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14. ABSTRACT Burn injuries represent a significant civilian and military health problem, ranking the seventh most common cause of unintentional injury. Thermal injury has constituted 5-10% of combat casualties incidences are expected to increase during future conflicts. Burn injuries cause significant tissue damage, resulting in hypovolemic shock and significant systemic inflammation, typically exceeding the body's natural antioxidant defense mechanisms, leading to multi-organ dysfunction and increased mortality. Vitamin C reduces inflammation and oxidative stress. Vitamin C is an essential, water-soluble micronutrient, is inexpensive, readily available and safe. In this multicenter, double-blind, randomized controlled trial of 666 patients with severe burns, patients will receive Vitamin C (50 mg/kg every 6 hrs for 96 hours) or placebo. We hypothesize that high dose intravenous vitamin C given in the early postburn period, in comparison with placebo, will significantly reduce organ dysfunction (e.g. kidneys, lung, and heart), mortality, and hospital length of stay, as well as improve quality of life 6 months after burn injury. This international trial already recruited >80 patients in 15 ICUs, has demonstrated to be feasible and safe and is expected to impact clinical practice to improve overall outcomes if burn injured patients worldwide.					
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1. INTRODUCTION:

We are conducting a multicentre, double-blind, randomized controlled trial of 666 (486 funded through this grant plus 180 Pilot trial patients funded from other sources) adult patients with severe burns randomly allocated to receive intravenous vitamin C (50 mg/kg every 6 hrs for 96 hours) or placebo (333 per group) to examine the effects of high dose vitamin C compared to placebo as part of resuscitation in adult patients with severe thermal burn injuries. The trial is being conducted in 40 burn units around the world. We hypothesize this inexpensive therapeutic strategy will be associated with less organ dysfunction, improved survival, and a quicker rate of recovery.

2. KEYWORDS:

Thermal burn injury, shock, vitamin C, resuscitation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Conduct a RCT of high dose IV vitamin C vs. placebo in 40 sites worldwide.

- Sub-task 1: Amend Pilot protocol and obtain regulatory approvals (months 1 – 15)
 - o Milestone: Amended protocol and consent finalized - COMPLETE
 - o Milestone: Health Canada and OHRO approval received at site #1 - COMPLETE
 - o Milestone: OHRO approval of all sites and protocols (months 1 – 15) – In Progress
 - One site is approved by OHRO to enroll in the trial and will begin recruiting patients in November 2023.
 - We are working with all other participating sites to obtain local IRB approval and subsequent OHRO approval.

Note: The pre-submission review process with the FDA was very protracted and delayed moving forward with the U.S. sites until FDA approval was received on 2023-Sep-22.

- Sub-task 2: Prepare sites to conduct the research protocol (months 1 – 15) – In Progress
 - o Milestone: All sites trained and activated (month 15) – In Progress
 - 16 sites are actively recruiting patients into the Pilot Trial. We are working with these sites to transition them to the Phase III trial.
- Sub-task 3: Conduct the study, recruit patients, collect data (months 1 – 45) – In Progress
- Sub-Task 4: Data Analysis – Not Started

What was accomplished under these goals?

The Pilot protocol and ICF were amended and submitted to regulatory authorities and approved as follows:

- Health Canada: 15-Oct-2022
- Site #1 Queen's University Health Sciences Research Ethics Board: 12-Dec-2022
- OHRO: 09-Jan-2023
- U.S. FDA: 22-Sep-2023
 - o The FDA pre-IND application was submitted 16-Feb-2023 and the initial response from the FDA was received on 17-May-2023. The following months resulted in unsubstantial changes to the protocol, and the full IND application submission 22-Aug-2023.
- EU Regulatory approval of the amended OHRO approved protocol is currently under review.
 - o This is a new, multi-step process that provides regulatory approval for all participating EU Member States. This process is longer but will result in all EU countries receiving approval.

Study procedure and training materials are prepared and being distributed to sites. Sites are being trained in preparation of activation to the Phase III Trial.

- We are behind with site activation and enrollments due to the regulatory delays above. We plan to catch up on both during the current funding year ('23 – '24),

What opportunities for training and professional development has the project provided?

- All investigators participating in this international trial were trained in formal classes to comply both Good Clinical Practice Standards and the Declaration of Helsinki, providing them with skills and certificates to conduct clinical research and to improve patient care.
 - Regular stakeholders meetings are held for researchers, providing updates towards the trial results and providing further opportunities for international research.
 - Regular meetings are held for interested researchers online or at large international conferences thereby providing valuable knowledge on the newest research in the area of burn injury and micronutrient strategies.

How were the results disseminated to communities of interest?

The regular stakeholders meeting as well as regular presentation on international conferences allows the progress of this study to be made public as well as disseminating the newest knowledge gains in this area.

What do you plan to do during the next reporting period to accomplish the goals?

Now that FDA approval has been received, we will move quickly to help Pilot Trial sites and new sites obtain local IRB approval and subsequent OHRO approval. As soon as EU Regulatory approval is received, we will work quickly with EU sites to obtain OHRO approval. With approvals, materials, and training in place, we will activate sites as soon as possible, encourage enrollments, and support sites to successfully conducting the trial. We will continue Monthly Stakeholder meetings via Zoom and continue Monthly Recruitment reporting to the Executive Committee with feedback to the sites.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The VICToRY trial did not yet impact clinical practice, but raised awareness and attracted a lot of interest in the burn and critical care, as well as nutrition communities. Our previous international, multi-center trial, RE-ENERGIZE trial, has been the largest clinical trial in this area to this day, was published in the New England Journal of Medicine, discussed at scientific meetings worldwide, and has significantly influenced current clinical practice. We expect the VICToRY trial, which is performed in the same manner and quality to do the same,

What was the impact on other disciplines?

This trial treats critically ill burn patients with a micronutrient and therefore is of great interest and relevance to all these disciplines: plastic and burn surgery, critical care medicine and medical nutrition therapy.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

We experienced significant time delays related to obtaining US FDA approval and EU Regulatory approval. We have now obtained FDA approval and initial EU Regulatory approval. The current DoD approved version of the study is under review by the EU Regulatory body with expected approval by the end of November 2023. We are actively working with sites to obtain local and OHRO approvals, provide materials and training so that sites may be activated and recruiting as quickly as possible.

Changes that had a significant impact on expenditures

Delays to site activation and recruitment have resulted in fewer than projected expenditures during this reporting period. We anticipate this will result in greater spending during the current 2023 – 2024 reporting period as more sites are activated and begin enrolling patients.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

There have not been significant changes in the approved protocol for the use or care of human subjects during this reporting period. Non-substantive changes were made to the protocol at the request of the US FDA. These revisions include the addition of references and new data related to the potential benefit of vitamin C to burn injured patients, more detailed description of events of interest, an increase from 1 to 2 interim analyses to ensure an even earlier stopping if there is a signal of harm, the addition of appendices that more fully describe the schedule of assessments and serious adverse event definitions. The revised protocol and a summary of revisions table were submitted to OHRO for review and approval. The determination was made by OHRO that these are non-substantive revisions that do not require approval.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

• Publications, conference papers, and presentations

Journal publications.

Radke DI, Homayr AL, Stoppe C, Elke G. Vitamin C in critical illness: end of the story or still a place? Curr Opin Crit Care. 2023 Aug 1;29(4):339-345. doi: 10.1097/MCC.0000000000001054. Epub 2023 Jun 9. PMID: 37306524.

Hill A, Starchl C, Dresen E, Stoppe C, Amrein K. An update of the effects of vitamins D and C in critical illness. Front Med (Lausanne). 2023 Jan 11;9:1083760. doi: 10.3389/fmed.2022.1083760. PMID: 36726354; PMCID: PMC9885715.

Lee ZY, Ortiz-Reyes L, Lew CCH, Hasan MS, Ke L, Patel JJ, Stoppe C, Heyland DK. Intravenous vitamin C monotherapy in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Ann Intensive Care. 2023 Mar 7;13(1):14. doi: 10.1186/s13613-023-01116-x. PMID: 36882644; PMCID: PMC9990974.

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

The background, concept, rationale was presented during the European Burn Association Congress in Nantes 2023 Sep.

Cancio LC, Dansereau M, Stoppe C, Pruskowski KA, Heyland DK. From RE-ENERGIZE to VICToRY: Building the first international consortium for clinical trials in burns. Submitted to Military Health System Research Symposium. Podium presentation at Military Health System Research Symposium; 2023; Kissimmee, FL.

“The VICToRY Trial” European Burn Association Meeting, Turin, Italy, September 9, 2022.

Presentation of study protocol and stakeholder meeting, Frankfurt, 09/2019

- **Website(s) or other Internet site(s)**

<https://www.criticalcarenutrition.com/> Critical Care Nutrition – an academic research organization that provides expertise in research methodology, project development, implementation and management and quality improvement initiatives in health care. Dedicated to improving nutrition practices through knowledge generation, synthesis, and translation, Dr. Heyland and his research team have partnered with researchers from around the world.

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Dr. Daren Heyland	-	no change
Dr. Leopoldo Cancio	-	no change
Dr. Christian Stoppe	-	no change
Maureen Dansereau	-	no change
Alfonso Ortiz	-	no change
Shawna Froese	-	no change
Steve Hunt	-	no change
Teddy Brown	-	no change
Xuran Jiang	-	no change
Andrew Day	-	no change

Name:	Dr. Aileen Hill
Project Role:	co-PI, Executive Committee member
Researcher ID:	ORCID 0000-0002-7013-3357
Person month worked:	1
Contribution:	Dr. Hill has provided input on the trial design and study protocol, review and feedback of/to regulatory agencies including the U.S. FDA, guidance and decisions related to study implementation and operation.
Funding Support:	In kind

Name:	Kaitlin Pruskowski, PharmD
Project Role:	Content Expert, Executive Committee member
Researcher ID:	ORCID: 0000-0003-3262-6457
Person month worked:	1
Contribution:	Dr. Pruskowski has provided expert input, review and feedback of/to regulatory agencies including the U.S. FDA, guidance and decisions related to study implementation and operation, specifically related to pharmacy procedures, guidance, and training.
Funding Support:	In kind

Name:	Ellen Dresen
Project Role:	European Project Management
Person month worked:	6
Contribution:	Ms. Dresen has worked on preparation of German and European regulatory documents, German site communication, training, and support, and general project management tasks in Germany.
Funding Support:	DFG (German funding)

Name:	Michael Melak
Project Role:	European Project Management
Person month worked:	6
Contribution:	Mr. Melak worked on preparation of German and European regulatory documents, German site communication, training, and support, and general project management tasks in Germany.
Funding Support:	DFG (German funding)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Sites:

- Hôpital l'Enfant-Jésus, Quebec, QC, Canada
- Hôtel Dieu de Montréal – CHUM, Montréal, QC, Canada
- Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico
- Merheim Medical Center, Cologne, Germany
- Harborview Medical Center, Seattle, WA
- The Ohio State University Medical Center, Columbus, OH
- Bridgeport Hospital, Bridgeport, CT
- University of Iowa, Iowa City, IA
- Mercy Hospital, St. Louis, Mo
- UT Southwestern, Dallas, TX
- Arizona Burn Center, Phoenix, AZ
- BG Klinik Ludwigshafen, Germany
- RWTH Aachen University, Aachen, Germany
- Queen Elizabeth II Hospital, Halifax, NS Canada
- Grand Hôpital de Charleroi, Belgium
- Ghent University Hospital, Belgium

Financial support:

- U.S. DoD (Department of Defense)
- Lotte & John Hecht Memorial Foundation, Canada
- DFG (Deutsche Forschungsgemeinschaft), Germany

Product support:

- McGuff Pharmaceuticals, Inc., California (vitamin C)
- Nova Biomedical (glucometers)

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

FY24_Quad_Chart_VICToRY_2023.09.29 attached as appendix 'f'.

9. APPENDICES:

- a.* Radke, DI et al 2023 – Vitamin C in critical illness, end of the story or still a place
- b.* Hill, A et al 2023 – An update of the effect of vitamins D and C in critical illness
- c.* Lee, ZY et al 2023 – Intravenous vitamin C monotherapy in critically ill patients
- d.* Cancio, LC et al - From re-energize to VICToRY – *presentation*
- e.* VICToRY Monthly Recruitment Report_2023-Sep
- f.* FY24_Quad_Chart_VICToRY_2023.09.29



Vitamin C in critical illness: end of the story or still a place?

David I. Radke^a, Anna Lulu Homayr^a, Christian Stoppe^{b,c} and Gunnar Elke^a

Purpose of review

Critical illness is associated with decreased micronutrient levels, including vitamin C, an essential antioxidant for systemic inflammation. This review discusses the most recent evidence of high-dose vitamin C monotherapy in critically ill adults.

Recent findings

Three randomized-controlled trials (RCTs) were published in 2022. A pilot study including 40 patients with septic shock could not detect significant differences in outcome parameters after administering vitamin C. A multicenter study with 124 septic patients showed no significant difference in 28-day mortality, while vitamin C was associated with an increased risk of acute kidney dysfunction. The LOVIT trial, an international prospective RCT in 872 septic patients, revealed an increased risk of the composite endpoint persistent organ dysfunction plus death at day 28 in the high-dose vitamin C group. Six systematic reviews and meta-analyses (SRMA), including up to 4740 patients published before and 2 SRMA publications including these RCTs showed divergent results on clinical endpoints including mortality.

Summary

The use of high-dose intravenous vitamin C cannot be recommended for the septic critically ill in clinical practice since the LOVIT trial. Further research is needed to evaluate its potential role in other critically ill patients.

Keywords

micronutrient, oxidative stress, pharmaconutrition, sepsis, vitamin C

INTRODUCTION

The water-soluble vitamin C, or ascorbic acid, is an essential micronutrient that must be ingested to maintain an adequate blood plasma level of more than 50 $\mu\text{mol/l}$ since endogenous production is impossible. In more detail, hypovitaminosis C starts at plasma levels less than 23 $\mu\text{mol/l}$ and a deficiency is defined as less than 11 $\mu\text{mol/l}$. To perpetuate plasma levels, a daily intake of 95–110 mg/day is recommended for healthy, nonsmoking adults [1]. Plasma levels below 20 $\mu\text{mol/l}$ may result in early symptoms of an inadequate vitamin supply [2]. Once orally administered, vitamin C is absorbed in the intestine via the symport carrier SVCT1 (sodium-dependent vitamin C transporter 1), followed by renal filtration and reabsorption in the proximal tubule. Cellular uptake into metabolic active tissues is performed by SVCT2 [3]. High intake and vitamin C concentrations in the plasma impair intestinal absorption and renal reabsorption, resulting in diminished utilization of the orally administered and an elevated

renal excretion rate of vitamin C, respectively [4]. As an essential cofactor of many enzymes, vitamin C is involved in synthesizing hormones and transmitters such as cortisol and catecholamines, as well as endothelial function, regulation of the vascular tone, and iron or folic acid metabolism [5] (Fig. 1). Yet, its best-known function is the protection from reactive oxygen species (ROS) as an antioxidant and ROS scavenger in the cytosol or extracellular space [6]. It also

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KEY POINTS

- The positive pleiotropic effects of vitamin C in the presence of frequently low plasma levels form the biochemically plausible rationale for its therapeutic use in critical illness.
- High-dose vitamin C specific adverse event rate is reported to be infrequent and involves artificial hyperglycemia, nephropathy and kidney stones in the critically ill.
- Most recent evidence of two randomized controlled trials (RCTs) revealed that high-dose i.v. vitamin C is associated with an increased risk of organ dysfunction plus mortality in sepsis while controversy concerning clinical outcome still prevails from SRMAs.
- Currently, recruiting trials will show if a high-dose vitamin C supplementation may be helpful for distinct subpopulations of critical illness.
- Although high-dose vitamin C cannot be recommended in patients with sepsis and septic shock, doses recommended for healthy individuals to secure daily intake should still be provided with medical nutrition therapy in the critically ill to allow an optimal function of the body's immune defense mechanisms.

reduces oxidized vitamin E in the plasma membrane, interacting synergistically [7]. Vitamin C is also thought to play an epigenetic and transcriptomic reprogramming role via its demethylation activity and as a cofactor of enzymes associated with DNA methylation, thereby impacting acute and chronic inflammation [8]. Critically ill patients, especially those suffering from sepsis, inflammation or other conditions of oxidative stress, have subnormal plasma levels of vitamin C due to increased metabolic consumption for antioxidant and anti-inflammatory processes, reduced absorption due to intestinal dysfunction, inefficient recycling of vitamin C metabolites, and increased losses due to medically necessary treatment measures [e.g., drainage, medication, renal replacement and extracorporeal membrane oxygenation (ECMO)] [9,10]. These findings have led to replenishing any deficiency to guarantee an optimal function of the body's immune defense mechanisms or even to attain supraphysiologic plasma levels of vitamin C in terms of pharmaconutrition [9,10]. At high daily doses, the vitamin C metabolite oxalate is excreted renally, which can cause epithelial or tubular cell damage. Impaired renal function may otherwise lead to the crystallization of calcium oxalate with the consecutive stone formation and nephropathy [11]. A scoping review from 2020 including 74 studies and 2801 adult patients receiving high-dose

vitamin C at a median dose of 22.5 g/day (455 mg/kg/day) reported ≥ 932 adverse events with high heterogeneity in the event rate among studies and no consistent evidence that high-dose vitamin C therapy is more harmful than placebo [12]. Besides oxalate nephropathy, adverse event reports included hypernatremia and glucometer error (false-high blood glucose).

While several recent studies and systematic reviews and meta-analyses (SRMA) elaborated on vitamin C therapy in combination with hydrocortisone and thiamine (HAT therapy) also within the last 12–18 months [13–15], no statistically significant effects of this combined antioxidative cocktail could be demonstrated [16,17]. This review provides an overview of recently published data focusing on (high-dose) intravenous monotherapy with vitamin C in critical illness.

RANDOMIZED-CONTROLLED TRIALS

Table 1 provides an overview of the three RCTs reviewed below according to the PICO format. The first double-blinded RCT in 2022 investigating the impact of vitamin C administration in septic shock included 40 patients as a pilot study [18[¶]]. Rosengrave *et al.* elaborated on diverse outcomes with 25 mg/kg vitamin C every 6 h for up to 96 h compared to placebo. Of note, all patients' baseline vitamin C status was deficient (median 9.2 $\mu\text{mol/l}$). Although vitamin C supplementation restored the deficit (median 264 $\mu\text{mol/l}$ after 24 h, median 408 $\mu\text{mol/l}$ after 72 h), plasma levels in the placebo arm decreased further (median 4.4 $\mu\text{mol/l}$ after 72 h). Regarding the multiple endpoints of this study, none of them reached statistical significance. The mean duration of vasopressor therapy was 48 h in the vitamin C and 54 h in the placebo group ($P=0.54$). Only shorter but nonsignificant lengths of intensive care unit (ICU) and hospital stay were observed. Interestingly, co-administration of hydrocortisone did not significantly alter the duration of vasopressor therapy. No adverse events occurred.

In a multicenter, double-blinded RCT, Wacker *et al.* [19^{¶¶}] included 167 adult patients within 24 h of vasopressor initiation for septic shock treatment randomized to either i.v. vitamin C (10 mg/ml in normal saline) administered as a 1000-mg bolus over 30 min followed by continuous infusion of 250 mg/h for 96 h or placebo of equal volumes of normal saline. In total, 124 patients could be included in the final analysis, with the primary outcome of all-cause 28-day mortality being lower in the vitamin C arm without reaching statistical significance (vitamin C 26.7%, placebo 40.6% $P=0.10$). In a post hoc

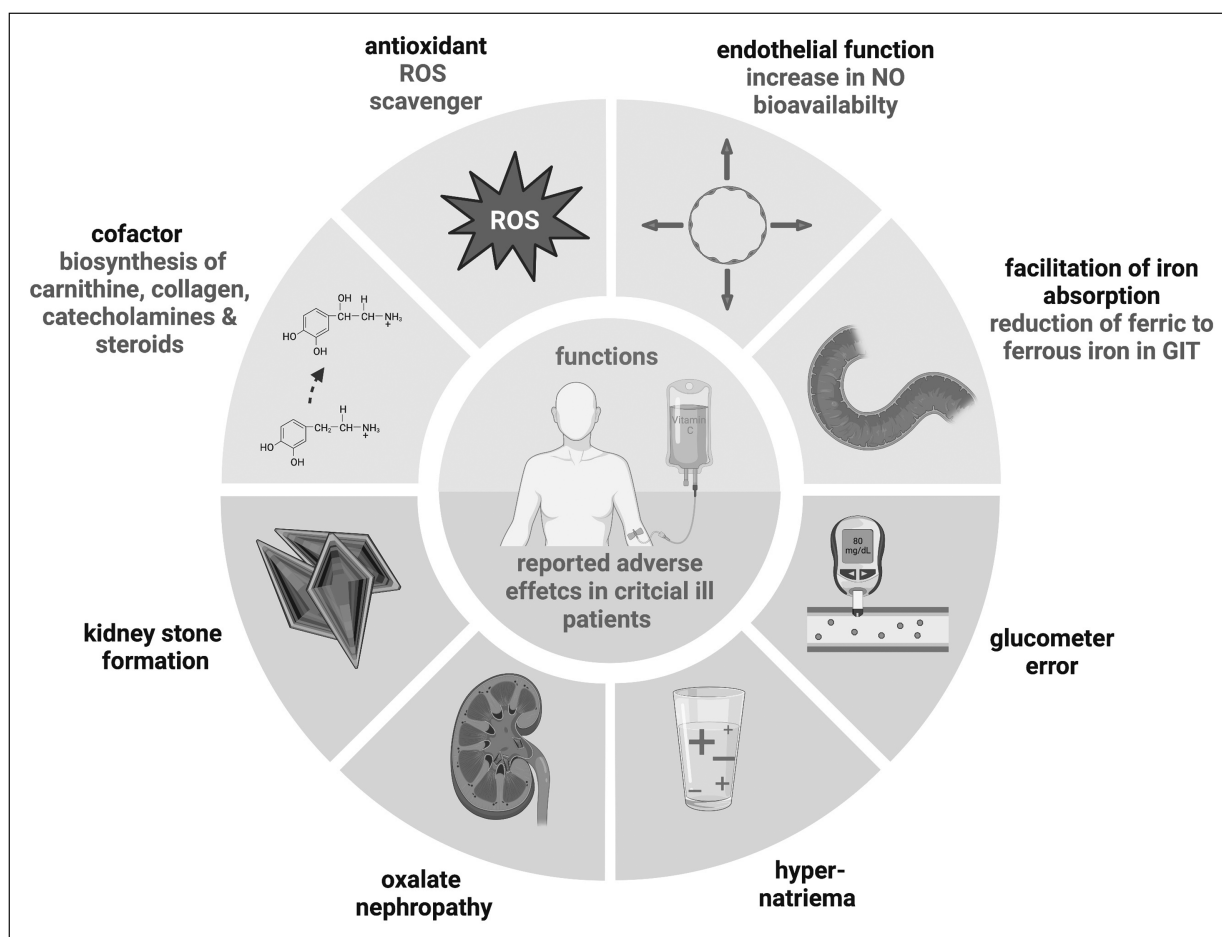


FIGURE 1. Overview on positive pleiotropic functions and potential adverse effects of (high-dose) vitamin C (created with <https://www.biorender.com>).

subgroup analysis, vitamin C was associated with a decrease in 28-day mortality among patients requiring positive-pressure ventilation at enrollment (vitamin C 36.3%, placebo 60.0%, $P=0.05$). However, initiation of renal replacement therapy (RRT) was higher in the vitamin C arm (vitamin C 16.7%, placebo 3.3%, $P=0.015$), as was the volume of fluid administration within 6 h of study drug initiation (vitamin C 1.07 l, placebo 0.76 l, $P=0.03$). There were no statistically significant differences in other secondary outcomes. Honore *et al.* [9] commented that examining the relative times of study drug initiation and RRT initiation indicates that most patients requiring RRT in the vitamin C group had it initiated or planned prior to study drug initiation. Thus, patients receiving vitamin C were already upon RRT and subject to vitamin C removal as vitamin C has a molecular weight of 176 Dalton and is exposed to significant clearance during RRT with the 6 g daily vitamin C dose (after the bolus) may not have reached the desired vitamin C plasma concentration as intended by the study investigators.

Later in 2022, the Lessening Organ Dysfunction with Vitamin C (LOVIT) RCT was published by Lamontagne *et al.* [20²²] as the largest RCT on high-dose intravenous vitamin C monotherapy in septic patients so far. 50 mg/kg vitamin C was administered every 6 h in the first 96 h and compared to placebo. This dosing strategy was built on a previously positive landmark study by Fowler *et al.* [21]. A total of 872 adult patients within 24 h after ICU admission were included if an infection was proven or suspected and vasopressor therapy was required. The combined primary endpoint was persistency of organ dysfunction (i.e. mechanical ventilation, sustained vasopressor-therapy, renal replacement therapy) plus death at day 28. Surprisingly, the intervention with high-dose vitamin C performed significantly worse concerning the combined primary endpoint [44.5 vs. 38.5%, risk ratio (RR) 1.21, 95% confidence interval (CI) 1.04–1.40, $P=0.01$]. There was no significant difference between the intervention and placebo groups for the individual components, 28-day mortality and persistent organ dysfunction. Neither analyses of

Table 1. Comparison of the three most recent randomized-controlled trials on intravenous vitamin C monotherapy.

PICO	Rosengrave's RCT [18 [•]]	Wacker's RCT [19 ^{••}]	LOVIT [20 ^{••}]
Patients	N= 40 (septic shock)	N= 124 (septic shock)	N= 872 (septic shock)
Interventions	Vitamin C (25 mg/kg) every 6 h in first 96 h	Vitamin C (1000 mg) bolus + 250 mg/h for 96 h	Vitamin C (50 mg/kg) bolus every 6 h in first 96 h
Control	Placebo	Placebo	Placebo
outcome	Intravenous vasopressor requirement (dose + duration) Mortality, LOS, SOFA	28-day mortality 10 secondary endpoints i.a. lactate clearance, RRT, LOS, i.v. fluid administration	Death + persistent organ dysfunction at day 28 5 secondary endpoints i.a. death at day 28 and 6 months, biomarkers, QOL
Results	48 h vs. 54 h; n.s. mortality 33% vs. 38% LOS 3.8 days vs. 7.1 days (ICU); 18 days vs. 22 days (hospital), n.s.	26.7% vs. 40.6%; n.s. RRT 16.7% vs. 3.3% i.v. fluid administration after 6 h 1.07 l vs. 0.76 l others n.s.	44.5% vs. 38.5%; P= 0.01 n.s.
Limitations	Small sample size Lower dose of vitamin C due to concerns of ethics committee Median 18 h until start of vitamin C supplementation after ICU admission	Time prior to shock treatment often unknown Underpowered for smaller differences No measurement of vitamin C levels RRT already planned or initiated in vitamin C group Non-White subjects underrepresented	13.3% in vitamin C group spent already 49 h in ICU Sepsis phenotypes not considered No measurement of vitamin C levels Information on pathogens, antimicrobial therapy, ARDS at baseline not collected Subjects from low- and middle-income countries underrepresented

ICU, intensive care unit; LOS, length of stay; n.s., nonsignificant; QOL, quality of life; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

SOFA score, inflammatory biomarkers, hypoglycemia rate, stage 3 acute kidney injury, 6-month survival, nor health-related quality of life showed significant differences between the study groups. Notably, safety outcomes were also similar in both groups and as opposed to the results from Wacker *et al.* [19^{••}], no evidence of increased acute kidney dysfunction was observed. Potential explanations for these unexpected results followed, including that in the LOVIT trial: (1) patients were sought to be excluded if >24 h in the ICU, but 13.3% of patients in the intervention group already spent 49 h in another hospital's ICU, so that the acute onset of sepsis may have occurred earlier, (2) imbalances in sepsis phenotypes may have contributed to the heterogeneity in response to vitamin C, (3) the average vitamin C level (measured in a sub-cohort) was in the normal but not deficient range [22].

Hemilä and Chalker conducted a secondary analysis of the LOVIT trial with the aim to determine whether the abrupt termination of high-dose vitamin C ("rebound effect") could explain the increased mortality in the vitamin C arm [23]. Driven by a previous re-analysis of the CITRIS-ALI trial where the authors showed a time-dependent

modification of the vitamin C effect by the termination of the vitamin treatment [24], Cox regression with two time periods to model the distribution of deaths over the first 11 days was used. Compared with the uniform difference between both groups over the 11-day follow-up period, adding a separate vitamin C effect starting from day 5 improved the fit of the Cox model used. While there was no in-between group difference in mortality during the 4-day vitamin C intervention, 57 deaths occurred in the vitamin C group and 32 deaths in the placebo group in the week after the vitamin C intervention was stopped. Thus, the authors concluded that the increased mortality in the vitamin C group in the LOVIT trial is attributed to the abrupt termination of vitamin C since, admittedly, rather old publications already discussed the effects of abrupt vitamin C withdrawal [25,26]. In a subsequent publication, the LOVIT trial was examined in more detail from a statistical point of view [27]. Sidebotham argued that the LOVIT trial group designed their trial with the hypothesis of a beneficial effect for vitamin C although the pretest probability for adverse consequences of the treatment was low – a possible pitfall of lower power when calculating the sample size. According to this, the risk of false positivity for the

harmful effect of vitamin C found in the LOVIT trial was high.

METAANALYSES

The LOVIT investigators provided an updated SRMA showing beneficial effects on early mortality after vitamin C administration [28^{***}]. In more detail, in-hospital mortality was reduced (21 RCTs, 2762 patients) in addition to 30-day mortality (24 RCTs, 3436 patients) and early mortality, that is, 30-day or before hospital discharge mortality (34 RCTs, 4366 patients). Yet, a detrimental effect was observed at 90 days in an analysis including a subset of 1722 patients (58% LOVIT contribution). Interestingly, the authors suggested harmful effects, whereas the respective analyzed data (five RCTs, 1722 patients) did not support this finding [28^{***}]. Most recently, Lee *et al.* published their SRMA with 16 RCTs (2130 patients), including the RCTs mentioned above [29^{***}]. They showed a significantly reduced overall mortality in patients receiving vitamin C monotherapy. However, no differences in duration of mechanical ventilation, ICU and hospital length of stay, SOFA score at 96 h or vasopressor dose were found. Dosing or duration of vitamin C treatment did not have any impact on the results. Lastly, they assumed a beneficial effect for patients with highest disease severity.

Six SRMAs of high-dose vitamin C monotherapy in the critically ill were published in 2021/2022, including 10–33 studies ($N=1737$ to $N=4740$ patients) [30–35], but not the RCTs by Rosengrave, Wacker and Lamontagne *et al.* In the SRMA by Sato *et al.*, 11 RCTs ($N=1737$ patients) were included and high-dose i.v. vitamin C was not associated with a significantly lower short-term mortality but significantly shorter duration of vasopressor use and a significantly greater decline in the Sepsis Organ Failure Assessment (SOFA) score at 72–96 h [33]. The SRMA by Li *et al.* [31] included 10 RCTs involving 1400 septic patients. Vitamin C was associated with an improved Δ SOFA within 72 h while there were neither in-between group differences on short (28–30 days) and long-term mortality (90 days) nor any other outcome measures. Patel *et al.* [32] analyzed fifteen studies involving 2490 critically ill patients. Compared with a placebo, vitamin C monotherapy was associated with a significant reduction in overall mortality. No trial in their SRMA reported an increase in adverse events related to i.v. vitamin C. Interestingly, a subgroup analysis showed reduced mortality in patients receiving higher doses of vitamin C ($\geq 10\,000$ mg/day, ≥ 6 g/day or ≥ 75 mg/kg body weight/day) – a dose similar to the LOVIT trial. In the SRMA by Shrestha [34], a total of 33 observational studies

($N=2603$ patients) and RCTs ($N=2137$ patients) were aggregated for the primary outcome of overall hospital mortality. Pooled data using a random effect model showed a 19% reduction in odds for hospital mortality, while among the 15 RCTs, this effect could not be observed. Feng *et al.* [30] included nine RCTs with a 584 septic patients and revealed no significant differences between the vitamin C and control group on the primary endpoint 28-day mortality or secondary endpoints including vasopressor dose and length of stay. Lastly, the SRMA by Xing *et al.* [35], including 18 RCTs with $N=2001$ critically ill patients, reported reduced ICU and hospital length of stay without significant effects on the longest follow-up mortality, hospital or ICU mortality and change in SOFA scores. In all these 2021/2022 SRMAs, vitamin C was not associated with a significant effect on the development of acute renal dysfunction.

In general, however, it should be noted that the available SRMAs and underlying studies on vitamin C monotherapy in critically ill patients show a high heterogeneity of methodology – particularly with study and patients selection criteria as well as start, dosage and treatment duration of vitamin C.

GUIDELINES

The heterogeneity of data on vitamin C supplementation or pharmaconutrition is also reflected in current guideline recommendations of international societies, all published before LOVIT. The ESPEN guideline on clinical nutrition in intensive care disapproves of high-dose antioxidative treatment, including vitamin C, without proof of a vitamin C deficiency [36]. In the current Surviving Sepsis campaign guideline, the use of i.v. vitamin C for adults with sepsis or septic shock is not recommended [37]. No comment was made on the supplementation of single vitamins in the American Society for Parenteral and Enteral Nutrition (ASPEN) guideline, but a more detailed consideration of this topic was put in prospect [38]. The German Society for Nutritional Medicine guideline also recommends against using (high-dose) pharmaconutrition with zinc, alpha-tocopherol, and vitamins A and C in critically ill patients [39]. In the ESPEN micronutrient guideline [1], the expert group states that vitamin C requirements in critically ill patients are still uncertain. Plasma concentrations may be measured when scurvy or chronic low intake is suspected and a minimum of 100 mg per day shall be administered in standard conditions. In patients with oxidative stress or assumed malabsorption, however, 200–500 mg of vitamin C per day may be appropriate, which should be escalated to a dose

of 2–3 g daily (parenteral) in cases of critical illness and acute phase of inflammation.

CONCLUSION

Due to its beneficial pleiotropic effects, high-dose vitamin C monotherapy has a biologically plausible rationale to counteract acute inflammation triggered by critical illness/sepsis. However, based on the LOVIT trial, high-dose vitamin C cannot be recommended in patients with sepsis and septic shock outside clinical trials, although questions about the observed adverse effects remain open. Whether this is the end of the story or there is still a place for high-dose vitamin C is a matter of current debate! Supported by recently published SRMAs, ongoing trials need to clarify whether there is a beneficial treatment effect in other patient cohorts, such as COVID-19, burn injury, and/or cardiac surgery. In addition, future trials on vitamin C or any other antioxidative intervention should focus on a more personalized approach (patient identification, dose regimens, treatment duration and risk-benefit ratio regarding clinical endpoints). Until then, vitamin C should be substituted in the dosage recommended for healthy individuals to secure daily intake with medical nutrition therapy in the critically ill.

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An update of the effects of vitamins D and C in critical illness

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Many critically ill patients are vitamin D and vitamin C deficient and the current international guidelines state that hypovitaminoses should be compensated. However, uncertainty about optimal dosage, timing and indication exists in clinical routine, mainly due to the conflicting evidence. This narrative review discusses both micronutrients with regards to pathophysiology, clinical evidence of benefits, potential risks, and guideline recommendations. Evidence generated from the most recent clinical trials are summarized and discussed. In addition, pragmatic tips for the application of these vitamins in the clinical routine are given. The supplementations of vitamin D and C represent cost-effective and simple interventions with excellent safety profiles. Regarding vitamin D, critically ill individuals require a loading dose to improve 25(OH)D levels within a few days, followed by a daily or weekly maintenance dose, usually higher doses than healthy individuals are needed. For vitamin C, dosages of 100–200 mg/d are recommended for patients receiving parenteral nutrition, but needs may be as high as 2–3 g/d in acutely ill patients.

KEYWORDS

critical care, vitamin D, vitamin C, medical nutrition therapy, micronutrients, review

1. Introduction

The Medical Nutrition Therapy (MNT) is an integral part of the complex care needed for patients in the intensive care unit (ICU). It is especially important for patients with high nutritional risk, for example patients who are chronically malnourished or sarcopenic, or for patients remaining on the ICU for a prolonged period. MNT encompasses the administration of macronutrients (carbohydrates, protein, and fats), as well as the supplementation of micronutrients, for example vitamins and trace elements.

The MNT in the ICU is anything but trivial, the optimal administration strategy frequently remains controversial due to inconclusive evidence. This is especially true for micronutrients, as many of them have been studied in heterogeneous ICU

populations in varying dosages, routes, and durations of administration at different perioperative and/or ICU times. In addition, reported outcomes differ from trial to trial, preventing rigorous evidence synthesis, for example in forms of well-conducted meta-analyses. Therefore, uncertainty remains about what needs to be considered and to be implemented in the daily clinical practice on ICU.

This article reviews current evidence and controversies about two very different micronutrients—vitamin D and vitamin C—in a narrative manner. Both vitamins are discussed with regards to pathophysiology, clinical evidence of benefits, potential risks, and guideline recommendations. Evidence generated from the most recent clinical trials are summarized. In addition, pragmatic tips for the application of these vitamins in the clinical routine are given.

2. Vitamin D

2.1. Supplementation with vitamin D in the ICU

Contrary to popular believe, vitamin D is not a vitamin but a steroid hormone with a wide range of cellular, anti-inflammatory, and immunomodulatory effects. It is one of the main regulators of the calcium and phosphate balance, and hence, plays a key role in maintaining a healthy bone metabolism. Moreover, the immunomodulatory features of this hormone are of particular interest for the critically ill patient.

The body obtains vitamin D either from fungi-based diet (vitamin D₂) or animal source (vitamin D₃), by endogen synthesis in sun-exposed skin (vitamin D₃) or by supplements. After that, the liver metabolizes either of them to 25(OH)D, which is further hydroxylated to the active form 1,25(OH)₂D in the kidneys. The active form of vitamin D has a half-life of about 1 h and exerts its manifold effects by binding to vitamin D-receptor (VDR), which is expressed by many tissues (1–3) (Table 1).

Vitamin D and its metabolites are essential immunomodulators that is involved in many biological processes of the innate and adaptive immune system (4). Immune cells such as lymphocytes, monocytes, macrophages, and dendritic cells express the VDR, which explains the major role of sufficient vitamin D levels for infections and cancer, respectively (5–7). Another key action of vitamin D₃ involves its potential to promote the killing of intracellular bacteria such as *Mycobacteria tuberculosis* and *M. leprae* in macrophages via toll-like-receptor 1 and 2, implicating a great capability for severely ill patients (8, 9).

Additionally, the VITAL study revealed that daily supplementation with 2,000 IU vitamin D over a course of 5 years appeared to reduce the incidence of autoimmune diseases (10), which could be explained by tolerogenic effects of

the hormone (4). Further, vitamin D exerts a protective impact on intestinal mucosa and influences thyroid diseases (6, 11) (see overview—Figure 1).

Vitamin D₃ acts *via* both genomic and non-genomic pathways. Basically, calcitriol is thought to exert its effects through interaction with the nuclear vitamin D receptor (nVDR). But there are also non-genomic actions taking place *via* the activation of signaling molecules for example phospholipases C and A₂, second messengers, activation of protein kinases or opening calcium or chloride channels. Another non-genomic action includes the binding to target proteins, which provides the basis for the immunoregulatory effects of vitamin D (12).

The actions of vitamin D in a neuronal cell line and the neuroprotective non-genomic effects of vitamin D and its metabolites is still investigated. Recent studies have shown a modulation of synaptic transmission in juvenile GnRH neurons by vitamin D₃ and additionally, calcipotriol (a vitamin D analog) has been shown to act as a neuroprotective agent in neuroblastoma cells (13, 14).

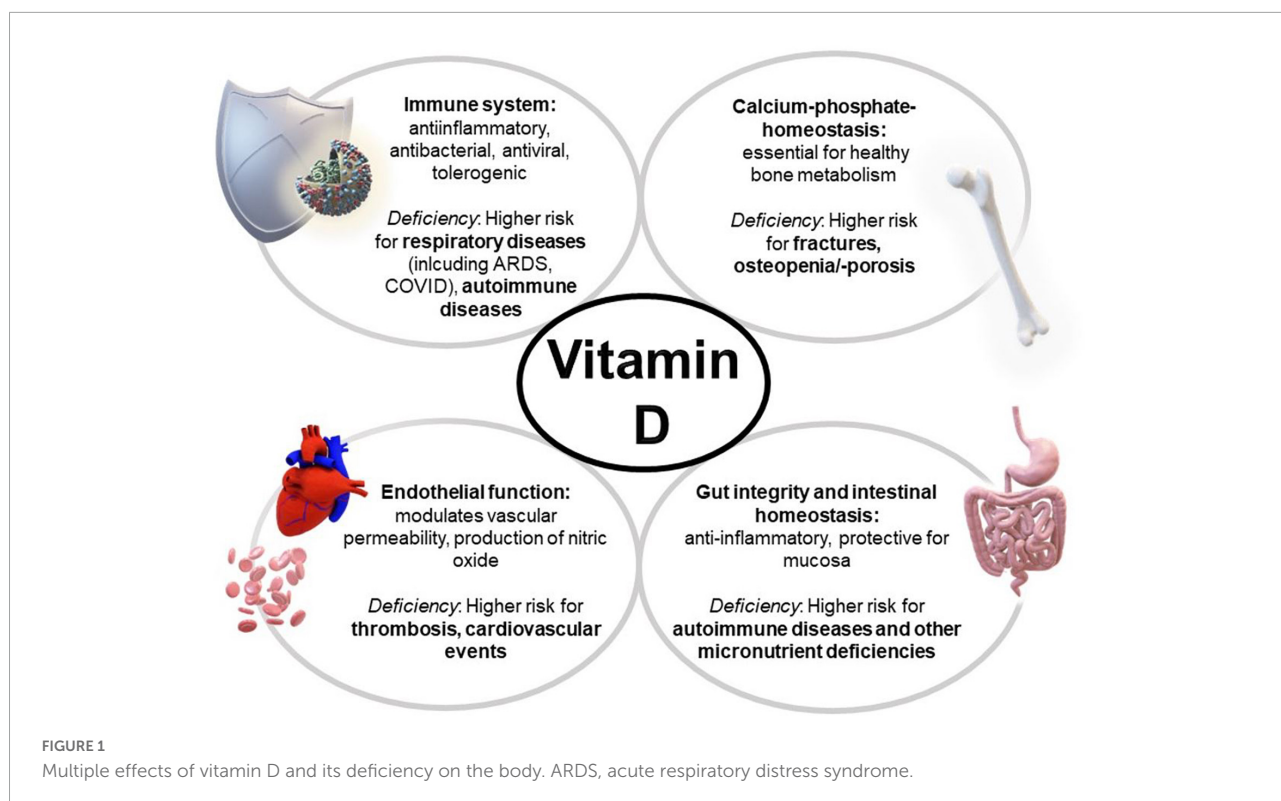
Furthermore, pharmacogenomics have a relevant impact on the pharmacokinetics and -dynamics of vitamins and influence the effectiveness of any supplementation. Vitamin D production strongly depends on renal 1 α -hydroxylase, which can be up-regulated by parathyroid hormone (PTH) and inhibited by calcitriol itself. Genetic polymorphisms in the encoding enzymes CYP27B1 as well as CYP24A1 have shown to influence significantly the concentration of vitamin D metabolites in circulation (15).

Also, genetic aberrations in the vitamin D binding protein (VDBP) have shown to be associated with a higher risk for Graves' disease (16) and have indicated a decreased risk for osteoporosis (17).

Other genetic polymorphisms in diverse CYP-enzymes can lead to remarkably reduced conversion to calcitriol, and genetic variations in the vitamin D receptor have been linked to increased incident of hip fracture, myocardial infarction, cancer and mortality overall. There is some indication that VDR polymorphisms modulate especially the risk for prostate, breast, colorectal and skin cancer (15, 18, 19).

2.2. Vitamin D deficiency

Vitamin D deficiency [defined as 25(OH)D levels below 20 ng/ml] is common and occurs in nearly half of the normal population and in about 70% of all intensive care patients (20, 21). Burn patients are particularly affected (22, 23). Vitamin D deficiency can be caused by low seasonal sun exposure or high air pollution (1), vegan diet (24), using sunscreen, staying indoors, wearing concealing clothing and reduced endogenous vitamin D production efficiency from solar UVB in older age.



Also, the bioavailability of vitamin D decreases in patients with obesity (25). In addition, obesity entails systemic inflammation, which may increase the need for exogenous vitamin D.

However, vitamin D deficiency seems to occur in ICU patients worldwide regardless of latitude, i.e., UV exposure (26). Pre-existing conditions, malnutrition, liver, renal or parathyroid dysfunction can lead to reduced vitamin D levels, as can therapeutic interventions and co-medications. All in all, this can result in increased mortality and poorer outcomes (1, 27).

A clear association between low vitamin D and poor clinical outcome in critically ill adults and children has been demonstrated repeatedly in observational studies. There is a higher risk for sepsis, acute respiratory failure, acute renal failure, prolonged ICU stay, as well as increased mortality and morbidity for patients with vitamin D deficiency (21, 28–32).

2.3. Previous RCTs in critical care/population settings and methodological issues

In 2014, the VITDAL study showed no benefit of vitamin D supplementation on the primary endpoint in 480 mixed critically ill patients with vitamin D deficiency (defined as 25OHD < 20 ng/ml), using a large upfront loading bolus of 540,000 IU followed by monthly maintenance doses of

90,000 IU. However, in the predefined subgroup with severe vitamin D deficiency (<12 ng/ml), 28-day mortality was significantly lower in the vitamin D group (34).

Several smaller trials followed, using different intervention protocols (oral, intramuscular, and single bolus), showing inconsistent results. The largest published RCT to date (>1,000 patients), the VIOLET study (35), showed no benefit of vitamin D in a less severely ill patient group (patients “with risk for ARDS” were included outside of the ICU, i.e., in the theater, the ward, or the emergency room). The intervention was a single large bolus dose of 540,000 IU vitamin D₃. Currently, the European VITDALIZE study (sample size target = 2,400 patients) is still recruiting in several countries including Austria and the United Kingdom using a large bolus dose followed by daily 4,000 IU in a severely deficient ICU population. A direct comparison of the VIOLET study (35) and VITDALIZE study is presented in Table 2.

In a meta-analysis published in 2022, Menger et al. found meaningful and significant benefits of vitamin D administration in critically ill patients for mortality (risk ratio 0.78), shorter ICU stay (−3.1 days), and shorter duration of ventilation (−5.1 days). The aggregated evidence further highlighted the importance of the different vitamin D metabolites and the route of administration (36).

Generally, clinical trials often showed no treatment benefit of vitamin D. Many previous intervention studies displayed multiple, fundamental methodological errors, including e.g.,

TABLE 1 Overview of available vitamin D preparations, adapted to Prietl B. et al. (4) indicated usual dosage recommendations apply to non-ICU patients.

	Daily dose	Indication	Overdose side effects	Half-life	Costs
Native vitamin D					
Unhydroxylated, inactive vitamin D ₃ Cholecalciferol Calcidiol/Calciol Very stable	400–4,000 IU	Vitamin D deficiency, osteoporosis, hypoparathyroidism, rickets prophylaxis.	Rarely hypercalcemia, hypercalciuria	Circulating: 2 days functional: 2–3 months	€
Unhydroxylated, inactive vitamin D ₂ Ergocalciferol Vitamin D ₂ Less stable during storage, cooking/baking	400–4,000 IU			Circulating: 2 days functional: 2 months or less (33)	€
Calcifediol	30–60 µg	Hyperparathyroidism, Vit D deficiency, renal failure CKD 3–4	Hypercalcemia, hypercalciuria	~2 weeks	
Active vitamin D					
Hydroxylated active vitamin D 1,25(OH) ₂ D ₃ (calcitriol) 1,α(OH)D ₃ (alfacalcidol)	0.25–1.0 µg	Advanced kidney disease with secondary hyperparathyroidism, (pseudo) hypoparathyroidism, not alone in vitamin D deficiency.	Narrower therapeutic range: hypercalcemia, hyperphosphatemia, hypercalciuria, nephrocalcinosis.	15 h	€€
Other active vitamin D analogs: Analogues to vitamin D ₂ : Paricalcitol, doxercalciferol Analogues to vitamin D ₃ : Falcacitriol, maxacalcitol		Advanced renal disease with secondary hyperparathyroidism,	Hypercalcemia possible, but less common than with other active forms	~15 h	€€€

Calcidiol is the storage form of vitamin D from which calcitriol is produced on demand and has the highest half-life of 3 weeks. CKD, chronic kidney disease.

investigation of a non-vitamin D deficient study population, very small case numbers, exaggerated/unrealistic effect sizes, very different specifications on dose and metabolites used (see overview [Table 1](#)), or an intake of vitamin D in the placebo group. Previous vitamin D studies were virtually always “underpowered” for the intended endpoint.

In 2014 Heaney published his guidelines with a system to standardize clinical studies of nutrient effects, taking into account the physiology of the investigated nutrient and necessary basics for nutrient study design (37).

For example, in the U.S. VITAL Study with a relatively healthy study population of 25,871 subjects who received vitamin D supplementation of 2,000 IU for 5 years with or without omega-3 fatty acids, neither of which demonstrated protection against falls, cardiovascular events, or cancer (38, 39). There were many problems with the design and analyses of the study, including that vitamin D status before the start of supplementation was normal and averaged 30.8 ng/ml, whereas only 12.7% of participants had levels below 20 ng/ml. One explanation could be that vitamin D is often added to American foods such as milk and participants were allowed to consume up to 800 IU (20 µg) of vitamin D daily, which is the usual daily recommendation for adults. Additionally, BMI overall was high and outcomes

were not evaluated individually concerning the particular 25OHD concentration.

However, secondary analysis concluded that all-cancer mortality rate was significantly reduced, especially in the cohort with normal weight. Obesity and being overweight seemed to obstruct this effect (40).

Another important variable is adequate sample size, which in randomized trials is primarily determined by the estimated effect of the intervention relative to the standard/placebo group, but also the desired power. For example, a very high number of cases is required to detect an effect on mortality. In the future, it might be helpful to use composite endpoints (primary endpoints consisting of several individual endpoints)—as it has been common practice in other fields, including critical care and cardiology, for a long time (41–43).

2.4. High dose bolus administration

By now, one-time high-dose supplementation is considered obsolete, as it has been shown to be ineffective, and in some settings even harmful (in contrast to a daily/weekly administered vitamin D dose). Not even the exemplary

TABLE 2 Comparison of the large intervention studies VIOLET and VITDALIZE—two studies that at first glance appear similar, but nevertheless have significant differences, regarding drug administration, inclusion criteria, and primary endpoints.

	VIOLET (NCT03096314)	VITDALIZE (NCT03188796)
Inclusion criteria	Vitamin D level ≤ 20 ng/ml	25(OH)D ≤ 12 ng/ml
Number of cases	Planned 3,000, aborted after 1,360 at first interim analysis due to “futility.” Analyzed 1,078	Planned 2,400, an interim analysis As of October 2022: 900 patients included
Population	Patients at risk for ARDS	ICU-patients
Bolus output	A single bolus of 540,000 IU	Bolus administration of 540,000 IU and additional daily administrations of 4,000 IU over a 90-day period (corresponding to a total vitamin D administration of 900,000 IU over a 90-day period).
Primary endpoint	90-day mortality	All-cause mortality after 28 days

In the VIOLET study, 1,360 patients were screened and found to have vitamin D levels of <20 ng/ml using point of care testing, but only 1,078 who actually had a vitamin D level <20 ng/ml in subsequent LC/MS testing were analyzed. However, in the previous VITDAL-ICU study, only the subgroup with levels <12 ng/ml showed significantly reduced 28-day mortality, not the subgroup with vitamin D between 12 and 20 ng/ml (34). Based on these results, the design of the VITDALIZE study was planned and created (correct subgroup, correct endpoint). Mention should also be made of the VITDALIZE-Kids study (NCT03742505), led by JD McNally in Canada, which has included critically ill children since 2019 (planned 766, as of October 2022: >200 ; primary endpoint: health related quality of life).

vitamin D deficiency disease—rickets—can effectively be treated with bolus administration (44). Biologically, this can probably be explained by the induced activation of catabolic enzymes 24-hydroxylase and FGF-23, both of which can inactivate vitamin D (45). Likewise, in the prevention of respiratory infections only daily or weekly low-dose administration is effective (46). Nevertheless, in the intensive care setting—since it is a time-critical situation—a high-dose loading dose could be given at the beginning, followed by maintenance therapy (47).

2.5. Implications for COVID-19

Patients with low vitamin D levels are at increased risk of becoming infected with SARS-CoV-2 and developing severe disease including ICU admission and death (48). A recent study by Gibbons et al. has shown that the supplementation of vitamin D2 and D3 reduced the risk for COVID-19 infection, as well as mortality. The benefits were even better in people receiving higher dosages, as well as in those with a more severe deficiency (49).

Vitamin D appears to have multiple effects on cells and tissues that have also been implicated in the progression of

COVID-19 and of ARDS. Vitamin D is a regulator of important genomic and non-genomic mechanisms in the immune system, is involved in the defense against respiratory infections, and also plays a controlling role in the renin-angiotensin-aldosterone system used by SARS-CoV-2 to invade host cells (50). Epithelial cells are the primary target of respiratory pathogens, and a seasonal decline of vitamin D could contribute to a higher rate of (lower) respiratory tract infections during winter. Two meta-analyses showed that vitamin D treatment can reduce the risk for respiratory tract infections (5, 46). Respiratory epithelial cells, as well as macrophages and monocytes express enzymes in response to inflammation, which are able to convert 25(OH)D into the active form 1,25(OH)₂D₂₅, which in turn induces the expression of the antibacterial and antiviral peptide cathelicidin and influences lymphocyte activity (51). 1,25(OH)₂D affects immunotolerance in antigen-presenting cells (APC) (52); hence, having a tolerogenic impact, by decreasing IL-12 production and increasing IL-10 (53).

Vitamin D-receptors are also expressed by blood vessels, whereby vitamin D modulates endothelial function as well as vascular permeability, and it is a transcriptional factor for endothelial nitric oxide production (54). Lack of vitamin D has been associated with thrombotic and cardiovascular events and has shown *in vitro* to influence the structure and formation of thrombi. In severe vitamin D deficiency, a high-dose cholecalciferol supplementation was associated with a reduction in thrombin generation (55, 56). This potential impact may play a role in the future in the prevention and treatment of COVID-19 patients, which often suffer from coagulopathy, thrombosis and microangiopathy.

A small RCT including 50 patients to evaluate high-dose calcifediol administration compared to standard therapy without calcifediol has shown to cause a significant reduction in the need for ICU treatment of hospitalized patients (57). Calcifediol is a more rapidly acting native vitamin D metabolite that is currently only available for routine purposes in some countries but is certainly interesting in the ICU population. Oral calcifediol increases the serum 25(OH)D levels more rapidly and is about 3.2-fold more potent than cholecalciferol, which means that lower dosages are needed. Also, intermittent oral calcifediol showed a higher rate of intestinal absorption and potentially a more stable serum 25(OH)D level than intermittent oral cholecalciferol intake (58).

A systematic review and meta-analysis including 2,078 COVID-19 patients found that 61 (10.5%) individuals in the vitamin D supplementation group died, compared to 386 (25.8%) in the non-treated group (OR: 0.60; 95% CI: 0.32–1.12; $p = 0.11$). Regarding ICU admission, 12.2% of the individuals in the treated group were admitted to ICU, compared to 26.3% in the non-treated group (OR: 0.33; 95% CI: 0.15–0.71; $p = 0.005$) (59).

Considering the multiple effects that vitamin D exerts throughout the human body and the data we have so far on the topic, the achievement of an adequate level of vitamin D could play a highly relevant role as an adjuvant tool to optimize immunologic responses to infection or vaccination. However, it may not be possible to show a small benefit during the pandemic because of the high financial and regulatory barriers and the time needed to collect such data.

2.6. Fracture risk and osteoporosis after critical illness

The risk of fracture after an ICU-stay is increased (60). Accelerated bone resorption, including changed bone turnover markers, bone mineral density and fragility fracture rate are issues in critically ill patients and predict mortality. The reasons include immobilization and resulting muscle loss, frequent vitamin D deficiency, inflammatory cytokines, but also malnutrition, as well as drugs such as steroids or proton pump inhibitors (PPI) (61, 62).

Early mobilization and restrained medication with PPIs and steroids are cornerstones of osteoporosis prophylaxis in this setting. Interestingly, bisphosphonates have been shown to significantly improve survival in patients at particularly high risk of mortality (63). In cases of prolonged immobilization, antiresorptive substances such as bisphosphonates or denosumab could be tried as a case-by-case decision (64). The basic prerequisite for this is an adequate vitamin D level as well as sufficient calcium intake, otherwise severe hypocalcemia may occur. The results of the currently recruiting Australian Bone Zone study will be highly relevant (NCT04608630) for the question if zoledronic acid or denosumab can improve bone health in this special setting.

2.7. Target levels

The target vitamin D level indicating optimal levels remains highly controversial and different targets may apply to different diseases. A high dose supplementation to reach pharmacological levels could be required to achieve some effects, but the potential for toxicity must be kept in mind when using such an approach.

2.8. Key messages (vitamin D)

- In case of (par)enteral nutrition, vitamins and trace elements should always be supplemented.
- Usual daily requirement for adults: 600–4,000 IU of vitamin D daily.
- Vitamin D deficiency is a rapidly modifiable risk factor in critically ill patients.

- The 25(OH)D level is a relatively stable and now readily available laboratory value after the hyperacute phase of acute illness/outside the initial phase of major surgery that reliably detects vitamin D deficiency (<20 ng/ml).
- Given the available evidence, we suggest a target level of 30–40 ng/ml and a repeat 25OHD measurement after a few weeks.
- Vitamin D deficiency has been described in the majority of ICU patients worldwide (children and adults).
- Vitamin D supplementation thus represents a cost-effective, simple intervention with an excellent safety profile that is involved in multiple biological processes of the immune system, bone health, and mortality, and thus could contribute significantly to improved outcomes in intensive care patients.
- Critically ill individuals may require a loading dose to improve 25(OH)D levels within a few days, followed by a daily or weekly maintenance dose, usually higher doses than healthy individuals are needed.
- For a reduction of the increased fracture risk after critical illness, antiresorptive substances such as bisphosphonates/denosumab should be considered as a case-by-case decision in prolonged immobilization; the basic prerequisite for this is an adequate vitamin D level as well as sufficient calcium intake, otherwise severe hypocalcemia may occur as an adverse event.
- In the future, calcifediol may play a more important role in the ICU setting, as it seems to increase 25(OH)D serum concentrations faster than oral vitamin D3.
- Side effects of vitamin D supplementation are rare and include:
 - Hypercalciuria/-calcemia.
 - Kidney damage and new formation of kidney stones.
 - Increased risk of falls and fractures has been described for infrequent or single ultrahigh doses.

3. Vitamin C

Vitamin C is the first recognized and first synthetically fabricated vitamin. The pharmacokinetics and metabolic pathways have been discussed extensively in several reviews (65, 66), therefore only a short summary is given here. Vitamin C is a water-soluble, essential micronutrient with a multitude of functions in the human body. Vitamin C has almost complete bioavailability after enteral resorption and is eliminated *via* the kidneys. In the plasma, it exists in two forms: ascorbic acid and its oxidized and biologically less active form dehydroascorbate. Vitamin C is quickly eliminated with an approximate half-life of 1 h after intravenous injection. Vitamin C is required for the function of more than 60 enzymes, among which are (65):

- The synthesis of norepinephrine, collagen, and carnitine.
- The function of vitamin C dependent mono- and dioxygenases involved in peptide amidation and tyrosine metabolism.
- The metabolism of cholesterol to bile acids and in steroid metabolism.
- The cytochrome P450 driven hydroxylation of aromatic drugs and carcinogens.
- The absorption of iron in the small intestine.
- Stem cell differentiation.

Vitamin C is also a strong antioxidant and counterbalances the influence of reactive oxygen species thus protecting cells and organs from damage in settings of oxidative stress and inflammation (65). A very condensed overview of vitamin C's influence on different organ systems is displayed in **Figure 2**. Within the specific contents of this manuscript, it is important to mention that vitamin C raises glutathione levels and may thereby increase the effect of vitamin D as well (67–71).

In the western-countries, patients with the full clinical symptoms of scurvy (gingivitis, hemorrhagic diathesis, immune deficiency pancytopenia, general weakness) are not to be expected frequently due to overall good supply situation (72). Nevertheless, in critical illness there are many different patient populations who may benefit from vitamin C supplementation, especially since ICU patients regularly show suboptimal vitamin C levels (73–75), which ultimately lead to

compromised function of the immune system and antioxidant defense mechanisms.

3.1. Potential benefits of vitamin C in critical illness

There are many different ICU subpopulations possibly profiting from vitamin C administration, as vitamin C has pleiotropic functions.

The greatest benefit of vitamin C is to be expected in patients with high extend of inflammation and oxidative stress, as vitamin C not only neutralizes free radicals and reactive oxygen species, but also restores other antioxidative molecules, such as vitamin E. Therefore, vitamin C may reduce cell and organ damage. A typical case is ischemia-and reperfusion injury (I/R-injury). As examples, benefits of a vitamin C supplementation were shown in cardiac surgery with the use of cardio-pulmonary-bypass (76–82), patients after cardio-pulmonary resuscitation or patients with surgeries requiring the clamping of large arterial vessels (65). In experimental models, such as ischemic stroke, vitamin C proved to be beneficial as well (83–85).

Another patient group who may potentially benefit from vitamin C administration, is patients experiencing systemic inflammation, for example after polytrauma, burn injury, or during sepsis and shock. In this patient group, vitamin C is involved in vasopressor synthesis, improves the endothelial

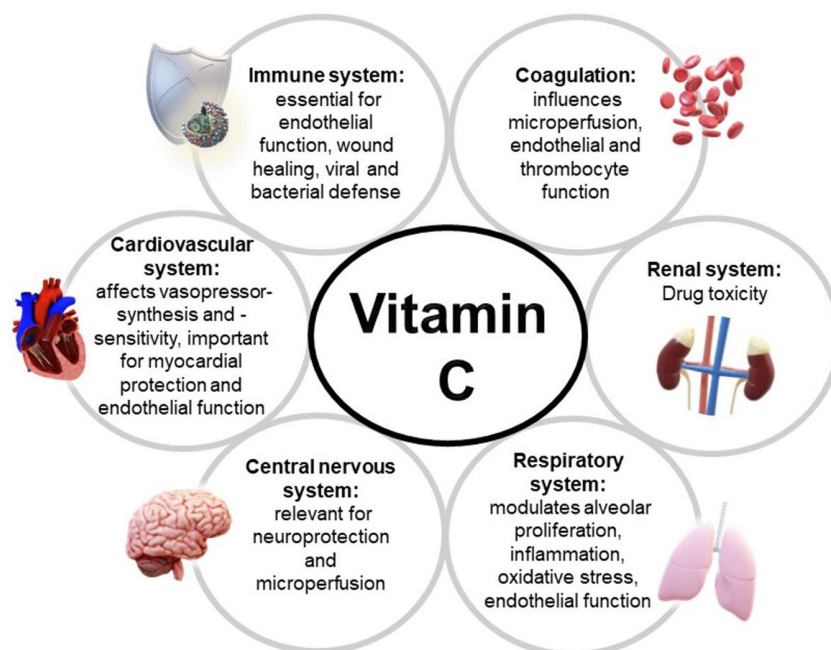


FIGURE 2
Vitamin C's influence of different organ systems.

sensitivity for vasopressors, as well as endothelial function and microperfusion, which in turn can reduce edema and volume demands (65, 86, 87).

The two mentioned clinical situations—oxidative stress and systemic inflammation—are attributed special attention in the new Micronutrient guidelines of the ESPEN (European Society for Clinical Nutrition and Metabolism) (47). These patients should receive 2–3 g/d vitamin C intravenously, whereas other patients should receive 100–200 mg/d (47). However, it must be acknowledged that these recommendations given are based on the evidence of predominantly smaller RCTs, which are known to overestimate the effects size.

In addition, patients who experience greater losses of water-soluble micronutrients, for example during extracorporeal circulation (e.g., with hemofiltration or extracorporeal membrane oxygenation or patients with significant exudation (large wound surface, thermal injury, open abdomen) may need a greater amount and parenteral administration of vitamin C when compared to other patients (88).

Two other mechanisms come in mind, where vitamin C supplementation could be useful, although here the pathomechanisms are less acute. Patients with chronically high oxidative stress, for example patients with coronary artery diseases or chronic obstructive pulmonary disease also benefited from vitamin C in past clinical trials (65). Furthermore, vitamin C reduced drug-toxicity in several settings, even though this currently finds sparse clinical application. Vitamin C reduced the risk of contrast-mediated nephropathy (89) and reduced drug-toxicity, apoptosis and DNA damage during radio- and/or chemotherapy (90, 91). The following table (Table 3) gives a condensed summary of the pathologies, pathomechanisms and the described benefits of vitamin C on different patient cohorts. It must be pointed out that this table does not discriminate the level of evidence between individual sources. The reason is simple: a rigorous and methodologically meticulous discussion of all high-level evidence regarding the administration of vitamin C across all the mentioned medical fields would be beyond the scope of this review and needs to be done elsewhere.

3.2. Potential harms of vitamin C?

Generally, vitamin C is regarded as safe and easy to use micronutrient. Adverse effects were mostly mentioned in case reports and especially after prolonged high-dosage administration. In patients with some hereditary diseases, vitamin C administration led to adverse effects: it can aggravate iron-overload in patients with hemochromatosis, as vitamin C is a co-factor for iron uptake. In patients with G6DP deficiency (glucose-6-phosphate dehydrogenase), which has a high-varying geographical prevalence, the vitamin may induce hemolysis. Patients with severe chronic kidney disease or history of kidney stones need a close monitoring of the kidney function

during high-dose vitamin C administration, as the formation of oxalate kidney stones may be induced (65).

High-dose of intravenous vitamin C may alter the measurements of some handheld blood glucose meters, which may measure false-high blood glucose levels. This needs special attention, as true hypoglycemia may be masked or truly euglycemic patients may receive insulin treatment due to false-high readings (65).

Other side effects of vitamin C, such as flatulence and diarrhea or false-positive readings of tests for occult blood in the stool can be attributed to enteral administration of vitamin C. In theory, vitamin C may act pro-oxidatively, although this has not been proven *in vivo* and it remains discussed whether this potential pro-oxidative character might not be beneficial as well (65, 118).

A systematic review of the harmful effects of high dose vitamin C (median 22.5 g/d) showed diverse rates of adverse events (numerically one higher, one equal and one lower in comparison to the control group in each one RCT). In 2,801 patients, five cases of oxalate nephropathy (0.18%), five cases of hypernatremia (0.18%), three cases of hemolysis in G6DP deficient patients (0.11%), two cases of glucometer error (0.07%), and one case of kidney stones (0.04%) were reported (119). In addition, the latest systematic reviews and meta-analyses have shown no difference in (serious) adverse effects in patients receiving vitamin C in clinical studies (76, 110, 111).

3.3. Current evidence for vitamin C

In 2017, a retrospective Study from Marik et al. administering a combination of hydrocortisone, vitamin C and thiamine (“HAT-therapy,” “Marik Cocktail”) to patients with severe sepsis and septic shock demonstrated a significant advantage of survival and reduced rate of organ dysfunction in those patients receiving vitamin C (87). Since then, the interest in vitamin C-research augmented largely. Mostly small studies (which in the majority cannot be discussed here for the sake of conciseness) with diverse dosing and administration regimens in heterogeneous patient populations aimed to demonstrate a treatment effect, whereas the reported outcomes and outcome measurement timepoints were as diverse as the rest of the studies.

As examples, the studies from Fowler et al. showed a reduction of inflammatory markers and organ dysfunction in septic patients (120), as well as a significant reduction of mortality in patients with ARDS (acute respiratory distress syndrome) in a large randomized controlled study, the “CITRIS-ALI”-trial (105) in the respective vitamin C groups. Combination therapies, for example with other antioxidants or vitamins (vitamin E, vitamin A), as well as other drugs (statins, acyl cysteine, omega-3 fatty acids, and β -blocker) have also been evaluated in clinical studies and have mostly shown neutral or even negative effects

TABLE 3 Role and potential benefits of vitamin C on various organ systems, adapted from; all described benefits were derived from clinical studies unless stated explicitly.

Patient group/Afflicted organ system	Special role of vitamin C in the organ system	Pathology/Condition studied	Pathophysiology related to potential usefulness of vitamin C	Benefits from vitamin C administration						
				Described benefits of vitamin C in the organ system/Condition	Described or potential mechanisms through which vitamin C may be beneficial					
					Mitigation of oxidative stress + restoration of other antioxidants	Improved endothelial function and microcirculation	Improved vasopressor response	Improved platelet function and decreased capillary plugging	Reduced extravasation and edema	Enhanced immune function and antibacterial properties
Central nervous system	- Elevated levels up to 80 times to protect neurons (92, 93) - Essential for the differentiation and myelination of neurons (94, 95)	Stroke/Cerebral ischemia	- I/R injury and subsequent oxidative stress - Shift of vitamin C from the intra- to extracellular compartment and intraneuronal vitamin C deficiency (75)	- Reduces infarct volume in experimental models (83–85) - Decreases ischemic stroke-related lipid peroxidation (96)	×	×		×	×	
		ICB Head trauma	- Hemorrhage/tissue damage - Increased ICP and subsequent reduction of cerebral perfusion	Inversely correlated with major diameter of lesion and severity of neurological impairment (97)	×	×	×	×	×	×
Cardiovascular system	- Frequent vitamin C deficiency (98) - Vasopressor synthesis	Cardiac surgery Post-reanimation	- I/R Injury and subsequent oxidative stress - Hemodilution and extracorporeal circulation - Compromised cardiac function and hemodynamics	- Decreases myocardial injury (99) and higher cardiac index (99) - Decreases rate of post-op arrhythmia (76–82), ICU (76, 79, 80) and hospital stay (76, 79–81, 100) and ventilation time (76, 77, 81) - Decreases bleeding (101)	×	×	×	×	×	×
		CAD and MI	Chronic inflammatory disease leading to increased need of antioxidants	- Promotes endothelial and NO dependent vasodilation - Reduces AKI after coronary angiography (89)	×	×	×	×		
Respiratory system	- High levels in alveolar type II cells and macrophages (102) - Collagen synthesis, endothelial restoration and alveolar proliferation (103)	ARDS Pneumonia COPD Asthma Cystic fibrosis	- Most common organ system to suffer from reactive oxygen species (103) - Acute or chronic inflammation leading to increased need of antioxidants - Plasma histamine levels correlate inversely with vitamin C levels (102)	- Reduces I/R injury and lung damage in experimental models (65) - Reduces pulmonary inflammation (104) - Reduces mortality in ARDS (105) - Prevents/ameliorates pneumonia (106, 107)	×	×	×		×	×

(Continued)

TABLE 3 (Continued)

Patient group/Afflicted organ system	Special role of vitamin C in the organ system	Pathology/Condition studied	Pathophysiology related to potential usefulness of vitamin C	Benefits from vitamin C administration						
				Described benefits of vitamin C in the organ system/Condition	Described or potential mechanisms through which vitamin C may be beneficial					
					Mitigation of oxidative stress + restoration of other antioxidants	Improved endothelial function and microcirculation	Improved vasopressor response	Improved platelet function and decreased capillary plugging	Reduced extravasation and edema	Enhanced immune function and antibacterial properties
Renal system	• Renal excretion	Contrast mediated nephropathy	• Drug toxicity	• Decreases risk for AKI (89)	×	×				
		COVID-19 SIRS	• Systemic inflammation and oxidative stress • Vitamin C can reduce the expression of ACE2, which hinders the entry of the virus into cells, and stabilizes blood pressure (108)	• In experimental models: protects kidneys from injuries caused by external factors, facilitates repair (108)	×	×				
Oncology	• Induces pluripotent stem cell differentiation • Drug metabolism	Chemo- and radiotherapy	• Reduced uptake due to anorexia and cachexia • Drug toxicity • Reduced organ function • Clotting disorder	• Decreases drug toxicity (90) • Attenuation of apoptosis and DNA damage (91) • Decreased intestinal mucosa damage in experimental design (109) • Increases chemosensitivity	×	×				x
Critical illness	• Frequent vitamin C deficiency (73–75) • Drug metabolism	Sepsis/septic shock,	• Systemic inflammation • Imbalance between vitamin C loss/requirements and vitamin C uptake	• Reduces vasopressor requirement (86, 87) • Reduces mortality (86, 87, 105, 110, 111) and organ failure (87) • Shortens ICU stay (111)	×	×	×	×	×	×
Burn injury	• Induces pluripotent stem cell differentiation • Collagen and carnitine synthesis	Severe thermal injury with large% TBSA burned Inhalation trauma	• I/R Injury and subsequent oxidative stress • Hemodilution • Large wound surfaces and increased losses • “After-burn” and disturbed microperfusion	• Reduction of resuscitation volume (112–114) • Shorter time to wound healing (115) • Reduces vasopressor requirement (113) • Increases urine output (113, 116) • Shorter mechanical ventilation (112) • Improved hospital survival (117)	×	×	×	×	×	×

ACE II, angiotensin converting enzyme II; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ICP, intracranial pressure; ICU, intensive care unit; ICB, intracranial bleeding; I/R, ischemia- and reperfusion; MI, myocardial infarction; NO, nitric oxide; SIRS, systemic inflammatory response syndrome; TBSA, total body surface area.

of these “cocktails” (65, 121–124). Regarding higher level of evidence, there was an equal flood of meta-analyses, which demonstrated benefits of high-dose vitamin C for example in cardiac surgery patients (76, 78–81, 100, 125) or in the common ICU population (110, 126, 127), some also calculated no clear influence of vitamin C on the individual outcomes.

However, this year, in a large randomized controlled trial, the “LOVIT- trial” from Lamontagne et al., vitamin C monotherapy in septic patients was associated with a significantly higher occurrence of the combined endpoint: “death + persistent organ dysfunction,” while the latter was defined as use of vasopressors, invasive mechanical ventilation, or new renal-replacement therapy at 28 days (128). Although this study with 872 patients led to doubts regarding the potential benefits of vitamin C, it should be mentioned that neither the single components of the composite endpoint nor inflammatory markers, nor 6 months-mortality nor quality of life were different between the groups and that the severity of illness was unevenly balanced, so that a null effect rather a harmful is currently discussed (129). In addition, commencement of vitamin C therapy was delayed (>10 h) and with high variance, limiting the generalizability of the findings.

Currently recruiting randomized controlled trials include trials in patients with ARDS, sepsis COVID-19, cardiac surgery, cardiac arrest and burn patients (NCT04138394). The currently registered 254 studies (www.clinicaltrials.gov, accessed October 3rd, 2022, under the search term “vitamin C”) will show if a vitamin C administration really has beneficial treatment effects in critically ill patients.

3.4. Vitamin C in the ICU routine

In summary of the above sections, it can be stated that vitamin C has a broad spectrum of potential benefits with relatively few risks of adverse effects. The administration of vitamin C is neither costly nor is it difficult to administer and is usually quickly eliminated *via* the kidneys in case of overdoses. In patients with G6DP-deficiency, hemochromatosis, history of kidney stones or chronic kidney disease, or if blood sugar cannot be determined with reliable devices, vitamin C should not be used in higher dosages. Pathophysiologically, a loading dose of vitamin C may be beneficial, as the greatest amount of inflammation and oxidative stress is usually the greatest in the most acute setting, however, there is no evidence on this strategy yet. Otherwise, the dosing for different patient populations is summarized in Table 4.

Studies have shown that in the general ICU populations, vitamin C levels are often suboptimal (73–75), suggesting that increased vitamin C supplementation might optimize the body's function. Nevertheless, especially in the setting of

TABLE 4 Recommendations for vitamin C dosing according to the ESPEN Micronutrient Guideline (47) and nutrition in the ICU guidelines.

Patient group	Examples	Dosage
Parenteral nutrition (47, 130, 131)	Supplementary or total parenteral nutrition	100–200 mg/d (2)
Patients with chronically elevated demands (47)	COPD, CAD, alcoholism, diabetes mellitus, smokers, heart failure, chronic dialysis	200–500 mg/d (2)
Patients in the acute phase of critical illness (47)	I/R Injury: cardiac surgery, stroke, resuscitation, clamping of large vessels, tourniquet Increased losses: extracorporeal circulation, exsudation Systemic inflammation: sepsis, shock, polytrauma	2–3 g/d (47)

CAD, coronary artery disease; COPD, chronic obstructive pulmonary diseases; I/R: ischemia-reperfusion.

critical illness the interpretation of serum or plasma vitamin C levels needs to be performed cautiously, as they are influenced by hemodilution and re-distribution (98). In addition, the measurement of vitamin C is hindered by its pH-, thermo-, temperature-, and UV-lability. Therefore, the measurement is relatively difficult to perform correctly in clinical routine and meticulous probe processing is required to obtain valid results (98). When measurement of the vitamin C status is needed, EDTA tubes should be used to collect plasma. The probes should be centrifuged the supernatant should be transferred into Eppendorf tubes. Afterward and depending on the standards of the collaborating laboratory, denaturation of proteins and additional centrifugation might be necessary. During the whole process, the probes should be cooled, e.g., stored on crushed ice and protected by light, for example through wrapping the probes with tinfoil. From drawing blood until storage at -80°C , the whole process should be performed in under 60 min (90 min in case of protein denaturation) (98).

There is not enough evidence to answer the question of the optimal administration strategy of vitamin C with regard to indication, dosage, route of administration, duration and monitoring. However, the following key messages give a summary for the use of vitamin C in clinical routine.

3.5. Key messages (vitamin C)

- Vitamin C has a central role for multiple enzymatic processes in the human biology and is important for an optimal immune function in the human body.
- Vitamin C has a broad spectrum of potential benefits with relatively low risks of adverse effects. The administration of vitamin C is simple and inexpensive, however it needs to be protected from light and heat to avoid degradation.

- Vitamin C deficiency is frequent among ICU patients and should be compensated to allow optimal enzymatic and immune function (47).
- The measurement of vitamin C in the clinical practice remains cumbersome: mistakes during probe-handling, hemodilution and compartment shifts of vitamin C may contribute to false-low measured plasma levels.
- If vitamin C is measured, probe processing needs to be performed quickly (<90 min), cooled and under light-protection.
- There is currently evidence for high dosages of vitamin C in the general ICU population and guidelines uniformly recommend against the use of vitamin C in pharmacologic dosages (47, 130, 131).
- Dosage should be as follows (47, 130, 131):
 - 100–200 mg/d in patients with parenteral nutrition.
 - 200–500 mg/d in patients with chronically elevated vitamin C demand.
 - 2–3 g/d in patients in the acute phase of critical illness.
- In case of vitamin C supplementation special attention should be paid to possible adverse effects:
 - Artificial hyperglycemia.
 - Nephropathy and kidney stones.
 - Hemolysis.
- Current evidence:
 - The recent LOVIT trial questions the benefits of high-dose vitamin C in patients with sepsis and septic shock.
 - Systematic reviews suggest benefits of high-dosed vitamin C if given alone in critically ill patients.
 - Currently recruiting trials will show if a high-dose vitamin C supplementation may be of use for distinct subpopulations of critically ill patients.
- Point of care tests, which would allow a rapid measurements of vitamin C levels, or its surrogates would be helpful to identify specific patient populations in need

for this treatment and/or assist to evaluate the success of this intervention.

Author contributions

AH and KA: concept. AH, CSa, CSo, and KA: first draft of the manuscript. CSa and AH: figures. AH, CSa, ED, CSo, and KA: proofreading and correction of content and language. All authors contributed to the article and approved the submitted version.

Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW

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Intravenous vitamin C monotherapy in critically ill patients: a systematic review and meta-analysis of randomized controlled trials with trial sequential analysis

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Abstract

Background A recent landmark randomized controlled trial (RCT) in septic patients demonstrated an increased risk of death and persistent organ dysfunction with intravenous Vitamin C (IVVC) monotherapy, which represents a disparate result from previous systematic reviews and meta-analyses (SRMA). We performed an updated SRMA of IVVC monotherapy to summarize and explore heterogeneity across current trials and conduct trial sequential analysis (TSA) to guard against type-I or type-II statistical errors.

Methods RCTs evaluating IVVC in adult critically ill patients were included. Four databases were searched from inception to 22 June 2022 without language restrictions. The primary outcome was overall mortality. Random effect meta-analysis was performed to estimate the pooled risk ratio. TSA for mortality was performed using the DerSimonian–Laird random effect model, alpha 5%, beta 10%, and relative risk reduction (RRR) of 30%, 25%, and 20%.

Results We included 16 RCTs ($n = 2130$). IVVC monotherapy is associated with significant reduction in overall mortality [risk ratio (RR) 0.73, 95% confidence interval (CI) 0.60–0.89; $p = 0.002$; $I^2 = 42\%$]. This finding is supported by TSA using RRR of 30% and 25%, and sensitivity analysis using fixed-effect meta-analysis. However, the certainty of our mortality finding was rated low using GRADE due to the serious risk of bias and inconsistency. In a priori subgroup analyses, we found no differences between single vs multicenter, higher ($\geq 10,000$ mg/day) vs lower dose and sepsis vs non-sepsis trials. *Post-hoc*, we found no differences in subgroup analysis of earlier (< 24 h) vs delayed treatment, longer (> 4 days) vs shorter treatment duration, and low vs other risk of bias studies. IVVC may have the greatest benefit in trials that enrolled patients above (i.e., $> 37.5\%$; RR 0.65, 95% CI 0.54–0.79) vs below (i.e., $\leq 37.5\%$; RR 0.89, 95% CI 0.68–1.16) median control group mortality (test for subgroup differences: $p = 0.06$), and TSA supported this.

Conclusions IVVC monotherapy may be associated with mortality benefits in critically ill patients, particularly in patients with a high risk of dying. Given the low certainty of evidence, this potentially life-saving therapy warrants further studies to identify the optimal timing, dosage, treatment duration, and patient population that will benefit most from IVVC monotherapy.

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Keywords Vitamin C, Ascorbic acids, Sepsis, Critical illness, Systematic review

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Introduction

Vitamin C is an essential micronutrient with pleiotropic functions and can serve as an antioxidant [1]. In critically ill patients, vitamin C level is depleted [2, 3] despite receipt of enteral and/or parenteral nutrition sources [4] and lower levels have been associated with worse clinical outcomes [3, 4].

In the last decade, metabolic resuscitation using high-dose intravenous vitamin C (IVVC) has been tested as a pharmacotherapeutic agent to modify the inflammatory cascade and improve clinical outcomes in critical illness [5]. Most trials have evaluated high-dose IVVC monotherapy or in combination with intravenous hydrocortisone and thiamine [5]. Previously, several systematic reviews and meta-analyses (SRMAs) of randomized controlled trials (RCTs) were performed to evaluate the effects of IVVC in critical illness [6–9]. Overall, no significant effect of IVVC on mortality was found. However, in a subgroup analysis, we previously demonstrated that IVVC monotherapy confers a greater benefit [relative risk (RR) 0.64, 95% confidence interval (CI) 0.49 to 0.83; $p=0.0006$], compared to combination therapy (RR 1.00, 95% CI 0.85 to 1.18; $p=0.99$), and the test for subgroup differences was significant ($p=0.004$) [8, 10], further enhance the signal of mortality benefit of IVVC monotherapy.

The Lessening Organ Dysfunction With VITamin C (LOVIT) study, a recent large, multicenter trial compared high-dose (200 mg/kg/day body weight for 96 h) IVVC monotherapy to placebo in patients with septic shock found IVVC monotherapy increased the risk of a composite endpoint of death or persistent organ dysfunction at day 28 (RR 1.21, 95% CI 1.05 to 1.40; $p=0.01$) [11]. However, an SRMA that included the results of LOVIT (published at the same time) found that IVVC monotherapy was still associated with a significant mortality benefit (RR 0.65, 95% CI 0.50–0.86; $p=0.002$), compared to combination therapy (RR 0.94, 95% CI 0.74–1.19; $p=0.58$), and there was still evidence for a significant test for subgroup differences ($p=0.04$) [12]. However, this SRMA included several studies with inappropriate study design or patient population: a quasi-trial [13], a study that excluded intubated patients [14], and a study that was published in abstract form [15], which may limit the confidence of the reported results.

The disparate findings from SRMAs of RCTs and a well-conducted landmark RCT of IVVC monotherapy are difficult to reconcile. It is possible that type-1 errors may have occurred in the IVVC monotherapy subgroup analyses of previous SRMAs, because each SRMA update entails repeated statistical testing which would increase the risk of random error. A statistical technique, Trial Sequential Analysis (TSA), that is analogous to interim

analyses in RCTs can be employed to control for type-I error, because it sets a more stringent statistical significance threshold for the initial trials and gradually reduces the threshold with each subsequent trial [16]. Another shortfall of previous SRMAs is that certain important effect modifiers are not robustly explored [12]. Therefore, we aim to perform an updated SRMA of RCTs specifically in critically ill patients and include TSA to robustly examine if the effects of IVVC monotherapy are modified by dose, timing, treatment duration, the included patient population, or the trial quality.

Methodology

We conducted this SRMA according to the PRISMA 2020 guidelines [17]. The PRISMA 2020 checklist is shown in the Additional file 1. The study protocol was registered in PROSPERO (CRD42022323880).

Eligibility criteria

RCTs among critically ill patients comparing IVVC monotherapy with placebo or usual care and reported at least one clinical outcome (mortality, infectious complications, duration of mechanical ventilation, and intensive care unit [ICU] or hospital length of stay) were included. Quasi-randomized trials, studies conducted among elective surgical or non-critically ill patients, studies that used any combination therapy, and studies published in abstract form were excluded.

Information source and search strategies

MEDLINE, EMBASE, CENTRAL and CINAHL were searched with relevant subject headings and keywords from database inception to 22 June 2022 without language restrictions. Personal files and the reference list of previous SRMAs were reviewed. Additional file 1: Table S1 shows the search strategies.

Study selection process

One author screened the title and abstract for potential eligible studies (ZYL). The potential studies were retrieved, and the full text were evaluated independently by two authors (ZYL, LOR). Disagreements were discussed with the senior author (DKH).

Data collection process and data items

Data items were collected independently by two authors (ZYL, LOR) in a standardized data abstraction form (Additional file 1). Two studies published in Chinese were abstracted by a single author that understands Chinese (ZYL) [18, 19]. Where needed, authors were contacted (up to two times) to obtain additional data.

Study quality and risk-of-bias assessment

The quality of the included trials was evaluated independently by two authors (ZYL, LOR) using the Canadian Critical Care Nutrition (CCN) Methodological Quality System [8], and the Cochrane Risk of Bias version 2 (ROB2) [20]. The use of CCN Methodological Quality System allow us to compare critical care nutrition trials across time and topics. Any disagreements were resolved by the senior author (DKH).

Statistical analysis and data handling

The primary outcome was overall mortality. The mortality timepoint was chosen in the following order: 28-day mortality, hospital mortality, ICU mortality, other mortality—if a study reported multiple mortality timepoints. Secondary outcomes were: 28-day mortality, longer term mortality (≥ 60 days and the longest follow-up reported), duration of mechanical ventilation, ICU and hospital length of stay, incidences of acute kidney injury and renal replacement therapy, SOFA score at 96 h, dose and duration of vasopressor used, and adverse events (as reported by the original manuscript).

Dichotomous outcomes were presented as risk ratio (RR), while continuous outcomes were presented as mean difference (MD) or standardized mean difference (SMD). The DerSimonian–Laird random-effect model was used to account for the different patients' characteristics, dosing, duration, and starting time of the IVVC [21]. For the analysis of continuous outcome, authors of the primary publication were contacted to obtain the mean and standard deviation (SD) if this information was not reported. Median and range are not converted to mean and SD for meta-analysis.

The following subgroup analyses were planned a priori: single vs multicenter center trial, higher (administering $\geq 10,000$ mg/day based on a 70 kg adult) vs lower dose of vitamin C [8, 22], and sepsis vs non-sepsis trial.

For studies that had >1 group of IVVC intervention with different dosages, the results of the two IVVC group were combined and compared with the control group. For subgroup analysis of higher vs lower doses of Vitamin C, the control group sample size was distributed proportionally to the two intervention groups [23]. For subgroup analysis of $\leq$ vs >24 h, it is assumed that the intervention was initiated >24 h for 4 studies with unclear reporting of this information [24–27].

Post-hoc—since LOVIT was a negative trial, which is in the opposite direction from other trials, [28] we performed a sensitivity analysis for our primary outcomes using the fixed-effect model (Mantel–Haenszel method), because this model assigns more weight to larger trials [28]. We also performed a sensitivity analysis in trials,

where the patients' mean, or median baseline vitamin C level was reported to be deficit (≤ 21 $\mu\text{mol/L}$ [22]). For subgroup analysis, we added six additional post-hoc analyses to further explore the source of heterogeneity in included trials: studies that enrolled patients above vs below the median overall control group mortality, $>$ vs $\leq$ median CCN score, low vs other risk of bias, duration of treatment $>$ or ≤ 4 days, commencement of the intervention $\leq$ vs >24 h of an event, and bolus vs continuous infusion.

Heterogeneity was quantified by the I^2 measure. Publication bias was visualized by the funnel plot. Egger's test was conducted for meta-analyses that included >10 studies [29], using STATA 16.1 (StataCorp LLC, Texas). All meta-analysis and test for subgroup differences were conducted using Revman 5.4 (Cochrane IMS, Oxford, UK). A two-sided p value of <0.05 was considered statistically significant, and a p value of <0.10 was considered a trend [30].

Trial sequential analysis

To control for type-I [31] and type-II errors and further confirming the results of our meta-analysis, TSA for overall mortality was performed with the following parameters [32]: alpha 5%, beta 10%, and the DerSimonian–Laird random effect model. Between-trial heterogeneity was adjusted by the diversity-estimate (D^2). The control group mortality was the observed mortality in this current meta-analysis (i.e., 35%), and the effect size [relative risk reduction (RRR)] of 30% was used based on the subgroup analysis of IVVC monotherapy in previous meta-analyses [8, 12], with sensitivity analyses for RRR of 25% and 20%. We also performed a sensitivity analysis using the Biggerstaff–Tweedie (BT) random-effect model as it attributes more weight to larger trials and less weight to smaller trials [16]. All TSA was performed using the TSA software (0.9.5.10 Beta, The Copenhagen Trial Unit, Denmark). (See Additional file 1 for detailed TSA explanation),

Certainty of the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the certainty of evidence for only the primary outcome [33]. Secondary outcomes were not evaluated, since most of the continuous outcomes were reported as medians (e.g., length of stay and SOFA score) and could not be statistically aggregated or were reported only in a few studies [e.g., incidences of acute kidney injury (AKI) or renal replacement therapy (RRT)]. The quality of the evidence was rated as high, moderate, low, and very low by considering the risk of bias, inconsistency, indirectness,

imprecision, and publication bias. GRADEpro was used to prepare the GRADE evidence profile table.

Results

Study selection

A total of 1361 records were found, and 66 full texts were assessed after the removal of duplicates and title/abstract screening. In addition, 451 articles were screened from citation searching and personal files, and 30 were retrieved. Therefore, a total of 96 articles were assessed for full-text. Finally, 16 RCTs ($n=2130$) were included (Additional file 1: Figure S1) [11, 18, 19, 24–27, 34–42]. Additional file 1: Table S2 lists the excluded studies.

Study characteristics

The study characteristics are summarized in Table 1. Ten (62.5%) studies enrolled patients with sepsis, and seven (43.8%) were multicenter trials. The mean/median age ranged from 29.4 to 73, where 11 (68.8%) of the studies had a mean/median age of >55 years. Ten studies reported the acute physiology and chronic health evaluation II (APACHE II) score (range: 13.5–24.5), and 11 studies reported the sequential organ failure assessment (SOFA) score (range: 5.9–13.3). Seven studies reported baseline plasma vitamin C levels (range: 3.4–129.3 $\mu\text{mol/L}$) in which patients in six studies were considered vitamin C deficient (range: 10–22 $\mu\text{mol/L}$) [11, 19, 27, 36, 41], one study had a very borderline vitamin C level (median: 22 $\mu\text{mol/L}$) and we also considered the patients were deficit in vitamin C [38], and one study had normal baseline vitamin C levels [26].

Study quality assessments

The CCN score of the studies ranged from 5 to 12, with a median score of 9. Additional file 1: Table S3 shows the detailed CCN score for all the included trials. In general, studies had low risk-of-bias in the extent of follow-up, treatment protocol, and outcome measurements; moderate risk-of-bias in randomization, baseline characteristics, analytical methods, and blinding; and high risk-of-bias in patient selection and co-interventions (Fig. 1A). Additional file 1: Figure S2 shows the ROB2 traffic light plot for each study. Overall, 3 (18.8%) studies had low risk of bias, 6 (37.5%) had some concerns, and 7 (43.8%) had high risk of bias. Most studies had risk of bias arising from the randomization process and in selection of the reported result (Fig. 1B).

Study intervention

Additional file 1: Table S4 summarizes the study interventions. Three studies had more than one group of vitamin C intervention [19, 35, 36] in which a lower and a higher dose of vitamin C were administered to different

groups of patients. The events before IVVC commencement were different in most studies (e.g., ICU admission/randomization/pressor initiation/post-abdominal surgery/head trauma/diagnosis of acute respiratory distress syndrome), and 7 studies started IVVC <24 h of an event, whereas 9 studies started IVVC >24 to ≤ 96 h after an event. The duration of intervention ranged from 3 to 7 days, with 11 studies administering IVVC for ≤ 4 days. The total vitamin C received per day ranged from 450 to 24,000 mg, with 7 (43.8%) studies administered high-dose IVVC ($\geq 10,000$ mg/day). Three studies administered IVVC through continuous infusion [26, 40, 42].

Additional file 1: Tables S5 and S6 summarize the clinical outcomes and adverse events, respectively.

Results of the primary outcome

In the aggregated estimate, we found evidence for a reduction in overall mortality (RR 0.73, 95% CI 0.60–0.89; $p=0.002$; $I^2=42\%$; 16 studies; Fig. 2A) associated with IVCC. In sensitivity analyses, there was still evidence for a reduction in overall mortality when fixed-effect model was used (RR 0.83, 95% CI 0.73–0.93; $p=0.002$; Fig. 2B). We found no evidence of subgroup differences in our predefined subgroups of single vs multicenter studies, sepsis vs non-sepsis patients, and higher vs lower dose of IVVC (Fig. 3 and Additional file 1: Figures S3–S5). In our *post-hoc* subgroup analyses we found no evidence of subgroup differences between subgroups of studies with > vs ≤ 9 CCN score, low vs other risk of bias, intervention commenced $\leq$ vs >24 h, duration of treatment of > vs ≤ 4 days, and bolus vs continuous infusion (Fig. 3 and Additional file 1: Figures S7–S11). In the subgroup analysis of above vs below median control group mortality, we observed a trend towards significant subgroup differences ($p=0.06$). That is, IVVC monotherapy may benefit sicker (RR 0.65, 95% CI 0.54–0.79; $p<0.00001$; $I^2=0\%$; 8 studies) but not the less sick patients (RR 0.89, 95% CI 0.68–1.16; $p=0.38$; $I^2=18\%$; 8 studies) (Additional file 1: Figure S6). In studies that reported baseline vitamin C deficit, we found no evidence of a treatment effect (Additional file 1: Figure S12). No evidence of funnel plot asymmetry was detected in the overall mortality analysis ($p=0.54$; Additional file 1: Figure S33).

Trial sequential analysis

The TSA graphs are presented in Fig. 4 and Additional file 1: Figures S34–S39 and summarized in Table 2. TSA confirmed the mortality benefits of IVVC monotherapy with high certainty for treatment effects of 30% and 25%. Although a larger sample size is required for a treatment effect of 20%, there was a trend towards significant mortality risk reduction (TSA adjusted RR 0.731, 95% CI 0.532–1.003). Sensitivity analysis using

Table 1 Study and baseline characteristics

Author, year (Country)	Population	Number of centers	n (Analyzed)	Age	M/F	APACHE II	SOFA	Baseline Vit C level (umol/L)	Vit C level after intervention (umol/L)	Weight in kg
1. Ferron-Celma 2008 (Spain)	Abdominal surgery with postop mortality risk > 30%	1	20	67.8 ± 4.5 vs 65.1 ± 3.6	11/9	NR	NR	NR	NR	NR
2. Razmkon 2011 (Iran)	Age ≥ 16, severe head injury (GCS ≤ 8). Exclude: G6PD, severe liver or renal disease	2	76 (Group A, B and D)	31.1 (16–67) vs 29.5 (19–75) vs 29.4 (16–68)	63/13	NR	NR	NR	NR	NR
3. Fowler 2014 (USA)	Severe sepsis with organ dysfunction	1	24	30–70 vs 49–92 vs 54–68	13/11	204 (12–23) vs 24.0 (12–33) vs 204 (15–29)	10.1 ± 2.0 vs 10.8 ± 4.4 vs 13.3 ± 2.9	All: 17.9 ± 2.4 20.2 (11–45) vs 16.7 (14–28) vs 17.0 (11–50)	Day 4: 331 (110–806) vs 3082 (1592–5722) vs 15.6 (7–27)	NR
4. Zabet 2016 (Iran)	Surgical ICU patients with septic shock requiring vasopressors	1	28	64.14 ± 15.98 vs 63.71 ± 13.84	21/7	19.07 ± 5.18 vs 23 ± 5.61	11.78 ± 2.22 vs 12.35 ± 3.00	NR	NR	NR
5. Chen 2019 (China)	Age ≥ 18, sepsis, ICU stay ≥ 96 h Exclude: G6PD, severe arrhythmia	2	122	69 ± 13.5 vs 67.4 ± 17.3 vs 72 ± 16.6	88/31	18.5 ± 5.1 vs 19.6 ± 6.0 vs 18.1 ± 5.7	6.3 ± 2.5 vs 7.0 ± 2.7 vs 6.3 ± 2.8	3.5 ± 2.0 vs 4.0 ± 3.2 vs 3.4 ± 2.5	48 h: 26.65 ± 18.94 vs 48.88 ± 31.43 vs 2.80 ± 2.91 96 h: 52.40 ± 56.03 vs 111.62 ± 64 vs 4.26 ± 3.22	64.8 ± 7.0 vs 65.5 ± 7.6 vs 65.3 ± 6.2
6. Fowler 2019 (USA)	Age ≥ 18, sepsis, mechanically ventilated with PF ratio < 300. Exclude: active kidney stone, DKA, interstitial lung disease	7	166	53 (39–67) vs 57 (44–70)	90/77	NR	mSOFA: 9.8 ± 3.2 vs 10.3 ± 3.1	22 (8–39) vs 22 (11–37)	48 h: 166 (88–376) vs 23 (9–37) 96 h: 169 (87–412) vs 26 (9–41) 168 h: 46 (19–66) vs 29 (12–39)	NR
7. Niu 2019 (China)	Age 18–75, sepsis in ICU. Exclude: immunocompromised, metastatic cancer	1	234	58.2 ± 14.1 ± 60.1 ± 14.2	116/118	22.0 (18.0–29.0) vs 24.0 (19.0–29.0)	8.3 ± 2.7 vs 8.7 ± 2.9	NR	NR	NR

Table 1 (continued)

Author, year (Country)	Population	Number of centers	n (Analyzed)	Age	M/F	APACHE II	SOFA	Baseline Vit C level (umol/L)	Vit C level after intervention (umol/L)	Weight in kg
8. Lv 2020 (China)	Age 18–75, ICU patients with sepsis. Exclude: immunocompromised	1	117	58.7 ± 14.2 vs 60.2 ± 14.1	59/58	21.0 (19.0–28.0) vs 23.0 (20.0–29.0)	8.6 ± 2.9 vs 8.9 ± 3.1	NR	NR	NR
9. Jamali Moghadam Siahkali 2021 (Iran)	Age ≥ 18, COVID-19 with clinical manifestation of ARDS or myocarditis. Exclude: G6PD, ESRF	1	60	57.53 ± 18.27 vs 61.00 ± 15.90	30/30	NR	NR	NR	NR	NR
10. Kassem 2021 (Egypt)	Age 18–64, TRALI ≤ 6 h of transfusion. Exclude: ever had kidney stone, G6PD, AKI, immunocompromised	2	80	52.6 ± 11.6 vs 47.2 ± 13.7	45/35	18.7 ± 8.1 vs 21.1 ± 7.1	6.7 ± 2.9 vs 5.9 ± 2.8	NR	NR	NR
11. Mahmood-poor 2021 (Iran)	Age: 18–80, severe pneumonia in ICU with CURB-65 score > 3. Exclude: vitamin C allergy, end-stage lung disease/malignancy, G6PD, DKA, active kidney stone	1	80	56.9 ± 12.3 vs 58.3 ± 13.1	46/34	24.5 ± 5.4 vs 22.7 ± 4.3	12.5 ± 2.7 vs 10.7 ± 2.7	117.1 ± 72.34 vs 129.3 ± 77.0	96 h: 449.7 ± 150.0 vs 93.0 ± 58.7	NR
12. Zhang 2021 (China)	Age ≥ 18 and < 80, COVID-19, PF ratio < 300. Exclude: G6PD, end-stage pulmonary disease	3	56	66.3 ± 11.2 vs 67.0 ± 14.3	36/20	13.5 (10.3–15.8) vs 14.0 (11.0–16.0)	NR	NR	NR	59.7 ± 11.2 vs 64.4 ± 9.3

Table 1 (continued)

Author, year (Country)	Population	Number of centers	n (Analyzed)	Age	M/F	APACHE II	SOFA	Baseline Vit C level (umol/L)	Vit C level after intervention (umol/L)	Weight in kg
13. Ap 2022 (India)	Sepsis defined by sepsis 3. Exclude: chronic kidney disease, chronic alcoholics, immunocompromised	1	40 (Group 1 and 4)	All: 52.4 ± 13.7	28/12	NR	NR	21.7 ± 10.0 vs 17.5 ± 7.9	Day 6: 22.8 ± 12.0 vs NR	NR
14. Rosengrave 2022 (New Zealand)	Septic shock with organ failure. Exclude: G6PD	1	40	69 (64–76) vs 66 (57–71)	27/13	SAPSII: 50 (41–49) vs 49 (42–58)	8.5 (6.8–11) vs 9.0 (7.8–10)	10 (4–13) vs 8.2 (4.7–11)	72 h: 408 (227–560) vs 4.4 (3.1–8.8)	Median weight: 80 kg
15. Wacker 2022 (USA)	Age ≥ 18, septic shock (≤ 24 h of diagnosis). Exclude: cardiac arrest, cardiac surgery 48 h, history of kidney stone, G6PD, ESRF	5	124	68.9 (60.1–79.9) vs 73.0 (60.9–80.0)	63/61	22 (16.5–28) vs 23 (17–28.5)	10 (7–11) vs 9 (7–12)	NR	NR	NR
16. Lamontagne 2022 (International)	Proven or suspected infection and receiving vasopressors ≤ 24 h of ICU admission. Exclude: known kidney stone within past 1 year	35	863	65.0 ± 14.0 vs 65.2 ± 13.8	538/324	24.2 ± 7.4 vs 24.1 ± 7.9	10.2 ± 3.4 vs 10.1 ± 3.7	20.6 ± 70.6 vs 19.1 ± 39.7	NR	84.9 ± 22.6 vs 85.6 ± 26.6

The results are presented in this sequence: intervention (low-dose vs high dose) vs control. Fowler 2019 reported mSOFA: no bilirubin score because of many missing values. To convert vitamin C from umol/L to mg/dL, divide values by 56.78

AKI acute kidney injury, DKA diabetic ketoacidosis, ESRF end-stage renal failure, F female, G6PD glucose-6-phosphate dehydrogenase deficiency, M male, NR not reported, TRALI transfusion-related acute lung injury

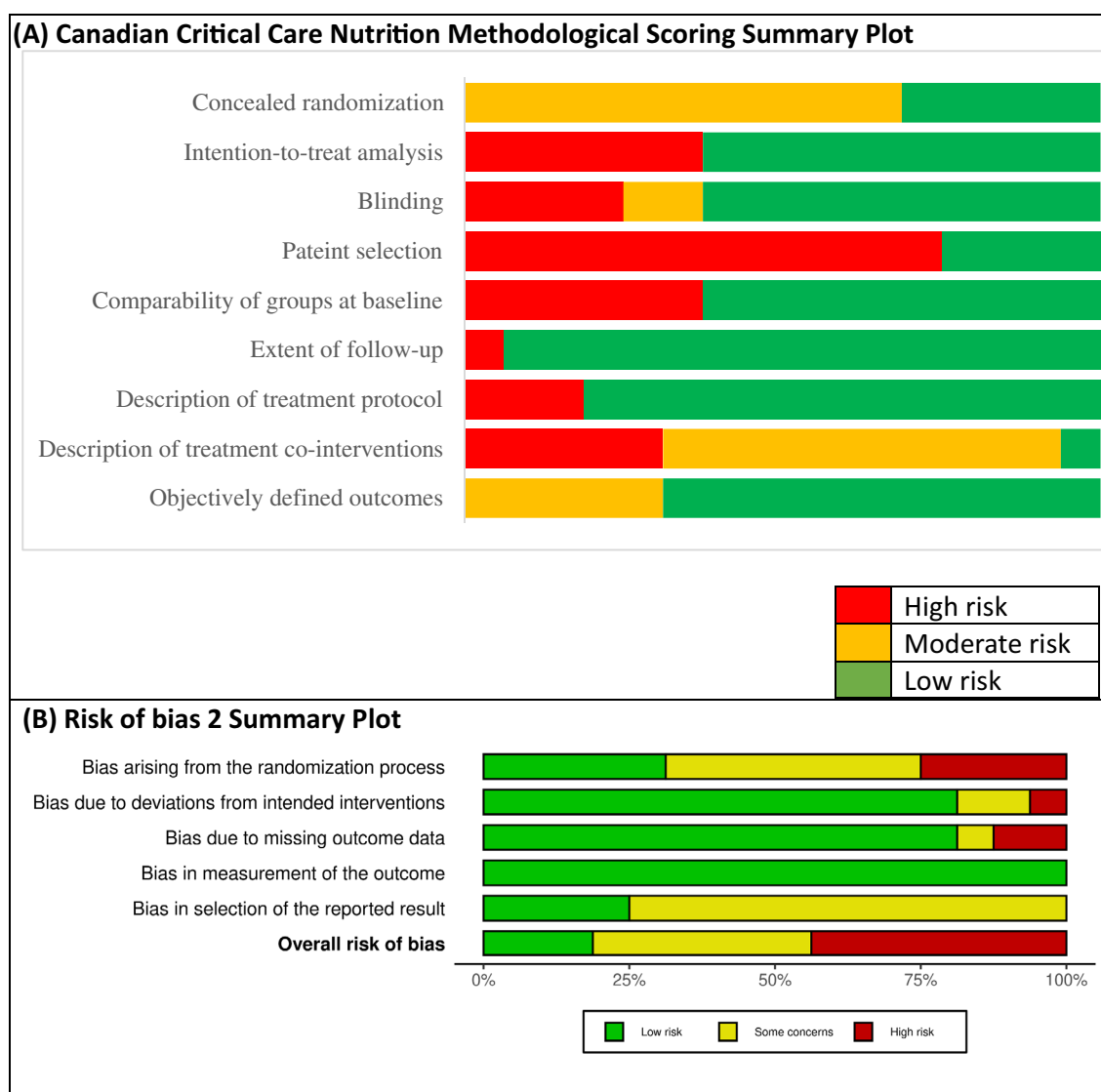


Fig. 1 Summary of **A** Canadian critical care nutrition methodological scoring and **B** risk of bias 2

the BT model (Additional file 1: Table S7) confirmed the mortality benefits of IVVC monotherapy with high certainty for treatment effects of 30%, 25% and 20%.

Similarly, TSA confirmed the mortality benefits of IVVC monotherapy with high certainty in the subgroup of studies that recruited patients with higher control group mortality for treatment effects of 30%, 25% and 20%, and similar results were shown in the sensitivity analysis using the BT model. In contrast, in the subgroup of studies that recruited patients with lower control group mortality, larger sample sizes are required for treatment effects of 30%, 25% and 20%. While the BT model showed that further trials are futile for treatment effect of 30% and 25%, and larger sample size is required for treatment effect of 20%

Result of the secondary outcomes

IVVC monotherapy is associated with significant reduction in 28-day mortality (RR 0.71, 95% CI 0.53, 0.95; $p=0.02$; $I^2=55\%$; 9 studies; Additional file 1: Figure S13). Similar to the main analysis, we found no evidence of subgroup differences for 28-day mortality for all the (Additional file 1: Figures S13–S21) subgroups analyses except for the subgroup analysis based on median control group mortality (Additional file 1: Figure S16). There was a significant subgroup differences for above vs below median control group mortality ($p=0.0003$) in which IVVC monotherapy was associated with significant mortality reduction in trials that enrolled sicker but not the less sick patients (Additional file 1: Figure S16). Additional file 1: Figure S22

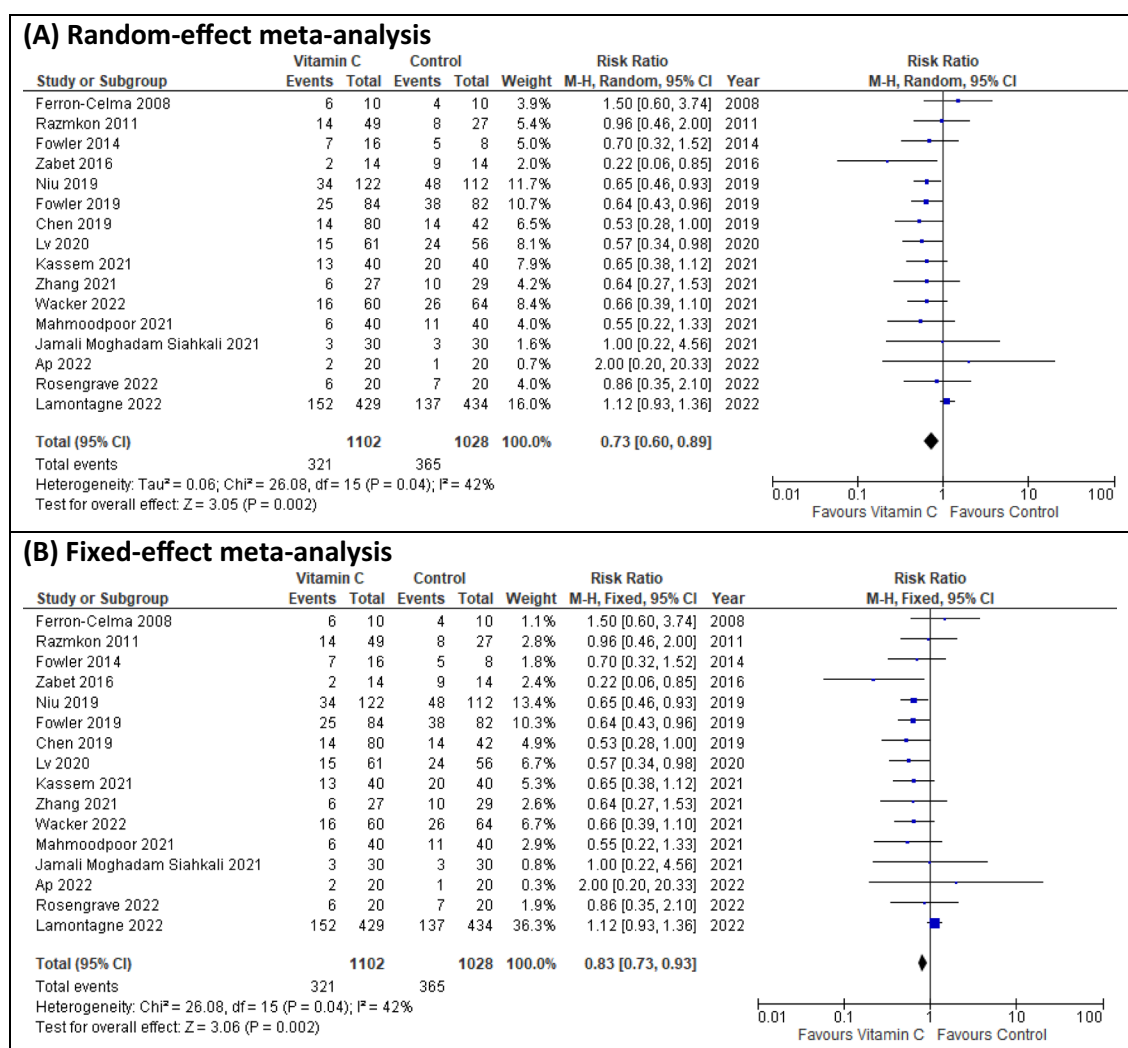


Fig. 2 Overall mortality. **A** Random-effect meta-analysis, and **B** sensitivity analysis with fixed-effect meta-analysis

shows the summary of the subgroup analysis for 28-day mortality.

We found no evidence that IVVC impacted longer term mortality (RR 0.98, 95% CI 0.82, 1.19; $p=0.86$; 4 studies) [11, 35, 38, 41], duration of mechanical ventilation (MD -1.71 , 95% CI -5.94 , 2.52; $p=0.43$; $I^2=95\%$; 3 studies), ICU (MD -0.63 , 95% CI -2.01 , 0.75; $p=0.37$; $I^2=35\%$; 7 studies) and hospital (MD -0.55 , 95% CI -3.09 , 2.88; $p=0.75$; $I^2=0\%$; 4 studies) length of stays. No significant differences were found for incidences of AKI (RR 0.95, 95% CI 0.81–1.11; $p=0.52$; $I^2=0\%$; 4 studies) [11, 25, 26, 40] and RRT (RR 2.00, 95% CI 0.59–6.77; $p=0.27$; $I^2=65\%$; 3 studies) [11, 40, 42]. (Additional file 1: Figures S23–S28).

In studies that reported the SOFA score, we observed a trend towards lower SOFA scores at the 96th hour for

the IVVC group (MD -0.82 , 95% CI -1.77 , 0.14; $p=0.09$; $I^2=63\%$; Additional file 1: Figure S29) [11, 19, 26, 41]. Four studies reported the dose of vasopressors used. The studies reported either the total vasopressors usage in 72 [37] or 96 [19]h in $\mu\text{g}/\text{min}$, or the mean vasopressor usage in $\mu\text{g}/\text{min}$ [26] or units/min [41]. When pooled, we found no difference in vasopressor usage between groups (SMD -0.26 , 95% CI -0.83 , 0.31; $p=0.37$; Additional file 1: Figure S30). Ten studies reported the duration of vasopressors but mean and SD were available in 3 studies [19, 26, 37]. When pooled, IVVC seemed to be associated with a reduced duration of vasopressors (MD -0.79 days, 95% CI -1.24 , -0.34 ; $p=0.0006$; Additional file 1: Figure S31). Additional descriptions of these results are available in the Additional file 1.

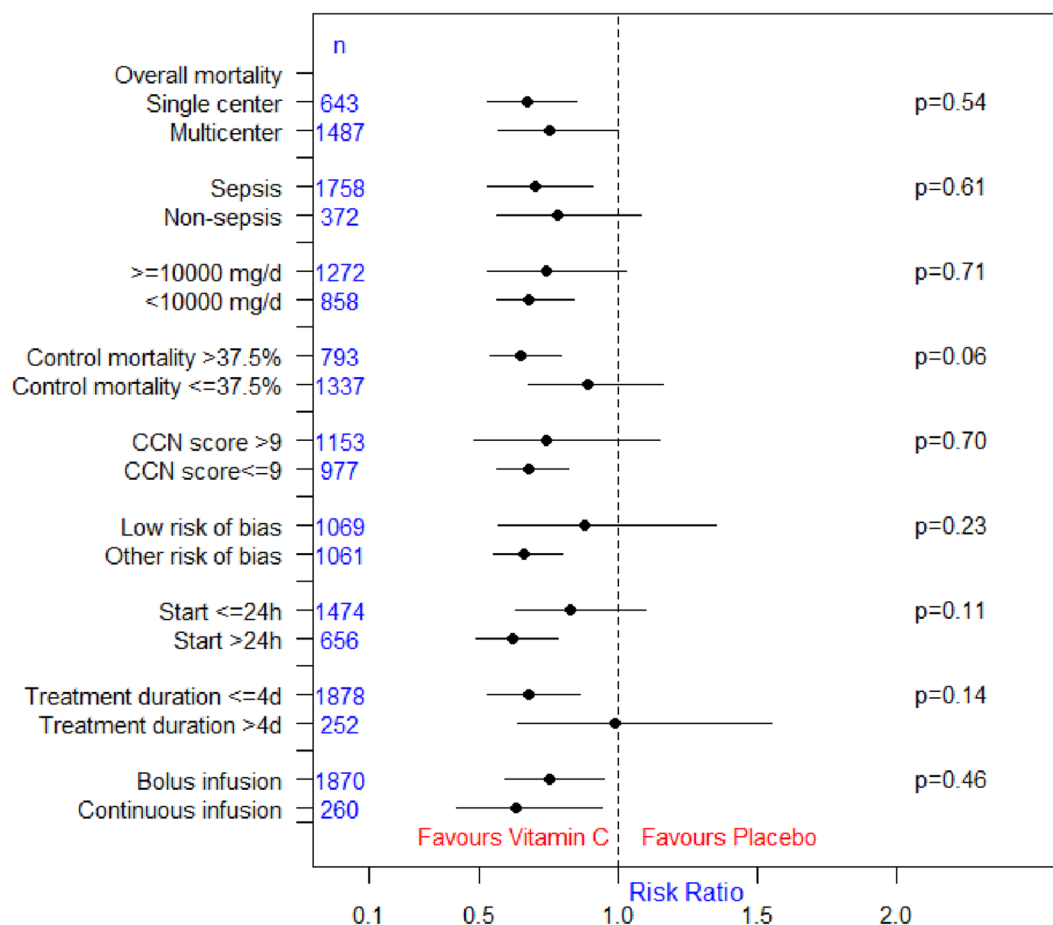


Fig. 3 Subgroup analysis for overall mortality. CCN critical care nutrition

Adverse events

The adverse event rate was similar between groups (RR 1.04, 95% CI 0.90, 1.20; $p=0.59$; $I^2=0\%$; 12 studies; Additional file 1: Figure S32).

Certainty of the evidence

The overall certainty of the evidence using GRADE was rated as low (Table 3). The certainty of the evidence was downgraded due to serious risk of bias (only 3/16 of the included trials are of low risk of bias) and inconsistency (heterogeneity I^2 is 42%)

Discussion

Summary of main findings

This SRMA of RCTs demonstrated that IVVC monotherapy is associated with a significant reduction in overall mortality. This finding is consistent with TSA and sensitivity analysis using the fixed-effect model meta-analysis. However, the certainty of evidence is low due to the serious risk of bias and inconsistency. On the other hand, based on limited analyzable studies, IVVC monotherapy did not affect the duration of mechanical ventilation, length of ICU and hospital stay, organ failure score at 96 h, vasopressors dose and duration, and incidences

(See figure on next page.)

Fig. 4 Trial sequential analysis for overall mortality. DARIS: diversity-adjusted required information size; RRR: relative risk reduction. The Z curve in blue measures the treatment effect (pooled relative risk). The green parallel lines are the boundaries of conventional naïve alpha of 5%, and the TSA boundaries are in red. A treatment effect outside the TSA boundaries of benefit or harm indicates that there is reliable evidence for a treatment effect, and a treatment effect within the futility zone (the triangle between the green parallel lines) indicates that there is reliable evidence of no treatment effect

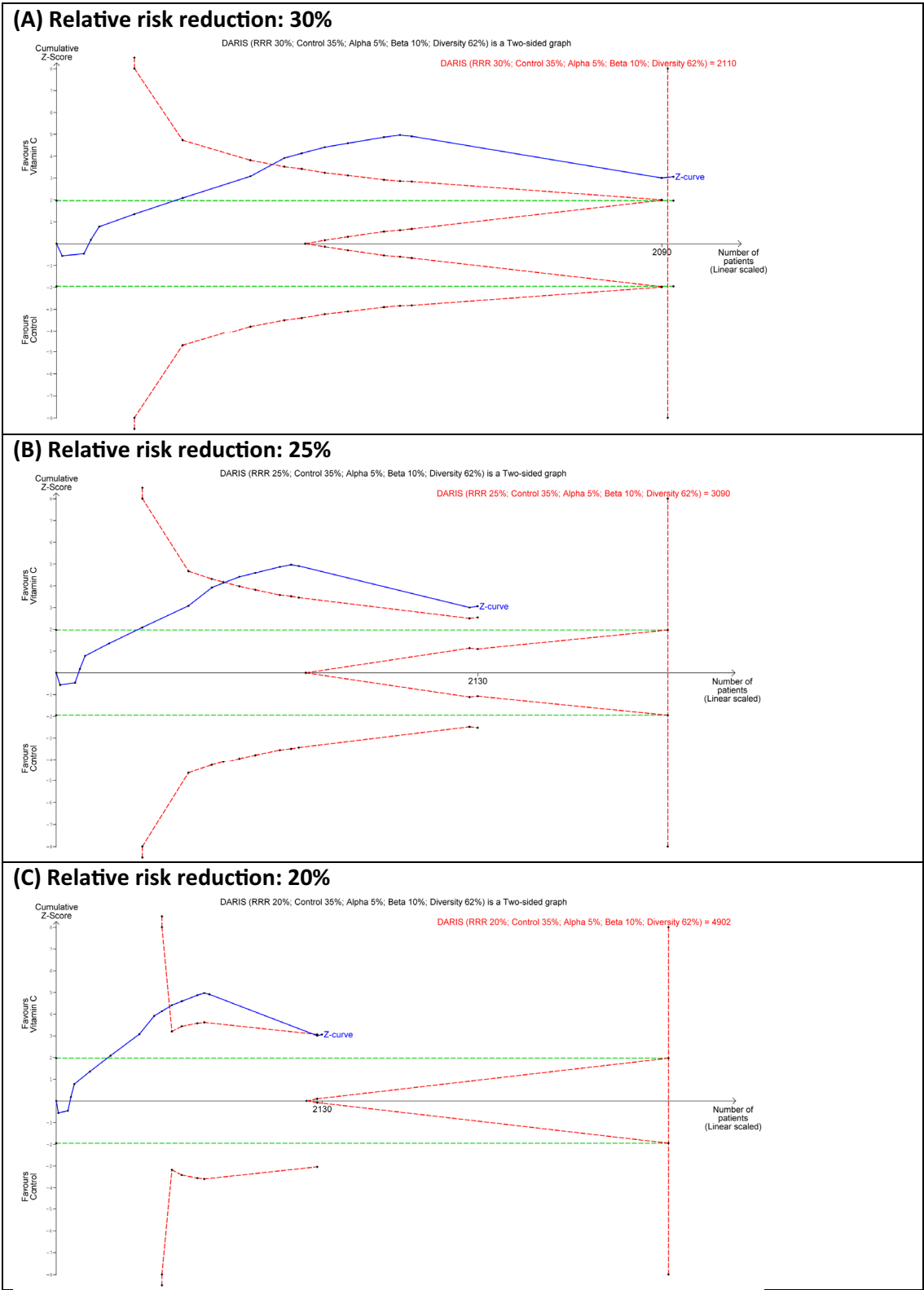


Fig. 4 (See legend on previous page.)

Table 2 Trial sequential analysis for overall mortality

Relative Risk reduction, %	Control group event rate, %	I^2 , %	D^2 , %	RIS	RIS achieved	TSA adjusted RR (95% CI)	Results
Overall analysis (16 studies; $n = 2130$)							
30%	35%	42	62	2110	-	0.731 (0.595–0.897)	Sig risk reduction
25%	35%	42	62	3090	-	0.731 (0.563–0.949)	Sig risk reduction
20%	35%	42	62	4902	43.5%	0.731 (0.532–1.003)	Trend to sig reduction
Subgroup with lower control group mortality (8 studies; $n = 1337$)							
30%	30%	18	60	2489	53.7%	0.889 (0.605–1.307)	Uncertain
25%	30%	18	60	3653	36.6%	0.889 (0.560–1.412)	Uncertain
20%	30%	18	60	5811	23.0%	0.889 (0.496–1.596)	Uncertain
Subgroup with higher control group mortality (8 studies; $n = 793$)							
30%	45%	0	0	545	-	0.651 (0.530–0.801)	Sig risk reduction
25%	45%	0	0	793	-	0.651 (0.535–0.793)	Sig risk reduction
20%	45%	0	0	1251	-	0.651 (0.506–0.839)	Sig risk reduction

DerSimonian–Laird Random effect model, Alpha 5%, beta 10%

RIS required information size, TSA Trial sequential analysis

of AKI and RRT. The signal of mortality reduction is not modified by the vitamin C dose administered, whether septic patients were included exclusively, single/multi-center trial, the trial quality based on median CCN score or ROB2, timing of commencement, or duration of treatment. However, in sicker patients (higher median control group mortality rate), IVVC monotherapy seemed to be associated with a significant reduction in overall mortality. IVVC did not specifically reduce mortality in the few available studies that reported patients with baseline vitamin C deficiency. No evidence of adverse events or safety issues was found.

Interpretation of the results in the context of other evidence

Our SRMA is the first to robustly explore the effects of IVVC monotherapy in critically ill patients through various subgroup analyses and TSA. In contrast, previous SRMA included trials that administered both IVVC monotherapy and combination therapy and found no significant effect of IVVC on 28-day to 1-year mortality [10]. The overall analysis of the most recent SRMA, among patients with severe infection, found a significant mortality reduction at hospital discharge or 30 days [12]. However, they concluded with moderate certainty that IVVC increased 90-day mortality (a non-statistical significant finding, RR 1.07, 95% CI 0.94–1.21) based on a meta-analysis of 5 trials with low risk of bias. Notably, 3 of these 5 trials investigated IVVC combination therapy [43–45]. They further compared IVVC monotherapy and combination therapy and found a significant test of subgroup differences in which IVVC monotherapy (but not combination therapy) had mortality benefits—a similar

finding in our previous SRMA [8, 12]. Statistically significant finding in meta-analysis may be a type-1 error due to low quality or inadequately powered trials, publication bias, and/or repeated significant testing [46]. The TSAs and sensitivity analysis in our SRMA indicated that the risk of type-1 error in finding a significant mortality benefits of IVVC monotherapy in our meta-analysis is very low.

Our SRMA included the most recent multicenter LOVIT trial [11] which found a higher incidence of a composite outcome of persistent organ dysfunction (need for vasopressor, renal replacement therapy and/or mechanical ventilation) plus death on trial day 28. The LOVIT trial did not demonstrate increased mortality at 28 days or 6 months, but when they combined 28-day mortality with persistent organ failure, they achieved a significant result on the composite outcome. It is worth pointing out that the authors acknowledged that the analysis of the primary outcome was very fragile; statistical significance was lost when analyzed using different adjustment techniques or when analyzed in unadjusted fashion. Nevertheless, when we examined the whole corpus of evidence including the LOVIT trial results, we found mortality benefits of IVVC monotherapy, albeit with low certainty. Furthermore, in this corpus of evidence, we found no evidence of more or persistent organ dysfunction, since we observed no differences in SOFA score at 96 h, dose of vasopressors, incidences of AKI and RRT, duration of mechanical ventilation, length of ICU and hospital stays, and longer term mortality. In addition, the days on vasopressors were significantly shorter. However, these secondary outcomes were from limited analyzable studies and these findings may be impacted by

Table 3 GRADE certainty assessment and summary of findings table for overall mortality

Certainty assessment					Summary of findings					
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With placebo	With Intravenous Vitamin C Monotherapy		Risk with placebo Risk difference with Intravenous Vitamin C Monotherapy
Overall mortality 2130 (16 RCTs)	Serious ^a	Serious ^b	Not serious	Not serious ^c	none		365/1028 (35.5%)	321/1102 (29.1%)	RR 0.73 (0.60 to 0.89)	96 Fewer per 1000 (from 142 to 39 fewer)

CI confidence interval, MD mean difference, RR risk ratio, SMD standardised mean difference

^a 3/16 of the included trials are of low risk of bias, accounting for 30.7% of the weight in random-effect meta-analysis, while 7/16 of the included trials are of high risk of bias, accounting for 40.6% of the weight in random-effect meta-analysis. However, result of the sensitivity analysis using fixed-effect meta-analysis (low risk of bias studies account for 48.5% of the weight) is consistent with the result of random-effect meta-analysis. Therefore, the result is downgraded by one instead of two levels

^b The overall heterogeneity I^2 is 42%

^c Both sensitivity analysis using the fixed-effect model meta-analysis, and the result of trial sequential analysis are similar to the main finding

survivorship bias [47]. Of note, the LOVIT investigators were unable to explain a putative mechanism of harm from their a priori defined biomarkers of tissue dysoxia, inflammation, and endothelial injury, which was measured up to day 7. Likely, the LOVIT trial did not harm patients but definitively showed a lack of treatment benefit.

One may argue that our findings could be influenced mainly by smaller studies. Indeed, 1 in 3 large RCTs did not agree with meta-analysis of previous smaller studies due to small study effects arising from publication bias or poor study conduct, leading to the exaggeration of the intervention benefit. However, this may not be the case for our review, since: (1) there was no subgroup differences between studies with higher vs lower quality score or low vs other risk-of-bias, (2) TSA showed very low risk of type-1 error, and (3) sensitivity analysis using the fixed effect model still showed the mortality benefit of IVVC monotherapy. That said, neither the analysis of the LOVIT trial nor our SRMA can explain the inconsistent findings of IVVC mechanistically, or from the perspective of trial or study intervention characteristics. One possible explanation is that LOVIT enrolled patients with a relatively lower risk of mortality, which is further discussed below.

Subgroup and sensitivity analyses

We were unable to demonstrate different treatment effects based on dose, timing, duration of treatment or method of IVVC infusion. Although some may dispute that our subgroup analysis of <24 h represents 'early' treatment within the pathophysiology of critical illness, as it was shown from a retrospective analysis that very early (<6 h of onset of septic shock) administration of IVVC may confer the greatest benefit [48], we were not able to perform such subgroup analysis as almost all of the included trials started IVVC therapy at least 12 h after ICU admission (Additional file 1: Table S4). We found that IVVC monotherapy is associated with a significant reduction in mortality in patients with higher baseline mortality risk, and TSA supported this finding. In contrast, this mortality benefit is not found in patients with lower baseline mortality risk and TSA suggested more studies are needed to reach the required information size for a more definitive conclusion. It is unfortunate that ongoing randomized trials of IVCC were stopped prematurely, presumably on the basis of LOVIT results [49–51].

The direction of the above results (based on baseline mortality risk) is similar to the subgroup analyses of the LOVIT trial in which patients with a lower (the lower 2 quartiles) predicted risk of death were found to have a higher rate of mortality or persistent organ dysfunction if they received IVVC, whereas patients with a higher

predicted risk of death were unaffected. Since our SRMA had greater power, we were able to demonstrate the mortality benefits of IVVC monotherapy in the high-mortality control group trial. That said, we did not have enough power to confirm the treatment effect of IVVC monotherapy in patients with lower baseline mortality.

It remains a compelling concept that only patients with documented vitamin C deficiency would benefit from IVVC supplementation. However, we could not demonstrate a beneficial effect of IVVC therapy in patients with reported baseline vitamin C deficiency, probably due to lack of power, since only a few studies reported the patients' baseline vitamin C level.

It must be noted that the studies including in this SRMA are investigating the administration of Vitamin C at supraphysiological dose (range: 3000–24,000 mg/day for a 70 kg adult, except for one study that administered a relatively lower dose of 450 mg/day [34]; Additional file 1: Table S4) through the intravenous route. Beyond acting as an essential nutrient, such high dose will exert a 'drug-like' effect to the body, this is known as pharmaconutrition. The mortality benefit observed may be due to the stronger effect of the anti-inflammation, immune-enhancing and wound healing functions, among others, exerted by the pharmaconutrition dose of Vitamin C [1, 52]; however, the exact underlying mechanism remained to be investigated. On the other hand, pharmaconutrition is not without any risk, which have to be considered carefully. In our analysis, however, we did not find an increased risk of adverse event, and this is further discussed below.

Adverse events

The lack of adverse events is consistent with the findings of a recent scoping review of 74 studies [53]. The scoping review included all studies that administered high-dose (6 g/d, 75 mg/kg/d or 3 g/m²/d) IVVC in adult patients. The specific adverse events attributed to high-dose IVVC found were oxalate nephropathy, hypernatremia, hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, glucometer error, and kidney stones. However, the authors found no evidence that IVVC is more harmful than placebo in double-blind RCTs. The authors recommended avoiding high-dose IVVC in patients with known or suspected G6PD deficiency. Our review identified 8/16 (50%) of the trials explicitly stated that patients with G6PD deficiency were excluded, and it is unclear if other studies exclude this group of patients. Due to a lack of data, the scoping review did not endorse the use of IVVC in critically ill patients, whereas we found no evidence of increased adverse events in our review of a large group of critically ill patients from RCTs.

Strengths and limitations

Our SRMA has several limitations. Although we did not detect a higher incidences of organ dysfunction associated with IVVC, we are unable to confirm whether organ dysfunction persisted for a longer period (i.e., 28 days) in patients with preexisting organ dysfunction as the follow-up period for organ failure was short (≤ 7 days) in most of the included trials. The limited number of low risk of bias studies and the high heterogeneity ($I^2=42\%$ and $D^2=62\%$) weaken the inferences we can make from our overall findings. In addition, TSA and several of our subgroup and sensitivity analyses were conducted *post-hoc*, and we did not adjust for multiplicity of testing (Additional file 1: Table S8). Accordingly, the results of such analysis should be considered hypothesis-generating. Furthermore, secondary outcomes are reported in smaller number of studies and not evaluated by TSA and GRADE. Therefore, their findings should not be overinterpreted.

The strength of our SRMA is demonstrated with the extensive subgroup and sensitivity analysis to explore the treatment effect of IVVC monotherapy. We also employed TSA to reduce the risk of type-1 or type-2 error in our findings.

Conclusion

Our SRMA found that IVVC monotherapy may be associated with reduced mortality in critically ill patients, a finding that is supported by TSA. However, the certainty of the evidence is low due to serious risk of bias and inconsistency of trial results. The use of IVVC monotherapy appears to be safe with no higher incidences of adverse events observed in these randomized trials. We found no evidence that IVVC monotherapy is associated with higher incidences of organ dysfunction in the short-term; its effect on long-term organ dysfunction remains to be fully investigated. Sicker patients may benefit the most from this therapy; however, this finding is considered hypothesis-generating. We suggest that the quest to search for the optimal dosage, timing, treatment duration as well as which critically ill patient population that may benefit the most from this therapy should be continued within the boundaries of well-designed RCTs.

Abbreviations

AKI	Acute kidney injury
APACHE II	Acute physiology and chronic health evaluation II
CCN	Critical Care Nutrition
CI	Confidence interval
G6PD	Glucose-6-phosphate dehydrogenase
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICU	Intensive care unit
IVVC	Intravenous vitamin C

LOVIT	Lessening organ dysfunction with VITamin C trial
MD	Mean difference
RCT	Randomized controlled trial
RIS	Required information size
ROB	Risk of bias
RR	Relative risk or risk ratio
RRR	Relative risk reduction
RRT	Renal replacement therapy
SD	Standard deviation
SMD	Standardized mean difference
SRMA	Systematic review and meta-analysis
SOFA	Sequential organ failure assessment
TSA	Trial sequential analysis

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-023-01116-x>.

Additional file 1: Methodology. PRISMA 2020 checklist. Results. **Table S1** Search strategy. **Table S2** List of excluded studies. **Table S3** Critical care nutrition methodological system. **Table S4** Intervention. **Table S5** Outcomes summary. **Table S6** Summary of adverse events. **Table S7** Trial sequential analysis for overall mortality (sensitivity analysis). **Table S8** Differences between protocol and review. **Figure S1** PRISMA flowchart. **Figure S2** Risk of bias 2 traffic light plot. **Figure S3** Overall mortality (single vs multicenter trials). **Figure S4** Overall mortality (sepsis vs non-sepsis). **Figure S5** Overall mortality (higher ≥ 10000 mg/day vs lower dose). **Figure S6** Overall mortality (median control group mortality $> vs \leq 37.5\%$). **Figure S7** Overall mortality (median CCN score $>9 vs \leq 9$). **Figure S8** Overall mortality (low vs other risk of bias). **Figure S9** Overall mortality (start of intervention $\leq vs >24$ h of ICU admission/septic shock/pressor initiation etc.). **Figure S10** Overall mortality (duration of treatment $> vs \leq 4$ days). **Figure S11** Overall mortality (bolus vs continuous infusion). **Figure S12** Overall mortality sensitivity analysis studies that measured and reported baseline vitamin C deficit. **Figure S13** 28-day mortality (single vs multicenter). **Figure S14** 28-day mortality (sepsis vs non-sepsis). **Figure S15** 28-day mortality (higher dose ≥ 10000 mg/day vs lower dose). **Figure S16** 28-day mortality (median control group mortality $> vs \leq 37.5\%$). **Figure S17** 28-day mortality (median CCN score $>9 vs \leq 9$). **Figure S18** 28-day mortality (low vs other risk of bias). **Figure S19** 28-day mortality (start of intervention $\leq vs >24$ h of ICU admission/septic shock/pressor initiation etc.). **Figure S20** 28-day mortality (Duration of treatment $> vs \leq 4$ days). **Figure S21** 28-day mortality (bolus vs continuous infusion). **Figure S22** Summary of subgroup analysis for 28-day mortality. **Figure S23** Longer term mortality (≥ 60 days). **Figure S24** Duration of mechanical ventilation. **Figure S25** ICU length of stay. **Figure S26** Hospital length of stay. **Figure S27** Incidence of acute kidney injury. **Figure S28** Incidence of renal replacement therapy. **Figure S29** Sequential organ failure assessment (SOFA) score at 96h. **Figure S30** Dose of vasopressors. **Figure S31** Days on vasopressors. **Figure S32** (a) Adverse events. (b) Adverse events (with continuity correction by adding 0.01 to cells with zero events). **Figure S33** Funnel plot for overall mortality. **Figure S34** TSA for overall mortality—subgroup analysis in trials with below median control group mortality—relative risk reduction 30%. **Figure S35** TSA for overall mortality—subgroup analysis in trials below median control group mortality ($\leq 37.5\%$)—Relative risk reduction 20%. **Figure S36** TSA for overall mortality—subgroup analysis in trials below median control group mortality ($\leq 37.5\%$)—Relative risk reduction 20%. **Figure S37** TSA for overall mortality—subgroup analysis in trials above ($>37.5\%$) median control group mortality—relative risk reduction 30%. **Figure S38** TSA for overall mortality—subgroup analysis in trials above ($>37.5\%$) median control group mortality—relative risk reduction 25%. **Figure S39** TSA for overall mortality—subgroup analysis in trials above ($>37.5\%$) median control group mortality—relative risk reduction 20%.

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Author contributions

ZYL and DKH contributed to the conception and design of this review, ZYL and LOR performed the literature screening, ZYL and LOR extracted the data and performed the quality assessment, ZYL, CCHL and DKH interpreted and synthesized the data, ZYL drafted the manuscript, ZYL, LOR, CCHL, MSH, LK, JP, CS, and DKH critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated and/or analyzed during the current study are included within the published article and its additional files. The standardized data abstraction form and the critical care nutrition methodology scoring system is available at www.criticalcarenutrition.com

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not applicable.

Competing interests

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From RE-ENERGIZE to VICToRY

Building the First International Consortium for Clinical Trials in Burns

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The views expressed in this presentation are those of the authors and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, DoD, or the U.S. Government.



Disclosures



- » L. Cancio is a co-inventor of Burn Navigator (Arcos Medical, Inc.), a burn resuscitation decision support software application. He has assigned his rights to the Army.
- » The authors are investigators on the VICToRY grant.
- » Dansereau, Stoppe, and Heyland were investigators on the RE-ENERGIZE grant.



Background



- » Burns represent 5-10% of combat casualties during conventional warfare and are projected to increase on the future battlefield
- » Conducting RCTs to improve combat casualty care is challenging
 - » Declining number of patients with large burns during peacetime
 - » Difficult to obtain informed consent from LAR under emergency conditions
- » A large, international, multicenter consortium was formed
 - » Recently completed RCT of glutamine therapy (RE-ENERGIZE)
 - » Ongoing RCT of moderately high-dose vitamin C (VICToRY)

RCT, randomized controlled trial; LAR, legally authorized representative



Methods



- » All research approved by local ethics committees/institutional review boards and is conducted in accordance with legal requirements in each participating country

- » Studies funded by
 - » US DoD
 - » Canadian Institutes of Health
 - » Lotte & John Hecht Memorial Foundation
 - » German Research Foundation



ORIGINAL ARTICLE

A Randomized Trial of Enteral Glutamine for Treatment of Burn Injuries

- » Double-blind, placebo-controlled phase III RCT
- » Evaluated the efficacy of enteral glutamine 0.5 mg/kg/day beginning within 72 h of admission
- » 1^o endpoint: time to discharge alive from hospital (censored at 90 days)
- » Enrolled 1209 burn patients
- » No difference in 1^o endpoint (40 days in glutamine group, 38 days in placebo group; $p=0.17$)
- » No difference in 6-month mortality (17.2% in glutamine group, 16.2% in placebo group)



VICToRY: benefits of Vitamin C



» Antioxidant

- » Protects neurons
- » Attenuates myocardial damage
- » Reduces vasopressor needs
- » Reduces ventilator days
- » Protects endothelial barrier
- » Reduces fluid needs

» Promotes wound healing

» Other

- » Restores platelet function
- » Inhibits bacterial growth

ORIGINAL ARTICLE

Reduction of Resuscitation Fluid Volumes in Severely Burned Patients Using Ascorbic Acid Administration

A Randomized, Prospective Study

Arch Surg 2000

Hideharu Tanaka, MD; Takayoshi Matsuda, MD; Yasusuke Miyagantani, MD;
Tetsuo Yukioka, MD; Hiroharu Matsuda, MD; Syuji Shimazaki, MD

*Comment: Use during hours 24-96 post-admission in VICToRY presumes treatment of **ongoing** oxidative stress, past the burn shock phase.*



VICToRY: study design



- » VICToRY is a double-blind, placebo-controlled phase III RCT
- » Interventions: Vitamin C 50 mg/kg IV q6h –OR– Placebo IV q6h for 96 hours
 - » Interventions must start within 24 hours of hospital admission
- » Primary endpoint: composite of persistent organ dysfunction (POD) and all-cause mortality at 28 days



VICToRY, cont.



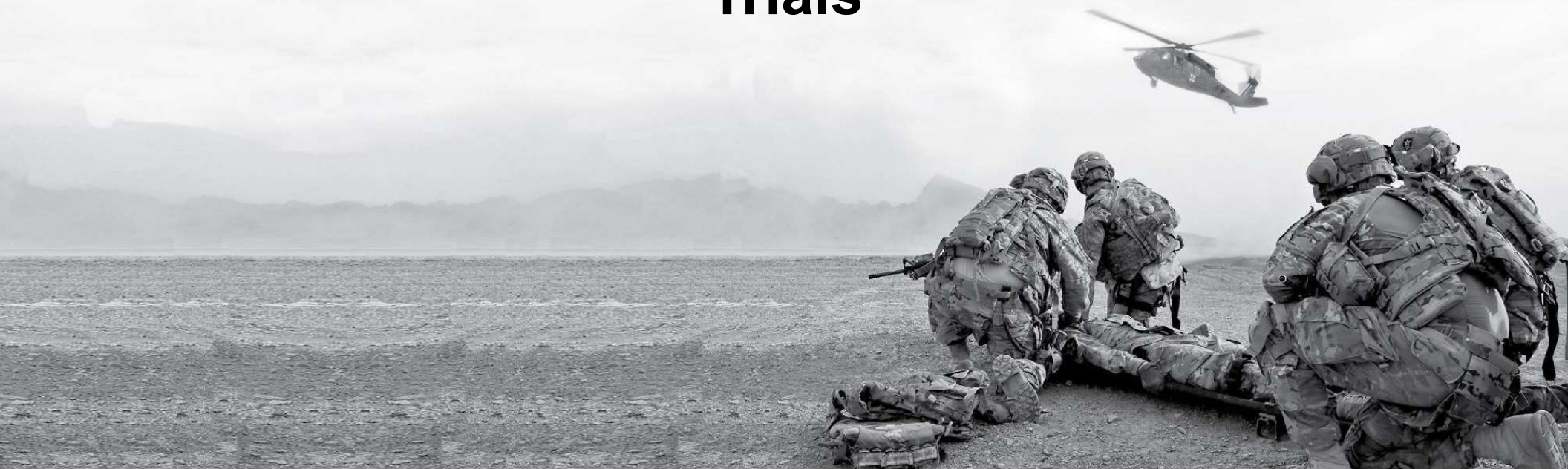
» **Secondary endpoints**

- » Time to discharge alive
- » 28-day POD and POD-free days in the first 28 days
- » ICU and hospital length of stay
- » Ventilator days
- » Bacteremia with Gram-negative bacilli
- » 6-month mortality
- » 6-month SF-36 (health-related quality of life and physical function domain)

POD, persistent organ dysfunction

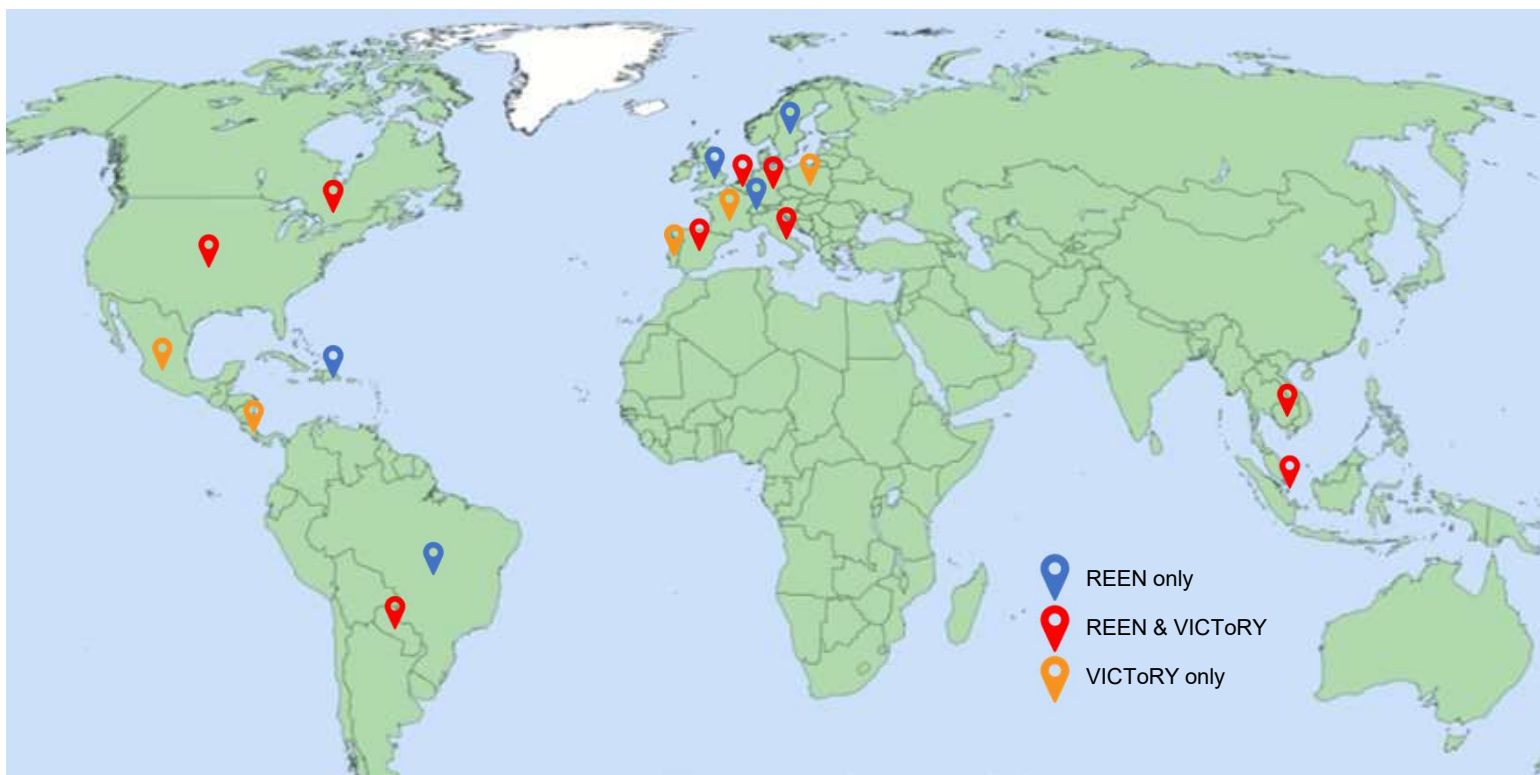


Building An International Consortium for Clinical Trials





Global Collaborative Research Infrastructure



Country	REEN Sites/ Country	VICToRY Sites/ Country*
Austria	1	
Belgium	2	4
Brazil	1	
Canada	6	5
Costa Rica		1
Dominican Republic	1	
France		5
Germany	2	9
Italy	1	6
Mexico		1
Paraguay	1	1
Poland		1
Portugal		2
Singapore	1	1
Spain	1	3
Sweden	1	
Switzerland	1	
Thailand	3	1
United Kingdom	6	
United States	26	10
Total	54	50

*includes active and in progress sites



Results – RE-ENERGIZE



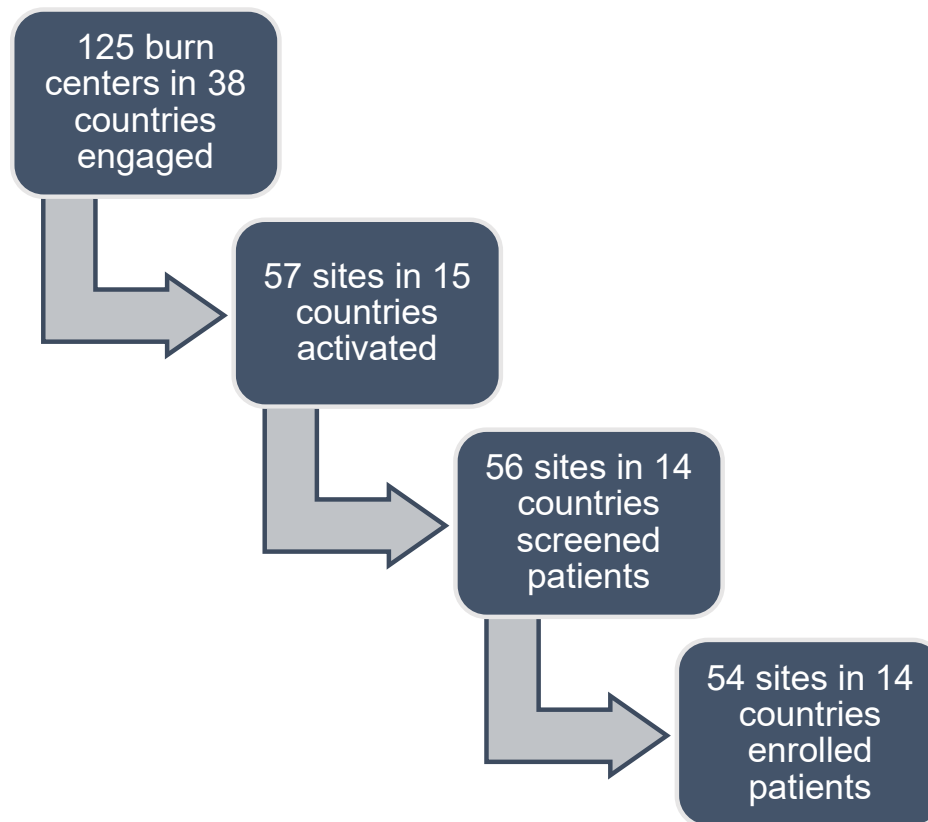
» **54 burn centers enrolled:**

- » US: 26
- » Europe: 15
- » Canada: 6
- » Asia: 4
- » Latin America: 3

» Number of enrolled patients: 1-95 per site

» **Enrollment rates:**

- » Pilot phase: **0.96** patients/site/month (range 0.68-1.31)
- » Definitive phase: **0.44** patients/site/month (range 0.08-1.74)





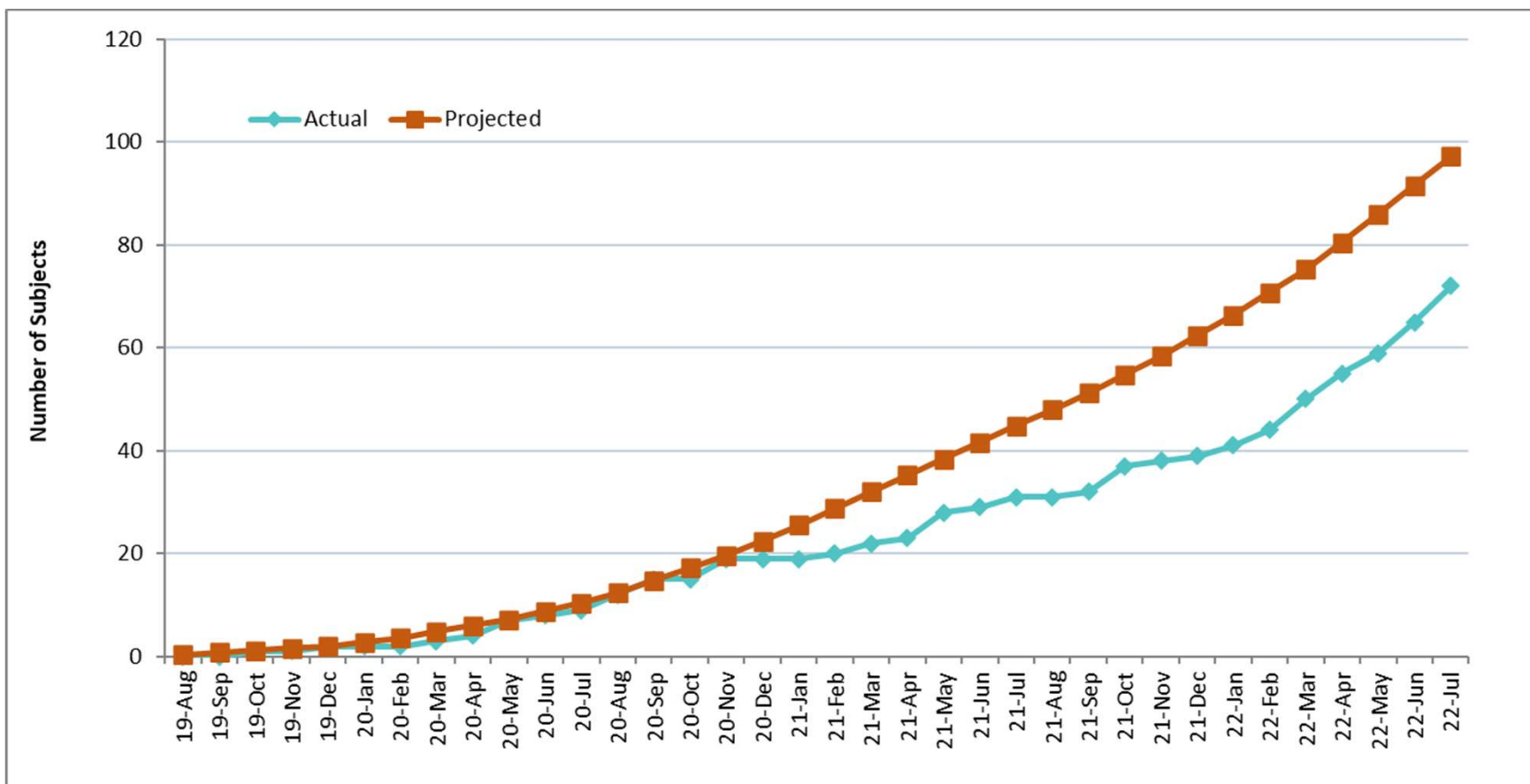
Results – VICToRY Trial



- » Currently enrolling in pilot phase
- » 138 burn centers in 32 countries engaged to participate
- » 14 sites in 4 countries currently enrolling
- » Enrollment rate: **0.7** patients/site/month



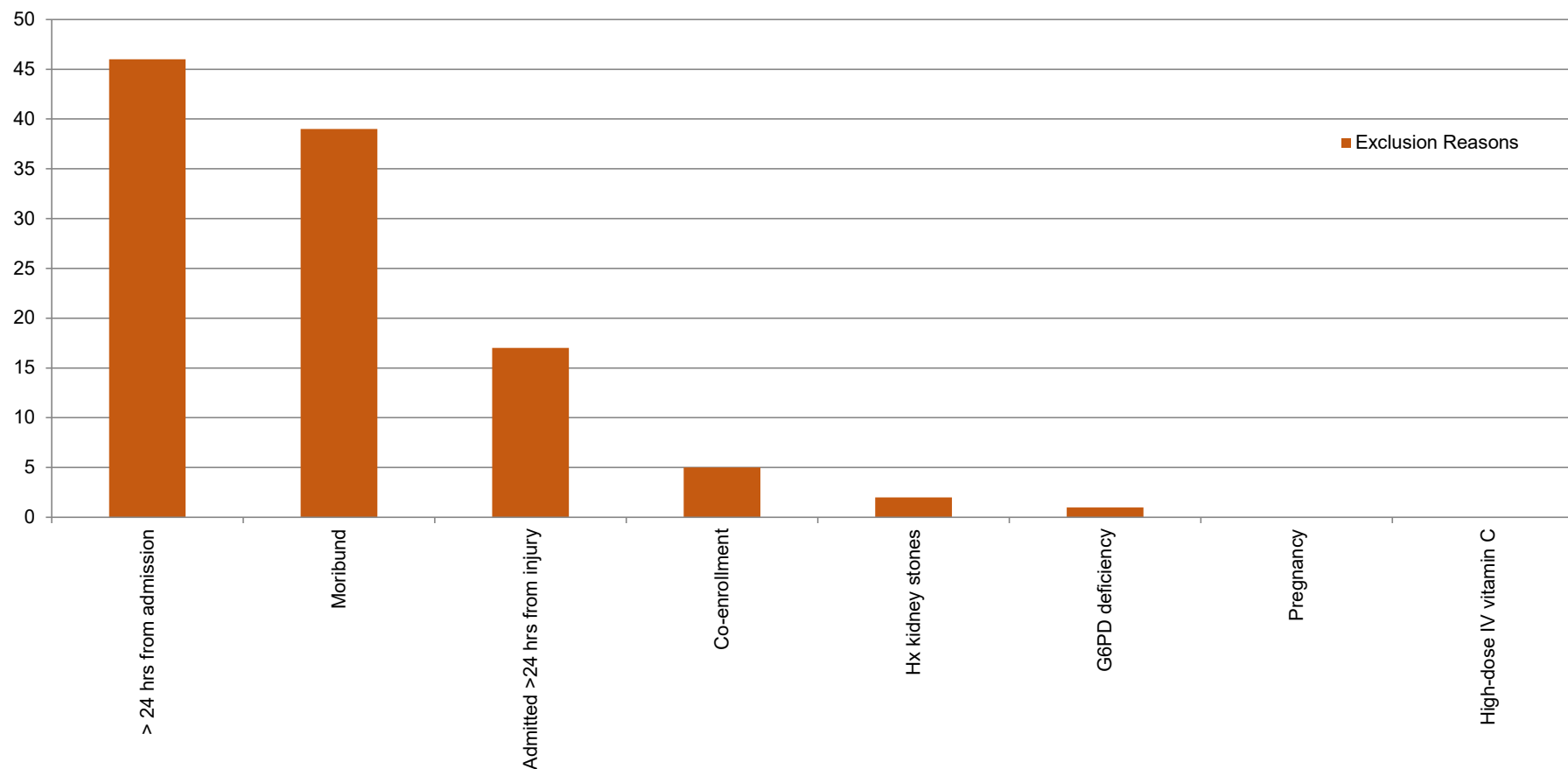
Cumulative Randomization: Actual vs. Projected



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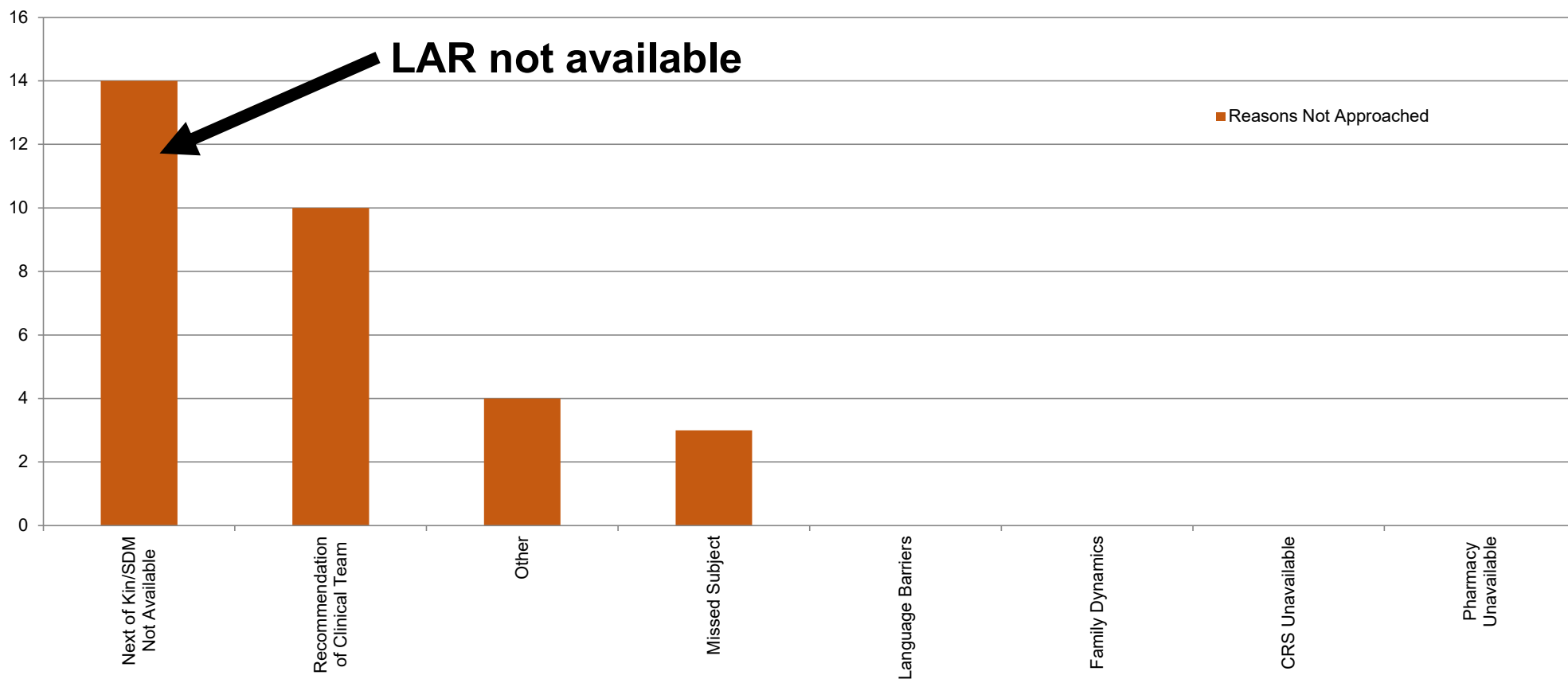


Enrollment Challenges: Reasons for Exclusion





Enrollment Challenges: Reasons Not Approached





Conclusion



- » RE-ENERGIZE changed the paradigm for burn-related RCTs
 - » Feasibility of conducting international studies
- » The RE-ENERGIZE network, in addition to new sites, is being leveraged for the VICToRY trial
- » Key to success is developing and maintaining **strong, positive relationships** with potential international partners and assisting them in overcoming obstacles unique to their environments
- » **Number 1 reason for missed enrollment: LAR not available**; rationale for EFIC in selected studies

LAR, legally authorized representative; EFIC, exception from informed consent



From RE-ENERGIZE to VICToRY

Building the First International Consortium for Clinical Trials in Burns

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Daren K. Heyland, MD, MSc, FRCPC



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Inclusion Criteria

18 years of age or older
Burn size $\geq$ 20% TBSA
Require skin grafting

Exclusion Criteria



Admitted >24 hours after injury
Intervention would be given >24 hours after hospital admission
Moribund
Pregnancy
Concomitant use of hydroxocobalamin
Concomitant administration of high-dose vitamin C
Known G6PD deficiency
History of kidney stones in last year



Recruitment Report

September 30, 2023

Recruitment Report

Site ID	Site Name	Date Activated	Date 1st Subject Screened	Date 1st Subject Randomized	Date Last Subject Randomized	# Not Eligible	Eligible but Not Randomized	Randomized	TOTAL Screened	% Randomized	Screening Rate # Screened / Month	Recruitment Rate # Enrolled / Month
1008	Hôpital l'Enfant-Jésus	31-May-21	31-May-21	31-May-21	02-May-23	20	5	14	39	36%	1.4	0.5
1099	Hotel-Dieu de Montreal - CHUM	18-Dec-20	08-Feb-21	30-Mar-21	26-Sep-23	21	2	13	36	36%	1.2	0.4
1152	Hospital Central Dr. Ignacio Morones Prieto, S	21-Jul-21	03-Nov-21	03-Nov-21	09-Mar-23	1	1	9	11	82%	0.5	0.4
1054	The Ohio State University Medical Center	12-Aug-21	21-Sep-21	08-Nov-21	14-Sep-23	22	3	7	32	22%	1.3	0.3
1177	Merheim Medical Center	30-Jan-23	22-Mar-23	22-Mar-23	04-Sep-23	0	0	7	7	100%	1.2	1.2
1097	Harborview Medical Center - Seattle	14-Dec-21	19-Feb-22	26-Feb-22	02-Aug-23	14	25	6	45	13%	2.4	0.3
1094	Arizona Burn Center - U of Arizona	24-Jul-20	18-Aug-20	26-Oct-20	17-Sep-21	7	11	6	24	25%	0.6	0.2
1098	Bridgeport Hospital	19-Sep-22	11-Oct-22	11-Oct-22	23-Jul-23	1	0	5	6	83%	0.5	0.5
1167	BG Klinik Ludwigshafen, Germany	03-Apr-23	05-Jun-23	05-Jun-23	03-Jul-23	0	0	5	5	100%	1.7	1.7
1017	University of Iowa	23-Feb-21	08-Nov-21	20-May-22	28-Aug-23	11	1	4	16	25%	0.7	0.2
1065	RWTH Aachen University, Aachen	22-Nov-22	31-Mar-23	31-Mar-23	18-Sep-23	3	1	3	7	43%	1.2	0.5
1027	Mercy Hospital St. Louis	01-Dec-21	30-Oct-22	15-Feb-23	17-Jul-23	13	5	2	20	10%	1.8	0.2
1061	Queen Elizabeth II, Halifax	19-Apr-23	03-Sep-23	03-Sep-23	03-Sep-23	0	0	1	1	100%	1	1
1131	Ghent University Hospital	21-Mar-23	07-Jun-23	-	-	2	0	0	2	0%	0.7	0
1113	UT Southwestern Medical Center	18-Aug-23	-	-	-	0	0	0	0	0%	0	0
1176	Grand Hopital de Charleroi	29-Sep-23	-	-	-	0	0	0	0	0%	0	0
# Sites Enrolling		16			TOTALS	115	54	82	251			
					%	45.8%	21.5%	32.7%				
									Average/Site	1	0.5	

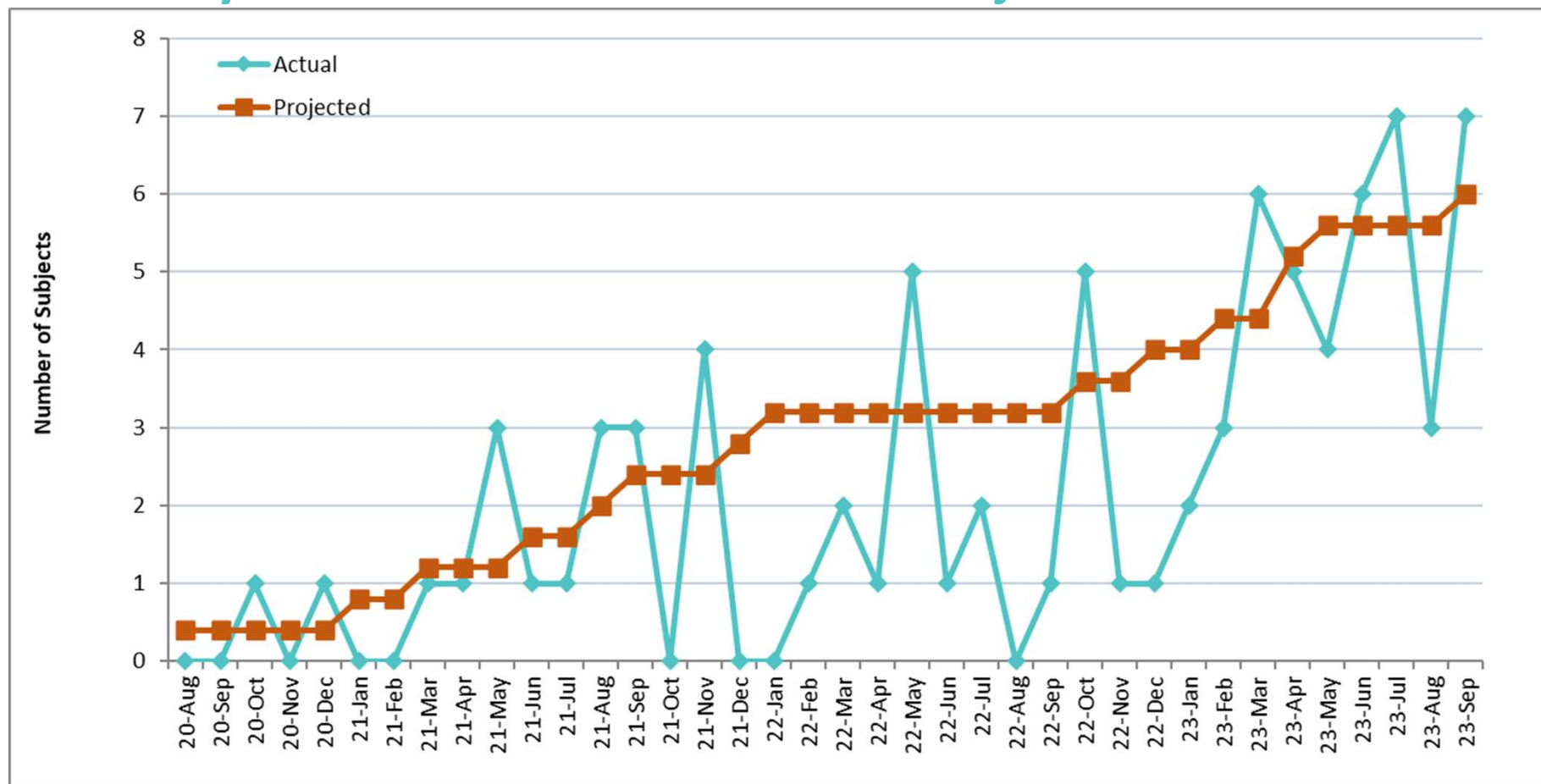


Monthly Recruitment

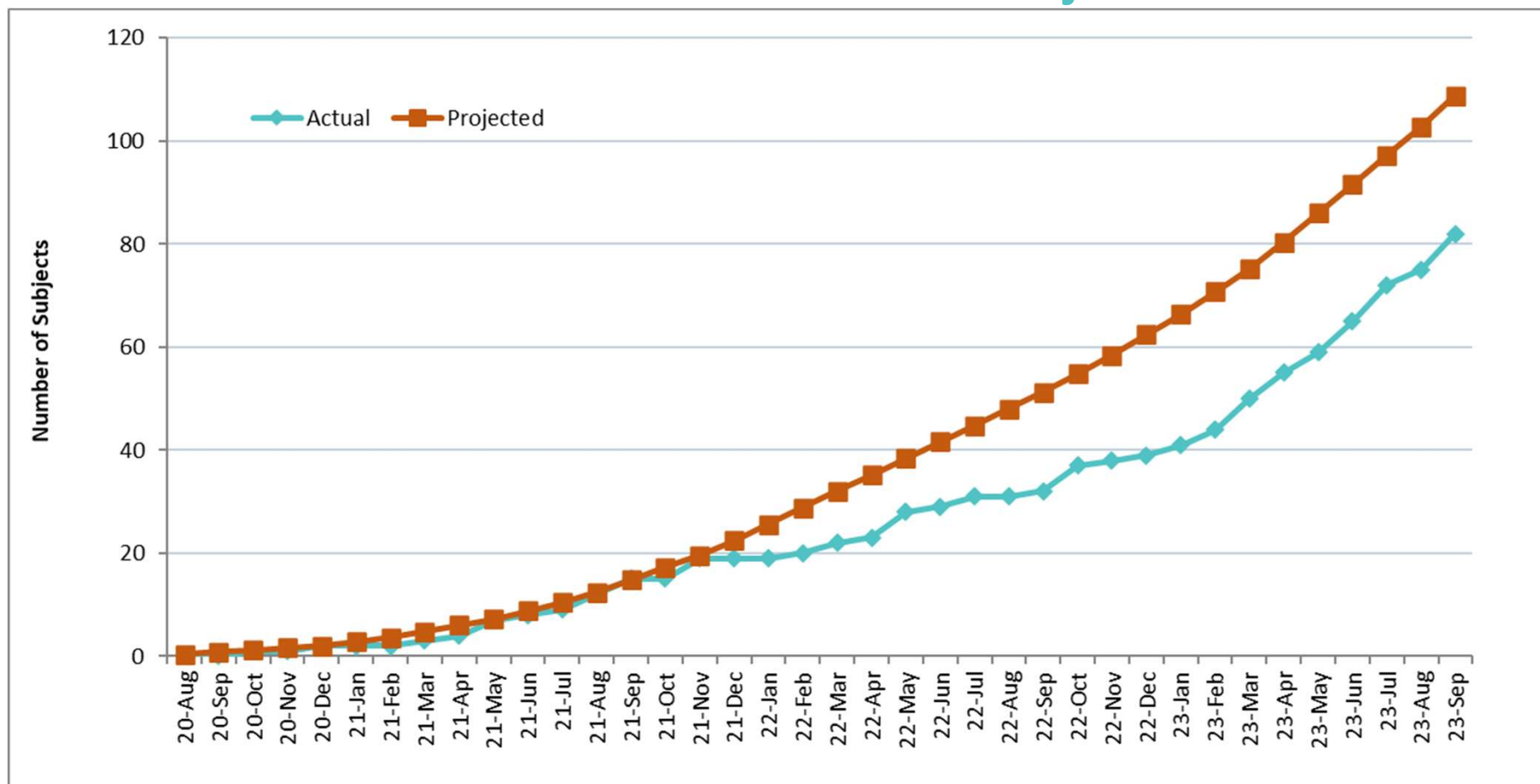
Site ID	Site Name	Date Activated	Date 1st Subject Screened	Date 1st Subject Randomized	Date Last Subject Randomized	# Not Eligible	Eligible but Not Randomized	Randomized	TOTAL Screened	% Randomized	Screening Rate # Screened / Month	Recruitment Rate # Enrolled / Month
1099	Hotel-Dieu de Montreal - CHUM	18-Dec-20	12-Sep-23	12-Sep-23	26-Sep-23	1	0	3	4	75%	4	3
1054	The Ohio State University Medical Center	12-Aug-21	14-Sep-23	14-Sep-23	14-Sep-23	1	0	1	2	50%	2	1
1065	RWTH Aachen University, Aachen	22-Nov-22	17-Sep-23	18-Sep-23	18-Sep-23	1	0	1	2	50%	2	1
1061	Queen Elizabeth II, Halifax	19-Apr-23	03-Sep-23	03-Sep-23	03-Sep-23	0	0	1	1	100%	1	1
1177	Merheim Medical Center	30-Jan-23	04-Sep-23	04-Sep-23	04-Sep-23	0	0	1	1	100%	1	1
1027	Mercy Hospital St. Louis	01-Dec-21	07-Sep-23	-	-	3	0	0	3	0%	3	0
1097	Harborview Medical Center - Seattle	14-Dec-21	08-Sep-23	-	-	0	3	0	3	0%	3	0
1131	Ghent University Hospital	21-Mar-23	21-Sep-23	-	-	1	0	0	1	0%	1	0
1008	Hôpital l'Enfant-Jésus	31-May-21	-	-	-	0	0	0	0	0%	0	0
1017	University of Iowa	23-Feb-21	-	-	-	0	0	0	0	0%	0	0
1094	Arizona Burn Center - U of Arizona	24-Jul-20	-	-	-	0	0	0	0	0%	0	0
1098	Bridgeport Hospital	19-Sep-22	-	-	-	0	0	0	0	0%	0	0
1113	UT Southwestern Medical Center	18-Aug-23	-	-	-	0	0	0	0	0%	0	0
1152	Hospital Central Dr. Ignacio Morones Prieto, S	21-Jul-21	-	-	-	0	0	0	0	0%	0	0
1167	BG Klinik Ludwigshafen, Germany	03-Apr-23	-	-	-	0	0	0	0	0%	0	0
1176	Grand Hopital de Charleroi	29-Sep-23	-	-	-	0	0	0	0	0%	0	0
# Sites Enrolling		16			TOTALS	7	3	7	17			
					%	41.2%	17.6%	41.2%				
									Average/Site	1.1	0.4	



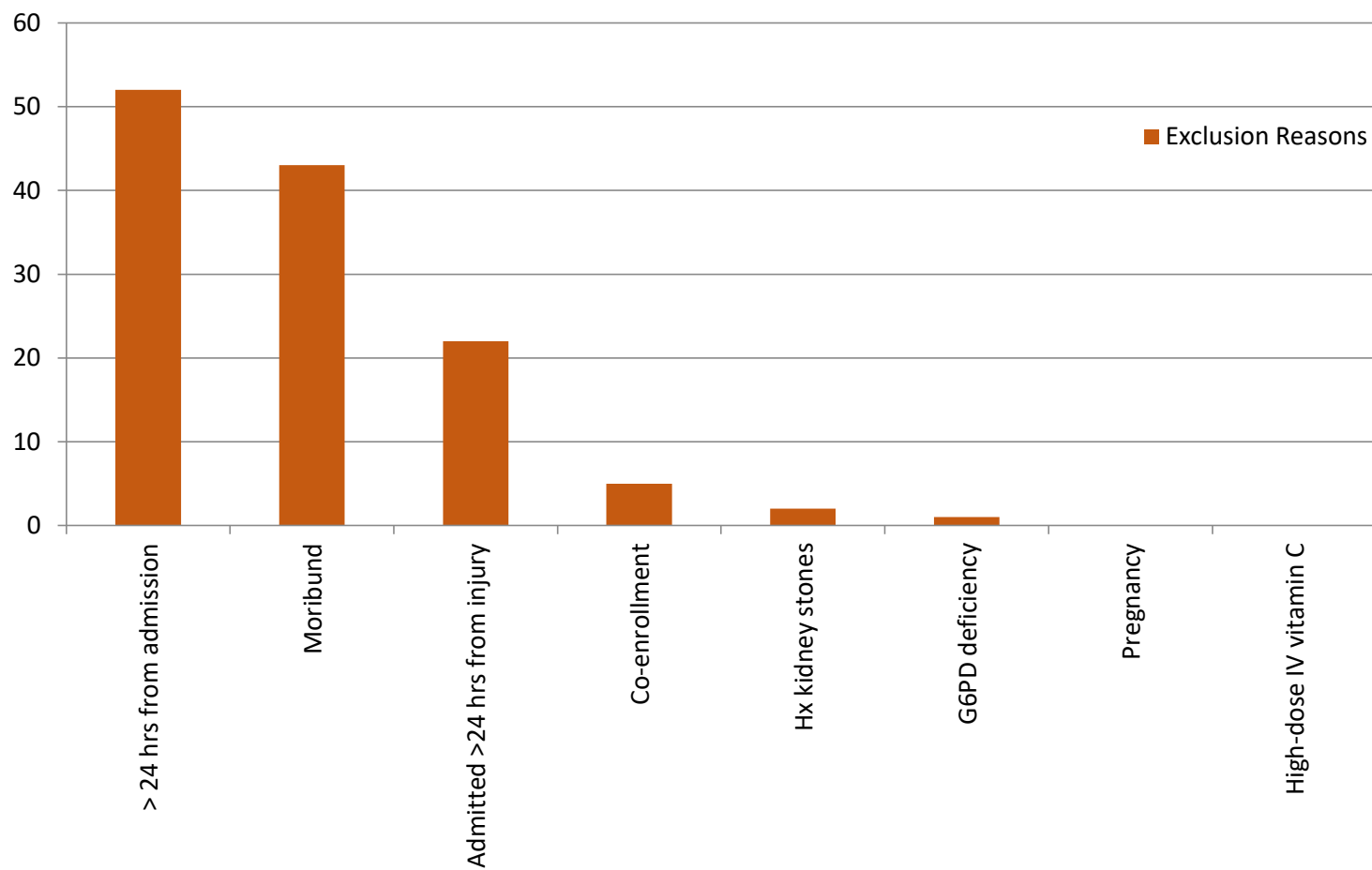
Monthly Randomization: Actual vs. Projected



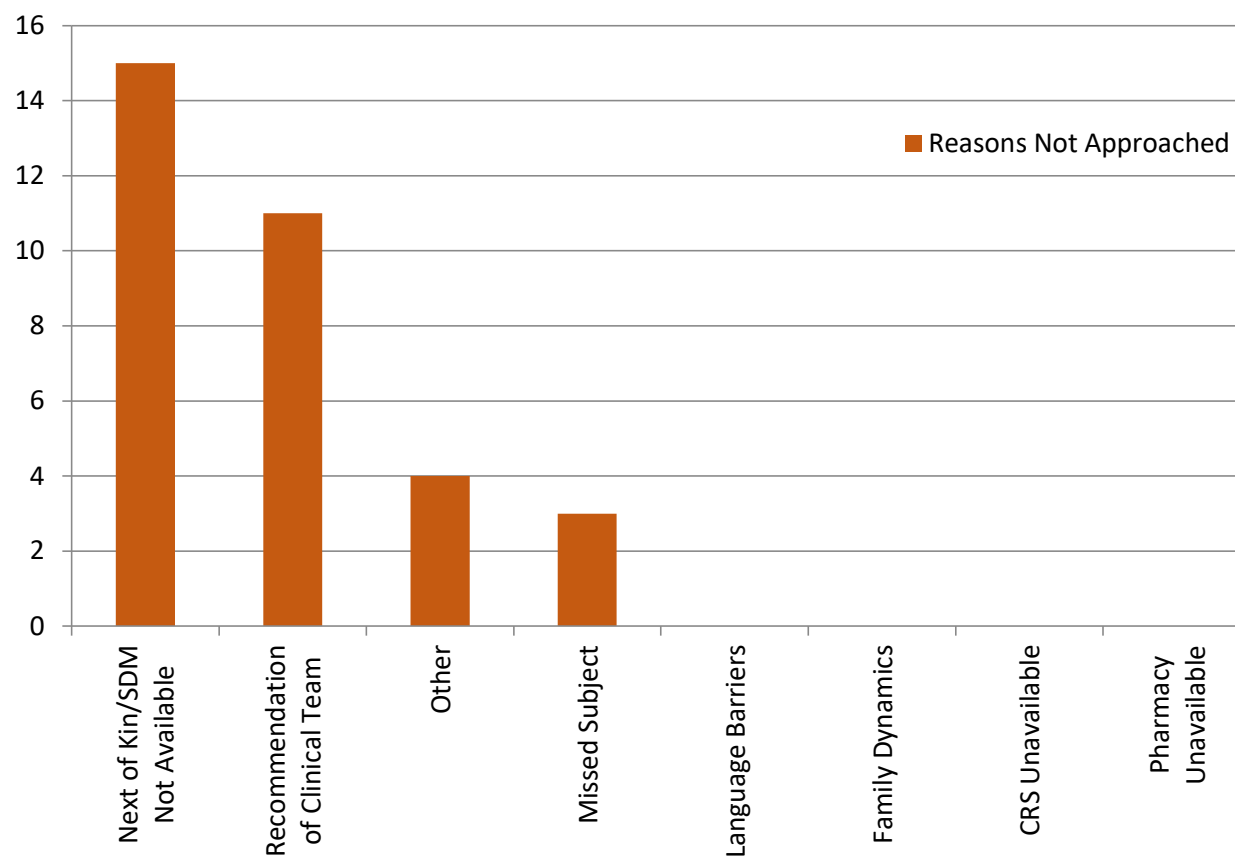
Cumulative Randomization: Actual vs. Projected



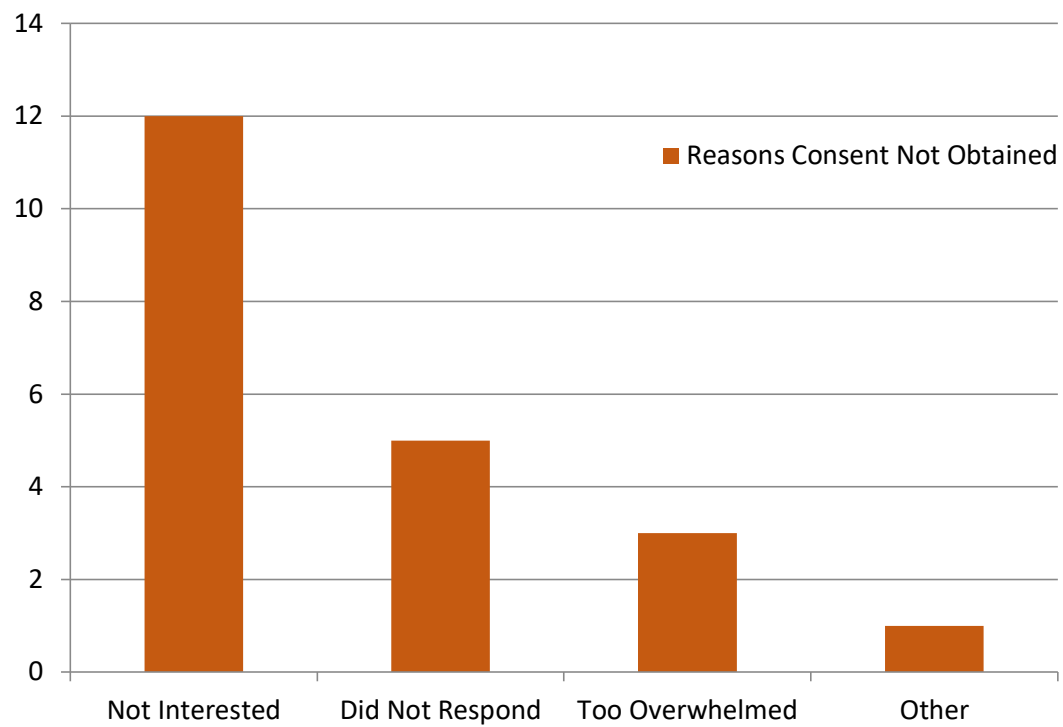
Reasons for Exclusions



Reasons Not Approached for Consent



Reasons Consent Not Obtained



Global Collaborative Research Infrastructure



Country	REEN Sites/ Country	VICTORY Sites/ Country*
Austria	1	
Belgium	2	4
Brazil	1	
Canada	6	5
Costa Rica		1
Dominican Republic	1	
France		5
Germany	2	9
Italy	1	6
Mexico		1
Paraguay	1	1
Poland		1
Portugal		2
Singapore	1	1
Spain	1	3
Sweden	1	
Switzerland	1	
Thailand	3	1
United Kingdom	6	
United States	26	10
Total	54	50

*includes active and in progress sites

-  REEN only
-  REEN & VICTORY
-  VICTORY only

Questions





Vitamin C in Thermal injury: The VICTORY Trial



Proposal #: MB210012
Total Budget: \$1,499,998

Laboratory/Division: (lab name/lab division)
PI: Dr. Daren Heyland **TA #:** (TA number, if applicable)

Technology Solution



The objective of this pivotal trial is to demonstrate efficacy of high-dose intravenous vitamin C administration in 486 severely burn injured patients globally. We aim to show that this inexpensive therapeutic strategy is safe and will significantly reduce the morbidity and mortality in civilians and military personnel with severe burns, and that the results of this randomized trial will have a significant impact on burn care world-wide, both on the battlefield and in the hospital.

- **Strategic Alignment:** Improve outcomes for burn injured personnel.
 - ❖ **Strategic Plan:** A randomized controlled trial of high-dose IV vitamin C versus placebo in 486 burn injured patients
 - ❖ **Technical Objective:** Demonstrate efficacy and safety of inexpensive therapeutic and widely available treatment, vitamin C.
- **Objective/Hypothesis:** We hypothesize that high-dose intravenous vitamin C given in the early postburn period, in comparison with placebo, will significantly reduce morbidity and mortality in civilians and military personnel with severe burns.
- **Aims:**
 - ❑ **Aim 1:** Reduce the burden of illness associated with significant burn injury in both civilian and military settings using a naturally occurring substance, vitamin C.
- **Risks & Mitigation Plan:** Primary risk is slow enrollment. Mitigation plan: recruit additional performance sites to enroll participants

Deliverables

- **FY24:**
 - ❑ Obtain OHRO approval of all sites and protocols.
 - ❑ Prepare and activate sites to conduct research protocol
 - ❑ Meet recruitment rate targets
- **FY25:**
 - ❑ Continue participant recruitment
 - ❑ Collect data and conduct source verification and site monitoring
- **FY26:**
 - ❑ Complete recruitment, clean and analyze data
- **FY27:**
 - ❑ Produce Final Report and publish research results

Operational Impact

Early administration of IV vitamin C to severely burn injured patients on the battlefield and in hospital targets pathophysiology of early postburn inflammation and organ dysfunction and will reduce morbidity and mortality.

Timeline

Legend: Deliverable # TRL Transition

Task	FY24	FY25	FY26
Conduct a randomized controlled trial of high dose I.V. vitamin C vs. placebo in 486 burn injured patients in 40 sites globally.			
Aim 1: Obtain approvals, train site personnel, activate sites, begin enrollment.			
Aim 2: Recruit participants, collect data, conduct quality assurance metrics.			
Aim 3: Complete recruitment, clean and analyze data, publish results.			
Funding per FY	\$500,000	\$500,000	\$499,998

Planned Transition (if applicable; TA required for 6.3)

TA Signed	TA ID	Transition Partner	TA Deliverable Name
MM/DD/YYYY	T.LABXX.2024.01	PMO/JTS	