

# World Journal of *Diabetes*

*World J Diabetes* 2020 April 15; 11(4): 90-149



**EDITORIAL**

- 90** Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out?

*Marik PE, Varon J, Surani SR*

- 95** Age of onset of diabetes and all-cause mortality

*Ang GY*

**REVIEW**

- 100** Glargine-300: An updated literature review on randomized controlled trials and real-world studies

*Ghosh S, Ghosh R*

- 115** Novel insight into perirenal adipose tissue: A neglected adipose depot linking cardiovascular and chronic kidney disease

*Huang N, Mao EW, Hou NN, Liu YP, Han F, Sun XD*

**ORIGINAL ARTICLE****Basic Study**

- 126** Lack of Syndecan-1 produces significant alterations in whole-body composition, metabolism and glucose homeostasis in mice

*Jaiswal AK, Sadasivam M, Aja S, Hamad ARA*

**SYSTEMATIC REVIEWS**

- 137** Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials

*Liang LR, Ma Q, Feng L, Qiu Q, Zheng W, Xie WX*

**ABOUT COVER**

Editorial Board Member of *World Journal of Diabetes*, Yashdeep Gupta, MD, Assistant Professor, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India

**AIMS AND SCOPE**

The primary aim of *World Journal of Diabetes* (WJD, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

**INDEXING/ABSTRACTING**

The WJD is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yu-Jie Ma*  
Proofing Production Department Director: *Xiang Li*

**NAME OF JOURNAL**

*World Journal of Diabetes*

**ISSN**

ISSN 1948-9358 (online)

**LAUNCH DATE**

June 15, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Timothy Koch

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

**EDITORIAL OFFICE**

Ruo-Yu Ma, Director

**PUBLICATION DATE**

April 15, 2020

**COPYRIGHT**

© 2020 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out?

Paul Ellis Marik, Joseph Varon, Salim R Surani

**ORCID number:** Paul Ellis Marik (0000-0001-5024-3949); Joseph Varon (0000-0002-7622-9974); Salim R Surani (0000-0001-7105-4266).

**Author contributions:** All authors have contributed to the preparation of the manuscript, literature search and review of manuscript.

**Conflict-of-interest statement:** The authors have no conflict of interest to disclose.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Received:** November 26, 2019

**Peer-review started:** November 26, 2019

**First decision:** December 23, 2019

**Revised:** December 24, 2019

**Accepted:** February 23, 2020

**Article in press:** February 23, 2020

**Published online:** April 15, 2020

**P-Reviewer:** Amiri M, Ghoch ME, Moretti R

**Paul Ellis Marik**, Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA 23507, United States

**Joseph Varon**, Department of Critical Care, United Memorial Medical Service, Houston, TX 77030, United States

**Salim R Surani**, Texas A and M University, Corpus Christi, TX 78413, United States

**Corresponding author:** Paul Ellis Marik, FRCP (C), MBChB, MD, Chairman, Full Professor, Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Av, Suite 410, Norfolk, VA 23507, United States. [marikpe@evms.edu](mailto:marikpe@evms.edu)

### Abstract

Sepsis and septic shock remain a major cause of morbidity and mortality among patients admitted in the intensive care unit. Diabetes is a major risk factor for the development of sepsis. The global mortality of sepsis remains high, despite significant interventions and guidelines. It has been known for decades that patients with sepsis have reduced levels of antioxidants, most notably vitamin C. Furthermore, experimental data has demonstrated multiple beneficial effects of vitamin C in sepsis. In addition, corticosteroids and thiamine may have synergistic biological effects together with vitamin C. Preliminary data suggests that therapy with hydrocortisone, ascorbic acid and thiamine improves the outcome of patients with sepsis with the potential to save millions of lives. However, this intervention has met with much resistance and has not been widely adopted. Ultimately, we await the final jury verdict on this simple, safe and cheap intervention.

**Key words:** Diabetes; Vitamin C; Ascorbic acid; Sepsis; Thiamine; Septic shock; Global burden of disease

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The combination of ascorbic acid (vitamin C), hydrocortisone and thiamine hold great promise for the treatment of sepsis. Despite, significant evidence there remains reluctance among the medical community to adopt this intervention. hydrocortisone, ascorbic acid and thiamine have the potential for saving millions of lives. We await the final jury verdict on this simple, safe and cheap intervention.

S-Editor: Dou Y  
L-Editor: A  
E-Editor: Liu MY



**Citation:** Marik PE, Varon J, Surani SR. Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out? *World J Diabetes* 2020; 11(4): 90-94

**URL:** <https://www.wjnet.com/1948-9358/full/v11/i4/90.htm>

**DOI:** <https://dx.doi.org/10.4239/wjd.v11.i4.90>

## INTRODUCTION

“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.” Max Planck, Theoretical Physicist (1858-1947).

According to the most recent estimates from the World Health Organization over 6 million citizens of the earth die from sepsis each year. As the greatest burden of sepsis is in middle- and low-income countries where accurate epidemiological data is lacking, this is likely an underestimate of the true global burden of this devastating syndrome<sup>[1-3]</sup>. The patients with diabetes have increased risk of developing sepsis<sup>[4]</sup>. The cornerstone of treatment of sepsis and septic shock is its early recognition, early appropriate antibiotics, early source control and a physiologic approach to fluid management<sup>[5]</sup>. Despite this approach the mortality of septic shock in resource rich countries approximates 30%, while that in resource poor countries the mortality is estimated to be about 60%. Sepsis is the commonest cause of death in children less than 5 years of age. Imagine for one moment that a simple, cheap and readily available intervention existed that could reduce the mortality from sepsis by 20% (conservatively). Such an intervention would save in excess of 1 million lives a year. Does such an intervention exist? We believe that the combination of hydrocortisone, ascorbic acid (vitamin C) and thiamine (HAT Rx) has the potential to prevent millions of deaths from sepsis each year and to reduce the severe life altering sequelae in the sepsis survivors<sup>[6-8]</sup>. Most importantly this intervention is cheap and without side effects (the side effects of a short course of low dose corticosteroids are minimal)<sup>[8,9]</sup>. So why has this simple, safe and cheap intervention not been more widely adopted? To answer this question, we need to question the established medical community and their power brokers. The commonest reasons cited are that the proposed benefits are not “biologically plausible” and the “jury is not out” on the benefits of this simple intervention<sup>[10,11]</sup>.

A jury is a body of people convened to render an impartial verdict (in a legal case) on the basis of evidence submitted to them by a court. The jurors evaluate the totality of the evidence presented to them and base their findings on the preponderance of evidence. In many cases there is no smoking gun [or randomized controlled trial (RCT)] so they base their assessment on the entire body of the evidence. Furthermore, the jury needs to ponder the consequences of an incorrect verdict. In a trial, if they wrongly convict, this could result in the wrong penalty. Similarly, in the case of “HAT Rx *vs* Sepsis” concluding that such therapy is biologically implausible and unsafe could potentially cost millions of lives.

So, what does the evidence to date demonstrate? Firstly, it should be recognized that humans (anthropoid primates) are unique amongst the animals that roam the earth, in they have lost the ability to synthesize vitamin C<sup>[12]</sup>. Vitamin C is an essential antioxidant and co-factor for many vital biological reactions. In non-human species, Vitamin C acts as a stress hormone with increased synthesis during stress which is likely protective. Secondly, over 400 basic science experiments have been performed demonstrating the benefit of vitamin C alone and in combination with hydrocortisone in attenuating the dysregulated immune response in sepsis, in limiting organ dysfunction and reducing death of the septic animals<sup>[8]</sup>. What is remarkable is that these medications act synergistically *via* multiple overlapping pathways. *In-vitro* studies have demonstrated the synergetic effects of the combination of corticosteroids and vitamin C<sup>[13,14]</sup>. In addition, vitamin C reverses the sepsis induced oxidation (and inactivation) of the glucocorticoid receptor, while corticosteroids increase the transcription of SVCT2, the pivotal vitamin C transporter<sup>[15,16]</sup>. Thiamine may act synergistically with glucocorticoids and vitamin C to limit mitochondrial oxidative injury and restore mitochondrial function and energy production<sup>[17]</sup>. Furthermore, vitamin C and thiamine may play a critical in limiting delirium and septic encephalopathy<sup>[17,18]</sup>. The key roles of vitamin C in sepsis is provided in [Table 1](#)<sup>[8]</sup>. Thirdly, the mortality benefit of vitamin C (alone) in reducing the mortality of septic shock and sepsis associated acute respiratory distress syndrome has recently been

demonstrated<sup>[19,20]</sup>. Fourthly, the benefit of HAT Rx has been demonstrated in multiple observational studies<sup>[6,20]</sup>. And fifthly, we have together treated over 2000 patients with severe sepsis and septic shock. We continue to witness the remarkable ability of this treatment strategy to reduce the dysregulated immune response and improve the outcome of patients with sepsis. We have absolutely no conflicts of interest and have no reason to provide false evidence to the court of science and public opinion. It is critical to emphasize that all three components of HAT Rx are Food and Drug Administration approved drugs, which in the recommended doses are completely devoid of side effects. We are unaware of any side-effects or complications associated with HAT Rx. It should, however, be noted that there are powerful forces at play attempting to invalidate and disprove the beneficial effects of HAT Rx<sup>[10,11]</sup>. This includes designing clinical trials that are doomed to fail, by using absurd dosing schedules or selectively enrolling patients likely to do poorly<sup>[21,22]</sup>.

---

## CONCLUSION

---

Shortly, the results of multi-center RCTs will be available<sup>[23-25]</sup>. Many will consider these trials to be the definitive evidence on which to judge the benefit of HAT Rx and to make a jury decision. However, while RCT's are considered the gold standard, it is important to realize that most RCT's do not replicate real world experience; mainly, due to the numerous exclusion criteria, enormous patient heterogeneity, non-standardized co-interventions and delays in instituting therapy. In the end, the thoughtful juror (clinician) must weigh the totality of the evidence before rendering a verdict.



Table 1 Summary of key roles of vitamin C in sepsis

Key role	Mechanism
Antioxidant	Scavenges extracellular, intracellular and mitochondrial ROS; limits oxidation of mitochondrial proteins, enzymes, lipoproteins, cell membrane, <i>etc.</i>
Anti-inflammatory	Inhibits activation of NFκB, decreases HMGB1, inhibits histamine, prevents NETosis, inactivates HIF-1α
Microcirculation	Increases eNOS, decreases iNOS, preserves tight junctions
Immune function	Supports lymphocyte proliferation, increases neutrophil bactericidal action, improves chemotaxis, stimulates interferon production, decreases T regulatory cells (Tregs), prevents lymphocyte apoptosis
Anti-thrombotic	Decreases platelet activation and tissue factor expression, increases thrombomodulin
Synthesis of catecholamines	Acts cofactor in synthesis of epinephrine, dopamine and vasopressin. Increases adrenergic sensitivity
Wound healing	Hydroxylation of procollagen, increased expression of collagen mRNA

Reproduced with permission from Nutrients<sup>[4]</sup>. ROS: Reactive oxygen species; NFκB: Nuclear factor κB; HIF-1α: Hypoxia-inducible transcription factor-1α; HMGB1: High mobility group box 1; eNOS: Endothelial nitric oxide synthetase; iNOS: Inducible nitric oxide synthetase; HO-1: Heme oxygenase-1; HIF-1α: Hypoxia-inducible transcription factor-1α.

## REFERENCES

- Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: barriers and potential solutions. *Crit Care* 2018; **22**: 232 [PMID: 30243300 DOI: 10.1186/s13054-018-2157-z]
- Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med* 2017; **377**: 414-417 [PMID: 28658587 DOI: 10.1056/NEJMp1707170]
- Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K; International Forum of Acute Care Trialists. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med* 2016; **193**: 259-272 [PMID: 26414292 DOI: 10.1164/rccm.201504-0781OC]
- Yende S, van der Poll T. Diabetes and sepsis outcomes--it is not all bad news. *Crit Care* 2009; **13**: 117 [PMID: 19291261 DOI: 10.1186/cc7707]
- Marik PE, Farkas JD. The Changing Paradigm of Sepsis: Early Diagnosis, Early Antibiotics, Early Pressors, and Early Adjuvant Treatment. *Crit Care Med* 2018; **46**: 1690-1692 [PMID: 30216303 DOI: 10.1097/CCM.0000000000003310]
- Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; **151**: 1229-1238 [PMID: 27940189 DOI: 10.1016/j.chest.2016.11.036]
- Blythe R, Cook D, Graves N. Scepticaemia: The impact on the health system and patients of delaying new treatments with uncertain evidence; a case study of the sepsis bundle. *F1000Res* 2018; **7**: 500 [PMID: 29904596 DOI: 10.12688/f1000research.14619.2]
- Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. *Nutrients* 2018; **10** [PMID: 30441816 DOI: 10.3390/nu10111762]
- Marik PE. The role of glucocorticoids as adjunctive treatment for sepsis in the modern era. *Lancet Respir Med* 2018; **6**: 793-800 [PMID: 30006071 DOI: 10.1016/S2213-2600(18)30265-0]
- Rubin R. Wide Interest in a Vitamin C Drug Cocktail for Sepsis Despite Lagging Evidence. *JAMA* 2019 [PMID: 31268477 DOI: 10.1001/jama.2019.7936]
- Møller MH, Laake JH, Myburgh JA, Alhazzani W, Perner A. The Magic Bullet in Sepsis or the Inflation of Chance Findings? *Chest* 2017; **152**: 222-223 [PMID: 28693775 DOI: 10.1016/j.chest.2017.04.181]
- Drouin G, Godin JR, Pagé B. The genetics of vitamin C loss in vertebrates. *Curr Genomics* 2011; **12**: 371-378 [PMID: 22294879 DOI: 10.2174/138920211796429736]
- Barabutis N, Khangoora V, Marik PE, Catravas JD. Hydrocortisone and Ascorbic Acid Synergistically Prevent and Repair Lipopolysaccharide-Induced Pulmonary Endothelial Barrier Dysfunction. *Chest* 2017; **152**: 954-962 [PMID: 28739448 DOI: 10.1016/j.chest.2017.07.014]
- Azari O, Kheirandish R, Azizi S, Farajli Abbasi M, Ghahramani Gareh Chaman S, Bidi M. Protective Effects of Hydrocortisone, Vitamin C and E Alone or in Combination against Renal Ischemia-Reperfusion Injury in Rat. *Iran J Pathol* 2015; **10**: 272-280 [PMID: 26351497]
- Okamoto K, Tanaka H, Makino Y, Makino I. Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 (L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl] hydrogen phosphate) potassium salt, via a redox-dependent mechanism. *Biochem Pharmacol* 1998; **56**: 79-86 [PMID: 9698091 DOI: 10.1016/S0006-2952(98)00121-X]
- Fujita I, Hirano J, Itoh N, Nakanishi T, Tanaka K. Dexamethasone induces sodium-dependant vitamin C transporter in a mouse osteoblastic cell line MC3T3-E1. *Br J Nutr* 2001; **86**: 145-149 [PMID: 11502226 DOI: 10.1079/bjn2001406]
- Moretti R, Peinkhofer C. B Vitamins and Fatty Acids: What Do They Share with Small Vessel Disease-Related Dementia? *Int J Mol Sci* 2019; **20** [PMID: 31752183 DOI: 10.3390/ijms20225797]
- Osiezagha K, Ali S, Freeman C, Barker NC, Jabeen S, Maitra S, Olagbemiro Y, Richie W, Bailey RK.

- Thiamine deficiency and delirium. *Innov Clin Neurosci* 2013; **10**: 26-32 [PMID: [23696956](#)]
- 19 **Zabet MH**, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J Res Pharm Pract* 2016; **5**: 94-100 [PMID: [27162802](#) DOI: [10.4103/2279-042X.179569](#)]
- 20 **Fowler AA 3rd**, Truitt JD, Hite RD, Morris PE, DeWilde C, Priday A, Fisher B, Thacker LR 2nd, Natarajan R, Brophy DF, Sculthorpe R, Nanchal R, Syed A, Sturgill J, Martin GS, Sevransky J, Kashouris M, Hamman S, Egan KF, Hastings A, Spencer W, Tench S, Mehkri O, Bindas J, Duggal A, Graf J, Zellner S, Yanny L, McPolin C, Hollrith T, Kramer D, Ojelo C, Damm T, Cassity E, Wieliczko A, Halquist M. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA* 2019; **322**: 1261-1270 [PMID: [31573637](#) DOI: [10.1001/jama.2019.11825](#)]
- 21 **Shin TG**, Kim YJ, Ryoo SM, Hwang SY, Jo JJ, Chung SP, Choi SH, Suh GJ, Kim WY. Early Vitamin C and Thiamine Administration to Patients with Septic Shock in Emergency Departments: Propensity Score-Based Analysis of a Before-and-After Cohort Study. *J Clin Med* 2019; **8** [PMID: [30654592](#) DOI: [10.3390/jcm8010102](#)]
- 22 **Litwak JJ**, Cho N, Nguyen HB, Moussavi K, Bushell T. Vitamin C, Hydrocortisone, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Analysis of Real-World Application. *J Clin Med* 2019; **8** [PMID: [30970560](#) DOI: [10.3390/jcm8040478](#)]
- 23 **Fujii T**, Udy AA, Deane AM, Luethi N, Bailey M, Eastwood GM, Frei D, French C, Orford N, Shehabi Y, Young PJ, Bellomo R; VITAMINS trial investigators. Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan. *Crit Care Resusc* 2019; **21**: 119-125 [PMID: [31142242](#)]
- 24 **Moskowitz A**, Andersen LW, Huang DT, Berg KM, Grossestreuer AV, Marik PE, Sherwin RL, Hou PC, Becker LB, Cocchi MN, Doshi P, Gong J, Sen A, Donnino MW. Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. *Crit Care* 2018; **22**: 283 [PMID: [30373647](#) DOI: [10.1186/s13054-018-2217-4](#)]
- 25 **Hager DN**, Hooper MH, Bernard GR, Busse LW, Ely EW, Fowler AA, Gaieski DF, Hall A, Hinson JS, Jackson JC, Kelen GD, Levine M, Lindsell CJ, Malone RE, McGlothlin A, Rothman RE, Viele K, Wright DW, Sevransky JE, Martin GS. The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol: a prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial. *Trials* 2019; **20**: 197 [PMID: [30953543](#) DOI: [10.1186/s13063-019-3254-2](#)]





Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-3991568  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

