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The Role of Antioxidants in Sepsis Management: A Review of Therapeutic Applications

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Abstract

Sepsis represents a life-threatening clinical condition characterized by a dysregulated host response to infection leading to organ dysfunction. It affects approximately 49 million people worldwide each year and contributes to an estimated 11 million deaths, accounting for 19.7% of global deaths. Despite the global decline in mortality rates, approximately 25% of patients still succumb to sepsis and hospital mortality in septic shock, a subset of sepsis, approaches 60%. Sepsis not only triggers a multifaceted immune imbalance involving both pro- and anti-inflammatory pathways, but also induces coagulation and complement cascades that collectively contribute to progressive tissue damage and multi-organ dysfunction. While advances have been made in the treatment of sepsis, mortality remains significantly high, ranging from 20% to 80%. The outcome of sepsis can be influenced by numerous factors, including the overall health status of the patient, the severity of sepsis, the organ systems affected and the timing of treatment initiated. Despite the potential of antioxidants such as melatonin, N-Acetylcysteine, vitamin C, vitamin E and selenium to manage oxidative stress in sepsis, further randomized controlled trials are warranted to clarify their dosage, timing and duration of administration and thereby improve our understanding and effective use of these agents in sepsis management. This review aims to examine the relationship between sepsis and antioxidants, specifically focusing on the role of antioxidants in the pathophysiology of sepsis and their potential therapeutic applications.

Keywords: Sepsis, Mortality Rates, Antioxidant Therapy, Septic Shock, Organ Dysfunction.

Introduction

Sepsis is a life-threatening clinical condition characterized by widespread physiological and biochemical disturbances. The Third International Consensus (Sepsis-3) defines sepsis as "organ dysfunction caused by a dysregulated host response to infection" and emphasizes for the first time the vital role of the innate and adaptive immune response in the development of the clinical syndrome (1). Approximately 49 million people are affected by sepsis each year, with an estimated 11 million deaths caused by the syndrome, up to 19.7% of all deaths (2). Globally, although mortality rates seem to be decreasing on

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average, 25% of patients still succumb to sepsis. Septic shock is a subgroup of sepsis characterized by circulatory, cellular and metabolic abnormalities, with a hospital mortality rate approaching 60% (3).

In contrast to an uncomplicated and localized infection, sepsis is a multifaceted disruption of the finely tuned immune balance of inflammation and anti-inflammation. Upregulation of pro- and anti-inflammatory pathways leads to system-wide release of cytokines, mediators and pathogen-related molecules, resulting in activation of coagulation and complement cascades (4). Recognition of pathogen-derived molecular patterns (PAMPs, e.g. endo- and exotoxins, lipids or DNA sequences) or endogenous host-derived danger signals (damage-associated molecular patterns; DAMPs) is the initial signal. These molecules activate specific receptors (toll-like receptors, TLRs) on the surface of antigen-presenting cells (APCs) and monocytes, thus initiating the clinical syndrome of sepsis through transcription of genes involved in inflammation, cell metabolism and adaptive immunity. As both pro-inflammatory and anti-inflammatory pathways are upregulated, the resulting inflammation leads to progressive tissue damage and ultimately causes multi-organ dysfunction. In many patients, concomitant immunosuppression caused by downregulation of activating cell surface molecules, increased apoptosis of immune cells and T cell exhaustion leads to "immunoparalysis" in the later stages of the disease, rendering affected patients susceptible to nosocomial infections, opportunistic pathogens and viral reactivation (5, 6).

This review aims to examine the relationship between sepsis and antioxidants, especially the role of antioxidants in the pathophysiology of sepsis and their potential therapeutic applications. Furthermore, the efficacy of antioxidants in the treatment of sepsis and the current scientific evidence in this field will also be discussed.

Clinical Features: Sepsis is usually characterized by prominent clinical signs such as fever, tachycardia and tachypnea, but these symptoms are far from specific and can also occur with various types of infection and other inflammatory conditions. Especially in elderly patients, these classic signs may be more vague or completely absent. Patients with sepsis often show neurologic signs such as changes in consciousness, confusion and agitation. This may be more pronounced especially in elderly individuals and in patients with immunodeficiency (7) .

Effects on the cardiovascular system are characterized by hypotension and increased heart rate, which means that circulation is compromised and tissues are not adequately perfused. This can lead to organ dysfunction and potentially life-threatening conditions. In particular, renal dysfunction in patients with sepsis can manifest as oliguria or anuria and increased serum creatinine levels. Hepatic dysfunction may be indicated by elevated bilirubin and transaminases, reflecting the involvement of the liver in the inflammatory response and removal of toxins (7, 8). The respiratory system may be severely affected during sepsis, resulting in rapid respiration and hypoxemia. Pulmonary infiltrates may be among the radiologic findings, especially in pulmonary infections such as bacterial pneumonia. Hematologically, sepsis has been associated with coagulopathy and disseminated intravascular coagulation (DIC), which can lead to hemorrhagic complications and microvascular thrombosis (9). There is a wide spectrum of clinical features of sepsis and this may vary depending on factors such as the patient's immune status, age, comorbid conditions, and the agent and site of infection. Therefore, early diagnosis and management of sepsis requires careful evaluation of clinical findings and laboratory data and rapid implementation of appropriate treatment strategies.

Sepsis and Mortality: Influencing Factors and Management Strategies: Despite new developments in the treatment of sepsis, the mortality

rate is high. Mortality rates have been reported to be between 20% and 80%. The different mortality rates reported in these studies are due to the heterogeneity of the study groups. The mortality rate is 45-50% in gram-negative bacterial sepsis, 20-30% in gram-positive bacterial sepsis and 15-30% in anaerobic sepsis. When shock, disseminated intravascular coagulation (DIC), Acute Respiratory Distress Syndrome (ARDS) and other organ failure complications develop, mortality rates range from 70% to 90%. Mortality rates also vary depending on the cause. The highest mortality rate has been reported in Pseudomonas aeruginosa sepsis (10).

The outcomes of sepsis vary depending on a number of factors including the general health status of the patient, severity of sepsis, affected organ systems and how early treatment is initiated. Sepsis may result in severe morbidity and mortality, especially if not recognized and managed early. The prognosis is often serious, especially in patients with septic shock and multiple organ failure. Septic shock can severely affect the patient's cardiovascular system, resulting in low blood pressure, low tissue perfusion and ultimately organ failure (7). Multiple organ failure is a common complication in patients with sepsis and may have serious effects on the kidneys, liver, lungs and other vital organs.

Many studies on sepsis outcomes have shown that early diagnosis and management, especially rapid initiation of appropriate antimicrobial therapy, can significantly improve patient outcomes. However, the management of patients with sepsis is not limited to early antibiotic therapy. Hemodynamic support, strategies to protect and support organ function, and appropriate supportive care are also critical (11).

In terms of long-term outcomes, patients who have survived sepsis may experience physical, cognitive and psychological problems. This condition, known as post-sepsis syndrome, is characterized by decreased quality of life, physical dysfunction and cognitive decline. In addition, patients with sepsis are at high risk for recurrent infections and long-term mortality (12).

Physiopathology: Sepsis is characterized by infectious agents and the systemic inflammatory response syndrome (SIRS) they trigger. The pathophysiology of sepsis is determined by the entry of microorganisms and their toxins into the body, followed by activation of inflammatory and immune responses. This process involves the release of proinflammatory and anti-inflammatory cytokines, coagulation factors and a number of other bioactive molecules (Figure 1).

The body develops a series of complex responses to infectious agents. This response is directed at destroying pathogens, regulating inflammation and repairing tissues. However, in the case of sepsis, this response can be excessive and dysregulated, often leading to harmful and potentially fatal consequences.

Innate immunity serves as the body's first line of defense against pathogens. During sepsis, immune cells such as macrophages and neutrophils phagocytize pathogens and release inflammatory mediators. However, over-activation can lead to systemic inflammation and endothelial damage.

Sepsis also has a significant impact on the coagulation system. Proinflammatory cytokines trigger a cascade that results in endothelial damage and thrombin generation. This can lead to microvascular thrombosis, disseminated intravascular coagulation (DIC) and ultimately organ dysfunction.

During sepsis, the body also engages anti-inflammatory mechanisms. This is intended to stabilize and control the inflammatory response. However, this process can also lead to immunosuppression, making patients more susceptible to secondary infections.

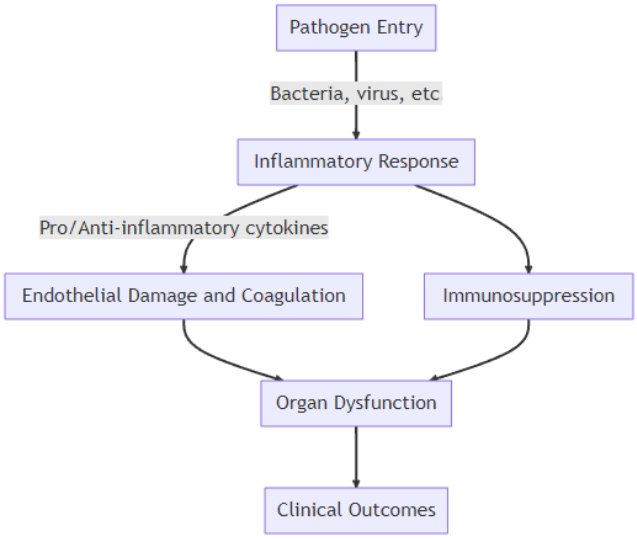

Figure 1. Pathogenesis of sepsis.

The end result of sepsis is a widespread organ failure, commonly known as multiple organ dysfunction syndrome (MODS). Disruptions in inflammatory and coagulation pathways lead to microvascular thrombosis, hypoperfusion and ultimately cellular death (13).

Treatment in Sepsis: Sepsis is a potentially life-threatening condition triggered by a serious infection in the body, leading to organ damage. Treatment of sepsis involves controlling the infection, supporting organ function and improving the general condition of the patient (Figure 2).

1. Control of Infection: Control of infection is critical in the treatment of sepsis and this is usually accomplished through two main strategies: antimicrobial therapy and control of the source of infection. In the context of antimicrobial therapy, early administration of broad-spectrum antibiotics and initial antibiotic selection considering the likely pathogens and local antibiotic resistance patterns are of vital importance (14). After the initial 48-72-hour treatment period, the antibiotic regimen should be re-evaluated according to clinical response and culture results and narrowed if necessary (15). The optimal duration of antibiotic treatment usually varies between 7-10 days, depending on the source of infection, pathogen and clinical response of the patient (16). On the other hand, the infection source control strategy involves surgical removal of infection sources such as infected devices or necrotic tissue (17). Procedures such as drainage of infected fluid collections and gastrointestinal decontamination may also be important in infection control (18). Furthermore, management of infected catheters and other medical devices plays a critical role in controlling infection and preventing secondary infections (19).

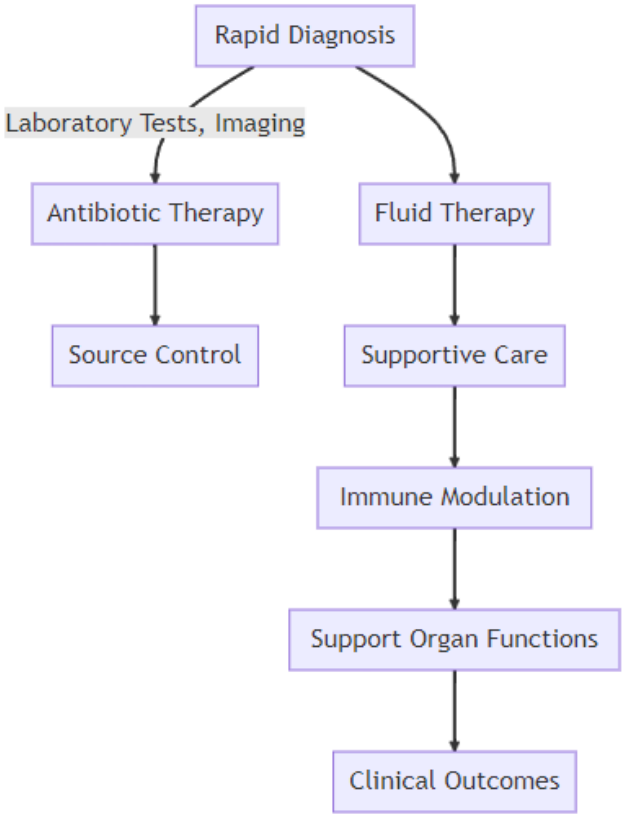

Figure 2. Treatment of Sepsis.

2. Hemodynamic Support and Fluid Management: Sepsis increases vascular permeability, leading to decreased intravascular volume and consequently hypotension, which compromises organ perfusion and can potentially lead to multiple organ dysfunction. Fluid resuscitation is generally considered the first step, which aims to stabilize the patient's hemodynamic status and optimize organ perfusion (20). Fluid therapy should be

guided by dynamic and static hemodynamic monitoring to assess the patient's volume status and perfusion (21). However, fluid management should be cautious because excessive fluid resuscitation may lead to complications, especially pulmonary edema and abdominal hypertension (22). Vasopressor agents, especially noradrenaline, are used in patients who do not respond to fluid resuscitation to maintain adecuate perfusion pressure (23). In addition, inotropic support (e.g. dobutamine) is also required in patients with myocardial dysfunction or characterized by low cardiac output despite fluid resuscitation and vasopressors (11). Hemodynamic support strategies should be individualized and continuously evaluated depending on the patient's clinical condition and response.

3. Organ Support: Respiratory Support: Acute Respiratory Distress Syndrome (ARDS) is a common complication in patients with sepsis, leading to alveolar damage, impaired oxygenation and the need for mechanical ventilation. From a physiologic perspective, using low tidal volumes (6 ml/kg ideal body weight) may reduce ventilator-related lung injury and this approach has reduced mortality in patients with ARDS (24). Positive end-expiratory pressure (PEEP) helps prevent alveolar collapse and improve oxygenation, but there is no consensus on the optimal level of PEEP and this requires titration according to the patient's hemodynamic status and oxygenation response (25).

Renal Support: Sepsis is frequently associated with acute kidney injury (AKI), which can lead to a number of complications including electrolyte imbalance, acidosis and fluid imbalance. Hemodialysis and continuous renal replacement therapies (CRRT) can support renal function and optimize metabolic homeostasis (26). CRRT may be preferred in hemodynamically unstable patients because it provides more stable fluid balance and azotemia control. Hemodialysis may provide faster azotemia control and better fluid output in more stable patients, but there is no clear evidence on the effect of these methods on mortality (27).

4. Metabolic and Nutritional Support: Sepsis leads to a significant increase in energy expenditure and thus catabolism, resulting in protein breakdown, loss of muscle mass and malnutrition. Physiologically, meeting patients' energy and protein requirements is critical to prevent muscle atrophy and promote recovery. Enteral nutrition is generally preferred to preserve gastrointestinal function and prevent bacterial translocation (28). However, optimal energy and protein intake is still a matter of debate in patients with sepsis and may require titration according to the metabolic status and requirements of individual patients (29).

5. Immunomodulation: Sepsis both superactivates and suppresses the immune system, putting the patient at risk for secondary infections and nosocomial infections. Immunomodulation can help the body fight infection more effectively by modulating macrophage activation, cytokine release and T cell function. However, the use of immunomodulatory agents should be cautious, especially regarding which patients will benefit from this treatment and which agents should be used. Several studies have investigated the role of immunomodulation in patients with sepsis, but the data in this area are complex and more research is needed (30).

Role of Antioxidant Therapy in Sepsis: Sepsis leads to the triggering of an excessive inflammatory response in the body and overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These reactive species can cause various biological damages associated with oxidative stress, such as lipid peroxidation, protein modification and DNA damage. Oxidative stress has been directly associated with cellular damage, organ dysfunction and death in sepsis (Figure 3) (31).

Antioxidants are components that can neutralize the harmful effects of ROS and RNS and thus reduce oxidative stress. In the context of sepsis, antioxidants can be used to reduce cell damage, modulate the inflammatory response and potentially improve patient prognosis (7, 31, 32). However, the role and efficacy of antioxidants in the treatment of sepsis is still being actively investigated in the current scientific literature.

Mitochondrion-targeted antioxidants (MitoQ, MitoE): Their Potential in Sepsis Management and ROS Mitigation: Given the significant role of the mitochondrial respiratory chain as a primary source of ROS in living cells and the notable involvement of mitochondrial dysfunction in the pathogenesis of sepsis, there's a growing interest in antioxidants targeting the intra-mitochondrial environment. This might be pivotal in mitigating the deleterious effects of sepsis. Many antioxidants are tethered to lipophilic cations like triphenylphosphonium (TPP) to enhance their penetration and concentration in the mitochondria. This is due to the high negative potential inside the inner mitochondrial membrane, which can lead to an increase in their accumulation by 100 to 500-fold (33).

In specific studies, administering mitochondrion-targeted antioxidants like MitoQ or MitoE, and melatonin, to rats infused with LPS/peptidoglycan G, has shown substantial improvements.

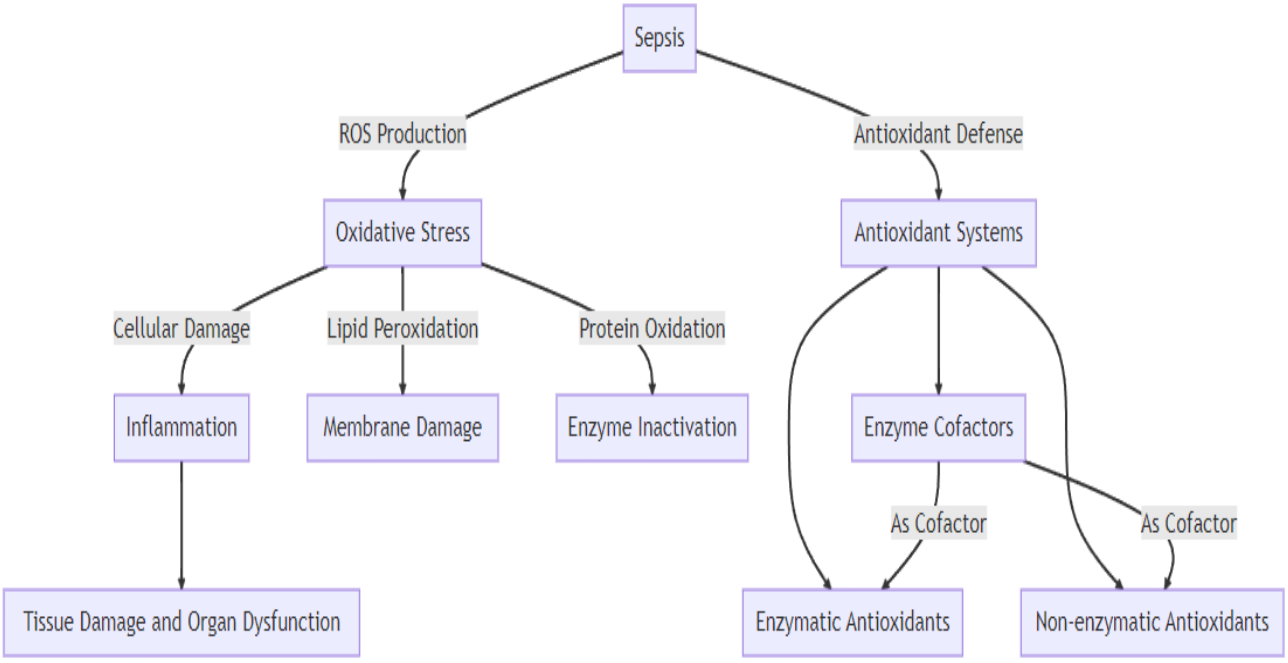

Figure 3. The role of antioxidant systems and enzyme cofactors in the management of sepsis and ROS generation.

These encompass better mitochondrial respiration, reduced oxidative stress, and diminished IL-6 levels due to the infused bacterial cell wall components. Additionally, antioxidant-treated rats demonstrated decreased plasma alanine amino-transferase and creatinine concentrations compared to their untreated counterparts (34). In another experiment, rats injected with LPS and treated with MitoQ exhibited prevention of endotoxin-induced reductions in cardiac mitochondrial function. Notably, this led to ameliorated oxygen consumption by cardiomyocytes, improved contractile functions, and reduced formation of protein carbonyl groups in cardiac tissue (35). Furthermore, long-term administration of MitoQ in mice primarily accumulated in the heart without manifesting symptoms of general toxicity or other

negative metabolic effects. Intriguingly, this long-term administration was associated with a decrease in visceral fat deposits and a reduction in plasma triglycerides (36). In particular, studies on the potential role of antioxidants such as vitamin C, melatonin, N-Acetylcysteine and vitamin E in the management of sepsis and septic shock provide important information in this regard (37-41) .

Melatonin's Protective Role in Sepsis: Oxidative Stress Mitigation and Cellular Restoration: Melatonin is known for its free radical scavenging properties and protects cell membrane lipids, cytosol proteins and nuclear and mitochondrial DNA. Melatonin administration has been observed to significantly reduce lipid peroxidation. The favorable effects of melatonin on sepsis have been associated with inhibition of apoptotic processes and reduction of oxidative stress (38, 39, 42). However, the mechanisms of action of melatonin are not yet fully known and more research is needed in this regard. In a separate research led by Escames et al., the potential therapeutic benefits of melatonin were assessed using an in vivo sepsis model in mice through cecal ligation and puncture (CLP). Findings revealed that sepsis led to an upregulation of iNOS and mtNOS expressions, which coincided with oxidative stress, disturbances in the respiratory chain, and diminished ATP generation, even though ATPase concentrations remained unchanged. Notably, the increase in mtNOS was linked to mitochondrial malfunctions specifically in the cardiac region. Importantly, administering melatonin mitigated the elevated expressions of iNOS/mtNOS triggered by sepsis, conserved mitochondrial balance during septic conditions, and reinstated ATP synthesis (43). In a related experiment involving rats subjected to the CLP method, sepsis led to a decline in GSH concentrations while causing a surge in MDA levels and increased MPO activity, indicating heightened neutrophil clustering. This was observed across multiple tissues including the liver, kidney, heart, lung, diaphragm, and brain. Concurrently, there was a rise in plasma AST, ALT, BUN, and Creatine levels. However, when the rats were treated with melatonin (10mg/kg i.p.) both 30 minutes before and 6 hours post-surgery, notable changes were observed. Specifically, the antioxidant effectively negated the heightened MDA levels across all examined tissues. It restored GSH concentrations to near-normal in the liver, kidney, diaphragm, and brain, although not in the heart and lungs. Furthermore, MPO activity was decreased across all tissues, and there was a significant reduction in elevated AST, ALT, BUN, and Cre values. The researchers posited that melatonin's ability to replenish GSH concentrations and curtail neutrophil accumulation might be behind these observed benefits (44).

N-Acetylcysteine (NAC): A Potential Antioxidant Shield Against Sepsis-Induced Organ Dysfunction and Inflammation: N-acetylcysteine (NAC), another antioxidant, has demonstrated protective qualities in sepsis scenarios. N-Acetylcysteine (NAC) can increase antioxidant capacity and shows a trend towards increasing glutathione (GSH) levels, but this difference is not statistically significant (45). NAC may reduce organ failure, confirming previous findings (46). In a particular study, NAC was given to subjects 20 minutes following the induction of sepsis via LPS injection. Throughout the subsequent 48 hours, researchers closely observed the mean arterial pressure (MAP) and HR. Key biochemical metrics, such as BUN, Cre, LDH, CPK, ALT, AST, TNF-a, IL-6, and IL-10 levels, were assessed. Results indicated that LPS introduction led to marked increases in BUN, Cre, LDH, CPK, ALT, AST, TNF-a, IL-6, and IL-10 levels, alongside HR, while causing a drop in MAP. Intriguingly, NAC administration counteracted some of these changes: it helped moderate the MAP decline, temper the HR surge, and reduce both organ injury indicators (like BUN, Cre, LDH, CPK, ALT, and AST)

and inflammatory markers (including TNF-a, IL-6, and IL-10) attributable to sepsis (47). In a separate study, NAC was administered an hour prior to exposing rats to endotoxin. Observations revealed that NAC reduced lung NF-kB activation in a dose-responsive manner (ranging from 200 to 1000 mg/kg) and curtailed cytokine-induced neutrophil chemoattractant mRNA expression within lung tissues. Consequently, NAC appears to lessen the pulmonary inflammatory response by suppressing NF-kB activity, offering potential relief from certain sepsis-associated respiratory issues (48).

The Roles of Vitamins, Polyphenols, and Other Nutritional Interventions: Common antioxidants, including vitamins C and E, have shown effectiveness in alleviating sepsis effects across multiple organs. The use of vitamin C in sepsis and septic shock is remarkable, especially in relation to its effects on organ dysfunction and mortality. Vitamin E tends to reduce lipid peroxidation (LPO) and carbonylation. This vitamin protects cell membranes from LPO and terminates the chain reaction. It also acts as an O2- and OH scavenger. Other antioxidants, such as polyphenols, β-glucan and antioxidants targeting mitochondria, selenium salts and selenium organ compounds may also be effective in ameliorating oxidative stress in sepsis (49).

In patients with sepsis, initially low vitamin C levels are frequently observed and this has been associated with organ failure and mortality (50). With the administration of vitamin C, restoration of normal vitamin levels and improvement in organ function have been observed. In particular, statistically significant differences were found with Vitamin C administration in patients with pneumonia (51, 52). However, the CITRIS-ALI study showed that Vitamin C administration did not improve in patients with acute respiratory distress syndrome (ARDS) and organ failure (53). These different results may be related to factors such as the timing of treatment initiation. A study involving rats revealed that administering ascorbic acid post-sepsis led to mitigated impacts on several liver functions and molecular markers. Notably, the mRNA expression of certain inflammatory indicators and hepatic enzymes was balanced with ascorbic acid treatment (54). Another study showed that both vitamin C, when given post-sepsis, and vitamin E, when provided before the septic event, stabilized liver functions and certain enzyme activities (55).

In separate research, the protective effect of b-glucan against sepsis-induced oxidative damage in rats was explored. Administered both pre and post a CLP procedure, b-glucan was found to effectively counteract the oxidative stress markers and tissue damages that sepsis typically causes (56).

Regarding nutritional interventions, a study on patients with severe sepsis showcased the potential of an antioxidant-rich liquid diet named ANOM1. Rich in polyphenols and essential vitamins and trace elements, ANOM1 was continuously infused to patients. Findings revealed that this diet not only enhanced vitamin C concentrations but also reduced oxidative stress markers, hinting at its potential to mitigate multi-organ failure in septic shock patients (57).

Roles and Implications of Selenium in Sepsis Management and Treatment Outcomes: Selenium stands as a vital micronutrient, playing a role in the function of over 30 selenoproteins . These proteins offer a range of biological roles, notably including cellular antioxidant defense, the regulation of thyroid hormones, and contributions to both the humoral and cellular branches of immunity. Breaking down serum selenium distribution, selenoprotein P (SePP) holds around 60%, GSH-Px carries about 30%, and albumin contains between 5-10%. The GSH-Px set of proteins is essential for reducing various hydroperoxides and collaborates with vitamin E to combat lipid peroxidation. The family of thioredoxin reductase enzymes aids in the transformation of H2O2

to water. During sepsis-induced endothelial dysfunction, SePP sticks to the endothelial cells, possibly as a protective action against oxidative stress-induced harm (58). Under catabolic conditions, the rate at which selenium is expelled through urine rises. There are observations suggesting that selenoproteins can suppress NF-κB through redox cellular signaling, thus cutting back on ROS/RNS production and the associated cytokine surge. Patients in critical condition due to sepsis often display diminished selenium levels (59) Measurements below 0.7 μmol/L have been linked to increased death rates and organ failures in ICU patients [6]. Kočan et al. [57] suggested that supplemental treatment using a constant 750 μg/24 h dosage of sodium selenite might offer advantages for septic patients grappling with acute lung injury (60). However, there's an ongoing debate over the solitary use of selenium as a therapeutic solution for sepsis. Kong et al. conducted a meta-analysis, revealing that while adding selenium to the primary treatment for severe sepsis or septic shock didn't alter mortality after 28 days, it did correlate with reduced overall mortality(61).

Conclucions

Sepsis remains a major source of morbidity and mortality worldwide. This complex and multifaceted condition leads to an excessive and dysregulated inflammatory response triggered by infection and ultimately organ dysfunction. Management of sepsis involves multiple components including infection control, hemodynamic support, organ support therapies, and appropriate nutritional and metabolic support. The key to sepsis treatment is early diagnosis and rapid intervention, because the earlier treatment is initiated, the more favorable the patient's prognosis.

Antioxidants can potentially play an important role in the management of sepsis, as these agents can reduce oxidative stress, which is prominent in sepsis and leads to cell damage, organ dysfunction and potentially death. Antioxidants such as melatonin, N-Acetylcysteine, vitamin C, vitamin E and selenium have shown promising results in models of sepsis and septic shock, but the clinical efficacy of these agents is still unclear and further research is needed.

Future research should consider factors such as dosage of antioxidants, timing of administration and duration of treatment, and more randomized controlled trials should be conducted to evaluate the clinical efficacy of these agents in sepsis and septic shock. In addition, the long-term outcomes and effects of antioxidants on quality of life in patients with sepsis should also be examined.

These and other novel strategies in the management of sepsis and septic shock may help optimize treatment and improve outcomes in this serious and common condition. However, more high-quality clinical research is needed to evaluate the efficacy and safety of these strategies. This will shape future advances in the management of sepsis and septic shock and provide critical information to help tackle these challenging conditions.

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Acknowledgements

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