreme confusion, and changes in mental status.

Figure 1: Worldwide burden of sepsis (Source: Global Sepsis Alliance)

RISK FACTORS, SIGNS, AND SYMPTOMS

Any kind of infection — viral, fungal, or bacterial — can lead to sepsis, although most cases derive from bacterial infections. Pneumonia, bloodstream infections, urinary infections, wounds, or infections of the digestive system are commonly associated with sepsis. Having cancer or being treated for cancer can also put you at a higher risk of developing an infection, which raises the risk of sepsis. (3)

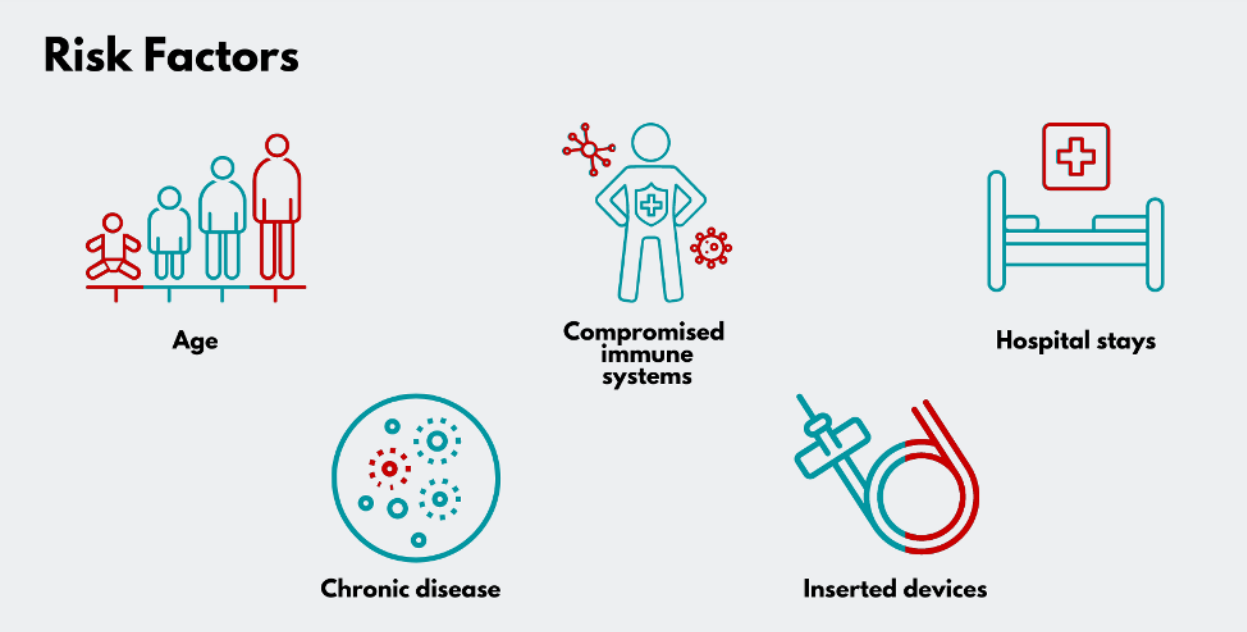


Figure 2: Some people are more at risk (Source: FLCCC)

Some conditions that increase the risk of sepsis include:

- Age – including infants and older adults (65+).
- Compromised immune systems – including people with decreased immune response, and those being treated for cancer.
- Chronic disease – including people with diabetes, kidney disease, and chronic obstructive pulmonary disease.
- Hospital stays – being admitted to an intensive care unit or needing a longer hospital stay puts people more at risk.
- Inserted devices — including catheters and breathing tubes.

The symptoms of sepsis are not specific and may vary from person to person. Common symptoms in adults may include:

- Fever
- Chills
- Uncontrolled shaking
- Confusion or a change in mental status

- Fast, shallow breathing and rapid heart rate
- Sweating for no clear reason
- Feeling lightheaded or headaches
- Tiredness
- Some symptoms are specific to the type of infection, such as painful urination from a urinary tract infection or a debilitating cough from pneumonia

Sepsis in children may appear differently than in adults. The Sepsis Alliance cautions that parents should suspect sepsis for any child who: (4)

- Feels abnormally cold to the touch
- Looks mottled, bluish, or has very pale skin
- Has a rash that does not fade when you press it
- Is breathing very fast
- Has a convulsion
- Is very lethargic or difficult to wake up

Similarly, sepsis may be suspected for any child under 5 who is not eating, vomits repeatedly, or has not urinated in 12 hours.

DIAGNOSING SEPSIS

No single diagnostic test exists for sepsis. Diagnosing sepsis requires clinical judgment based on the evidence of an infection or organ dysfunction. Providers will use measures such as a chest radiograph (pneumonia), urine and blood cultures, and laboratory tests to aid in the diagnosis of sepsis.

A complete blood count (CBC) with a differential count is very useful in the diagnosis of sepsis; a high neutrophil to lymphocyte ratio (N/L ratio) and more than 5% band forms are highly suggestive of sepsis. (5) In addition, the serum procalcitonin (PCT) level has a high positive predictive value for the diagnosis of sepsis; a level > 0.5 ug/l is highly suggestive of sepsis. A PCT > 2ug/l is almost diagnostic of bacterial infection. (6)

Procalcitonin is a biomarker that is released in response to bacterial infections and can be used to differentiate the etiology of infectious processes. PCT can also be employed as a tool to guide appropriate antibiotic therapy and thus has a role in antibiotic stewardship.

How to Treat Sepsis: Hospital Setting

Inpatient (MHAT)

Melatonin: 6-10 mg nightly.

Hydrocortisone: 50 mg intravenously every 6 hours, for at least 4 days and until patients are off vasopressors. If treatment is less than 10 days, a taper is not required.

Ascorbic acid: 1.5 g intravenously every 6 hours for a minimum of 12 doses, ideally 16 doses. Should treatment be initiated in excess of 6 hours after presentation to the hospital, the dose should be increased to 3 g intravenously every 6 hours. With delays in treatment of greater than 24 hours, mega-dose vitamin C should be considered, namely 20-25 g intravenously every 12 hours.

Thiamine: 200 mg intravenously every 12 hours.

How to Treat Sepsis: Outpatient Setting

Outpatient (MCAZ+)

Melatonin: 10 mg nightly.

Ascorbic acid (Vitamin C): 1 g orally every 2-4 hours (6 times a day) for 2 weeks. Intravenous vitamin C (1.5-3 g every 6-12 hours or 12-15 g daily) can be considered when feasible.

Antibiotics: Empiric antibiotics started as soon as possible. Dosed according to the specific antibiotic chosen.

Zinc: 75-100 mg daily for no longer than 2 weeks.

PLUS

Quercetin*: 500 mg twice daily for 2 weeks.*

Nano curcumin*: 500 mg twice daily.*

Pre- and Probiotics*: Daily bifidobacterium probiotics together with prebiotics are recommended to normalize the microbiome.*

TREATMENT APPROACHES

Options exist for both inpatient and outpatient treatment of sepsis. Some general principles apply to both options, as follows:

- Sepsis is a time-sensitive disease. Waiting until the diagnosis is confirmed will lead to excess morbidity and mortality.
- Treatment should begin immediately upon suspicion of sepsis — with empiric antibiotics (antibiotics targeted to treat a suspected bacterial infection) and the therapies described below.
- If the patient is proven not to have sepsis, antibiotics can be stopped with no adverse effects.
- Source control is essential. Sepsis cannot be cured until the source of infection is removed.
- Empiric antibiotics should be based on the likely source of sepsis and the likelihood of hospital vs. community pathogens.
- If a surgical source is suspected, consult with the hospital emergency room, surgery, and/or Interventional Radiology.
- Procalcitonin (PCT) and complete blood count (CBC) with differential white cell count are recommended. The trends in these biomarkers are essential in determining the response to therapy and the discontinuation of antibiotics.

Inpatient Treatment: MHAT protocol

(Melatonin, Hydrocortisone, Ascorbic Acid, Thiamine)

1. A physiologic-guided approach to fluid administration is suggested. Large-volume resuscitation will lead to “salt-water drowning” and excess mortality.
2. Early use of norepinephrine is recommended in patients with sepsis-induced hypotension/septic shock, targeting a mean arterial pressure of 65 mmHg. Short-term administration of pressors using a large bore peripheral venous catheter is suggested.
3. Monitor electrolytes daily. Ensure that magnesium concentration > 2.2 mmol/l.
4. Check a serum ferritin concentration to exclude sepsis-induced Hemophagocytic Lymphocytic Histiocytosis (HLH).
5. The following protocol is best initiated at the time of diagnosis and concurrent with the first dose of antibiotics. The response is attenuated with a delay in therapy.

Melatonin: 6-10 mg nightly.

Hydrocortisone: 50 mg intravenously every 6 hours, for at least 4 days and until patients are off vasopressors. If treatment is less than 10 days, a taper is not required.

Ascorbic acid (Vitamin C): 1.5 g intravenously every 6 hours for a minimum of 12 doses, ideally 16 doses. Should treatment be initiated in excess of 6 hours after presentation to the hospital, the dose should be increased to 3 g intravenously every 6 hours. With delays in treatment of greater than 24 hours, mega-dose vitamin C should be considered, namely 20-25 g intravenously every 12 hours.

Thiamine: 200 mg intravenously every 12 hours.

Effectiveness of MHAT

Vitamin C is an essential “stress hormone” for most mammals. (7) Goats, for example, produce around 2-4 g of vitamin C per day in their livers, and when they are stressed vitamin C synthesis increases significantly. Humans, however, have lost the ability to synthesize vitamin C, leaving us with an impaired stress response.

The inability to produce vitamin C has serious implications for patients with sepsis. Vitamin C acts synergistically with corticosteroids and together they aid in restoring the stress response and improving survival.

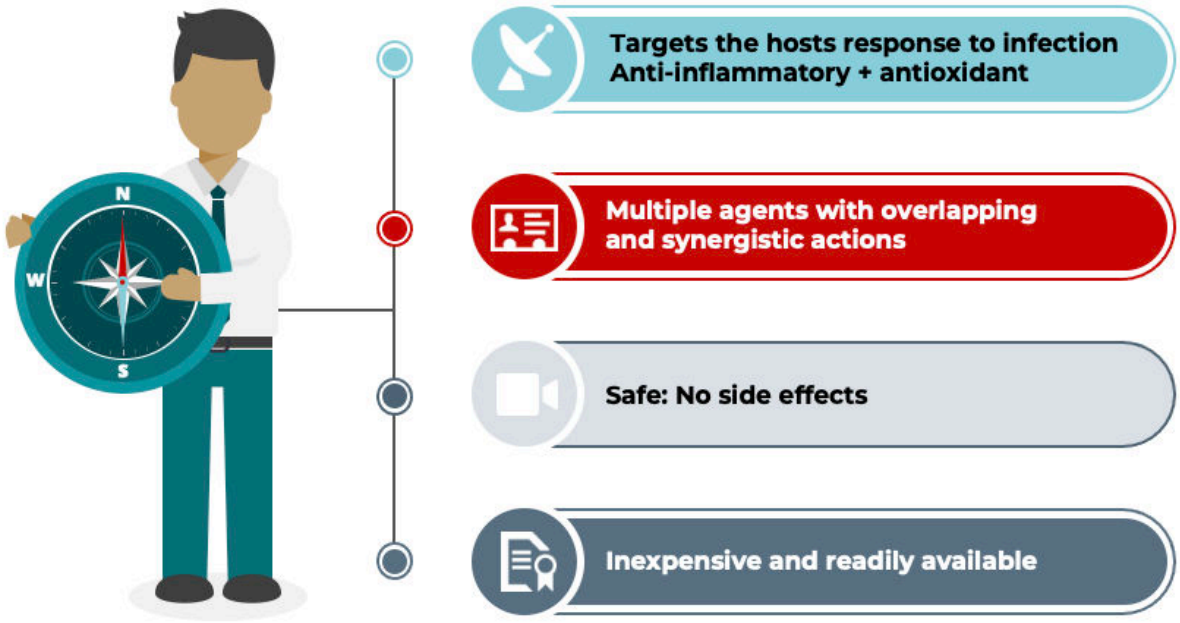


Figure 3: Philosophy behind MHAT (Source: FLCCC)

Hospital mortality increases as the patient transitions from sepsis to severe sepsis to septic shock. The mortality of severe sepsis is between 20% and 40%, while that for septic shock is between 40% and 60%. (8, 9) As Table 1 below indicates, this protocol could reduce the risk of dying by at least half.

HAT Rx: Characteristics of RCTs

Study	n	Mean time to Rx	Mortality	SOFA/Pressor
Marik (2017)	94	< 6 hours	8.5 vs. 40.4%	YES
Vitamins (2020)	216	> 18 hours	28.6 vs. 24%	NO
Oranges (2020)	137	< 10 hours	16.4 vs. 19%	YES
ACTS (2020)	205	> 14.5 hours	34.7 vs. 29.3	NO
Wani (2020)	100	< 10 hours	40 vs. 42%	YES
VICTAS (2021)	501	> 14.7 hours	22 vs.24%	NO
Feng (2021)	136	1.7 hours	8 vs. 15%	YES
Lamontagne (2022)	862	> 22 hours	35.4 vs 31.6	NO

Table 1: Randomized Controlled Trials of the HAT protocol

In early 2016, the mHAT protocol became the standard of care in the main ICU at Sentara Norfolk General Hospital (SNGH) in Virginia. (10) The graph below (Figure 4) was produced from data by Truven Health Analytics, a company that provided healthcare data and analytics services to hospitals, clinicians, government agencies, and pharmaceutical, biotech, and medical device companies.

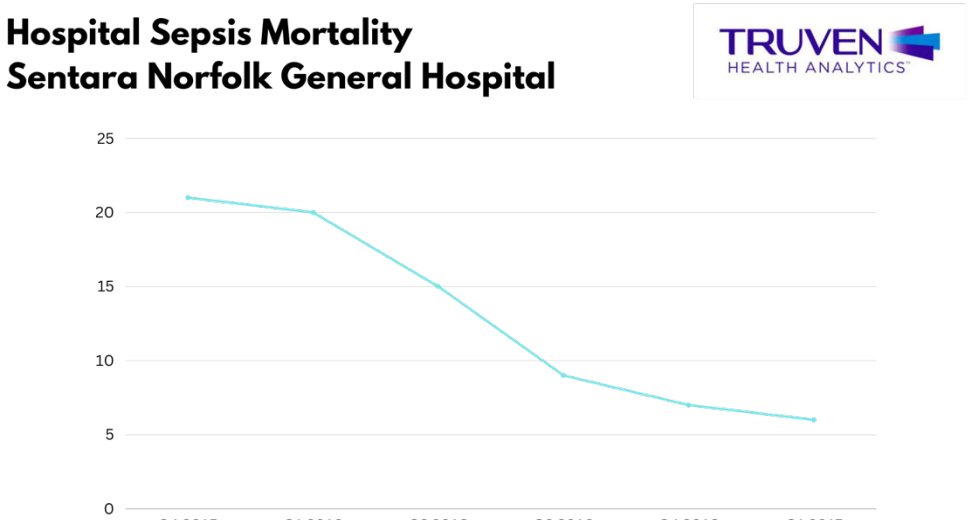


Figure 4: Hospital Mortality from Sepsis at Sentara Norfolk General Hospital after HAT protocol was introduced

Using Medicare data, it tracks the sepsis mortality reported at SNGH before and after the protocol was introduced. It should be noted that sepsis patient care at SNGH was directed by the ICU service prior to admission to the ICU.

The chart below (Figure 5) was compiled from data on 166 septic shock patients treated with the HAT protocol. The expected mortality (orange bars) is calculated from a highly validated scoring tool (APACHE) based on numerous physiologic variables. The ratio of the observed mortality (blue bars) compared to the expected mortality (O/E ratio) increases with delays in initiation. (11)

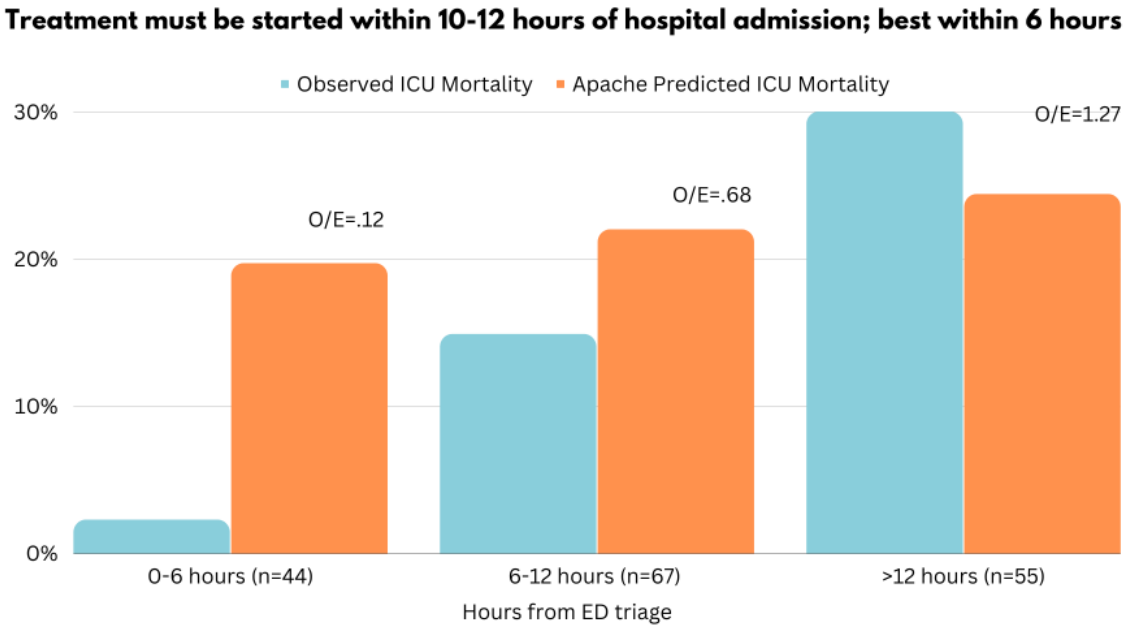


Figure 5: Sepsis is a time-sensitive disease. (Source: Long, et al; Critical Care and Shock. 2020; 23.)

Outpatient Treatment: MCAZ+ protocol

(Melatonin, Vitamin C, Antibiotics, Zinc, + supplements)

Melatonin: 10 mg at night.

Ascorbic acid (Vitamin C): 1 g orally every 2-4 hours (6 times a day) for 2 weeks. Stay well hydrated. Caution in patients with known kidney stones. Intravenous vitamin C at a dose of 1.5 to 3 g every 6-12 hours (optimal) or 12-15 g daily can be considered when practically feasible. Access to out-of-hospital intravenous infusions is available through some private home infusion companies or at private practice clinics of providers from various disciplines.

Antibiotics: Empiric antibiotics, targeted to treat the suspected infection, should be started as soon as possible, dosed according to the specific antibiotic selected.

Zinc: 75-100 mg daily for no longer than 2 weeks**.** Zinc supplements come in various forms, including zinc sulfate, zinc citrate, zinc gluconate, and zinc oxide.

Quercetin: 500 mg twice daily for 2 weeks.

Curcumin/Nano-curcumin: 500 mg twice daily.

Pre- and Probiotics: Daily bifidobacterium probiotics (e.g., Daily Body Restore) together with prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) are recommended to normalize the microbiome. Suggested probiotics include Megasporebiotic (Microbiome labs), TrueBifidoPro (US Enzymes) and Yourgutplus+, as well as soluble and insoluble fiber (glucomannan).

Mechanisms of action

Melatonin

Melatonin has anti-inflammatory, antioxidant, immunomodulating, and metabolic effects that are likely important in the mitigation of infections. (12-16)

Some patients are intolerant to melatonin, having very disturbing and vivid dreams; in these patients, it may be best to start with a 1-2 mg slow-release tablet and increase slowly, as tolerated. Melatonin undergoes significant first-pass metabolism in the liver with marked individual variation; this explains the wide dosing requirement. Slow- or extended-release preparations are preferred, as this minimizes the risk of bad dreams.

Hydrocortisone

A number of studies have found benefits for corticosteroids when included as part of general septic shock management, improving clinical outcomes such as time to shock reversal and ventilator-free days. (17-20)

The biological basis for including hydrocortisone in this treatment approach is based on potential synergies between ascorbic acid and hydrocortisone. Glucocorticoid binding to glucocorticoid receptors is negatively affected by oxidizing molecules. Ascorbic acid has been shown to restore glucocorticoid receptor function. (21)

Vitamin C

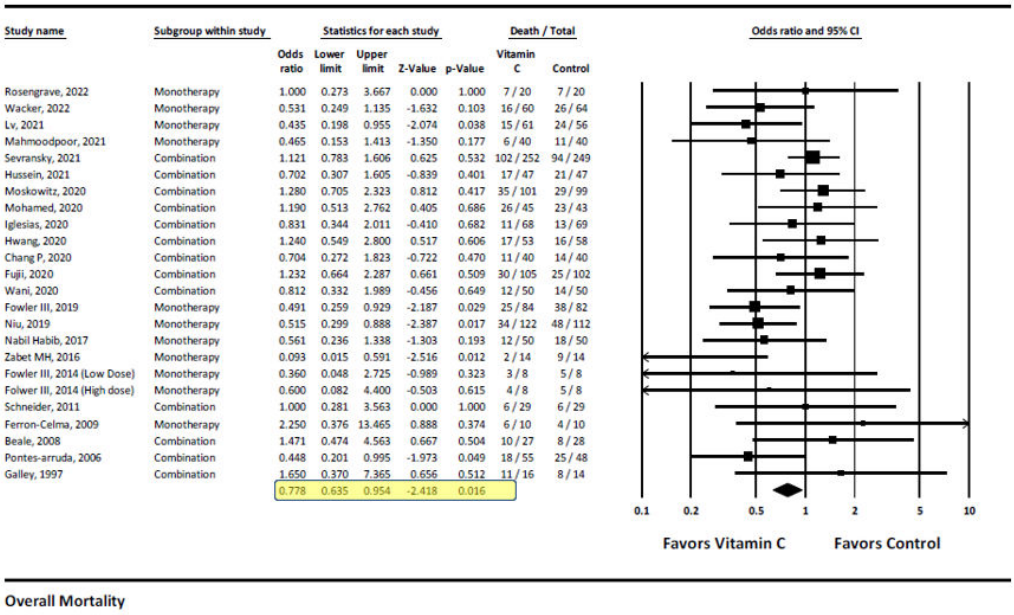
Ascorbic acid (Vitamin C) is a water-soluble vitamin that the body uses for a number of essential processes. It is a powerful antioxidant that scavenges free radicals and limits the oxidation of mitochondrial proteins, enzymes, lipoproteins, and cell membranes. Its antioxidant effects also improve micro- and macrovascular function and encourage wound healing.

Vitamin C also benefits the immune system, reducing inflammatory mediators, regulating macrophage function, supporting lymphocyte proliferation, increasing neutrophil bacteriocidal action, improving chemotaxis, stimulating interferon production, and decreasing T regulatory cells (Tregs). (22)

The meta-analysis below by Muhammed et al (Table 2) demonstrates that vitamin C significantly reduces the risk of death in patients with sepsis.

Article

The Role and Efficacy of Vitamin C in Sepsis: A Systematic Review and Meta-Analysis



Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Vitamin C	Control
Rosengrave, 2022	Monotherapy	1.000	0.273	3.667	0.000	1.000	7 / 20	7 / 20
Wacker, 2022	Monotherapy	0.531	0.249	1.135	-1.632	0.103	16 / 60	26 / 64
Lv, 2021	Monotherapy	0.435	0.198	0.955	-2.074	0.038	15 / 61	24 / 56
Mahmoodpoor, 2021	Monotherapy	0.465	0.153	1.413	-1.350	0.177	6 / 40	11 / 40
Sevransky, 2021	Combination	1.121	0.783	1.606	0.625	0.532	102 / 252	94 / 249
Hussein, 2021	Combination	0.702	0.307	1.605	-0.839	0.401	17 / 47	21 / 47
Moskowitz, 2020	Combination	1.280	0.705	2.323	0.812	0.417	35 / 101	29 / 99
Mohamed, 2020	Combination	1.190	0.513	2.762	0.405	0.686	26 / 45	23 / 43
Iglesias, 2020	Combination	0.831	0.344	2.011	-0.410	0.682	11 / 68	13 / 69
Hwang, 2020	Combination	1.240	0.549	2.800	0.517	0.606	17 / 53	16 / 58
Chang P, 2020	Combination	0.704	0.272	1.823	-0.722	0.470	11 / 40	14 / 40
Fujii, 2020	Combination	1.232	0.664	2.287	0.661	0.509	30 / 105	25 / 102
Wani, 2020	Combination	0.812	0.332	1.989	-0.456	0.649	12 / 50	14 / 50
Fowler III, 2019	Monotherapy	0.491	0.259	0.929	-2.187	0.029	25 / 84	38 / 82
Niu, 2019	Monotherapy	0.515	0.299	0.888	-2.387	0.017	34 / 122	48 / 112
Nabil Habib, 2017	Monotherapy	0.561	0.236	1.338	-1.303	0.193	12 / 50	18 / 50
Zabet MH, 2016	Monotherapy	0.093	0.015	0.591	-2.516	0.012	2 / 14	9 / 14
Fowler III, 2014 (Low Dose)	Monotherapy	0.360	0.048	2.725	-0.989	0.323	3 / 8	5 / 8
Folwer III, 2014 (High dose)	Monotherapy	0.600	0.082	4.400	-0.503	0.615	4 / 8	5 / 8
Schneider, 2011	Combination	1.000	0.281	3.563	0.000	1.000	6 / 29	6 / 29
Ferron-Celma, 2009	Monotherapy	2.250	0.376	13.465	0.888	0.374	6 / 10	4 / 10
Beale, 2008	Combination	1.471	0.474	4.563	0.667	0.504	10 / 27	8 / 28
Pontes-arruda, 2006	Combination	0.448	0.201	0.995	-1.973	0.049	18 / 55	25 / 48
Galley, 1997	Combination	1.650	0.370	7.365	0.656	0.512	11 / 16	8 / 14
		0.778	0.635	0.954	-2.418	0.016		

Muhammed M, et al. *Adv Resp Med* 2022;90:281

Table 2: A Meta-analysis of the role of Vitamin C in the Treatment of Sepsis

Thiamine

Thiamine (also known as vitamin B1) is a water-soluble vitamin that is critical to the metabolic processes of cells. Critically ill patients are often deficient in thiamine, and this deficiency may be associated with a higher risk of mortality. Administering thiamine during critical illness may improve organ function. (23)

Beriberi, a disease caused by thiamine deficiency, affects the cardiovascular or central nervous systems and bears several similarities to sepsis, including peripheral vasodilation, cardiac dysfunction, and elevated lactate levels. (24)

Zinc

Zinc is the second most abundant mineral in the body after iron and plays a crucial role in immune function. Since the body is unable to store zinc, it must be supplemented. Zinc not only supports a healthy immune system, it also promotes cell growth and tissue repair to aid in wound healing and is essential for the synthesis of proteins, which in turn help with the growth and repair of tissues.

Quercetin

Quercetin is a plant phytochemical (flavonoid) with broad-spectrum anti-inflammatory, antioxidant, antiviral, anticoagulant, and immune-modulatory properties. In addition, quercetin is a zinc ionophore, meaning it transports zinc particles across the cell wall barrier into the center of the cell, where zinc has the greatest effect on the immune system.

The major limitation of supplemental quercetin is its poor solubility and low oral absorption. (25) A lecithin-based formulation (Quercetin Phytosome®, Life Extension Bio-Quercetin) and a nanoparticle formulation have shown markedly improved bioavailability.

Curcumin/Nano-curcumin

Curcumin, the active ingredient in turmeric, has anti-inflammatory and immune-modulating properties. Curcumin has low solubility in water and is poorly absorbed by the body; consequently, it is traditionally taken with full-fat milk and black pepper, which enhance its absorption. Nano-curcumin preparations or formulations designed to enhance absorption are recommended. Due to the rare complication of hepatic injury (hepatitis), long-term treatment (more than 14 days) is not suggested.

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