

Emerging Adjunctive Approach for the Treatment of Sepsis: Vitamin C and Thiamine

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KEYWORDS

• Sepsis • Septic shock • Adjuvant treatment • Vitamin C • Thiamine

KEY POINTS

- Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection.”
- Sepsis affects approximately 1.5 million people each year in the United States.
- Sepsis is the most expensive condition being treated in US hospitals, costing more than \$24 billion in 2014.
- Vitamin C has been hypothesized to be a cost-effective and novel adjuvant therapy that can be used to ameliorate the effects of inflammation and oxidative stress in sepsis.

INTRODUCTION

Sepsis is a clinical condition that remains highly lethal. It is most often seen in critically ill patients and trauma victims. Sepsis and septic shock is a systemic and dysregulated inflammatory response to infection that can lead to hemodynamic instability, multiple organ dysfunction syndrome, and death.

In the late 1970s, it was estimated that 164,000 cases of sepsis occurred in the United States each year.¹ Since the 1970s, it is reported that rates of sepsis globally have increased.^{2–4}

Today, according to the Centers for Disease Control and Prevention (CDC) 2017⁵

- More than 1.5 million people get sepsis each year in the United States
- About 250,000 Americans die from sepsis each year
- One in three patients who die in a hospital has sepsis
- A CDC evaluation found 7 in 10 patients with sepsis had recently used health care services or had chronic diseases requiring frequent medical care

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The incidence of sepsis is rising for several different reasons: the aging population, the increase in the use of invasive and immunosuppressive treatments in the older patient, and the increase in education and awareness campaigns for sepsis.^{1,6–8} Neonates, the elderly, and those with weakened immune systems are most likely to get sepsis. Patients aged 65 years or older account for the majority (60%–85%) of all incidence of sepsis.¹ It is also highly likely that the incidence of sepsis will continue to increase in the future because of the aging population.^{1,7} Unfortunately, treatment for sepsis is significantly challenging and is becoming even more so as drug-resistant infections become more widespread. According to the Agency for Healthcare Research and Quality, sepsis is the most expensive condition being treated in US hospitals, costing more than \$24 billion in 2014.⁹

Sepsis and Septic Shock Defined

In 2016, a new definition of sepsis, Sepsis-3, was published in *The Journal of the American Medical Association (JAMA)*. This published definition presented a drastic change from the prior sepsis definitions published in 1991 (Sepsis-1) and 2001 (Sepsis-2). The Sepsis-3 consensus definition makes no division between sepsis and the condition described by Sepsis-2 as severe sepsis (that is, sepsis with acute organ dysfunction).¹⁰ According to the Sepsis-3 consensus, sepsis and severe sepsis are synonymous terms; therefore, currently there are only sepsis and septic shock.¹⁰ The new classifications define sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection. Septic shock is currently defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities substantially increase mortality.¹⁰ The new definitions for sepsis and septic shock reveal significant advances made in the pathophysiology, management, and epidemiology of sepsis. These concise definitions describe the life-threatening conditions more precisely and are aimed at achieving greater precision and consistency in how sepsis is diagnosed, reported, and treated.¹⁰

Pathophysiology

The normal host response to infection is a multifaceted process that confines and controls a bacterial invasion as the injured tissue begins to heal.¹¹ Sepsis results when the response to the infection becomes systemic and affects normal tissues and organ systems distant from the initial injury or infection.¹¹ Patients then present an immune response that starts the activation of biochemical cytokines and mediators associated with an inflammatory response. Proinflammatory and antiinflammatory cytokines released during the inflammatory response directly influence the endothelium, cardiovascular, hemodynamic, and coagulation mechanisms.¹¹ It is known that widespread distribution of proinflammatory mediators play an important role in the pathogenesis and high morbidity and mortality associated with sepsis. The immune system goes into overdrive, overwhelming normal processes in the blood. Increased capillary permeability and vasodilation interrupt the body's ability to provide adequate perfusion, oxygen, and nutrients to the tissues and cells. The result is that small blood clots form, blocking blood flow to vital organs, which often lead to complete organ failure.¹¹ In addition to the imbalance of the inflammatory response, major vitamins are overwhelmingly consumed. An excessive inflammatory response indeed enhances metabolic turnover of vitamin C. As a result, patients with severe sepsis often have very low plasma vitamin C levels that sometimes enter the "scurvy" zone.¹¹

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