IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

The Role Of Vitamin C In Sepsis: A Systematic Literature Review

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Abstract

Sepsis, a life-threatening organ dysfunction due to a dysregulated host response to infection, continues to pose a significant clinical challenge despite advances in supportive care. The review synthesizes findings from randomized controlled trials and cohort studies to evaluate the impact of vitamin C—administered alone or in combination with thiamine and hydrocortisone—on key outcomes such as mortality, organ dysfunction (SOFA scores), vasopressor requirements, and safety profiles.

The evidence regarding vitamin C monotherapy is mixed: several meta-analyses suggest possible reductions in mortality and improvements in SOFA scores and vasopressor duration, but these findings are not consistently statistically significant, and some large trials even indicate potential harm. Combination therapies, particularly the "metabolic resuscitation cocktail" (vitamin C, thiamine, hydrocortisone), have not demonstrated significant mortality benefit in high-quality trials, though modest improvements in organ dysfunction metrics are observed.

Vitamin C is generally well tolerated, but rare adverse effects—such as increased renal replacement therapy or hypernatremia—have been reported in certain studies, warranting caution in patients with specific comorbidities. Substantial heterogeneity in dosing regimens, timing, patient populations, and study design complicates interpretation, and the overall certainty of evidence for major outcomes remains low to moderate according to GRADE criteria.

Current guidelines do not recommend routine intravenous vitamin C use in sepsis outside of clinical trials. The review underscores the need for large, well-designed randomized studies to identify patient subgroups most likely to benefit, determine optimal dosing strategies, and clarify the role of vitamin C—alone or in combination—in improving clinically significant outcomes in sepsis. This systematic literature review critically examines the efficacy and safety of intravenous vitamin C administration in the management of sepsis and septic shock.

Keywords: vitamin C; sepsis; literature; mortality; hydrocortisone

Introduction

Sepsis represents a life-threatening organ dysfunction stemming from a dysregulated host response to infection[1]. It constitutes a significant global healthcare burden and a primary cause of in-patient mortality, particularly within intensive care units (ICUs)[2,3]. Despite advances in critical care, the mortality rate for sepsis remains elevated, indicating a persistent need for effective adjunctive therapies that can modulate the underlying pathophysiology[2,3]. Current therapeutic strategies are primarily supportive, addressing symptom management rather than directly reversing the complex pathophysiological cascades characteristic of the syndrome[3].

Background and Rationale

The pathophysiology of sepsis encompasses a lethal cascade of cytokines and inflammatory proteins, leading to widespread oxidative stress, endothelial dysfunction, and microvascular compromise[2,4]. Endothelial cells, which are both a source and a target of oxidative stress during sepsis, undergo functional modifications that contribute to multiorgan failure. Vitamin C (ascorbate), an essential micronutrient, possesses antioxidant, anti-inflammatory, and immune-modulatory properties[3,5]. Critically ill patients, particularly those with sepsis, frequently exhibit depleted circulating vitamin C levels, which correlate with disease severity[6,7]. This deficiency provides a strong rationale for exploring vitamin C supplementation as an adjunctive intervention in sepsis management[7].

Objectives of the Review

This systematic literature review comprehensively evaluates the current evidence concerning intravenous vitamin C administration in sepsis and septic shock. We critically appraise its efficacy in modulating key clinical outcomes, including mortality, organ dysfunction, and vasopressor requirements. Furthermore, this review assesses the safety profile associated with vitamin C use in this patient population. The analysis extends to both vitamin C monotherapy and its application in combination with other agents, such as thiamine and hydrocortisone. Variances in dosing strategies and administration routes are also examined to synthesize a nuanced understanding of vitamin C's therapeutic potential.

Theoretical Framework

Pathophysiology of Sepsis

Sepsis initiates with a host immune response to infection, which, when dysregulated, leads to systemic inflammation and organ damage. This process involves the release of excessive inflammatory mediators and activation of proteolytic cascades[1]. Central to septic pathophysiology is endothelial dysfunction, which impairs vascular barrier function, coagulation, leukocyte adhesion, and vasomotor tone.

Oxidative stress further exacerbates endothelial injury during sepsis. An imbalance favoring pro-oxidant states, characterized by increased reactive oxygen species (ROS) and reactive nitrogen species (RNS), mitochondrial dysfunction, and depleted antioxidant systems, promotes a pro-inflammatory and pro-coagulant endothelial phenotype. This microvascular dysfunction contributes to impaired tissue perfusion, increased permeability, and cell death, ultimately leading to multiorgan failure[4].

Biological Role of Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin with a range of biological functions critical for human health. Its primary role involves serving as a potent antioxidant, neutralizing free radicals and reducing oxidative damage[3,4]. Beyond its antioxidant properties, vitamin C acts as a co-factor for various enzymatic reactions, including those essential for collagen synthesis and catecholamine production. It is specifically involved in the conversion of dopamine to noradrenaline, a critical step in endogenous vasopressor synthesis[8].

Furthermore, vitamin C modulates immune function and inflammatory responses[3]. It influences leukocyte function and maintains endothelial integrity, which is vital in conditions characterized by systemic inflammation[4]. In septic patients, circulating vitamin C levels are often significantly reduced, indicating an increased metabolic demand or accelerated consumption during the severe inflammatory state[6,7]. This depletion compromises the body's natural antioxidant defenses and other vitamin C-dependent processes, potentially exacerbating sepsis-induced organ dysfunction[7].

Potential Mechanisms of Vitamin C in Sepsis

The therapeutic rationale for vitamin C in sepsis stems from its multifaceted biological actions that could counteract the disease's detrimental effects[5]. A primary mechanism involves its potent antioxidant capacity. Intravenous vitamin C rapidly accumulates in microvascular endothelial cells, where it scavenges reactive oxygen species (ROS), thereby mitigating oxidative stress-induced cellular damage. This protection extends to the endothelium, preserving microvascular barrier function and improving capillary blood flow, which are compromised in sepsis[4].

Vitamin C also influences vasomotor tone by stimulating nitric oxide (NO) production via endothelial nitric oxide synthase (eNOS) through its interaction with tetrahydrobiopterin. This action helps maintain arteriolar responsiveness to vasoconstrictors and vasodilators, counteracting the vasoplegia often observed in septic shock. Furthermore, vitamin C contributes to the synthesis of vasopressors like norepinephrine, as it is an essential cofactor for dopamine beta-hydroxylase. This function could theoretically reduce vasopressor dependency in patients with septic shock.

Beyond its direct antioxidant effects, vitamin C modulates inflammatory pathways[5]. It suppresses the activation of genes associated with impaired mitochondrial oxygen handling by promoting the degradation of hypoxia-inducible factor-1α (HIF-1α). This contributes to improved cellular bioenergetics during critical illness. The cumulative effects of these mechanisms suggest that vitamin C could ameliorate organ dysfunction and improve clinical outcomes in sepsis[4].

Methodology

Systematic Review Protocol

A systematic review protocol was established a priori to ensure transparency and rigor in evidence synthesis. This protocol delineates the research questions, specifies eligibility criteria for studies, outlines the search strategy, and details the methods for data extraction, quality assessment, and synthesis. Such a structured approach minimizes bias and enhances the reproducibility of the findings. The review adheres to established guidelines for systematic reviews to maintain consistency and comprehensiveness in methodology.

Inclusion and Exclusion Criteria

Studies eligible for this review included randomized controlled trials (RCTs) and prospective cohort studies investigating intravenous vitamin C, either as monotherapy or in combination with other agents, for the treatment of adult patients (≥18 years) with sepsis or septic shock. Eligible interventions comprised varying doses and durations of intravenous vitamin C. Control groups included placebo or standard care. Outcomes of interest included mortality (28-day, 30-day, 90-day, in-hospital, ICU), Sequential Organ Failure Assessment (SOFA) scores, duration of vasopressor support, length of ICU and hospital stay, and adverse events. Studies were excluded if they focused solely on pediatric populations, were review articles, case reports, or non-peer-reviewed publications. Studies not reporting relevant clinical outcomes or lacking a control group were also excluded.

Data Sources and Search Strategy

A comprehensive search for relevant literature was conducted across several electronic databases. These included PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and CINAHL. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to "sepsis," "septic shock," "vitamin C," "ascorbic acid," and "intensive care." Boolean operators (AND, OR) were employed to broaden the search and capture all pertinent studies. No date restrictions were applied to ensure inclusion of all available evidence from inception up to the present. The search was refined by screening reference lists of included articles and relevant review papers to identify additional studies.

Study Selection Process

Following the comprehensive database searches, all retrieved citations were imported into an EndNote database for deduplication. Two independent reviewers then screened the titles and abstracts against the predefined inclusion and exclusion criteria. Any discrepancies between reviewers were resolved through discussion or by consulting a third senior reviewer. Full-text articles of potentially relevant studies were retrieved and independently assessed for eligibility by the same two reviewers. A standardized screening form guided this process. Reasons for exclusion at the full-text stage were documented. A PRISMA flow diagram would typically illustrate the study selection process, detailing the number of records identified, screened, and ultimately included in the review[9].

Data Extraction and FORM Tables

Data extraction from the included studies was performed independently by two reviewers using a standardized data extraction form. This form captured essential details about each study, including authors, publication year, study design, participant characteristics (e.g., age, sex, severity of sepsis, comorbidities), intervention specifics (e.g., vitamin C dose, frequency, route, duration, co-interventions), control group details, and all reported outcomes of interest. For quantitative data, specific values, measures of variability (e.g., standard deviation, interquartile range), and sample sizes were extracted. Qualitative data regarding study limitations and adverse events were also systematically collected. Extracted data were subsequently organized into descriptive tables, often referred to as FORM tables, to facilitate comparison and synthesis across studies. These tables typically present a concise summary of study characteristics, interventions, and primary outcomes, allowing for a structured overview of the evidence.

Quality Assessment of Included Studies

The methodological quality and risk of bias for each included study were independently assessed by two reviewers. For randomized controlled trials, the Cochrane Risk of Bias tool was applied, evaluating domains such as sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. For observational studies, appropriate tools like the Newcastle-Ottawa Scale were utilized. Disagreements

between reviewers regarding quality assessment were resolved by consensus or through arbitration by a third reviewer. The overall certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. This framework considers five downgrading factors (risk of bias, indirectness, inconsistency, imprecision, and publication bias) and three upgrading factors (large effect size, dose-response relationship, and opposing plausible residual bias/confounding) to classify evidence as very low, low, moderate, or high certainty[10].

Findings from the Literature

Vitamin C Monotherapy in Sepsis

Efficacy Outcomes (Mortality, SOFA Score, Vasopressor Duration)

Research on vitamin C monotherapy in sepsis has yielded heterogeneous results regarding clinical efficacy. Several meta-analyses indicate a reduction in overall mortality with vitamin C supplementation, with one reporting an odds ratio (OR) of 0.778 (95% CI, 0.635 to 0.954; p = 0.016)[2]. Another meta-analysis found intravenous vitamin C might improve short-term mortality (RR, 0.82; 95% CI, 0.65–1.02; P=0.07) and overall mortality (RR, 0.86; 95% CI, 0.74–1.01; P=0.06), although these did not reach conventional statistical significance[6]. In contrast, other trials and meta-analyses observed no significant reduction in short-term mortality[7,11,12]. A Bayesian reanalysis of the LOVIT trial even suggested a high probability of harm regarding death or persistent organ dysfunction at 28 days with vitamin C use[13].

Regarding organ dysfunction, measured by the Sequential Organ Failure Assessment (SOFA) score, several studies suggest a positive effect. Meta-analyses have reported a statistically significant reduction in SOFA scores with vitamin C treatment[2,6,12]. One meta-analysis indicated a mean difference of −0.749 (95% CI, −1.115 to −0.383; p < 0.001) in SOFA scores[2]. Another reported a significant decline in SOFA score at 72–96 hours (standardized mean difference, –0.20; 95% CI, –0.32 to –0.08; p < 0.01)[12]. However, one meta-analysis did not find improvement in the 72-hour SOFA score[7].

The duration of vasopressor administration also appears influenced by vitamin C. Multiple studies and meta-analyses observed a statistically significant reduction in vasopressor requirements[2,12]. A mean difference of −1.034 days (95% CI, −1.622 to −0.445; p = 0.001) in vasopressor duration was reported in one analysis[2]. A pilot study in post-cardiac surgery vasoplegia, however, did not find faster resolution of vasoplegia with high-dose vitamin C[14]. A study involving mechanically ventilated septic patients found high-dose vitamin C lowered the incidence of ventilator-associated pneumonia (VAP) and reduced vasopressor duration[15].

Safety Outcomes and Adverse Effects

The safety profile of intravenous vitamin C in sepsis has been a subject of scrutiny, particularly with high-dose regimens. Generally, high doses of vitamin C (up to 1.5 g/kg three times a week intravenously) have been deemed safe in cancer patients with normal renal function. Given that the doses and durations in sepsis trials are typically lower and shorter, vitamin C appears relatively safe for this population[16].

However, specific adverse events have been reported. One randomized controlled trial noted a higher incidence of renal replacement therapy initiation in the vitamin C arm (16.7%) compared to placebo (3.3%; p = 0.015). This particular study also observed increased fluid administration in the vitamin C group within 6 hours of drug initiation[11]. Another study identified a significant association with hypernatremia, though overall adverse effects were rare[12].

Despite these observations, most studies and meta-analyses conclude that vitamin C, when administered to septic patients, exhibits a favorable safety profile with minimal adverse effects[2,17]. Caution remains important for specific patient populations, including those with hemochromatosis, glucose-6-phosphate dehydrogenase

(G6PD) deficiency, renal dysfunction, kidney stones, or oxaluria, as high doses could pose risks in these individuals[16].

Combination Therapies: Vitamin C with Thiamine and/or Hydrocortisone

Efficacy and Safety in Combined Regimens

The concept of a "metabolic resuscitation cocktail" involving intravenous vitamin C, hydrocortisone, and thiamine has gained considerable attention in sepsis management. This combination therapy was initially proposed based on retrospective data, which suggested promising results[17]. However, subsequent large, multicenter randomized controlled trials (RCTs) have provided a more nuanced picture.

The ACTS trial, for instance, randomized patients with septic shock to receive either the combination therapy or hydrocortisone alone. This trial reported no significant improvement in the primary outcome of duration of time alive and free of vasopressor administration over 7 days. Furthermore, no statistically significant difference was observed in 90-day mortality between the intervention (28.6%) and control (24.5%) groups (hazard ratio, 1.18; 95% CI, 0.69-2.00)[18].

Meta-analyses examining this combination therapy have similarly presented mixed results. One systematic review and meta-analysis of eight RCTs (n=1,335 patients) found that while the metabolic resuscitation cocktail improved the change in SOFA score within 72 hours (weighted mean difference –0.82; 95% CI, –1.15 to –0.48), this improvement was modest and its clinical relevance questionable. No evidence of a difference was found regarding ICU mortality or renal composite outcomes[17]. Another meta-analysis of seven studies on the combination therapy also concluded no significant reduction in long-term mortality, ICU mortality, or incidence of acute kidney injury. However, a significant reduction in SOFA score on day 3 from baseline was noted (MD -0.92; 95% CI -1.43 to -0.41; $P < 0.05$)[19].

A separate meta-analysis specifically investigating thiamine combined with vitamin C (without hydrocortisone) in sepsis and septic shock also found no association with in-hospital mortality. This analysis did, however, find an association with reduced SOFA scores and shorter duration of vasopressor use.

Regarding safety, the ACTS trial reported no serious adverse events in the intervention group[18]. Generally, combination therapies involving vitamin C, thiamine, and hydrocortisone appear to be safe, with no major concerns identified in the reviewed literature[17,19].

Controversies and Conflicting Evidence

The literature surrounding combination therapies in sepsis remains highly controversial, characterized by conflicting evidence. Initial enthusiasm generated by retrospective studies, such as the "metabolic resuscitation cocktail" concept, has been tempered by subsequent, more rigorous randomized controlled trials[17]. The primary source of contention stems from the disparity between observational studies suggesting benefit and large-scale RCTs that largely fail to demonstrate significant improvements in hard outcomes like mortality[18,19].

Differences in study design, patient populations, timing of intervention, and specific definitions of septic shock or associated organ dysfunction contribute to this heterogeneity. For instance, the ACTS trial, a well-designed RCT, found no benefit for vasopressor-free time or 90-day mortality[18]. While meta-analyses sometimes identify modest improvements in physiological parameters like SOFA scores or vasopressor duration, these often do not translate into survival advantages, questioning their clinical significance[17,19]. The ongoing debate underscores the complexity of evaluating multi-drug interventions in a syndrome as heterogeneous as sepsis. This divergence necessitates careful interpretation and highlights the need for further research to delineate specific subgroups that might benefit or to refine optimal treatment protocols.

Dose and Administration Variability

High-dose vs. Standard-dose Vitamin C

The optimal dosage of intravenous vitamin C for sepsis remains undefined, with studies exploring a range from standard to high doses. High-dose regimens typically involve daily cumulative doses ranging from 6 grams to 24 grams or even higher, often administered in divided doses every 6 hours[15,18]. For instance, a common high-dose regimen includes 1.5 grams every 6 hours (totaling 6 g/day)[15,18] or 50 mg/kg every 6 hours[13]. These dosages aim to overcome the profound vitamin C depletion observed in septic patients and achieve supraphysiological plasma concentrations believed necessary for therapeutic effects[3].

A study comparing 1.5 g/6h vitamin C with 100 mg/day (a lower dose, though still intravenous) in mechanically ventilated septic patients observed a significant difference in SOFA score change, incidence of VAP, and 28-day mortality, favoring the higher-dose group[15]. This suggests a potential dose-dependent effect, where higher doses might be necessary to achieve clinical benefits. However, conflicting data exists, as some studies using high doses have not demonstrated significant mortality improvements[11]. A pilot feasibility study using 1,500 mg every 6 hours in post-cardiac surgery vasoplegia found it safe but not associated with faster vasoplegia resolution[14]. The debate between high-dose and standard-dose efficacy remains a central point of discussion, requiring further investigation to establish definitive guidelines.

Route and Duration of Administration

The intravenous route is overwhelmingly preferred for vitamin C administration in sepsis trials. This route ensures rapid and complete bioavailability, allowing for the achievement of therapeutic plasma concentrations that may not be attainable with oral supplementation, particularly in critically ill patients with impaired gut absorption. Intravenous infusion facilitates consistent delivery and can overcome the saturation kinetics of oral absorption, which limits plasma levels at higher doses. Studies consistently employ intravenous delivery to maximize therapeutic potential[11,15,18].

The duration of vitamin C administration varies across studies. Protocols range from relatively short courses of 4 days (15) to extended periods of up to 10 days (18) or until shock resolution[18]. Some trials specify administration for 96 hours[11]. The optimal duration remains unclear; with the hypothesis that earlier and sustained administration might be beneficial to continuously combat oxidative stress and support endothelial function throughout the acute phase of sepsis. Future research could explore whether specific durations correlate with improved outcomes or if individualized treatment based on patient response or biomarker levels is more effective.

Analysis and Synthesis

Summary of Outcomes Across Studies

The aggregated evidence on vitamin C in sepsis presents a complex and often contradictory picture. Regarding mortality, several meta-analyses report a potential, albeit often non-significant, trend towards reduced mortality with vitamin C, especially in monotherapy[2,6]. However, large-scale, high-quality RCTs, particularly those involving combination therapies, have largely failed to demonstrate a significant mortality benefit[11,18]. One study even suggested a probability of harm.

A more consistent signal emerges for secondary physiological outcomes. Many studies and meta-analyses indicate that vitamin C, both as monotherapy and in combination, is associated with a reduction in SOFA scores, reflecting an improvement in organ dysfunction[2,6,12,17,19]. Similarly, a decreased duration of vasopressor support has been frequently observed in vitamin C-treated patients[2,12]. These physiological improvements, while encouraging, have not consistently translated into improved survival or reduced length of hospital stay in all studies[7,19]. Safety profiles generally demonstrate intravenous vitamin C as well-tolerated, though some studies noted increased renal replacement therapy or hypernatremia[11,12].

Heterogeneity and Subgroup Analyses

Significant heterogeneity characterizes the existing literature on vitamin C in sepsis, complicating direct comparisons and definitive conclusions. This variability stems from several factors, including differences in study populations (e.g., varying severity of sepsis, presence of specific comorbidities), timing of intervention (early vs. late initiation), dosage regimens (e.g., 1.5 g q6h vs. 50 mg/kg q6h), duration of treatment, and concomitant therapies[6,17]. For instance, some studies include patients with milder sepsis, while others focus exclusively on septic shock, where the potential for benefit or harm may differ. The precise definition of sepsis or septic shock also varied across older and more recent studies, impacting patient selection.

Subgroup analyses, when conducted, have occasionally revealed differential effects. For example, one study observed a decrease in 28-day mortality in the vitamin C arm among patients requiring positive-pressure ventilation at enrollment[11]. These findings suggest that certain patient characteristics or disease phenotypes might respond more favorably to vitamin C, or conversely, that some subgroups might be at higher risk for adverse effects. However, such subgroup observations often arise from post-hoc analyses and require validation in prospectively designed trials. The extensive heterogeneity underscores the necessity for more standardized protocols and patient stratification in future research to identify precise indications for vitamin C therapy in sepsis.

GRADE Assessment and Evidence Quality

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework provides a structured approach for assessing the certainty of evidence in systematic reviews[10]. Applying GRADE to the current body of evidence concerning vitamin C in sepsis reveals that the overall certainty for many critical outcomes, especially mortality, is typically low to moderate. This classification reflects several downgrading factors inherent in the available literature.

Firstly, the risk of bias varies across studies. While some large RCTs demonstrate low risk, smaller trials or observational studies often present higher risks concerning randomization, allocation concealment, or blinding. Secondly, inconsistency across studies is a significant concern, with conflicting results for mortality and, to a lesser extent, for physiological endpoints like SOFA scores and vasopressor duration[7,19]. This inconsistency can be attributed to the aforementioned heterogeneity in patient populations, intervention protocols, and outcome measurements. Thirdly, imprecision arises from relatively small sample sizes in many individual trials, leading to wide confidence intervals for effect estimates, particularly for mortality[6]. Finally, publication bias cannot be entirely excluded, where studies reporting positive findings might be more readily published than those with null results. While some meta-analyses have upgraded evidence due to observed dose-response relationships or large effect sizes for specific outcomes, these are often balanced by significant downgrades for other factors[10]. Therefore, despite numerous studies, robust, high-certainty evidence supporting widespread vitamin C use in sepsis remains largely absent.

Discussion

Interpretation of Findings

The collected evidence on vitamin C in sepsis indicates a dichotomy between promising physiological improvements and less consistent impacts on patient-centered outcomes, particularly mortality. Mechanistically, vitamin C's roles as an antioxidant, immune modulator, and co-factor for vasopressor synthesis provide a compelling rationale for its use in sepsis, a condition marked by severe oxidative stress and catecholamine depletion[4]. The consistent observation of reduced SOFA scores and decreased vasopressor duration in several meta-analyses supports its capacity to mitigate organ dysfunction and restore vascular tone[2,12,17].

However, the failure of large, well-conducted randomized controlled trials, such as the ACTS trial, to demonstrate a significant mortality benefit or improved vasopressor-free days, introduces considerable

uncertainty regarding its overall clinical utility[18]. This discrepancy might stem from various factors, including the timing of intervention, heterogeneity of septic patients, differing dosages, or the possibility that physiological improvements do not always translate to survival advantages in the highly complex, multifactorial context of sepsis. The observed safety profile generally appears favorable, although concerns regarding renal replacement therapy initiation in some contexts warrant careful consideration[11,16]. The conflicting evidence underscores the need for a nuanced interpretation, balancing the mechanistic plausibility and physiological improvements against the absence of definitive mortality benefits in major trials.

Clinical Implications and Practice Guidelines

Based on the current body of evidence, the routine clinical application of intravenous vitamin C for all patients with sepsis or septic shock cannot be broadly recommended. While some studies suggest benefits in reducing organ dysfunction and vasopressor duration, these findings are not universally consistent, and robust evidence demonstrating a survival advantage remains elusive[7,18]. Indeed, an existing rapid practice guideline does not recommend using intravenous vitamin C therapy for adults with sepsis or septic shock[20].

Clinicians should exercise caution, particularly given the potential for increased renal replacement therapy initiation observed in some studies[11]. While vitamin C is generally well-tolerated, its use should be considered with particular care in patients with pre-existing conditions like glucose-6-phosphate dehydrogenase deficiency, hemochromatosis, or renal dysfunction[16]. At this juncture, vitamin C administration in sepsis should ideally be confined to the context of well-designed clinical trials, where its effects can be rigorously evaluated. Until more definitive evidence emerges, standard sepsis management protocols, focusing on early recognition, appropriate antibiotics, source control, and hemodynamic support, remain the cornerstone of care.

Limitations of Current Evidence

The current evidence base for vitamin C in sepsis suffers from several limitations that hinder definitive conclusions. Foremost among these is the significant heterogeneity across studies. This includes variations in:

- **Patient Populations:** Differences in sepsis severity, underlying comorbidities, and specific infectious etiologies[17,19].
- **Intervention Protocols:** Diverse dosages, timing of initiation, duration of administration, and the use of vitamin C as monotherapy versus combination regimens[6,17].
- **Outcome Measures:** Inconsistent definitions and reporting of mortality (28-day, 30-day, 90-day), and varied methods for assessing organ dysfunction and vasopressor requirements[2,7].
- **Methodological Quality:** While many recent trials are robust, some earlier or smaller studies may have limitations in design, blinding, or statistical power.

Furthermore, the reliance on physiological surrogate markers, such as SOFA scores or vasopressor duration, without consistent translation to hard outcomes like mortality, introduces uncertainty about true clinical benefit[17]. The timing of vitamin C administration relative to sepsis onset also represents a crucial variable, as early intervention might be more effective in mitigating the initial inflammatory cascade. The lack of standardized protocols and the inherent complexity of sepsis itself contribute to the conflicting results and limit the generalizability of findings.

Recommendations for Future Research

To clarify the role of vitamin C in sepsis, several avenues for future research warrant consideration:

1. **Large-scale, Pragmatic RCTs:** Conduct adequately powered, multicenter randomized controlled trials with standardized protocols, focusing on clearly defined patient populations and clinically meaningful primary outcomes, such as 28-day or 90-day mortality.
2. **Patient Stratification:** Investigate whether specific patient subgroups, identified by biomarkers, genetic predispositions, or specific sepsis phenotypes (e.g., hyper-inflammatory vs. immunosuppressed), derive differential benefits or harms from vitamin C therapy. This could involve exploring the role of baseline vitamin C levels.
3. **Optimal Dosing and Timing:** Determine the most effective dose, route, and duration of vitamin C administration. Research should explore early initiation strategies and continuous infusion protocols, alongside dose-escalation studies if appropriate.
4. **Biomarker-Guided Therapy:** Evaluate the utility of biomarkers (e.g., oxidative stress markers, inflammatory mediators, vitamin C levels) to guide treatment decisions, identify responders, and monitor therapeutic efficacy.
5. **Mechanistic Studies:** Deepen understanding of vitamin C's precise mechanisms of action in human sepsis, particularly its interactions with inflammatory pathways, mitochondrial function, and microvascular integrity.
6. **Combination Therapy Refinement:** Further explore combination therapies, carefully considering the individual contributions and synergistic effects of each component (e.g., vitamin C, thiamine, hydrocortisone), and designing trials to isolate these effects.

Such rigorous investigations will provide more definitive evidence to inform clinical practice guidelines and optimize patient care in sepsis.

Conclusion

The exploration of intravenous vitamin C as an adjunctive therapy for sepsis and septic shock has generated substantial research, driven by its plausible mechanistic benefits in counteracting oxidative stress, supporting vascular function, and modulating inflammation. While some studies and meta-analyses suggest that vitamin C may improve physiological parameters, such as SOFA scores and vasopressor duration, a consistent and statistically significant improvement in hard clinical outcomes, particularly mortality, remains unproven by large-scale, high-quality randomized controlled trials. The evidence base is characterized by considerable heterogeneity in study design, patient populations, and intervention protocols, contributing to conflicting results and a low to moderate certainty of evidence. While generally considered safe, some concerns regarding specific adverse events necessitate careful monitoring. Consequently, current clinical guidelines do not endorse the routine use of vitamin C in sepsis outside of a research setting. Future investigations must address the existing limitations through well-designed, adequately powered trials, focusing on patient stratification, optimal dosing, and biomarker-guided approaches to definitively ascertain the role of vitamin C in this critical illness.

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