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## Role of Vitamin C and D in acute respiratory distress syndrome (ARDS) and Covid-19

**ID of request:** 26928  
**Date of request:** 7th January, 2021  
**Date of completion:** 7th January, 2021

If you would like to request any articles or any further help, please contact:  Angela Page at [angela.page@hhft.nhs.uk](mailto:angela.page@hhft.nhs.uk)

Please acknowledge this work in any resulting paper or presentation as: Evidence search: Role of Vitamin C and D in acute respiratory distress syndrome (ARDS) and Covid-19. Angela Page. ( 7th January, 2021). WINCHESTER, UK: Hampshire Healthcare Library Service.

**Sources searched**  
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### [B. Search History](#SearchHistory)

## A. Original Research

1. **Could SARS-CoV-2-induced lung injury be attenuated by vitamin D?**  
   Xiao Dongqiong International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2021;102:196-202.

A novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has been confirmed as having the capacity to transmit from humans to humans, causing acute respiratory distress syndrome (ARDS) and acute lung injury. Angiotensin converting enzyme-2 (ACE2) is known to be expressed on type II pneumocytes. As a counter-regulatory arm of the renin-angiotensin system (RAS), ACE2 plays critical roles in the pathogenesis of ARDS and acute lung injury. The affinity of the spike protein receptor binding domain (RBD) of SARS-CoV-2 for human ACE2 (hACE2) largely determines the degree of clinical symptoms after infection by SARS-CoV-2. Previous studies have shown that regulating the ACE2/RAS system is effective in the treatment of severe acute respiratory syndrome coronavirus (SARS-CoV)-induced ARDS and acute lung injury. Since ACE2 is the host cell receptor for both SARS-CoV-2 and SARS-CoV, regulating the ACE2/RAS system may alleviate ARDS and acute lung injury caused by SARS-CoV-2 as well as SARS-CoV. Vitamin D was found to affect ACE2, the target of SARS-CoV-2; therefore, we propose that vitamin D might alleviate ARDS and acute lung injury induced by SARS-CoV-2 by modulating ACE2.

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1. **Effects of vitamin D on macrophages and myeloid-derived suppressor cells (MDSCs) hyperinflammatory response in the lungs of COVID-19 patients**  
   Kloc M. Cellular Immunology 2021;360:No page numbers.

Vitamin D regulates homeostasis, anti-microbial response, and inflammation. The vitamin D receptors are expressed in the macrophages and other immune cells, regulating the transcription of many different genes, including those coding the anti-microbial peptides. One of the most severe complications of the SARS-CoV-2 infection is the acute respiratory distress syndrome (ARDS) caused by the hyperinflammatory response (commonly called cytokine storm) of the lung macrophages. Studies showed that Vitamin D deficiency increases the severity of the ARDS in COVID-19 infection. We discuss here how the vitamin D supplementation may influence macrophage and myeloid-derived suppressor cells (MDSCs) inflammatory response, subdue the hyperinflammatory response, and lessen the ARDS in COVID-19 patients.<br/>Copyright &#xa9; 2020 Elsevier Inc.

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1. **Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?**  
   Shakoor Hira Maturitas 2021;143:1-9.

The world is currently in the grips of the coronavirus disease (COVID-19) pandemic, caused by the SARS-CoV-2 virus, which has mutated to allow human-to-human spread. Infection can cause fever, dry cough, fatigue, severe pneumonia, respiratory distress syndrome and in some instances death. COVID-19 affects the immune system by producing a systemic inflammatory response, or cytokine release syndrome. Patients with COVID-19 have shown a high level of pro-inflammatory cytokines and chemokines. There are currently no effective anti-SARS-CoV-2 viral drugs or vaccines. COVID-19 disproportionately affects the elderly, both directly, and through a number of significant age-related comorbidities. Undoubtedly, nutrition is a key determinant of maintaining good health. Key dietary components such as vitamins C, D, E, zinc, selenium and the omega 3 fatty acids have well-established immunomodulatory effects, with benefits in infectious disease. Some of these nutrients have also been shown to have a potential role in the management of COVID-19. In this paper, evidence surrounding the role of these dietary components in immunity as well as their specific effect in COVID-19 patients are discussed. In addition, how supplementation of these nutrients may be used as therapeutic modalities potentially to decrease the morbidity and mortality rates of patients with COVID-19 is discussed.

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1. **Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19**  
   Kumar R. Virus Research 2021;292:No page numbers.

The first incidence of COVID-19 was reported in the Wuhan city of Hubei province in China in late December 2019. Because of failure in timely closing of borders of the affected region, COVID-19 spread across like a wildfire through air travel initiating a pandemic. It is a serious lower respiratory track viral infection caused by highly contagious, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Coronavirus including COVID-19 causing SARS-CoV-2 causes zoonotic diseases and thought to be originated from bats. Since its first incidence, the virus has spread all across the world, causing serious human casualties, economic losses, and disrupting global supply chains. As with SARS-CoV, COVID-19 causing SARS-CoV-2 follows a similar path of airborne infection, but is less lethal and more infectious than SARS and MERS. This review focusses on the pathogenesis of SARS-CoV-2, especially on the dysfunctional immune responses following a cytokine storm in severely affected persons. The mode of entry of SARS-CoV-2 is via the angiotensin converting enzyme 2 (ACE-2) receptors present on the epithelial lining of lungs, gastrointestinal tract, and mucus membranes. Older persons with weaker immune system and associated co-morbidities are more vulnerable to have dysfunctional immune responses, as most of them concomitantly have severe hypovitaminosis D. Consequently, causing severe damage to key organs of the body including lungs and the cardiovascular system. Since, vast majority of persons enters to the intensive care units and died, had severe vitamin D deficiency, thus, this area must be investigated seriously. In addition, this article assesses the role of vitamin D in reducing the risk of COVID-19. Vitamin D is a key regulator of the renin-angiotensin system that is exploited by SARS-CoV-2 for entry into the host cells. Further, vitamin D modulates multiple mechanisms of the immune system to contain the virus that includes dampening the entry and replication of SARS-CoV-2, reduces concentration of pro-inflammatory cytokines and increases levels of anti-inflammatory cytokines, enhances the production of natural antimicrobial peptide and activates defensive cells such as macrophages that could destroy SARS-CoV-2. Thus, this article provides the urgency of needed evidences through large population based randomized controlled trials and ecological studies to evaluate the potential role of vitamin D in COVID-19.<br/>Copyright &#xa9; 2020 Elsevier B.V.

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1. **"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".**  
   Entrenas Castillo Marta The Journal of steroid biochemistry and molecular biology 2020;203:105751.

OBJECTIVEThe vitamin D endocrine system may have a variety of actions on cells and tissues involved in COVID-19 progression especially by decreasing the Acute Respiratory Distress Syndrome. Calcifediol can rapidly increase serum 25OHD concentration. We therefore evaluated the effect of calcifediol treatment, on Intensive Care Unit Admission and Mortality rate among Spanish patients hospitalized for COVID-19.DESIGNParallel pilot randomized open label, double-masked clinical trial.SETTINGUniversity hospital setting (Reina Sofia University Hospital, Córdoba Spain.) PARTICIPANTS: 76 consecutive patients hospitalized with COVID-19 infection, clinical picture of acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).PROCEDURESAll hospitalized patients received as best available therapy the same standard care, (per hospital protocol), of a combination of hydroxychloroquine (400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days), azithromycin (500 mg orally for 5 days. Eligible patients were allocated at a 2 calcifediol:1 no calcifediol ratio through electronic randomization on the day of admission to take oral calcifediol (0.532 mg), or not. Patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. Outcomes of effectiveness included rate of ICU admission and deaths.RESULTSOf 50 patients treated with calcifediol, one required admission to the ICU (2%), while of 26 untreated patients, 13 required admission (50 %) p value X2 Fischer test p < 0.001. Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment versus without Calcifediol treatment: 0.02 (95 %CI 0.002-0.17). Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003-0.25). Of the patients treated with calcifediol, none died, and all were discharged, without complications. The 13 patients not treated with calcifediol, who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged.CONCLUSIONOur pilot study demonstrated that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease, but larger trials with groups properly matched will be required to show a definitive answer.

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1. **A 29-year-old male with a fatal case of covid-19 acute respiratory distress syndrome (Cards) and ventilator-induced lung injury (vili)**  
   Deliwala S.S. American Journal of Case Reports 2020;21:1-6.

Patient: Male, 29-year-old Final Diagnosis: Acute respiratory distress syndrome (ARDS) \* COVID-19 \*multi organ failure/septic shock \* pneumothorax Symptoms: Cough \* dyspnea \* fatigue \* myalgia Medication: - Clinical Procedure: Mechanical ventilation \* thoracentesis Specialty: Critical Care Medicine Objective: Unknown ethiology Background: COVID-19 patients that develop acute respiratory distress syndrome (ARDS) "CARDS" behave differently com-pared to patients with classic forms of ARDS. Recently 2 CARDS phenotypes have been described, Type L and Type H. Most patients stabilize at the milder form, Type L, while an unknown subset progress to Type H, resem-bling full-blown ARDS. If uncorrected, phenotypic conversion can induce a rapid downward spiral towards pro-gressive lung injury, vasoplegia, and pulmonary shrinkage, risking ventilator-induced lung injury (VILI) known as the "VILI vortex". No cases of in-hospital phenotypic conversion have been reported, while ventilation strategies in these patients differ from the lung-protective approaches seen in classic ARDS. Case Report: A 29-year old male was admitted with COVID-19 pneumonia complicated by severe ARDS, multi-organ failure, cytokine release syndrome, and coagulopathy during his admission. He initially resembled CARDS Type L case, although refractory hypoxemia, fevers, and a high viral burden prompted conversion to Type H within 8 days. Despite ventilation strategies, neuromuscular blockade, inhalation therapy, and vitamin C, he remained asyn-chronous to the ventilator with volumes and pressures beyond accepted thresholds, eventually developing a fatal tension pneumothorax. <br/>Conclusion(s): Patients that convert to Type H can quickly enter a spiral of hypoxemia, shunting, and dead-space ventilation towards full-blown ARDS. Understanding its nuances is vital to interrupting phenotypic conversion and entry into VILI vortex. Tension pneumothorax represents a poor outcome in patients with CARDS. Further research into monitoring lung dynamics, modifying ventilation strategies, and understanding response to various modes of ventilation in CARDS are required to mitigate these adverse outcomes.<br/>Copyright &#xa9; Am J Case Rep, 2020;.

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1. **A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19.**  
   Malek Mahdavi Aida Reviews in medical virology 2020;30(5):e2119.

The novel coronavirus disease 2019 (COVID-19) is rapidly expanding and causing many deaths all over the world with the World Health Organization (WHO) declaring a pandemic in March 2020. Current therapeutic options are limited and there is no registered and/or definite treatment or vaccine for this disease or the causative infection, severe acute respiratory coronavirus 2 syndrome (SARS-CoV-2). Angiotensin-converting enzyme 2 (ACE2), a part of the renin-angiotensin system (RAS), serves as the major entry point into cells for SARS-CoV-2 which attaches to human ACE2, thereby reducing the expression of ACE2 and causing lung injury and pneumonia. Vitamin D, a fat-soluble-vitamin, is a negative endocrine RAS modulator and inhibits renin expression and generation. It can induce ACE2/Ang-(1-7)/MasR axis activity and inhibits renin and the ACE/Ang II/AT1R axis, thereby increasing expression and concentration of ACE2, MasR and Ang-(1-7) and having a potential protective role against acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Therefore, targeting the unbalanced RAS and ACE2 down-regulation with vitamin D in SARS-CoV-2 infection is a potential therapeutic approach to combat COVID-19 and induced ARDS.

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1. **A dissection of SARS-CoV2 with clinical implications (Review)**  
   Stancioiu F. International Journal of Molecular Medicine 2020;46(2):489-508.

We are being confronted with the most consequential pandemic since the Spanish flu of 1918-1920 to the extent that never before have 4 billion people quarantined simultaneously; to address this global challenge we bring to the forefront the options for medical treatment and summarize SARS-CoV2 structure and functions, immune responses and known treatments. Based on literature and our own experience we propose new interventions, including the use of amiodarone, simvastatin, pioglitazone and curcumin. In mild infections (sore throat, cough) we advocate prompt local treatment for the naso-pharynx (inhalations; aerosols; nebulizers); for moderate to severe infections we propose a tried-and-true treatment: the combination of arginine and ascorbate, administered orally or intravenously. The material is organized in three sections: i) Clinical aspects of COVID-19; acute respiratory distress syndrome (ARDS); known treatments; ii) Structure and functions of SARS-CoV2 and proposed antiviral drugs; iii) The combination of arginine-ascorbate.<br/>Copyright &#xa9; 2020 Spandidos Publications. All rights reserved.

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1. **Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation (AVoCaDO). NCT04357782**  
   Davis ClinicalTrials.gov 2020;:0.

"Previous research has shown that high dose intravenous vitamin C (HDIVC) may benefit patients with sepsis, acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS). However, it is not known if early administration of HDIVC could prevent progression to ARDS. We hypothesize that HDIVC is safe and tolerable in Coronavirus disease 2019 (COVID-19) subjects given early or late in the disease course and may reduce the risk of respiratory failure requiring mechanical ventilation and development of ARDS along with reductions in supplemental oxygen demand and inflammatory markers."

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1. **Ascorbate as Prophylaxis and Therapy for COVID-19-Update From Shanghai and U.S. Medical Institutions.**  
   Cheng Richard Z. Global advances in health and medicine 2020;9:2164956120934768.

BackgroundNo validated treatments have been identified for the COVID-19 pandemic virus; several are currently in randomized clinical trials. Diagnostic instruments are rapidly evolving. Symptoms range from those of a common cold to acute respiratory distress syndrome (ARDS), to sepsis arising from the flood of inflammatory bacterial and viral pathogens in the blood. Mortality generally arises from cytokine storms of uncontrolled inflammation, oxidative injury, and damage to the alveolar-capillary barrier, with secondary bacterial infection. To address the indisputably urgent need for therapeutics for COVID-19, a specialized interdisciplinary medical panel convened in Shanghai in March 2020 to consider all relevant clinical and experimental evidence on the possible utility of intravenous (IV) ascorbate in the treatment of COVID-19-related ARDS.MethodsThe panel convened multidisciplinary medical experts and reviewed all relevant in vitro, in vivo, clinical studies and randomized controlled trials on IV ascorbate and issued a consensus report on 23 March 2020 noting that substantial differences in serum concentrations of ascorbate are achieved through IV administration in contrast with the oral route.FindingsThe Shanghai panel, and a parallel medical group in Guangzhou, are advising the use of high-dose IV ascorbate for the treatment of ARDS, along with other supportive therapies, including Vitamin D and zinc. We report preliminary progress in using this treatment for 50 consecutive cases treated in Shanghai hospitals, consistent with earlier reports from a meta-analysis of the use of IV ascorbate to treat sepsis. We provide an instructive clinical anecdote regarding a single family where one elderly member with cardiac and other major comorbidities developed and survived ARDS-related sepsis following daily treatments that included 15 g of IV ascorbate. None of her adult caregivers who had ingested between 2 and 10 g of ascorbate daily developed COVID-19.

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1. **Association Between Vitamin D and Novel SARS-CoV-2 Respiratory Dysfunction - A Scoping Review of Current Evidence and Its Implication for COVID-19 Pandemic.**  
   Santaolalla Aida Frontiers in physiology 2020;11:564387.

ObjectivesTo assess the association between vitamin D deficiency and increased morbidity/mortality with COVID-19 respiratory dysfunction.DesignScoping review.Data SourcesOvid MEDLINE (1946 to 24 of April 2020) and PubMed (2020 to 17 of September 2020).Eligibility Criteria for Selecting StudiesA search using the search terms: [(cholecalciferol or ergocalciferol or vitamin D2 or vitamin D3 or vitamin D or 25OHD) and (SARS-CoV-2 or coronavirus or COVID or betacoronavirus or MERS-CoV or SARS-CoV or respiratory infection or acute respiratory distress syndrome or ARDS)]m.p. was conducted on the 24/04/2020 (Search A) and 17/09/2020 (Search B).Results91 studies were identified as being concerned with Acute Respiratory Infection (ARI)/Acute Respiratory Distress Syndrome (ARDS) and vitamin D, and 25 publications specifically explored the role of vitamin D deficiency in the development and progression of SARS-CoV-2/COVID-19 related ARDS. Search "A" identified three main themes of indirect evidence supporting such an association. Consistent epidemiological evidence exists linking low vitamin D levels to increased risk and severity of respiratory tract infections. We also report on plausible biological processes supporting such an association; and present weaker evidence supporting the benefit of vitamin D supplementation in reducing the risk and severity of ARIs. Uncertainty remains about what constitutes an appropriate dosing regimen in relation to reducing risk/severity of ARI/ARDS. More recent evidence (Search B) provided new insights into some direct links between vitamin D and COVID-19; with a number of cohort and ecological studies supporting an association with PCR-positivity for SARS-CoV-2 and vitamin D deficiency. The exact efficacy of the vitamin D supplementation for prevention of, or as an adjunct treatment for COVID-19 remains to be determined; but a number of randomized control trials (RCTs) currently underway are actively investigating these potential benefits.ConclusionOur rapid review of literature supports the need for observational studies with COVID-19 infected populations to measure and assess vitamin D levels in relation to risk/severity and outcomes; alongside RCTs designed to evaluate the efficacy of supplementation both in preventive and therapeutic contexts. The overlap in the vitamin D associated biological pathways with the dysregulation reported to drive COVID-19 outcomes warrants further investigation.

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1. **Can a Combination of AT1R Antagonist and Vitamin D Treat the Lung Complication of COVID-19?**  
   Rafiullah Mohamed The American journal of the medical sciences 2020;360(4):338-341.

Severe Acute Respiratory Distress Syndrome caused by a novel human coronavirus SARS-CoV-2 named COVID-19 and declared as a pandemic. This paper reviews the possibility of repurposing angiotensin type 1 receptor (AT1R) antagonists and vitamin D to treat COVID-19. ACE2 protein found on the cell membranes is the target of SARS-CoV-2 for entering into the host cells. Viral spike protein-binding with ACE2 down-regulates it. As ACE2 is known to protect the lung from injuries, SARS-CoV-2-induced ACE2 deficiency may expose patients to lung damage. AT1R antagonists and vitamin D increase the expression of ACE2 independently. Besides, vitamin D suppresses the compensatory increase in renin levels following the inhibition of the renin-angiotensin system by AT1R antagonists. Therefore, a combination of AT1R antagonists and vitamin D may offer protection against COVID-19 induced lung injury.

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1. **Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: Lessons from SARS and MERS, and potential therapeutic interventions**  
   Jafarzadeh A. Life Sciences 2020;257:No page numbers.

The COVID-19-, SARS- and MERS-related coronaviruses share many genomic and structural similarities. However, the SARS-CoV-2 is less pathogenic than SARS-CoV and MERS-CoV. Despite some differences in the cytokine patterns, it seems that the cytokine storm plays a crucial role in the pathogenesis of COVID-19-, SARS- and MERS. Monocytes and macrophages may be infected by SARS-CoV-2 through ACE2-dependent and ACE2-independent pathways. SARS-CoV-2 can effectively suppress the anti-viral IFN response in monocytes and macrophages. Since macrophages and dendritic cells (DCs) act as antigen presenting cells (APCs), the infection of these cells by SARS-CoV-2 impairs the adaptive immune responses against the virus. Upon infection, monocytes migrate to the tissues where they become infected resident macrophages, allowing viruses to spread through all organs and tissues. The SARS-CoV-2-infected monocytes and macrophages can produce large amounts of numerous types of pro-inflammatory cytokines and chemokines, which contribute to local tissue inflammation and a dangerous systemic inflammatory response called cytokine storm. Both local tissue inflammation and the cytokine storm play a fundamental role in the development of COVID-19-related complications, such as acute respiratory distress syndrome (ARDS), which is a main cause of death in COVID-19 patients. Here, we describe the monocytes and macrophage responses during severe coronavirus infections, while highlighting potential therapeutic interventions to attenuate macrophage-related inflammatory reactions in possible approaches for COVID-19 treatment.<br/>Copyright &#xa9; 2020 Elsevier Inc.

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1. **Coronavirus disease-2019 (COVID-19): An updated review**  
   Rudrapal M. Drug Research 2020;70(9):389-400.

The current outbreak of novel Coronavirus Disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major pandemic situation and a catastrophe for humans. COVID-19 is a severe infectious disease particularly of the respiratory system characterized by fatal complications such as severe acute respiratory distress syndrome (SARS), pneumonia, cardiac arrhythmia, kidney failure/ multiple organ failure and even death. Since its discovery, the SARS-CoV-2 has spread across 213 countries or territories, causing more than 8.5 million people with a rising death toll over 5.5 million people (as of June 2020, WHO). In fact, the current looming crisis of COVID-19 has become an increasingly serious concern to public health. It has affected lives of millions of people with severe impact on health systems and economies globally. Since there are no specific drugs and/or vaccines available so far, combating COVID-19 remains to be a major challenging task. Therefore, development of potential and effective treatment regimens (prophylactic/therapeutic) is urgently required which could resolve the issue. In this review, we summarize the current knowledge about the coronavirus, disease epidemiology, clinical manifestations and risk factors, replication of the virus, pathophysiology and host immune responses of SARS-CoV-2 infection. The therapeutic interventions and prophylactic measures along with precautionary measures are the frontline approaches that could be undertaken in order to control and prevent the spread of the deadly and highly contagious COVID-19 are also detailed herein.<br/>Copyright &#xa9; 2020 American Institute of Physics Inc.. All rights reserved.

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1. **Could vitamins help in the fight against covid-19?**  
   Jovic T.H. Nutrients 2020;12(9):1-30.

There are limited proven therapeutic options for the prevention and treatment of COVID-19. The role of vitamin and mineral supplementation or "immunonutrition" has previously been explored in a number of clinical trials in intensive care settings, and there are several hypotheses to support their routine use. The aim of this narrative review was to investigate whether vitamin supplementation is beneficial in COVID-19. A systematic search strategy with a narrative literature summary was designed, using the Medline, EMBASE, Cochrane Trials Register, WHO International Clinical Trial Registry, and Nexis media databases. The immune-mediating, antioxidant and antimicrobial roles of vitamins A to E were explored and their potential role in the fight against COVID-19 was evaluated. The major topics extracted for narrative synthesis were physiological and immunological roles of each vitamin, their role in respiratory infections, acute respiratory distress syndrome (ARDS), and COVID-19. Vitamins A to E highlighted potentially beneficial roles in the fight against COVID-19 via antioxidant effects, immunomodulation, enhancing natural barriers, and local paracrine signaling. Level 1 and 2 evidence supports the use of thiamine, vitamin C, and vitamin D in COVID-like respiratory diseases, ARDS, and sepsis. Although there are currently no published clinical trials due to the novelty of SARS-CoV-2 infection, there is pathophysiologic rationale for exploring the use of vitamins in this global pandemic, supported by early anecdotal reports from international groups. The final outcomes of ongoing trials of vitamin supplementation are awaited with interest.<br/>Copyright &#xa9; 2020 by the authors. Licensee MDPI, Basel, Switzerland.

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1. **COVID-19 and Vitamin D: A lesson from the skin.**  
   Slominski Radomir M. Experimental dermatology 2020;29(9):885-890.

The negative outcomes of COVID-19 diseases respiratory distress (ARDS) and the damage to other organs are secondary to a "cytokine storm" and to the attendant oxidative stress. Active hydroxyl forms of vitamin D are anti-inflammatory, induce antioxidative responses, and stimulate innate immunity against infectious agents. These properties are shared by calcitriol and the CYP11A1-generated non-calcemic hydroxyderivatives. They inhibit the production of pro-inflammatory cytokines, downregulate NF-κΒ, show inverse agonism on RORγ and counteract oxidative stress through the activation of NRF-2. Therefore, a direct delivery of hydroxyderivatives of vitamin D deserves consideration in the treatment of COVID-19 or ARDS of different aetiology. We also recommend treatment of COVID-19 patients with high-dose vitamin D since populations most vulnerable to this disease are likely vitamin D deficient and patients are already under supervision in the clinics. We hypothesize that different routes of delivery (oral and parenteral) will have different impact on the final outcome.

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1. **Covid-19 susceptibility and severity might be modified by vitamin d status: Theoretical and practical considerations**  
   Tanner A. Current Respiratory Medicine Reviews 2020;16(2):93-101.

Background: The recently identified SARS-CoV-2 coronavirus has resulted in the Covid-19 pandemic with severe morbidity and high mortality, particularly in certain sections of the population. The co-morbidity patterns associated with adverse outcomes are multiple and complex and there is emerging epidemiological, nutritional and molecular biological evidence that an inadequate vitamin D status is a contributing factor. <br/>Objective(s): The aim was to review the role of vitamin D in immune function with particular reference to the mechanisms whereby it supports immune efficiency, host protection and immune modulation. The evidence for the possible benefit of vitamin D supplementation to ameliorate the severity of respiratory infection by SARS-CoV-2 and other pathogens was also reviewed with a view to making a recommendation. <br/>Method(s): PubMed, MEDLINE and Google Scholar were searched using the terms: Covid-19, coronavirus, SARS-CoV-2, vitamin D, calcitriol, deficiency, adaptive immunity, innate immunity, ventilation, critical care, intensive care, acute respiratory distress syndrome, cytokine storm, respiratory viruses, respiratory tract infection, respiratory syncytial virus, influenza, supplementation. Papers for inclusion were selected on the basis of relevance and quality. <br/>Finding(s): Vitamin D insufficiency is widespread in many parts of the world. Vitamin D is needed for normal protective and surveillance immune function and there is evidence that deficiency increases the risk of some respiratory infections, probably including Covid-19. By binding with dedicated receptors on immune cells vitamin D influences several strands of immune function, including the production of anti-microbial peptides and several cytokines that promote an appropriate immune response. Vitamin D supplementation probably reduces the risk of respiratory infection, with persuasive biological, epidemiological and observational evidence for possible benefit against Covid-19. <br/>Conclusion(s): Despite the lack of direct evidence specific to Covid-19 a cogent theoretical case can be made for giving adults from selected groups, and arguably all adults, routine supplementation with vitamin D to improve immune efficiency and reduce the incidence and severity of respiratory infections. This could be particularly important in sections of the population with a high prevalence of vitamin D insufficiency. Targeted research is required to provide firm evidence to guide practice.<br/>Copyright &#xa9; 2020 Bentham Science Publishers.

1. **Cytokine storm in aged people with CoV-2: possible role of vitamins as therapy or preventive strategy.**  
   Fiorino Sirio Aging clinical and experimental research 2020;32(10):2115-2131.

BACKGROUNDIn December 2019, a novel human-infecting coronavirus, SARS-CoV-2, had emerged. The WHO has classified the epidemic as a "public health emergency of international concern". A dramatic situation has unfolded with thousands of deaths, occurring mainly in the aged and very ill people. Epidemiological studies suggest that immune system function is impaired in elderly individuals and these subjects often present a deficiency in fat-soluble and hydrosoluble vitamins.METHODSWe searched for reviews describing the characteristics of autoimmune diseases and the available therapeutic protocols for their treatment. We set them as a paradigm with the purpose to uncover common pathogenetic mechanisms between these pathological conditions and SARS-CoV-2 infection. Furthermore, we searched for studies describing the possible efficacy of vitamins A, D, E, and C in improving the immune system function.RESULTSSARS-CoV-2 infection induces strong immune system dysfunction characterized by the development of an intense proinflammatory response in the host, and the development of a life-threatening condition defined as cytokine release syndrome (CRS). This leads to acute respiratory syndrome (ARDS), mainly in aged people. High mortality and lethality rates have been observed in elderly subjects with CoV-2-related infection.CONCLUSIONSVitamins may shift the proinflammatory Th17-mediated immune response arising in autoimmune diseases towards a T-cell regulatory phenotype. This review discusses the possible activity of vitamins A, D, E, and C in restoring normal antiviral immune system function and the potential therapeutic role of these micronutrients as part of a therapeutic strategy against SARS-CoV-2 infection.

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1. **Cytokine Storm in Novel Coronavirus Disease (COVID-19): Expert Management Considerations.**  
   Mehta Yatin Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 2020;24(6):429-434.

Aim/objective/introductionCytokine storm or cytokine release syndrome (CRS) is inevitable in severe and critically ill patients with novel coronavirus disease-2019 (COVID-19). This review aimed to discuss current therapeutic options for the management of CRS in COVID-19.BackgroundCytokine storm is caused by the colossal release of proinflammatory cytokines [e.g., IL (interleukin)-2, IL-6, IL-8 TNF (tumor necrosis factor)-α, etc.] causing dysregulated, hyperimmune response. This immunopathogenesis leads to acute lung injury and acute respiratory distress syndrome (ARDS). Targeting cytokine storm with the therapies that are already available in India with the support of published guidelines and consensus can assist in achieving a better outcome in COVID-19.Review resultsWe predominantly included published guidelines or consensus recommendations about the management of cytokine storm in COVID-19. From the existing literature evidence, it is observed that among the currently available agents, low-dose corticosteroids and heparin can be beneficial in managing cytokine storm. The use of serine protease inhibitors such as ulinastatin has been advised by some experts. Though therapies such as high-dose vitamin C and interleukin-6 inhibitors (e.g., tocilizumab) have been advised, the evidence regarding their use for cytokine storm in COVID-19 is limited. Therapies such as Janus kinase inhibitors (JAK) inhibitors and Neurokinin-1 receptor (NK-1) antagonists are still in research. Besides, pharmaceutical treatments, use of blood purification strategies, and convalescent plasma may be life-saving options in some of the critically ill COVID-19 patients. For these therapies, there is a need to generate further evidence to substantiate their use in CRS management.ConclusionCurrent management of COVID-19 is preventive and supportive. Different therapies can be used to prevent and treat the cytokine storm. More research is needed for further supporting the use of these treatments in COVID-19.How to cite this articleMehta Y, Dixit SB, Zirpe KG, Ansari AS. Cytokine Storm in Novel Coronavirus Disease (COVID-19): Expert Management Considerations. Indian J Crit Care Med 2020;24(6):429-434.

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1. **Does vitamin D deficiency increase the severity of COVID-19?**  
   Weir E. Kenneth Clinical medicine (London, England) 2020;20(4):e107.

The severity of coronavirus 2019 infection (COVID-19) is determined by the presence of pneumonia, severe acute respiratory distress syndrome (SARS-CoV-2), myocarditis, microvascular thrombosis and/or cytokine storms, all of which involve underlying inflammation. A principal defence against uncontrolled inflammation, and against viral infection in general, is provided by T regulatory lymphocytes (Tregs). Treg levels have been reported to be low in many COVID-19 patients and can be increased by vitamin D supplementation. Low vitamin D levels have been associated with an increase in inflammatory cytokines and a significantly increased risk of pneumonia and viral upper respiratory tract infections. Vitamin D deficiency is associated with an increase in thrombotic episodes, which are frequently observed in COVID-19. Vitamin D deficiency has been found to occur more frequently in patients with obesity and diabetes. These conditions are reported to carry a higher mortality in COVID-19. If vitamin D does in fact reduce the severity of COVID-19 in regard to pneumonia/ARDS, inflammation, inflammatory cytokines and thrombosis, it is our opinion that supplements would offer a relatively easy option to decrease the impact of the pandemic.

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1. **Early nutrition protocol during Covid-19 pandemic**  
   Bursi S. Clinical Nutrition ESPEN 2020;40:511-512.

Rationale: At the end of February 2020 the first SARS-COV2 related pneumonia was diagnosed in Italy and soon the disease spread all over the country. It is well demonstrated that malnutrition is related to worse outcomes in many acute and chronic diseases and that ICU stay is often associated to worsening of nutritional status leading to ICU acquired weakness. Peculiar COVID-19 clinical feature is the Cytokine Storm leading to a Systemic Inflammatory Response Syndrome with multiple organ impairment and metabolic imbalances. Other typical symptoms that may worsen nutritional status are anosmia, ageusia, anorexia and diarrohea. The most of hospitalized patients needed some kind of respiratory therapy, ranging from oxygen delivering nasal cannulae to mechanical ventilation if ARDS or respiratory failure occurred. In the early phases of the pandemic our Clinical Nutrition Unit at the Maggiore Hospital in Bologna (Italy) developed a protocol for early nutrition treatment for COVID-19 inpatients: the aim was to provide a useful tool, fast and easy to perform in Intensive Care Units (ICUs) and general medicine wards. <br/>Method(s): Publication from Scientific Association on Clinical Nutrition in ICU and Internal Medicine setting were searched online on PubMed. Recently published recommendations and guidelines regarding Clinical Nutrition and micronutrient function in COVID-patients were also screened and evaluated. Upon these bases we developed a specific Nutritional Protocol for COVID-19 inpatients. <br/>Result(s): The multistep protocol considered three different scenarios depending on the route of nutrient administration: oral feeding, enteral feeding via nasogastric tube, parenteral nutrition. The protocol was intended to be used by non nutrition specialists to start early nutrition therapy (ideally in the first 24-48 hours of hospitalization) We decided to use hypercaloric and high-protein Oral Nutrition Supplements, enteral formulas and parenteral formulas to restrict fluids, all enriched with immunomodulatory components (i.e. omega-3 fatty acids EPA and DHA). Due to high vitamin and trace elements requirements during acute stress every patient should be provided with thiamine and with one high dose intramuscular injection of vitamin D. <br/>Conclusion(s): During the recent COVID-19 pandemic the importance of continuous clinical updating, flexibility and adaptation to new clinical settings was crucial to develop an Early Nutrition Protocol; this was intended to be a fast and easy to use tool to help non-nutritionist physicians in performing a first nutritional assessment in a large number of patients in emergency setting. Disclosure of Interest: None declared<br/>Copyright &#xa9; 2020

1. **Eculizumab treatment in patients with COVID-19: Preliminary results from real life ASL Napoli 2 Nord experience**  
   Diurno F. European Review for Medical and Pharmacological Sciences 2020;24(7):4040-4047.

- OBJECTIVE: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2)-re-lated pneumonia, referred to as COVID-19 (Coronavirus Disease 19), is a public health emergency as it carries high morbidity, mortality, and has no approved specific pharmacological treatments. In this case series, we aimed to report preliminary data obtained with anti-complement C5 therapy with eculizumab in COVID-19 patients admitted to intensive care unit (ICU) of ASL Napoli 2 Nord. <br/>PATIENTS AND METHODS: This is a case series of patients with a confirmed diagnosis of SARS-CoV2 infection and severe pneumonia or ARDS who were treated with up to 4 infusions of eculizumab as an off-label agent. Patients were also treated with anticoagulant therapy with Enoxaparin 4000 IU/day via subcutaneous injection, antiviral therapy with Lopinavir 800 mg/day + Ritonavir 200 mg/day, hydroxychloroquine 400 mg/ day, ceftriaxone 2 g/day IV, vitamine C 6 g/day for 4 days, and were on Non-Invasive Ventilation (NIV). <br/>RESULT(S): We treated four COVID-19 patients admitted to the intensive care unit because of severe pneumonia or ARDS. All patients successfully recovered after treatment with eculizumab. Eculizumab induced a drop in inflammatory markers. Mean C Reactive Protein levels dropped from 14.6 mg/dl to 3.5 mg/dl and the mean duration of the disease was 12.8 days. <br/>CONCLUSION(S): Eculizumab has the potential to be a key player in treatment of severe cases of COVID-19. Our results support eculizumab use as an off-label treatment of COVID-19, pending confirmation from the ongoing SOLID-C19 trial.<br/>Copyright &#xa9; 2020 Verduci Editore s.r.l. All rights reserved.

1. **Effects of Micronutrients or Conditional Amino Acids on COVID-19-Related Outcomes: An Evidence Analysis Center Scoping Review.**  
   Rozga Mary Journal of the Academy of Nutrition and Dietetics 2020;:No page numbers.

Recent narrative reviews have described the potential efficacy of providing individuals infected with coronavirus disease 2019 (COVID-19) with additional micronutrients to reduce disease severity. Although there are compelling reasons why providing additional micronutrients or conditional amino acids may affect COVID-19-related outcomes, evidence is lacking. The objective of this scoping review is to explore and describe the literature examining the effect of providing additional micronutrients or conditional amino acids (glutamine, arginine) in adults with conditions or infections similar to COVID-19 infection on COVID-19-related health outcomes. A literature search of the MEDLINE database and hand search of Cochrane Database of systematic reviews retrieved 1,423 unique studies, and 8 studies were included in this scoping review. Four studies examined a target population with ventilator-related pneumonia and acute respiratory distress syndrome, and the other 4 studies included patients who were at risk for ventilator-associated pneumonia. Interventions included intravenous ascorbic acid, intramuscular cholecalciferol, enteral and intramuscular vitamin E, enteral zinc sulfate, and oral and parenteral glutamine. In 6 of the 8 included studies, baseline status of the nutrient of interest was not reported and, thus, it is uncertain how outcomes may vary in the context of nutrient deficiency or insufficiency compared with sufficiency. In the absence of direct evidence examining efficacy of providing additional micronutrients or conditional amino acids to standard care, registered dietitian nutritionists must rely on clinical expertise and indirect evidence to guide medical nutrition therapy for patients infected with COVID-19.

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1. **Emerging pharmacological therapies for ARDS: COVID-19 and beyond.**  
   Horie Shahd Intensive care medicine 2020;46(12):2265-2283.

ARDS, first described in 1967, is the commonest form of acute severe hypoxemic respiratory failure. Despite considerable advances in our knowledge regarding the pathophysiology of ARDS, insights into the biologic mechanisms of lung injury and repair, and advances in supportive care, particularly ventilatory management, there remains no effective pharmacological therapy for this syndrome. Hospital mortality at 40% remains unacceptably high underlining the need to continue to develop and test therapies for this devastating clinical condition. The purpose of the review is to critically appraise the current status of promising emerging pharmacological therapies for patients with ARDS and potential impact of these and other emerging therapies for COVID-19-induced ARDS. We focus on drugs that: (1) modulate the immune response, both via pleiotropic mechanisms and via specific pathway blockade effects, (2) modify epithelial and channel function, (3) target endothelial and vascular dysfunction, (4) have anticoagulant effects, and (5) enhance ARDS resolution. We also critically assess drugs that demonstrate potential in emerging reports from clinical studies in patients with COVID-19-induced ARDS. Several therapies show promise in earlier and later phase clinical testing, while a growing pipeline of therapies is in preclinical testing. The history of unsuccessful clinical trials of promising therapies underlines the challenges to successful translation. Given this, attention has been focused on the potential to identify biologically homogenous subtypes within ARDS, to enable us to target more specific therapies 'precision medicines.' It is hoped that the substantial number of studies globally investigating potential therapies for COVID-19 will lead to the rapid identification of effective therapies to reduce the mortality and morbidity of this devastating form of ARDS.

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1. **Evidence Supports a Causal Role for Vitamin D Status in Global COVID-19 Outcomes**  
   Davies MedRxiv preprint server 2020;:0.

Please note: this article is a preprint and has not been peer-reviewed. Abstract: Background: The COVID-19 pandemic caused by the coronavirus SARS-CoV-2 seemed to affect locations in the northern hemisphere most severely appearing to overlap with the pattern of seasonal vitamin D deficiency. Integrating available knowledge, we hypothesised that vitamin D status could play a causal role in COVID-19 outcomes. Objectives We set out to analyse the relationship between COVID-19 severity and latitude, and construct a causal inference framework to validate this hypothesis. Methods: We analysed global daily reports of fatalities and recoveries from 239 locations from 22nd Jan 2020 to 9th April 2020. We quantified local COVID-19 outbreak severity to clearly distinguish the latitude relationship and identify any outliers breaking this pattern, and analysed the timeline of spread. We then used a causal inference framework to distinguish correlation from cause using observational data with a hypothetico-deductive method of proof. We constructed two contrasting directed acyclic graph (DAG) models, one causal and one acausal with respect to vitamin D and COVID-19 severity, allowing us to make 19 verifiable and falsifiable predictions for each. Results: Our analysis confirmed a striking correlation between COVID-19 severity and latitude, and ruled out the temporal spread of infection as an explanation. We compared observed severity for 239 locations with our contrasting model. In the causal model, 16 predictions matched observed data and 3 predictions were untestable; in the acausal model, 14 predictions strongly contradicted observed data, 2 appeared to contradict data, and 3 were untestable. Discussion: We show in advance of RCTs that observed data strongly match predictions made by the causal model but contradict those of the acausal model. We present historic evidence that vitamin D supplementation prevented past respiratory virus pandemics. We discuss how molecular mechanisms of vitamin D action can prevent respiratory viral infections and protect against ARDS. We highlight vitamin D’s direct effect on the renin-angiotensin-system (RAS), which in concert with additional effects, can modify host responses thus preventing a cytokine storm and SARS-CoV-2-induced pathological changes. Emerging clinical research confirms striking correlations between hypovitaminosis D and COVID-19 severity, in full alignment with our study. Conclusions: Our novel causal inference analysis of global data verifies that vitamin D status plays a key role in COVID-19 outcomes. The data set size, supporting historical, biomolecular, and emerging clinical research evidence altogether suggest that a very high level of confidence is justified. Vitamin D prophylaxis potentially offers a widely available, low-risk, highly-scalable, and cost-effective pandemic management strategy including the mitigation of local outbreaks and a second wave. Timely implementation of vitamin D supplementation programmes worldwide is critical with initial priority given to those who are at the highest risk, including the elderly, immobile, homebound, BAME and healthcare professionals. Population-wide vitamin D sufficiency could also prevent seasonal respiratory epidemics, decrease our dependence on pharmaceutical solutions, reduce hospitalisations, and thus greatly lower healthcare costs while significantly increasing quality of life.

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1. **Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths.**  
   Grant William B. Nutrients 2020;12(4):No page numbers.

The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

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1. **Exploring links between vitamin D deficiency and COVID-19.**  
   Mohan Mradul PLoS pathogens 2020;16(9):e1008874.

Coronavirus Disease 2019 (COVID-19) pandemic remains a major public health threat in most countries. The causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus can lead to acute respiratory distress syndrome and result in mortality in COVID-19 patients. Vitamin D is an immunomodulator hormone with established effectiveness against various upper respiratory infections. Vitamin D can stall hyper-inflammatory responses and expedite healing process of the affected areas, primarily in the lung tissue. Thus, there are ecological and mechanistic reasons to promote exploration of vitamin D action in COVID-19 patients. As no curative drugs are available currently for COVID-19, we feel that the potential of vitamin D to alter the course of disease severity needs to be investigated. Clinical studies may be undertaken to address the value of vitamin D supplementation in deficient, high-risk COVID-19 patients.

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1. **Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial.**  
   Liu Fang BMJ open 2020;10(7):e039519.

INTRODUCTIONThe rapid worldwide spread of COVID-19 has caused a global health crisis. To date, symptomatic supportive care has been the most common treatment. It has been reported that the mechanism of COVID-19 is related to cytokine storms and subsequent immunogenic damage, especially damage to the endothelium and alveolar membrane. Vitamin C (VC), also known as L-ascorbic acid, has been shown to have antimicrobial and immunomodulatory properties. A high dose of intravenous VC (HIVC) was proven to block several key components of cytokine storms, and HIVC showed safety and varying degrees of efficacy in clinical trials conducted on patients with bacterial-induced sepsis and acute respiratory distress syndrome (ARDS). Therefore, we hypothesise that HIVC could be added to the treatment of ARDS and multiorgan dysfunction related to COVID-19.METHODS AND ANALYSISThe investigators designed a multicentre prospective randomised placebo-controlled trial that is planned to recruit 308 adults diagnosed with COVID-19 and transferred into the intensive care unit. Participants will randomly receive HIVC diluted in sterile water or placebo for 7 days once enrolled. Patients with a history of VC allergy, end-stage pulmonary disease, advanced malignancy or glucose-6-phosphate dehydrogenase deficiency will be excluded. The primary outcome is ventilation-free days within 28 observational days. This is one of the first clinical trials applying HIVC to treat COVID-19, and it will provide credible efficacy and safety data. We predict that HIVC could suppress cytokine storms caused by COVID-19, help improve pulmonary function and reduce the risk of ARDS of COVID-19.ETHICS AND DISSEMINATIONThe study protocol was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (identifiers: Clinical Ethical Approval No. 2020001). Findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.TRIAL REGISTRATION NUMBERNCT04264533.

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1. **Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome.**  
   Boretti Alberto PharmaNutrition 2020;12:100190.

The recent outbreak of Covid19 has required urgent treatments for numerous patients. No suitable vaccines or antivirals are available for Covid19. The efficiency against Covid19 of WHO therapies of choice, that are two antivirals developed for other pathologies, is controversial. Therefore, alternative approaches are required. Intravenous (IV) Vitamin C (Vit-C) has emerged as one of the other alternatives for this purpose. Here we review the effects of IV Vit-C on the immune system response, the antiviral properties of IV Vit-C, and finally the antioxidant properties of IV Vit-C to specifically address the cytokines' storm characteristic of the Acute Respiratory Distress Syndrome (ARDS) that occur in the later cycle of the Covid19 infectious disease.

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1. **MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19.**  
   Bilezikian John P. European journal of endocrinology 2020;183(5):R133.

The SARS-CoV-2 virus responsible for the COVID-19 pandemic has generated an explosion of interest both in the mechanisms of infection leading to dissemination and expression of this disease, and in potential risk factors that may have a mechanistic basis for disease propagation or control. Vitamin D has emerged as a factor that may be involved in these two areas. The focus of this article is to apply our current understanding of vitamin D as a facilitator of immunocompetence both with regard to innate and adaptive immunity and to consider how this may relate to COVID-19 disease. There are also intriguing potential links to vitamin D as a factor in the cytokine storm that portends some of the most serious consequences of SARS-CoV-2 infection, such as the acute respiratory distress syndrome. Moreover, cardiac and coagulopathic features of COVID-19 disease deserve attention as they may also be related to vitamin D. Finally, we review the current clinical data associating vitamin D with SARS-CoV-2 infection, a putative clinical link that at this time must still be considered hypothetical.

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1. **Pathways in the Pathophysiology of Coronavirus 19 Lung Disease Accessible to Prevention and Treatment.**  
   Eisenhut Michael Frontiers in physiology 2020;11:872.

Background: In COVID 19 related lung disease, which is a leading cause of death from this disease, cytokines like tumor necrosis factor-alpha (TNF alpha) may be pivotal in the pathogenesis. TNF alpha reduces fluid absorption due to impairment of sodium and chloride transport required for building an osmotic gradient across epithelial cells, which in the airways maintains airway surface liquid helping to keep airways open and enabling bacterial clearance and aids water absorption from the alveolar spaces. TNF alpha can, through Rho-kinase, disintegrate the endothelial and epithelial cytoskeleton, and thus break up intercellular tight junctional proteins, breaching the intercellular barrier, which prevents flooding of the interstitial and alveolar spaces with fluid. Hypotheses: (1) Preservation and restoration of airway and alveolar epithelial sodium and chloride transport and the cytoskeleton dependent integrity of the cell barriers within the lung can prevent and treat COVID 19 lung disease. (2) TNF alpha is the key mediator of pulmonary edema in COVID 19 lung disease. Confirmation of hypothesis and implications: The role of a reduction in the function of epithelial sodium and chloride transport could with regards to chloride transport be tested by analysis of chloride levels in exhaled breath condensate and levels correlated with TNF alpha concentrations. Reduced levels would indicate a reduction of the function of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and a correlation with TNF alpha levels indicative of its involvement. Anti-TNF alpha treatment with antibodies is already available and needs to be tested in randomized controlled trials of COVID 19 lung disease. TNF alpha levels could also be reduced by statins, aspirin, and curcumin. Chloride transport could be facilitated by CFTR activators, including curcumin and phosphodiesterase-5 inhibitors. Sodium and chloride transport could be further regulated to prevent accumulation of alveolar fluid by use of Na(+)/K(+)/2Cl(-) cotransporter type 1 inhibitors, which have been associated with improved outcome in adults ventilated for acute respiratory distress syndrome (ARDS) in randomized controlled trials. Primary prevention of coronavirus infection and TNF alpha release in response to it could be improved by induction of antimicrobial peptides LL-37 and human beta defensin-2 and reduction of TNF alpha production by vitamin D prophylaxis for the population as a whole.

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1. **Pharmacological management of COVID-19 patients with ARDS (CARDS): A narrative review**  
   Matera M.G. Respiratory Medicine 2020;171:No page numbers.

Coronavirus disease 2019 (COVID-19) is highly infectious. It has been highlighted that if not expertly and individually managed with consideration of the vasocentric features, a COVID-19 patient with an acute respiratory distress syndrome (CARDS) may eventually develop multiorgan failure. Unfortunately, there is still no definite drug for CARDS that is capable of reducing either short-term or long-term mortality and no specific treatments for COVID-19 exist right now. In this narrative review, based on a selective literature search in EMBASE, MEDLINE, Scopus, The Cochrane Library, Web of Science, and Google Scholar and ClinicalTrials.gov, we have examined the emerging evidence on the possible treatment of CARDS. Although numerous pharmacologic therapies to improve clinical outcomes in CARDS have been studied also in clinical trials, none have shown efficacy and there is great uncertainty about their effectiveness. There is still no recommendation for the therapeutic use of any specific agent to treat CARDS because no drugs are validated to have significant efficacy in clinical treatment of COVID-19 patients in large-scale trials. However, there exist a number of drugs that may be useful at least in some patients. The real challenge now is to link the right patient to the right treatment.<br/>Copyright &#xa9; 2020 Elsevier Ltd

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1. **Possible association of vitamin D status with lung involvement and outcome in patients with COVID-19: a retrospective study.**  
   Abrishami Alireza European journal of nutrition 2020;:No page numbers.

PURPOSEVitamin D deficiency has been reported as a key factor in the development of infectious diseases such as respiratory tract infections and inflammatory processes like acute respiratory distress syndrome. However, the impact of vitamin D on the severity and outcome of COVID-19 is still not fully known. Herein, we aimed to evaluate the prognostic role of serum vitamin D concentration on the extent of lung involvement and final outcome in patients with COVID-19.METHODSSeventy-three subjects with confirmed diagnosis of COVID-19 were investigated in this study. The patients had been admitted to our academic hospital from February 28, 2020 to April 19, 2020. Demographic and clinical data, serum 25(OH)D levels, and findings of initial chest computed tomography were recorded. Linear and binary logistic regression, cox regression and ROC curve tests were used for statistical analysis.RESULTSThe mean age of patients was 55.18 ± 14.98 years old; 46.4% were male. Mean serum 25(OH)D concentration was significantly lower in the deceased (13.83 ± 12.53 ng/ mL compared with discharged patients (38.41 ± 18.51 ng/mL) (P < 0.001). Higher levels of 25(OH)D were associated with significantly less extent of total lung involvement (β = - 0.10, P = 0.004). In addition, vitamin D deficiency [25(OH) D < 25 ng/mL] was associated with a significant increase in the risk of mortality (hazard ratio = 4.15, P = 0.04).CONCLUSIONThis study suggests that serum vitamin D status might provide useful information regarding the clinical course, extent of lung involvement and outcome of patients with COVID-19. However, further studies with larger sample size are needed to confirm these findings.

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1. **Possible role of vitamin D in Covid-19 infection in pediatric population.**  
   Panfili F. M Journal of endocrinological investigation 2020;:No page numbers.

PURPOSECovid-19 is a pandemic of unprecedented proportion, whose understanding and management is still under way. In the emergency setting new or available therapies to contrast the spread of COVID-19 are urgently needed. Elderly males, especially those affected by previous diseases or with comorbidities, are more prone to develop interstitial pneumonia that can deteriorate evolving to ARDS (acute respiratory distress syndrome) that require hospitalization in Intensive Care Units (ICUs). Even children and young patients are not spared by SARS-CoV 2 infection, yet they seem to develop a milder form of disease. In this setting the immunomodulatory role of Vitamin D, should be further investigated.METHODSWe reviewed the literature about the immunomodulatory role of Vitamin D collecting data from the databases Medline and Embase.RESULTSVitamin D proved to interact both with the innate immune system, by activating Toll-like receptors (TLRs) or increasing the levels of cathelicidins and β-defensins, and adaptive immune system, by reducing immunoglobulin secretion by plasma cells and pro-inflammatory cytokines production, thus modulating T cells function. Promising results have been extensively described as regards the supplementation of vitamin D in respiratory tract infections, autoimmune diseases and even pulmonary fibrosis.CONCLUSIONSIn this review, we suggest that vitamin D supplementation might play a role in the prevention and/or treatment to SARS-CoV-2 infection disease, by modulating the immune response to the virus both in the adult and pediatric population.

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1. **Pre-exposure prophylaxis for COVID-19 infection: Current concepts and strategies**  
   Uthman A.T. Systematic Reviews in Pharmacy 2020;11(9):860-865.

The current pandemic of COVID-19 disease has spread, in a matter of a few months to nearly 200 countries, and the absence of a treatment has put the world in jeopardy. To date, more than 42 million people worldwide have been infected with severe acute respiratory distress syndrome coronavirus 2 (SARS CoV-2) and nearly 1.25 million have died from COVID-19 Pandemic. Many countries moved toward resuming work activities and social interaction to rescue economy. This makes population continue suffering severe losses in the absence of strict prophylaxis strategy against this pandemic. It is well known that prevention is better than cure, therefore, we plan to display the current strategies that should be implemented prior to exposure to infection and underlines its effectiveness in containing the infection. Repurposed vaccines and SARS-CoV-2 specific vaccines are also mentioned, to keep up with the most recent updates that are being carried out.<br/>Copyright &#xa9; 2020 EManuscript Technologies. All rights reserved.

1. **Rejuveinix Shows a Favorable Clinical Safety Profile in Human Subjects and Exhibits Potent Preclinical Protective Activity in the Lipopolysaccharide-Galactosamine Mouse Model of Acute Respiratory Distress Syndrome and Multi-Organ Failure.**  
   Uckun Fatih M. Frontiers in pharmacology 2020;11:594321.

Background: New treatment platforms that can prevent acute respiratory distress syndrome (ARDS) or reduce its mortality rate in high-risk coronavirus disease 2019 (COVID-19) patients, such as those with an underlying cancer, are urgently needed. Rejuveinix (RJX) is an intravenous formulation of anti-oxidants and anti-inflammatory agents. Its active ingredients include ascorbic acid, cyanocobalamin, thiamine hydrochloride, riboflavin 5' phosphate, niacinamide, pyridoxine hydrochloride, and calcium D-pantothenate. RJX is being developed as an anti-inflammatory and anti-oxidant treatment platform for patients with sepsis, including COVID-19 patients with viral sepsis and ARDS. Here, we report its clinical safety profile in a phase 1 clinical study (ClinicalTrials.gov Identifier: NCT03680105) and its potent protective activity in the lipopolysaccharide galactosamine (LPS-GalN) mouse model of ARDS. Methods: A phase 1, double-blind, placebo-controlled, randomized, two-part, ascending dose-escalation study was performed in participating 76 healthy volunteer human subjects in compliance with the ICH (E6) good clinical practice guidelines to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RJX (Protocol No. RPI003; ClinicalTrials.gov Identifier: NCT03680105). The ability of RJX to prevent fatal shock, ARDS, and multi-organ failure was examined in the well-established LPS-GalN mouse model of sepsis and ARDS. Standard methods were employed for the statistical analysis of data in both studies. Findings: In the phase 1 clinical study, no participant developed serious adverse events (SAEs) or Grade 3-Grade 4 adverse events (AEs) or prematurely discontinued participation in the study. In the non-clinical study, RJX exhibited potent and dose-dependent protective activity, decreased the inflammatory cytokine responses (interleukin-6, tumor necrosis factor alpha, transforming growth factor beta), and improved survival in the LPS-GalN mouse model of sepsis and ARDS. Histopathological examinations showed that RJX attenuated the LPS-GalN induced acute lung injury (ALI) and pulmonary edema as well as liver damage. Conclusion: RJX showed a very favorable safety profile and tolerability in human subjects. It shows potential to favorably affect the clinical course of high-risk COVID-19 by preventing ARDS and its complications.

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1. **Role of vitamin D in pathogenesis and severity of COVID-19 infection.**  
   Honardoost Maryam Archives of physiology and biochemistry 2020;:1-7.

Coronavirus disease (COVID-19) is an infectious disease caused by a new virus that causes respiratory illness. Older adults and individuals who have pre-existing chronic medical conditions are at higher risk for more serious complications from COVID-19. Hypovitaminosis D is attributed to the increased risk of lung injury and acute respiratory distress syndrome (ARDS) as well as diabetes, cardiovascular events and associated comorbidities, which are the main causes of severe clinical complications in COVID-19 patients. Considering the defensive role of vitamin D, mediated through modulation of the innate and adaptive immune system as well as inhibition of the Renin Angiotensin System (RAS), vitamin D supplementation might boost the immune system of COVID-19 patients and reduce severity of the disease in vitamin D deficient individuals.

1. **The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging".**  
   Meftahi Gholam Hossein Inflammation research : official journal of the European Histamine Research Society ... [et al.] 2020;69(9):825-839.

PURPOSENovel Coronavirus disease 2019 (COVID-19), is an acute respiratory distress syndrome (ARDS), which is emerged in Wuhan, and recently become worldwide pandemic. Strangely, ample evidences have been shown that the severity of COVID-19 infections varies widely from children (asymptomatic), adults (mild infection), as well as elderly adults (deadly critical). It has proven that COVID-19 infection in some elderly critical adults leads to a cytokine storm, which is characterized by severe systemic elevation of several pro-inflammatory cytokines. Then, a cytokine storm can induce edematous, ARDS, pneumonia, as well as multiple organ failure in aged patients. It is far from clear till now why cytokine storm induces in only COVID-19 elderly patients, and not in young patients. However, it seems that aging is associated with mild elevated levels of local and systemic pro-inflammatory cytokines, which is characterized by "inflamm-aging". It is highly likely that "inflamm-aging" is correlated to increased risk of a cytokine storm in some critical elderly patients with COVID-19 infection.METHODSA systematic search in the literature was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science, as well as Google Scholar pre-print database using all available MeSH terms for COVID-19, Coronavirus, SARS-CoV-2, senescent cell, cytokine storm, inflame-aging, ACE2 receptor, autophagy, and Vitamin D. Electronic database searches combined and duplicates were removed.RESULTSThe aim of the present review was to summarize experimental data and clinical observations that linked the pathophysiology mechanisms of "inflamm-aging", mild-grade inflammation, and cytokine storm in some elderly adults with severe COVID-19 infection.

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1. **Therapeutic Options Against the New Coronavirus: Updated Clinical and Laboratory Evidences**  
   Fernandes A.C.L. Frontiers in Medicine 2020;7:No page numbers.

The pandemic caused by the new coronavirus (SARS-Cov-2) has encouraged numerous in vitro studies and clinical trials around the world, with research groups testing existing drugs, novel drug candidates and vaccines that can prevent or treat infection caused by this virus. The urgency for an effective therapy is justified by the easy and fast viral transmission and the high number of patients with severe respiratory distress syndrome who have increasingly occupied intensive care hospital beds, leading to a collapse in health systems in several countries. However, to date, there is no sufficient evidence of the effectiveness of any researched therapy. The off-label or compassionate use of some drugs by health professionals is a reality in all continents, whose permission by regulatory agencies has been based on the results of some clinical trials. In order to guide decision-making for the treatment of COVID-19, this review aims to present studies and guidelines on the main therapies that have been and are currently being tested against SARS-CoV-2 and to critically analyze the reported evidences.<br/>&#xa9; Copyright &#xa9; 2020 Fernandes, Vale, Guzen, Pinheiro, Cobucci and de Azevedo.

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1. **Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials.**  
   Horowitz Richard I. Medical hypotheses 2020;143:109851.

PURPOSEAsymptomatic or minimally symptomatic infection with COVID-19 can result in silent transmission to large numbers of individuals, resulting in expansion of the pandemic with a global increase in morbidity and mortality. New ways of screening the general population for COVID-19 are urgently needed along with novel effective prevention and treatment strategies.HYPOTHESISA hypothetical three-part prevention, diagnostic, and treatment approach based on an up-to-date scientific literature review for COVID-19 is proposed. Regarding diagnosis, a validated screening questionnaire and digital app for COVID-19 could help identify individuals who are at risk of transmitting the disease, as well as those at highest risk for poor clinical outcomes. Global implementation and online tracking of vital signs and scored questionnaires that are statistically validated would help health authorities properly allocate essential health care resources to test and isolate those at highest risk for transmission and poor outcomes. Second, regarding prevention, no validated protocols except for physical distancing, hand washing, and isolation exist, and recently ivermectin has been published to have anti-viral properties against COVID-19. A randomized trial of ivermectin, and/or nutraceuticals that have been published to support immune function including glutathione, vitamin C, zinc, and immunomodulatory supplements (3,6 Beta glucan) could be beneficial in preventing transmission or lessening symptomatology but requires statistical validation. Third, concerning treatment, COVID-19 induced inflammation and "cytokine storm syndrome" with hemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) have resulted in extreme morbidity and mortality in those with certain comorbidities, secondary to "acute respiratory distress syndrome" (ARDS) and multiorgan dysfunction with disseminated intravascular coagulation (DIC). Deficiency in red blood cell, serum and alveolar glutathione has been published in the medical literature for ARDS, as well as viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress. A randomized controlled trial of blocking NF-κB and cytokine formation using glutathione precursors (N-acetyl-cysteine [NAC] and alpha lipoic acid) and PO/IV glutathione with associated anti-viral effects should be performed, along with an evaluation of Nrf2 activators (curcumin, sulforaphane glucosinolate) which have been scientifically proven to lower inflammation. Since high mortality rates from sepsis induced DIC due to COVID-19 infection has also been associated with thrombotic events and elevated levels of D-dimer, randomized controlled trials of using anticoagulant therapy with heparin is urgently required. This is especially important in patients on ventilators who have met certain sepsis induced coagulopathy (SIC) criteria. The use of acetazolamide with or without sildenafil also needs to be explored with or without heparin, since increased oxygen delivery to vital organs through prevention of thrombosis/pulmonary emboli along with carbonic anhydrase inhibition may help increase oxygenation and prevent adverse clinical outcomes.CONCLUSION AND IMPLICATIONSA three-part prevention, diagnostic, and treatment plan is proposed for addressing the severe complications of COVID-19. Digital monitoring of symptoms to clinically diagnose early exposure and response to treatment; prevention with ivermectin as well as nutritional therapies that support a healthy immune response; treatment with anti-inflammatory therapies that block NF-κB and activate Nrf2 pathways, as well as novel therapies that address COVID-19 pneumonia and ARDS with DIC including anticoagulation and/or novel respiratory therapies with or without acetazolamide and sildenafil. These three broad-based interventions urgently need to be subjected to randomized, controlled trials.

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1. **Unusual early recovery of a critical COVID-19 patient after administration of intravenous vitamin C**  
   Khan H.M.W. American Journal of Case Reports 2020;21:1-6.

Objective: Unusual clinical course Background: Coronavirus disease 2019 (COVID-19) continues to spread, with confirmed cases now in more than 200 coun-tries. Thus far there are no proven therapeutic options to treat COVID-19. We report a case of COVID-19 with acute respiratory distress syndrome who was treated with high-dose vitamin C infusion and was the first case to have early recovery from the disease at our institute. Case Report: A 74-year-old woman with no recent sick contacts or travel history presented with fever, cough, and shortness of breath. Her vital signs were normal except for oxygen saturation of 87% and bilateral rhonchi on lung auscultation. Chest radiography revealed air space opacity in the right upper lobe, suspicious for pneumonia. A nasopharyngeal swab for severe acute respiratory syndrome coronavirus-2 came back positive while the patient was in the airborne-isolation unit. Laboratory data showed lymphopenia and elevated lactate dehydroge-nase, ferritin, and interleukin-6. The patient was initially started on oral hydroxychloroquine and azithromycin. On day 6, she developed ARDS and septic shock, for which mechanical ventilation and pressor support were started, along with infusion of high-dose intravenous vitamin C. The patient improved clinically and was able to be taken off mechanical ventilation within 5 days. <br/>Conclusion(s): This report highlights the potential benefits of high-dose intravenous vitamin C in critically ill COVID-19 patients in terms of rapid recovery and shortened length of mechanical ventilation and ICU stay. Further studies will elaborate on the efficacy of intravenous vitamin C in critically ill COVID-19.<br/>Copyright &#xa9; Am J Case Rep, 2020.

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1. **Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome.**  
   Chiscano-Camón Luis Critical care (London, England) 2020;24(1):522.

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1. **Vitamin D can prevent COVID-19 infection-induced multiple organ damage.**  
   Aygun Hatice Naunyn-Schmiedeberg's archives of pharmacology 2020;393(7):1157-1160.

Vitamin D is an immunomodulator hormone with an anti-inflammatory and antimicrobial effect with a high safety profile. A lot of COVID-19 infected patients develop acute respiratory distress syndrome (ARDS), which may lead to multiple organ damage. These symptoms are associated with a cytokine storm syndrome. The aim of this letter is to note the 5 crucial points that vitamin D could have protective and therapeutic effects against COVID-19. For that reason, COVID-19 infection-induced multiple organ damage might be prevented by vitamin D.

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1. **Vitamin D Deficiency and ARDS after SARS-CoV-2 Infection.**  
   Faul J. L Irish medical journal 2020;113(5):84.

1. **Vitamin D in COVID - 19: Dousing the fire or averting the storm? - A perspective from the Asia-Pacific.**  
   Chandran Manju Osteoporosis and sarcopenia 2020;6(3):97-105.

COVID-19, the acute respiratory tract infection (RTI) caused by the Coronavirus, Sars-CoV-2, has swept around the world. No country has been spared from its onslaught. Treatments that can reduce the risk of infection and mortality from the disease are desperately needed. Though high quality randomized controlled trials are lacking, some observational and interventional studies that explore the link between vitamin D and RTIs exist. Vitamin D modulates both innate as well as adaptive immunity and may potentially prevent or mitigate the complications associated with RTIs. Evidence linking vitamin D to COVID-19 include that the outbreak occurred in winter in the northern hemisphere at a time when vitamin D levels are lowest in resident populations, that blacks and minority ethnic individuals who are known to have lower levels of vitamin D appear to be disproportionately affected and have more severe complications from the disease, that vitamin D deficiency has been shown to contribute to acute respiratory distress syndrome and that case fatality rates increase with age and in populations with comorbid conditions such as diabetes, hypertension, and cardiovascular disease, all of which are associated with lower vitamin D levels. This narrative review summarizes the current knowledge about the epidemiology and pathophysiology of COVID-19, the evidence linking vitamin D and RTIs, especially COVID-19, the mechanistic reasons behind the possible protective effect of vitamin D in COVID-19, and the evidence with regard to vitamin D supplementation in RTIs. It concludes with some recommendations regarding supplementation of vitamin D in patients with COVID-19.

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1. **Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020\_166.**  
   Quesada-Gomez Jose Manuel The Journal of steroid biochemistry and molecular biology 2020;202:105719.

Coronavirus infection is a serious health problem awaiting an effective vaccine and/or antiviral treatment. The major complication of coronavirus disease 2019 (COVID-19), the Acute Respiratory Distress syndrome (ARDS), is due to a variety of mechanisms including cytokine storm, dysregulation of the renin-angiotensin system, neutrophil activation and increased (micro)coagulation. Based on many preclinical studies and observational data in humans, ARDS may be aggravated by vitamin D deficiency and tapered down by activation of the vitamin D receptor. Several randomized clinical trials using either oral vitamin D or oral Calcifediol (25OHD) are ongoing. Based on a pilot study, oral calcifediol may be the most promising approach. These studies are expected to provide guidelines within a few months.

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1. **Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series.**  
   Ohaegbulam Kim C. American journal of therapeutics 2020;27(5):e485.

BACKGROUNDCoronavirus disease 2019 (COVID-19) has infected more than 4.4 million people and caused more than 300,000 deaths partly through acute respiratory distress syndrome with propensity to affect African American and Hispanic communities disproportionately. Patients with worse outcomes have exhibited higher blood plasma levels of proinflammatory cytokines. Activation of the vitamin D receptor expressed on immune cells has been shown to directly reduce the secretion of inflammatory cytokines, such as interleukin-6, and indirectly affect C-reactive protein.AREAS OF UNCERTAINTYThe significance of the vitamin D pathway in patients diagnosed with COVID-19.THERAPEUTIC INNOVATIONVitamin D supplementation in patients after diagnosis of COVID-19.PATIENTS AND PHARMACOLOGICAL INTERVENTIONSWe report 4 vitamin D deficient patients diagnosed with COVID-19 in April 2020 who were provided with either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation.CLINICAL OUTCOMESPatients that received a high dose of vitamin D supplementation achieved normalization of vitamin D levels and improved clinical recovery evidenced by shorter lengths of stay, lower oxygen requirements, and a reduction in inflammatory marker status.CONCLUSIONSVitamin D supplementation may serve as a viable alternative for curtailing acute respiratory distress syndrome in patients in underserved communities where resources to expensive and sought-after medications may be scarce. Randomized clinical trials will serve as an appropriate vessel to validate the efficacy of the therapeutic regimen and dissection of the pathway.

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1. **Vitamin D3 as Potential Treatment Adjuncts for COVID-19.**  
   Malaguarnera Lucia Nutrients 2020;12(11):No page numbers.

Severe acute respiratory syndrome coronavirus type (SARS-CoV2, also known as COVID-19), which is the latest pandemic infectious disease, constitutes a serious risk to human health. SARS-CoV2 infection causes immune activation and systemic hyperinflammation which can lead to respiratory distress syndrome (ARDS). ARDS victims are characterized by a significant increase in IL-6 and IL-1. Macrophage activation, associated with the "cytokine storm", promotes the dysregulation of the innate immunity. So far, without vaccines or specific therapy, all efforts to design drugs or clinical trials are worthwhile. Vitamin D and its receptor vitamin D receptor (VDR) exert a critical role in infections due to their remarkable impact on both innate and adaptive immune responses and on the suppression of the inflammatory process. The protective properties of vitamin D supplementation have been supported by numerous observational studies and by meta-analysis of clinical trials for prevention of viral acute respiratory infection. In this review, we compare the mechanisms of the host immune response to SARS-CoV2 infection and the immunomodulatory actions that vitamin D exerts in order to consider the preventive effect of vitamin D supplementation on SARS-CoV2 viral infection.

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1. **What Can Cellular Redox, Iron, and Reactive Oxygen Species Suggest About the Mechanisms and Potential Therapy of COVID-19?**  
   Muhoberac B.B. Frontiers in Cellular and Infection Microbiology 2020;10:No page numbers.

Accumulating evidence suggests that there are important contributions to coronavirus disease (COVID-19) from redox imbalance and improperly coordinated iron, which cause cellular oxidative damage and stress. Cells have developed elaborate redox-dependent processes to handle and store iron, and their disfunction leads to several serious diseases. Cellular reductants are important as reactive oxygen species (ROS) scavengers and to power enzymatic repair mechanisms, but they also may help generate toxic ROS. These complicated interrelationships are presented in terms of a cellular redox/iron/ROS triad, including ROS generation both at improperly coordinated iron and enzymatically, ROS interconvertibility, cellular signaling and damage, and reductant and iron chelator concentration-dependent effects. This perspective provides the rational necessary to strongly suggest that COVID-19 disrupts this interdependent triad, producing a substantial contribution to the ROS load, which causes direct ROS-induced protein and phospholipid damage, taxes cellular resources and repair mechanisms, and alters cellular signaling, especially in the more critical acute respiratory distress syndrome (ARDS) phase of the infection. Specific suggestions for therapeutic interventions using reductants and chelators that may help treat COVID-19 are discussed.<br/>&#xa9; Copyright &#xa9; 2020 Muhoberac.

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The links to internet sites in this document are 'live' and can be opened by holding down the CTRL key on your keyboard while clicking on the web address with your mouse

### Full text papers

Links are given to full text resources where available. For some of the papers, you will need an **NHS OpenAthens Account**. If you do not have an account you can [register online](https://openathens.nice.org.uk/).

You can then access the papers by simply entering your username and password. If you do not have easy access to the internet to gain access, please let us know and we can download the papers for you.

### Guidance on searching within online documents

Links are provided to the full text of each document. Relevant extracts have been copied and pasted into these results. Rather than browse through lengthy documents, you can search for specific words as follows:

**Portable Document Format / pdf / Adobe**  
Click on the Search button (illustrated with binoculars). This will open up a search window. Type in the term you need to find and links to all of the references to that term within the document will be displayed in the window. You can jump to each reference by clicking it.

**Word documents**  
Select Edit from the menu, the Find and type in your term in the search box which is presented. The search function will locate the first use of the term in the document. By pressing 'next' you will jump to further references.

## B. Search History

|  | **Source** | **Criteria** | **Results** |
| --- | --- | --- | --- |
| 1. | Medline | \*"RESPIRATORY DISTRESS SYNDROME, ADULT"/ | 15169 |
| 2. | Medline | ("respiratory distress syndrome").ti,ab | 27836 |
| 3. | Medline | (ards).ti,ab | 13196 |
| 4. | Medline | (1 OR 2 OR 3) | 36258 |
| 5. | Medline | exp "ASCORBIC ACID"/ | 42577 |
| 6. | Medline | ("ascorbic acid").ti,ab | 32220 |
| 7. | Medline | ("vitamin c").ti,ab | 21763 |
| 8. | Medline | exp "VITAMIN D"/ | 60042 |
| 9. | Medline | ("vitamin d\*").ti,ab | 70399 |
| 10. | Medline | (cholecalciferol).ti,ab | 2554 |
| 11. | Medline | (ergocalciferol).ti,ab | 565 |
| 12. | Medline | (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11) | 153508 |
| 13. | Medline | exp CORONAVIRUS/ | 45340 |
| 14. | Medline | "CORONAVIRUS INFECTIONS"/ | 44265 |
| 15. | Medline | (coronavirus\*).ti,ab | 43004 |
| 16. | Medline | (covid\*).ti,ab | 75978 |
| 17. | Medline | (sars-cov-2).ti,ab | 23098 |
| 18. | Medline | (13 OR 14 OR 15 OR 16 OR 17) | 103465 |
| 19. | Medline | (4 AND 12 AND 18) | 44 |
| 20. | Medline | 19 [Languages English] | 44 |
| 21. | EMBASE | \*"ADULT RESPIRATORY DISTRESS SYNDROME"/ | 16438 |
| 22. | EMBASE | ("respiratory distress syndrome").ti,ab | 37298 |
| 23. | EMBASE | (ards).ti,ab | 22114 |
| 24. | EMBASE | (21 OR 22 OR 23) | 47665 |
| 25. | EMBASE | exp "ASCORBIC ACID"/ | 93308 |
| 26. | EMBASE | ("ascorbic acid").ti,ab | 36178 |
| 27. | EMBASE | ("vitamin c").ti,ab | 26319 |
| 28. | EMBASE | exp "VITAMIN D"/ | 147087 |
| 29. | EMBASE | ("vitamin d").ti,ab | 94999 |
| 30. | EMBASE | (cholecalciferol).ti,ab | 4047 |
| 31. | EMBASE | (ergocalciferol).ti,ab | 975 |
| 32. | EMBASE | (25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31) | 260349 |
| 33. | EMBASE | exp CORONAVIRINAE/ | 22742 |
| 34. | EMBASE | (coronavirus\*).ti,ab | 43187 |
| 35. | EMBASE | (covid\*).ti,ab | 76215 |
| 36. | EMBASE | (sars-cov-2).ti,ab | 22626 |
| 37. | EMBASE | (33 OR 34 OR 35 OR 36) | 104123 |
| 38. | EMBASE | (24 AND 32 AND 37) | 79 |
| 39. | EMBASE | 38 [English language] | 77 |

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