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DOI 10.14200/jrm.2020.0102

INTRODUCTION

By the time you read this paper, millions of people globally will have tested positive for the coronavirus, with the United States leading the world in confirmed cases and fatalities.

The pulmonary and other systemic complications of the novel coronavirus (SARS-CoV-2) have created a worldwide emergency. Effective, targeted antiviral drugs are lacking, and symptomatic support is the only therapeutic approach available for the severe acute respiratory infection (SARI)[1] this virus causes. The current guidelines of the National Institutes of Health (NIH) state there is insufficient evidence to either recommend or advise against any particular antiviral, immunomodulatory, or anti-inflammatory therapy in patients with severe coronavirus disease 2019 (COVID-19) infection.[2] A recent NIH report on an ongoing clinical trial of remdesivir says patients receiving the intervention had a 31% faster time to recovery than those who received placebo, and that there is a trend toward decreasing mortality. More comprehensive data regarding this trial will be available in a forthcoming report,[3] but we have at hand something with a remarkable safety record, as well as an array of beneficial clinical effects worth considering for this condition: ascorbic acid.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ASCORBIC ACID

Years of research have shown ascorbic acid (otherwise known as vitamin C or ascorbate – this paper will use these terms interchangeably) to be extremely safe in humans at very high doses. Ascorbic acid is an essential nutrient with important and diverse physiological effects. At high doses (≥7500 mg/day), especially when producing high micromolar or millimolar concentrations, it has been shown to have pharmacological properties. Among its many actions, it plays a role in reducing inflammation (a precipitating factor in SARI), supporting various aspects of the immune system, and having a direct antiviral effect.[4–10]

ANTIVIRAL EFFECTS OF ASCORBIC ACID

A number of studies describe multiple mechanisms by which ascorbic acid enhances the function of leukocytes including chemokinesis and chemotaxis[11]; phagocytosis[12]; lysosomal enzyme production[13]; generation of reactive oxygen species

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(ROS)[14] and microbial killing[15]; up-regulation of the antibody response[16]; and increasing interferon.[8] These effects, along with enhanced neutrophil chemotactic action,[17,18] have been documented in humans receiving either intravenous (IV) vitamin C or taking gram doses orally.

In addition, studies have shown that vitamin C lowers the risk of infection.[19,20] Studies in animal models have demonstrated that parenteral ascorbate improves sepsis and sepsis-induced multiple-organ dysfunction syndrome by preventing cellular immunosuppression.[21] Studies in septic mice suggest that increased survival occurs by activation of Nrf2/HO-1 signals.[22]

In vitro observations with pharmacologic concentrations (millimolar range) suggest a direct antiviral effect of ascorbate[23] that is consistent with clinical observations of patients with Epstein–Barr viral (EBV) infection. Pharmacologic IV ascorbate therapy was associated with a significant reduction in EBV antibodies.[24] Moreover, IV ascorbic acid has demonstrated clinical benefits against a variety of viral infections.[25–28]

THE HUMAN DISADVANTAGE

Most vertebrates respond to physiological stress such as sepsis with a dramatic increase in the synthesis of ascorbate. This is done by converting glucose via the enzyme l-gulono-g-lactone oxidase (GLO). When sufficient ascorbate is present, it helps control excess inflammation, support leukocyte function, inhibit microbial pathogen growth, and neutralize harmful ROS. Humans, however, lack both the necessary gene and the GLO enzyme,[29] and are not able to synthetize ascorbate. This means we must supplement with nutritional doses or acquire pharmacologic doses according to the particular physiologic demands at hand.

ABSORPTION AND PLASMA CONCENTRATIONS IN HEALTH AND DISEASE

Absorption of ascorbic acid in the intestinal membrane occurs either as ascorbate (ASC) by sodium-coupled active transport via the SVCT1 transporter, or as dehydroascorbic acid (DHA) through facilitated diffusion via GLUT1 or GLUT3 transporters.[30] In addition to being a co-factor required for many physiological functions, ascorbic acid has high electron-donating and hydrogen-donating power. This capacity to move electrons gives ascorbic acid great versatility and makes it a formidable RedOx molecule. Ascorbate concentrations in body fluids and tissues are regulated via intestinal absorption, cellular transport, and excretion. Plasma and tissue concentrations are controlled by various mechanisms including absorption, tissue rate of accumulation, tissue utilization, and renal reabsorption.

The amount of vitamin C needed to prevent scurvy is very small, and generally considered to be obtainable from most western-type diets. However, data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) show that the prevalence of inadequate plasma vitamin C concentrations in the USA are as high as 22%–33%, with 7%–14% of people showing scorbutogenic deficiency.[31,32] Signs and symptoms of scurvy occur with plasma ascorbate levels below 1.5 mg/L (0.0085 mM),[33] or below 1.9 mg/L [0.011 mM (11 μM)].[34] People with marginal ascorbate hypovitaminosis, characterized by ascorbate concentrations below 23 μmol/L, can easily develop scurvy when challenged with physiological stressors.[35,36] Adequate levels to support health are anything above 23 μmol/L, or more specifically, as recommended in several European countries, about 50 μmol/L to compensate for metabolic losses.[37–39] Consuming five to nine servings of fruits and vegetables daily, or taking a 200-mg ascorbate supplement have been estimated to produce steady-state ascorbate plasma concentrations of 70–80 μmol/L.[40]

In healthy volunteers who took 3 g of vitamin C orally every day for 6 days, peak values did not exceed 220 μmol/L.[41] It was only when a supra-physiological (millimolar) concentration of ascorbic acid was achieved by high-gram IV dosing that pharmacologic properties were noted.[42–46]

Table 1 shows the correlation of plasma ascorbate concentrations, doses, and the clinical implications ranging from scorbutogenic deficiency to pharmacologic concentrations.

Table 1: Ascorbate plasma levels.

Description	Concentration
Scorbutogenic deficiency – weakness, tiredness, anemia, gingivitis, poor wound healing, ecchymosis	<1.5 mg/L (<8.5 μM)[33] <1.9 mg/L[34]
Low plasma level (suboptimal minimal reserves)	1.5–5 mg/L (8.5–28 μM)[35,36]
Sub-clinical vitamin C insufficiency (nonspecific symptoms, i.e. fatigue, irritability, depression)	<4 mg/L (23 μmol/L)[37]
Adequate plasma level (from diet or dietary supplements)	>5 mg/L (28 μM)[37]
Five to nine servings of fruits and vegetables or 200 mg oral supplement daily	>23 μM, 50 μmol/L[37,38] Achieve steady state 70–80 μmol/L[39]
Low pharmacologic (high-dose dietary supplement) 3 g 6 times a day oral supplement	220 μmol/L micromolar[40]
Moderate-high pharmacologic (intravenous doses) 50 g and higher	>10,000 μmol/L (10 mM) millimolar[42–46]

Clinicians will tell you that sick patients are able to take higher doses of ascorbic acid orally without getting loose stool than they are able to tolerate when well. It has been shown that at least 80% of adult patients will tolerate 10–15 g of ascorbic acid per day without reaching bowel tolerance when it is dissolved in water and taken in divided doses. In the case of serious or very toxic disease states, dosing may need to be every half hour. Short delays in taking these doses may prolong the disease process.[47] Absorption and distribution of ascorbate into diseased tissue presumably occurs because of increased ascorbate metabolism. Frequent dosing is, therefore, thought to meet metabolic demand.[48]

ASCORBIC ACID IN CLINICAL TRIALS FOR SEPSIS

Cytokine storm refers to a severe immune reaction in which the body rapidly releases floods of inflammatory cytokines into the blood causing sepsis. The result is an overwhelming production of ROS that damage multiple organelles, cells, and tissues, leading to progressive organ failure. Cytokine storm is one of the most dangerous complications of COVID-19 infection.[49] Over 500 peer-reviewed papers reporting on both experimental and clinical studies clearly demonstrate the biological and pharmacologic mechanisms by which vitamin C alone, or combined with other agents, can be used in the management of sepsis and other inflammatory disorders.[49,50]

A coagulopathy is commonly observed in patients with severe COVID-19 infection[51] that correlates with a rise in inflammatory markers [C-reactive protein (CRP)].[52] Low-molecular-weight heparin (LMWH) is used to treat it. Interestingly, ascorbic acid has been shown to restore impaired fibrinolysis in heavy smokers, whose endothelial capacity to acutely release tissue plasminogen activator (t-PA) is significantly impaired.[53]

A comprehensive randomized study using IV ascorbic acid in 167 patients with severe acute respiratory failure demonstrated a significant reduction in mortality in the ascorbic acid group, from the fourth day onward, compared to the placebo group (P=0.023).[54]

In this study, Fowler *et al*. gave participants 50 mg/kg of ascorbic acid intravenously every 6 hours, which amounted to a range of 3500–5000 mg every 6 hours for a total of 14,000–20,000 mg every 24 hours, with no unexpected treatment-related side effects.[54]

Recent studies suggest that ascorbic acid, as part of a protective protocol for COVID-19 patients hospitalized with sepsis, may reduce mortality[55] and length of stay in the intensive care unit (ICU),[56] and significantly reduce the time to resolution of shock.[57]

The use of ascorbic acid as a reliable antiviral in many different acute infectious diseases has been documented since 1949. Frederick R. Klenner, MD demonstrated that vitamin C consistently neutralized any toxin when sufficiently dosed and administered for a long enough period of time.[58] This included curing 60 out of 60 patients of polio within 4 days of intramuscular and oral administration of ascorbic acid.[59] In 1951, he reported using ascorbic acid to cure patients with advanced polio and its associated flaccid paralysis.[60]

Marcial-Vega *et al*. reported on the efficacy and safety of 25–50 g of IV ascorbic acid plus hydrogen

peroxide in the treatment of 56 patients with Chikungunya-related arthralgia. Results showed a greater than 71% post-infusion reduction in pain with no adverse effects reported.[61]

These results are consistent with earlier *in vitro* studies which showed that ascorbic acid inactivated the polio,[62] herpes,[63] vaccinia,[64,65] tobacco mosaic,[66] bacteriophage,[67–70] entero,[71] influenza,[7] and rabies[72] viruses. The antiviral effects of ascorbate have also been shown in animal models including rabies in guinea pigs,[73] and VEE virus in mice.[74]

Previous clinical studies showed that ascorbic acid can resolve polio,[9–11,75,76] acute hepatitis,[77–79] viral encephalitis,[80–83] measles,[84] mumps,[85] herpes,[86] and influenza.[87] There are also case reports in humans of IV vitamin C being used to successfully treat influenza,[17] mononucleosis,[24] Chikungunya,[88] and Zika.[89]

ASCORBIC ACID AND COVID-19 STUDIES AND RECOMMENDATIONS

An NIH-funded study that will take place in Wuhan, China, will investigate using 12 g IV ascorbic acid for patients with severe COVID-19 pneumonia.[90] A study using 10 g of IV vitamin C in patients hospitalized with COVID-19 began in Italy in March.[91]

The Shanghai Expert Consensus on COVID-19 Treatment organized by the Shanghai Medical Association has included ascorbic acid as a treatment for COVID-19-associated pneumonia.[92]

The Shanghai Guidelines for the Treatment of COVID-19 Infection, an official document endorsed by the Shanghai Medical Association and the Shanghai City government, reveals that thus far in 2020, 50 COVID-19 patients out of 358 cases have been treated with IV ascorbic acid (IVAA), using 10–20 g infused over 24 hours. One patient who continued to deteriorate was put on a 50-g infusion over a 4-hour period. This patient made a complete recovery and was eventually discharged. All patients who received IVAA improved, and had on average a 5-day shorter stay (25 days vs. 30 days) than patients who did not receive IVAA. No mortalities or adverse events were reported in the IVAA treatment group.[92]

An International Pulmonologist Consensus Group has stated that a moderate dose of IV vitamin C along with other nutrients (1.5 g ascorbic acid IV every 6 hours, plus 200 mg IV thiamine every 12 hours) could be considered as an adjunct protocol for treatment of COVID-19 pneumonia.[93]

IV ascorbic acid has a long track record of safety.[94] It has been used historically in the management of viral infections and more recently for sepsis. Ongoing clinical trials in the United States, Canada, China, Italy, and other countries will hopefully support its widespread use for patients with COVID-19 infection in the larger medical community.

REFERENCES

1. CDC Information for Clinicians on Investigational Therapeutics for Patients with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html.
2. National Institutes of Health, COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/critical-care/pharmacologic-interventions/.
3. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19.
4. Levine M, Padayatty SJ, Espey MG. Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries. *Adv Nutr*. 2011;2:78–88.
5. Sun L, Igarashi T, Tetsuka R, *et al*. Pilot clinical study of ascorbic acid treatment in cardiac catheterization. *J Radiat Res*. 2019;60:573–8.
6. Nakajima M, Kojiro M, Aso S, *et al*. Effect of high-dose vitamin C therapy on severe burn patients: a nationwide cohort study. *Crit Care*. 2019;23:407.
7. Cheng LL, Liu YY, Li B, Ran PX. [An in vitro study on the pharmacological ascorbate treatment of influenza virus]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2012;35:520–3.
8. Kim Y, Kim H, Bae S, *et al*. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-α/β at the initial stage of

influenza A virus (H3N2) infection. *Immune Netw*. 2013;13:70–4.

9. Sorice A, Guerriero E, Capone F, *et al*. Ascorbic acid: its role in immune system and chronic inflammation diseases. *Mini Rev Med Chem*. 2014;14:444–52.

10. Feigen G, Smith B, Dix C, *et al*. Enhancement of antibody production and protection against systemic anaphylaxis by large doses of vitamin C. *Res Commun Chem Pathol Pharmacol*. 1982;38:313–33.

11. Schwager J, Bompard A, Weber P, Raederstorff D. Ascorbic acid modulates cell migration in differentiated HL-60 cells and peripheral blood leukocytes. *Mol Nutr Food Res*. 2015;59:1513–23.

12. Shilotri PG. Phagocytosis and leukocyte enzymes in ascorbic acid deficient guinea pigs. *J Nutr*. 1977;107:1513–6.

13. Anderson R. Effects of ascorbate on normal and abnormal leucocyte functions. *Int J Vitam Nutr Res*. Suppl. 1982;23:23–34.

14. Sharma P, Raghavan SA, Saini R, Dikshit M. Ascorbate-mediated enhancement of reactive oxygen species generation from polymorphonuclear leukocytes: modulatory effect of nitric oxide. *J Leukoc Biol*. 2004;75:1070–8.

15. Vilchèze C, Kim J, Jacobs Jr WR. Vitamin C potentiates the killing of mycobacterium tuberculosis by the first-line tuberculosis drugs isoniazid and rifampin in mice. *Antimicrob Agents Chemother*. 2018;62:e02165–17.

16. Mitsuzumi H, Kusamiya M, Kurimoto T, Yamamoto I. Requirement of cytokines for augmentation of the antigen-specific antibody responses by ascorbate in cultured murine T-cell-depleted splenocytes. *Jpn J Pharmacol*. 1998;78:169–79.

17. Anderson R, Oosthuizen R, Maritz R, *et al*. The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune functions in normal volunteers. *Am J Clin Nutr*. 1980;33:71–6.

18. Bozonet SM, Carr AC, Pullar JM, Vissers MCM. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. *Nutrients.* 2015;7:2574–88.

19. Vorilhon P, Arpajou B, Vaillant Roussel H, *et al*. Efficacy of vitamin C for the prevention and treatment of upper respiratory tract infection. A meta-analysis in children. *Eur J Clin Pharmacol*. 2019;75:303–11.

20. Kim GN, Yoo WS, Park MH, *et al*. Clinical features of herpes simplex keratitis in a Korean tertiary referral center: efficacy of oral antiviral and ascorbic acid on recurrence. *Korean J Ophthalmol*. 2018;32:353–60.

21. Gao YL, Lu B, Zhai JH, *et al*. The parenteral vitamin C improves sepsis and sepsis-induced multiple organ dysfunction syndrome via preventing cellular immunosuppression. *Mediators Inflamm*. 2017;2017:4024672.

22. Kim SR, Ha YM, Kim YM, *et al*. Ascorbic acid reduces HMGB1 secretion in lipopolysaccharide-activated RAW 264.7 cells and improves survival rate in septic mice by activation of Nrf2/HO-1 signals. *Biochem Pharmacol*. 2015;95:279–89.

23. Furuya A, Uozaki M, Yamasaki H, *et al*. Antiviral effects of ascorbic and dehydroascorbic acids in vitro. *Int J Mol Med*. 2008;22:541–5.

24 Mikirova N, Hunninghake R. Effect of high dose vitamin C on Epstein-Barr viral infection. *Med Sci Monit*. 2014;20:725–32.

25. Schencking M, Vollbracht C, Weiss G, *et al*. Intravenous vitamin C in the treatment of shingles: results of a multicenter prospective cohort study. *Med Sci Monit*. 2012;18:CR215–24.

26. Chen S, Zhao W, Zhang B, *et al*. Clinical effect of intravenous vitamin C on viral myocarditis in children: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2019;23:3082437.

27. Gonzalez MJ, Berdiel MJ, Duconge J, *et al*. High dose intravenous vitamin C and influenza: a case report. *J Orthomol Med*. 2018;33:1–3.

28. Marcial-Vega V, Gonzalez-Terron I, Levy TE. Intravenous ascorbic acid and hydrogen peroxide in the management of patients with Chikungunya. *Bol Asoc Med*. 2017;107:20–4.

29. Nishikimi M, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. *Am J Clin Nutr*. 1991;54(6 Suppl):1203S–8S.

30. Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. *Nutrients*. 2019;11:2412.

31. Schleicher RL, Carroll MD, Ford ES, *et al*. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 National Health and Nutrition Examination Survey (NHANES). *Am J Clin Nutr*. 2009;90:1252–63.

32. Cahill L, Corey PN, El-Sohemy A. Vitamin C deficiency in a population of young Canadian adults. *Am J Epidemiol*. 2009;170:464–71.

33. Hagel AF, Albrecht H, Dauth W, *et al*. Plasma concentrations of ascorbic acid in a cross section of the German population. *J Int Med Res*. 2018;46:168–74.

34. Food and Nutrition Board, Institute of Medicine. Vitamin C. In: *DRI Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press; 2000. pp. 95–185.

35. Carr AC, Pullar JM, Bozonet SM, Vissers MC. Marginal ascorbate status (hypovitaminosis C) results in an attenuated response to vitamin C supplementation. *Nutrients*. 2016;8:341.

36. Lykkesfeldt J, Poulsen HE. Is vitamin C supplementation beneficial? Lessons learned from randomized controlled trials. *Br J Nutr*. 2010;103:1251–9.

37. Krajcovicova-Kudlackova M, Babinska K, Valachovicova M, *et al*. Vitamin C protective plasma value. *Bratisl Lek Listy*. 2007;108:265–8.

38. Brubacher D, Moser U, Jordan P. Vitamin C concentrations in plasma as a function of intake: a meta-analysis. *Int J Vitam Nutr Res*. 2000;70:226–37.

39. Tetens I. Scientific opinion on dietary reference values for vitamin C. *EFSA J*. 2013;11:3418.

40. Levine M, Conry-Cantilena C, Wang Y, *et al*. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci U S A*. 1996;93:3704–9.

41. Padayatty SJ, Sun H, Wang Y, *et al*. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med*. 2004;140:533–7.

42. González MJ, Mora EM, Miranda-Massari JR, *et al*. Inhibition of human breast carcinoma cell proliferation by ascorbate and copper. *P R Health Sci J*. 2002;21:21–3.

43. Chen Q, Espey MG, Krishna MC, *et al*. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc Natl Acad Sci U S A*. 2005;102:13604–9.

44. Welsh JL, Wagner BA, van't Erve TJ, *et al*. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial. *Cancer Chemother Pharmacol*. 2013;71:765–75.

45. Wirapakorn C, Singkham-In U, Taratummarat S, *et al*. The cooperation of pharmacologic-dose ascorbate with ceftriaxone against Staphylococcus aureus through bactericidal synergy and enhanced macrophage killing activity. *Asian Pac J Allergy Immunol*. 2019;37:94–101.

46. Mikirova NA, Casciari JJ, Hunninghake RE, Riordan NH. Intravenous ascorbic acid protocol for cancer patients: scientific rationale, pharmacology, and clinical experience. *Funct Food Health Dis*. 2013;3:344–66.

47. Cathcart RF. The method of determining proper doses of vitamin C for the treatment of disease by titrating to bowel tolerance. *Othomol Psychiat*. 1981;10125–32.

48. Mehta P, McAuley DF, Brown M, *et al*. HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033–4.

49. Marik PE. Vitamin C for the treatment of sepsis: the scientific rationale. *Pharmacol Therapeut*. 2018;189:63–70.

50. Marik PE. Hydrocortisone. Ascorbic acid and thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients*. 2018;10:1762.

51. Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–9.

52. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, *et al*. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020. doi: 10.1002/ajh.25829. [Epub ahead of print].

53. Kaehler J, Koeke K, Karstens M, *et al*. Impaired capacity for acute endogenous fibrinolysis in smokers is restored by ascorbic acid. *Free Radic Biol Med*. 2008;44:315–21.

54. Fowler AA, Truwit JD, Hite RD, *et al*. 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;322:1261–70.

55. Marik PE, Khangoora V, Rivera R, *et al*. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151:1229–38.

56. Mitchell AB, Ryan TE, Gillion AR, *et al*. Vitamin C and thiamine for sepsis and septic shock. *Am J Med*. 2020;133:635–8.

57. Iglesias J, Vassallo AV, Patel VV, *et al*. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. *Chest*. 2020. doi:10.1016/j.chest.2020.02.049 [Epub ahed of print].

58. Klenner FR. Observations on the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathology. *J Appl Nutr.* 1971;23.

59. Klenner FR. The treatment of poliomyelitis and other viral diseases with vitamin C. *South Med Surg*. 1949;209.

60. Klenner FR. Massive doses of vitamin C and the virus diseases. *South Med Surg*. 1951;113:101–7.

61. Marcial-Vega V, Idxian Gonzalez-Terron G, Levy TE. Intravenous ascorbic acid and hydrogen peroxide in the management of patients with Chikungunya. *Bol Asoc Med P R*. 2015;107:20–4.

62. Jungeblut CW. Inactivation of poliomyelitis virus in vitro by crystalline vitamin C (ascorbic acid). *J Exp Med*. 1935;62:517–21.

63. Holden M, Molloy E. Further experiments on the inactivation of herpes virus by vitamin C (l-ascorbic acid. *J Immunol*. 1937;33:251–7.

64. Kligler IJ, Bernkopf H. Inactivation of vaccinia virus by ascorbic acid and glutathione. *Nature*. 1937;139:965–6.

65. Turner G. Inactivation of vaccinia virus by ascorbic acid. *J Gen Microbiol*. 1964;35:75–80.

66. Lojkin M. A study of ascorbic acid as an inactivating agent of tobacco mosaic virus. *Contr Boyce Thompson Inst Pl Res*. 1936;8:455.

67. Lominski I. Inactivation du bacteriophage par l'acide ascorbiqu. *J Nutr Sci Vi ascorbique*. *C r Seanc Soc Biol*. 1936;122:766.

68. Murata A, Oyadomari R, Ohashi T, Kitagawa K. Mechanism of inactivation of bacteriophage deltaA containing single-stranded DNA by ascorbic acid. *J Nutr Sci Vitaminol* (Tokyo). 1975;21:261–9.

69. Morgan AR, Cone RL, Elgert TM. The mechanism of DNA strand breakage by vitamin C and superoxide and the protective roles of catalase and superoxide dismutase. *Nucleic Acids Res*. 1976;3:1139–49.

70. Richter HE, Loewen PC. Rapid inactivation of bacteriophage T7 by ascorbic acid is repairable. *Biochim Biophys Acta*. 1982;697:25–30.

71. Salo RJ, Cliver DO. Inactivation of enteroviruses by ascorbic acid and sodium bisulfite. *Appl Environ Microbiol*. 1978;36:68–75.

72. Amato G. Azione dell'acido ascorbico sul virus fisso della rabia e sulla tossina tetanica. *Giornale di Batteriologia, Virologia et Immunologia* (Torino). 1937;19:843–7.

73. Banic S. Prevention of rabies by vitamin C. *Nature*. 1975;258:153–4.

74. Valero N, Mosquera J, Alcocer S, *et al*. Melatonin, minocycline and ascorbic acid reduce oxidative stress and viral titers and increase survival rate in experimental Venezuelan equine encephalitis. *Brain Res*. 2015;1622:368–76.

75. Greer E. Vitamin C in acute poliomyelitis. *Med Times*. 1955;83:1160–1.

76. Baur H. Poliomyelitis therapy with ascorbic acid. *Helv Med Acta*. 1952;19:470–4.

77. Dalton WL. Massive doses of vitamin C in the treatment of viral diseases. *J Indiana State Med Assoc*. 1962;55:1151–4.

78. Orens S. Hepatitis B—A ten day "cure". A personal history. *Bull Phila Cty Dent Socc*. 1983;48:4–5.

79. Klenner F. Significance of high daily intake of ascorbic acid in preventive medicine. *J Int Acad Prev Med.* 1974;1:45–69.

80. Klenner F. The treatment of poliomyelitis and other virus diseases with vitamin C. *South Med Surg*. 1949;111:209–14.

81. Klenner F. Massive doses of vitamin C and the virus diseases. *South Med Surg.* 1951;103:101–7.

82. Klenner F. The use of vitamin C as an antibiotic. *J Appl Nutr*. 1953;6:274–8.

83. Klenner F. Observations of the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathology. *J Appl Nutr*. 1971;23:61–88.

84. Joffe MI, Sukha NR, Rabson AR. Lymphocyte subsets in measles. Depressed helper/inducer subpopulation reversed by in vitro treatment with levamisole and ascorbic acid. *J Clin Invest*. 1983;72:971–80.

85. Karam F. Vitamins B1 and C in the treatment of mumps. *Rev Bras Med*. 1953;10:285–6.

86. Zureick M. [Therapy of herpes and herpes zoster with intravenous vitamin C]. *J Prat Rev Gen Clin Ther*. 1950;64:586.

87. Cai Y, Li YF, Tang LP, *et al*. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. *Biomed Res Int*. 2015;2015:675149.

88. Adrover-López PA, Gonzalez MJ, Miranda-Massari JR, *et al*. Inflammatory sequelae after Chikungunya virus infection: proposed. *J Restor Med*. 2016;5:39–45.

89. González MJ, Berdiel MJ, Miranda-Massari JR, *et al*. High dose intravenous vitamin C treatment for Zika fever. *J Orthomolec Med*. 2016;31:19–22.

90. Peng Z. (PI), Wuhan University. Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia. https://clinicaltrials.gov/ct2/show/NCT04264533.

91. Corrao S. (PI), University of Palermo. Use of ascorbic acid in patients with COVID 19. https://www.clinicaltrials.gov/ct2/show/NCT04323514.

92. Shanghai Expert Group. Clinical treatment of new coronavirus disease. *Chin J Infect Dis*. 2020;38. doi: 10.3760/cma.j.issn.1000-6680.2020.0016. [Epub ahead of print].

93. Marik P. EVMS critical care COVID-19 management protocol. https://www.evms.edu/covid-19/covid_care_for_clinicians/.

94. Padayatty SJ, Sun AY, Chen Q, *et al*. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS One*. 2010;5:e11414.