

Do the Math: "MATH+" Saves Lives

by Michael Passwater
Orthomolecular Medicine News Service

Complete References

1. Front Line COVID-19 Critical Care Alliance <https://covid19criticalcare.com>
2. Kory P, Meduri GU, Iglesias J, Varon J, Marik PE. Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. Journal of Intensive Care Medicine. <https://doi.org/10.1177/0885066620973585>
3. FLCC Alliance (2020) I-MASK+ Protocol. <https://hardball.parkoffletter.org/wp-content/uploads/2020/12/FLCCC-I-MASK-Protocol-v6-2020-12-09-ENGLISH.pdf>
4. The Nobel Prize in Physiology or Medicine 2015. NobelPrize.org. Nobel Media AB 2020. <https://www.nobelprize.org/prizes/medicine/2015/summary>
5. Tay MYF, Fraser JE, Chan WKK, et al. (2013) Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Research. 99:301-306. <https://pubmed.ncbi.nlm.nih.gov/23769930>
6. Varghese FS, Kaukinen P, GlÃ¤sker S, et al. (2016) Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Research. 126:117-124. <https://pubmed.ncbi.nlm.nih.gov/26752081>
7. Wagstaff KM, Sivakumaran H, Heaton SM, et al. (2012) Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochemical Journal. 443:851-856. <https://pubmed.ncbi.nlm.nih.gov/22417684>
8. King CR, Tessier TM, Dodge MJ, et al. (2020) Inhibition of Human Adenovirus Replication by the Importin alpha/beta1 Nuclear Import Inhibitor Ivermectin. Journal of Virology. 94:e00710-20. <https://pubmed.ncbi.nlm.nih.gov/32641484>
9. Caly L, Druce JD, Catton MG, et al. (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 178:104787. <https://pubmed.ncbi.nlm.nih.gov/32251768>
10. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF (2020) SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS ONE 15:e0239252. <https://doi.org/10.1371/journal.pone.0239252>
11. Mercola J, Grant WB, Wagner CL. (2020) Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. Nutrients, 12:3361. <https://www.mdpi.com/2072-6643/12/11/3361>



12. Zhang J, Taylor EW, Bennett K, Saad R, Rayman MP. (2020) Association between regional selenium status and reported outcome of COVID-19 cases in China. *Am J Clin Nutr*, 111:1297-1299. <https://doi.org/10.1093/ajcn/nqaa095>
13. Moghaddam A, Heller RA, Sun Q, et al. (2020) Selenium deficiency is associated with mortality risk from COVID-19. *Nutrients* 12:2098. <https://doi.org/10.3390/nu12072098>
14. Heller RA, Sun Q, Hackler J et al. (2021) Prediction of survival odds in COVID-19 by zinc, age, and selenoprotein P as composite biomarker. *Redox Biology* 38:101764. Online ahead of print. <https://pubmed.ncbi.nlm.nih.gov/33126054>
15. Merzon E. (2020) Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. *FEBS J.* 287:3693-3702. <https://pubmed.ncbi.nlm.nih.gov/32700398>
16. Castillo ME, Costa LME, Barrios JMV, et al. (2020) Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. *J Steroid Biochem Mol Biol* 203:105757. <https://pubmed.ncbi.nlm.nih.gov/32871238>
17. Jungreis I, Kellis M. (2020) Mathematical analysis of Cordoba calcifediol trial suggest strong role for vitamin D in reducing ICU admissions of hospitalized COVID-19 patients. *MedRxiv* preprint. <https://doi.org/10.1101/2020.11.08.20222638>
18. Grassroots Health Nutrient Research Institute. <https://www.grassrootshealth.net>
19. Polonikov, A. (2020) Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in COVID-19 patients. *ACS Infect Dis* 2020, 6, 7, 1558-1562. <https://doi.org/10.1021/acsinfecdis.0c00288>
20. Horowitz RI, Freeman PR, Bruzzese J. (2020) Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respir Med Case Rep* 2020, 101063. <https://doi.org/10.1016/j.rmc.2020.101063>
21. Zhao B, Fei J, Chen Y, et al. (2014) Vitamin C treatment attenuates hemorrhagic shock related multi-organ injuries through the induction of heme oxygenase-1. *BMC Complementary and Alternative Medicine* 2014, 14:442-454. <https://pubmed.ncbi.nlm.nih.gov/25387896>
22. Oudemans-van Straaten HM, Spoelstra-de Man AME, de Waard MC. (2014) Vitamin C revisited. *Critical Care* 18:460-473. <https://pubmed.ncbi.nlm.nih.gov/25185110>
23. Fowler AA, Syed AA, Knowlson S, Natarajan R, et al. (2014) Phase I Safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of Translational Medicine*, 12:32. <https://pubmed.ncbi.nlm.nih.gov/24484547>
24. Gu W, Cheng A, Barnes H, Kuhn B, Schivo M. (2014) Vitamin C Deficiency Leading to Hemodynamically Significant Bleeding. *JSM Clinical Case Reports*. 2:1046. <http://www.jscimedcentral.com/CaseReports/casereports-2-1046.pdf>
25. Manning J, Mitchell B, Appaduras DA, May JM, et al. (2013) Vitamin C Promotes Maturation of T-Cells. *Antioxid Redox Signal*. 19:2054-2067. <https://pubmed.ncbi.nlm.nih.gov/23249337>
26. Ladumer A, Schmitt CA, Schachner D, et al. (2012) Ascorbate stimulates endothelial nitric oxide synthase enzyme activity by rapid modulation of its phosphorylation status. *Free Radic Biol Med*. 2012 May 15; 52:2082-2090. <https://pubmed.ncbi.nlm.nih.gov/22542797>
27. Reddell L, Cotton BA. (2012) Antioxidant and micronutrient supplementation in trauma patients. *Curr Opin Clin Nutr Metab Care*. 15:181-187. <https://pubmed.ncbi.nlm.nih.gov/22261953>

28. May JM, Qu ZC. (2010) Ascorbic Acid Prevents Increased Endothelial Permeability Caused by Oxidized Low Density Lipoprotein. Free Radical Res. 44:1359-1368. <https://pubmed.ncbi.nlm.nih.gov/20815791>
29. Duconge J, Miranda-Massari JR, Gonzalez MJ, et al. (2008) Pharmacokinetics of vitamin C: insights into the oral and intravenous administration of ascorbate. P R Health Sci J. 27:7-19. <http://prhsj.rcm.upr.edu/index.php/prhsj/article/view/13>
30. Deicher R, Ziai F, Begknayer C, et al. (2005) Low Total Vitamin C Plasma Level Is a Risk Factor for Cardiovascular Morbidity and Mortality in Hemodialysis Patients. J Am Soc Nephrol. 16:1811-1818. <https://pubmed.ncbi.nlm.nih.gov/15814831>
31. Heller R, Munscher-Paulig F, Grabner R, Till V. (1999) L-Ascorbic Acid Potentiates Nitric Oxide Synthesis in Endothelial Cells. J Biol Chem, 274:8254-8260. <https://pubmed.ncbi.nlm.nih.gov/10075731>
32. Leibovitz B, Siegel BV. (1978) Ascorbic acid, neutrophil function, and the immune response. Int J Vitam Nutr Res. 48:159-164. <https://pubmed.ncbi.nlm.nih.gov/357320>
33. Klenner FR. (1971) Observations on the Dose and Administration of Ascorbic Acid When Employed Beyond the Range of a Vitamin in Human Pathology. J Applied Nutrition, 1971, Vol 23:61-87. https://jeffreydachmd.com/wp-content/uploads/2013/07/Ascorbic_Acid_Fred_klenner_1971.pdf
34. Lee RE. (1961) Ascorbic Acid and the Peripheral Vascular System. Ann N Y Acad Sci. 92:295-301. <https://pubmed.ncbi.nlm.nih.gov/13760268>
35. Lee RE, Holze EA. (1951) Nutritional factors in hemodynamics: dissociation of pressor response and hemorrhage resistance in avitaminosis C. Proc Soc Exp. Biol Med. 76:325-329. <https://pubmed.ncbi.nlm.nih.gov/14827915>
36. McCormick WJ. (1951) Vitamin C in the Prophylaxis and Therapy of Infectious Diseases. Arch Pediatr, 68:1-9.
37. Klenner FR. (1949) The Treatment of Poliomyelitis and Other Virus Diseases with Vitamin C. Journal of Southern Medicine and Surgery, 111:209-214. <https://pubmed.ncbi.nlm.nih.gov/18147027> https://www.seanet.com/~alexs/ascorbate/194x/klenner-fr-southern_med_surg-1949-v111-n7-p209.htm
38. Klenner FR. (19448) Virus Pneumonia and its Treatment with Vitamin C. Journal of Southern Medicine and Surgery, 110:36-38. <https://pubmed.ncbi.nlm.nih.gov/18900646> https://www.mv.helsinki.fi/home/hemila/CP/Klenner_1948_ch.pdf
39. Lee RE, Lee NZ. (1947) The peripheral vascular system and its reactions in scurvy; an experimental study. Am J Physiol, 149:465-475. <https://pubmed.ncbi.nlm.nih.gov/20239975>
40. Jungeblut CW. (1935) Inactivation of Poliomyelitis Virus in vitro by Crystalline Vitamin C (Ascorbic Acid). J Exp Med, 62:517-521. <https://pubmed.ncbi.nlm.nih.gov/19870431>
41. Colunga Biancatelli RM, Berrill M, Catravas JD, Marik PE. (2020) Quercetin and Vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Front Immunol, 11:1451. <https://pubmed.ncbi.nlm.nih.gov/32636851>
42. Colunga Biancatelli RM, Berrill M, Marik PE. (2020) The antiviral properties of vitamin C. Expert Rev Anti Infect Ther, 18:99-101. <https://pubmed.ncbi.nlm.nih.gov/31852327>
43. Barabutis N, Khangoora V, Marik PE, Catravas JD. (2017) Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. Chest, 152:954-962. <https://pubmed.ncbi.nlm.nih.gov/28739448>

44. de Melo AF, Homem-de-Mello M. (2020) High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection. Crit Care, 24:500. <https://pubmed.ncbi.nlm.nih.gov/32792018>
45. Marik PE. (2018) Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. Nutrients, 10:1762. <https://pubmed.ncbi.nlm.nih.gov/30441816>
45. May JM, Qu ZC. (2011) Ascorbic acid prevents oxidant-induced increases in endothelial permeability. Biofactors, 37:46-50. <https://pubmed.ncbi.nlm.nih.gov/21328627>
46. Utoguchi N, Ikeda K, Saeki K et al. (1995) Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. J Cell Physiol, 163:393-399. <https://pubmed.ncbi.nlm.nih.gov/7706381>
47. Han M, Pendem S, Teh SL, Sukumaran DK, Wu F, Wilson JX. (2010) Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. Free Radic Biol Med 2010; 48:128-35. <https://pubmed.ncbi.nlm.nih.gov/19840845>
48. Khan HMW, Parikh N, Megah SM, Predeteanu GS. (2020) Unusual Early Recovery of a Critical COVID-19 After Administration of Intravenous Vitamin C. Am J Case Rep, 21:e925521 <https://pubmed.ncbi.nlm.nih.gov/32709838>
49. Bharara A, Grossman C, Grinnon D, et al. (2016) Intravenous Vitamin C Administered as Adjunctive Therapy for Recurrent Acute Respiratory Distress Syndrome. Case Rep Crit Care. 2016:8560871. <https://pubmed.ncbi.nlm.nih.gov/27891260>
50. May JM, Harrison FE. (2013) Role of Vitamin C in the Function of the Vascular Endothelium. Antioxid Redox Signal. 19:2068-2083. <https://pubmed.ncbi.nlm.nih.gov/23581713>
51. Marik PE, Khangoora V, Rivera R, et al. (2017) Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest, 151:1229-1238. <https://pubmed.ncbi.nlm.nih.gov/27940189>
52. Barabutis N, Khangoora V, Marik PE, Catravas JD. (2017) Hydrocortisone and Ascorbic Acid Synergistically Prevent and Repair Lipopolysaccharide-Induced Pulmonary Endothelial Barrier Dysfunction. Chest, 152:954-962. <https://pubmed.ncbi.nlm.nih.gov/28739448>
53. Parker WH, Rhea EM, Qu ZC, Hecker MR, May JM. (2016) Intracellular ascorbate tightens the endothelial permeability barrier through Epac1 and the tubulin cytoskeleton. Am J Physiol Cell Physiol. 311:C652-C662. <https://pubmed.ncbi.nlm.nih.gov/27605450>
54. Ferry M, Coley N, Andrieu S, et al. (2013) How to design nutritional intervention trials to populations and apply for efficacy claims: a statement from the international academy on nutrition and aging task force. J Nutr Heal Aging. 17:619-523. <https://pubmed.ncbi.nlm.nih.gov/23933873>
55. Bieri JG. (1964) Synergistic effects between antioxidants and selenium or vitamin E. Biochem Pharmacol. 13:1465-1470. <https://pubmed.ncbi.nlm.nih.gov/14239620>
56. Badmaev V, Majeed M, Passwater RA. (1996) Selenium: A Quest for Better Understanding. Altern Ther Health Med. 2:59-62, 65-67. <https://pubmed.ncbi.nlm.nih.gov/8795924>
57. Taylor, E.W. RNA viruses vs. DNA synthesis: a general viral strategy that may contribute to the protective antiviral effects of selenium. Preprints 2020, 10.20944/preprints202006.0069.v1, 2020060069, <http://doi.org/10.20944/preprints202006.0069.v1>
58. Luxwolda MF, Kuipers RS, Kema IP, Dijck-Brouwer DA, Muskiet FA. (2012) Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. Br J Nutr. 108:1557-1561. <https://pubmed.ncbi.nlm.nih.gov/22264449>

59. The Nobel Prize in Physiology or Medicine 1903. NobelPrize.org. Nobel Media AB 2020. <https://www.nobelprize.org/prizes/medicine/1903/summary>
60. Dean C (2017) The Magnesium Miracle, 2nd Ed. Ballantine Books. ISBN-13 : 978-0399594441
61. Deng X, Song Y, Manson JE, et al. (2013) Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. BMC Med, 11:187. <https://pubmed.ncbi.nlm.nih.gov/23981518>
62. Flore R, Ponziani FR, Di Renzo TA, et al. (2013) Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis. Eur Rev Med Pharmacol Sci. 17:2433-2440. <https://pubmed.ncbi.nlm.nih.gov/24089220>
63. Schwalfenberg GK. (2017) Vitamins K1 and K2: The Emerging Group of Vitamins Required for Human Health. J Nutr Metab. 2017:6254836. <https://pubmed.ncbi.nlm.nih.gov/28698808>
64. Bosworth C, de Boer IH. (2013) Impaired vitamin D metabolism in CKD. Semin Nephrol. 33:158-168. <https://pubmed.ncbi.nlm.nih.gov/23465502>
65. Reinhardt W, Dolff S, Benson S, et al. (2015) Chronic Kidney Disease Distinctly Affects Relationship Between Selenoprotein P Status and Serum Thyroid Hormone Parameters. Thyroid. 25:1091-1096. <https://pubmed.ncbi.nlm.nih.gov/26348725>
66. Schäfze N, Fritsche J, Ebert-Dumig R, et al. (1999) The selenoprotein thioredoxin reductase is expressed in peripheral blood monocytes and THP1 human myeloid leukemia cells-- regulation by 1,25-dihydroxyvitamin D3 and selenite. Biofactors, 10:329-338, <https://pubmed.ncbi.nlm.nih.gov/10619700>
67. Jain SK, Micinski D. (2013) Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes. Biochem Biophys Res Commun 437:7-11, <https://pubmed.ncbi.nlm.nih.gov/23770363>
68. Alvarez JA, Chowdhury R, Jones DP, et al. (2014) Vitamin D status is independently associated with plasma glutathione and cysteine thiol/disulphide redox status in adults. Clin Endocrinol (Oxf) 81:458-466. <https://pubmed.ncbi.nlm.nih.gov/24628365>
69. Parsanathan R, Jain SK. (2019) Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice. Sci Rep. 9:14784. <https://pubmed.ncbi.nlm.nih.gov/31616013>
70. Fan YG, Pang ZQ, Wu TY, et al. (2020) Vitamin D deficiency exacerbates Alzheimer-like pathologies by reducing antioxidant capacity. Free Radic Biol Med. 161:139-149. <https://pubmed.ncbi.nlm.nih.gov/33068737>
71. Jain SK, Parsanathan R, Achari AE, et al. (2017) Glutathione Stimulates Vitamin D Regulatory and Glucose Metabolism Genes, Lowers Oxidative Stress and Inflammation, and Increases 25-Hydroxy-Vitamin D Levels in Blood: A Novel Approach to Treat 25-Hydroxyvitamin D Deficiency. Antioxid Redox Signal. 29:1792-1807. <https://pubmed.ncbi.nlm.nih.gov/30160165>
72. Guillen OM, Vindry C, Ohlmann T, Chavatte L. (2019) Selenium, Selenoproteins, and Viral Infection. Nutrients, 11:2101. <https://doi.org/10.3390/null092101>
73. Huang Z, Rose AH, Hoffman PR. (2012) The Role of Selenium in Inflammation and Immunity: From Molecular Mechanisms to Therapeutic Opportunities. Antioxid Redox Signal. 16:705-743. <https://pubmed.ncbi.nlm.nih.gov/21955027>
74. Cantorna MT, Snyder L, Lin YOD, Yang L. (2015) Vitamin D and 1,25(OH)2D Regulation of T cells. Nutrients, 7:3011-3021. <https://pubmed.ncbi.nlm.nih.gov/25912039>

75. Looman KIM, Jansen MAE, Voortman T, et al. (2017) The role of vitamin D on circulating memory T cells in children: The generation R Study. *Pediatr. Allergy Immunol.* 28:579-587. <https://pubmed.ncbi.nlm.nih.gov/28686349>
76. Taylor EW, Radding W. (2020) Understanding Selenium and Glutathione as Antiviral Factors in COVID-19: Does the Viral M pro Protease Target Host Selenoproteins and Glutathione Synthesis? *Front Nutr* 7:143. <https://pubmed.ncbi.nlm.nih.gov/32984400>
77. Bellinger FP, Ramoy AV, Reeves MA, Berry MJ. (2009) Regulation and function of selenoproteins in human disease. *Biochem J*, 422:11-22. <https://pubmed.ncbi.nlm.nih.gov/19627257>
78. Hiffler L, Rakotoambinina B. (2020) Selenium and RNA viruses interactions: Potential implications for SARSCov-2 infection (COVID-19). *Front Nutr*. 7:164. <https://pubmed.ncbi.nlm.nih.gov/33015130>
79. Beck MA, Levander OA, Handy J. (2003) Selenium deficiency and viral infection. *J Nutr.* 133(5 Suppl 1):1463S-1467S. <https://pubmed.ncbi.nlm.nih.gov/12730444>
80. Cunningham-Rundles S, McNeeley DF, Moon A. (2005) Mechanisms of nutrient modulation of the immune response. *J Allergy Clin Immunol.* 115:1119-1128; quiz 1129. <https://pubmed.ncbi.nlm.nih.gov/15940121>
81. Hoffmann PR, Berry MJ. (2008) The influence of selenium on immune responses. *Mol Nutr Food Res.* 52:1273-1280. <https://pubmed.ncbi.nlm.nih.gov/18384097>
82. Taylor AK, Cao W, Vora KP, et al. (2013) Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. *J Infect Dis.* 207:501-510. <https://pubmed.ncbi.nlm.nih.gov/22949306>
83. Beck MA, Handy J, Levander OA. (2004) Host nutritional status: the neglected virulence factor. *Trends Microbiol.* 12:417-423. <https://pubmed.ncbi.nlm.nih.gov/15337163>
84. Harthill M. (2011) Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. *Biol Trace Elem Res.* 143:1325-1336. <https://pubmed.ncbi.nlm.nih.gov/21318622>
85. Mak TW, Grusdat M, Duncan GS, et al. (2017) Glutathione Primes T cell Metabolism for Inflammation. *Immunity.* 46:675-689, 1089-1090. <https://pubmed.ncbi.nlm.nih.gov/28423341>, <https://pubmed.ncbi.nlm.nih.gov/28636957>
86. Leibovitz B, Siegel BV. (1978) Ascorbic acid, neutrophil function, and the immune response. *Int J Vitam Nutr Res.* 48:159-164. <https://pubmed.ncbi.nlm.nih.gov/357320>
87. Manning J, Mitchell B, Appadurai DA, et al. (2013) Vitamin C Promotes Maturation of T-Cells. *Antioxid Redox Signal.* 19:2054-2067. <https://pubmed.ncbi.nlm.nih.gov/23249337>

