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EFFECTS OF ANTIVIRALS, GLUCOCORTICOIDS AND VARIOUS SUPPLEMENTS IN MANAGEMENT OF COVID-19

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ABSTRACT

The COVID-19 infection pandemic has resulted in significantly raised economic and public health issues. Moreover, there is an associate degree pressing out to discover effective medication, prevention and control methods due to the high death toll of this new corona virus infection. Acute respiratory tract infections that mainly include lower respiratory tract infections and pneumonia are the leading cause of millions of deaths worldwide. The role of micronutrients, together with trace components, in stimulating the human immune system has been well established. Numerous vitamins like vitamin C, D, folate and microelements which includes zinc, plays essential physiological roles in promoting the immune system. It also helps regulate gene transcription, such as DNA replication, RNA transcription, cell division and cell activation in the human biological system. **Methods:** Previously published articles regarding Covid-19. **Observations:** Remdesivir (Antiviral) is a broad spectrum antiviral agent that has previously demonstrated antiviral activity against SARS-CoV-2 in vitro. Glucocorticoids can be useful in prevent cytokine-induced alveolar / pulmonary damage and chemokine storm. Zinc plays essential physiological roles in promoting the immune system, an indispensable microelement essential for a complete physiological enzymatic process. Vitamin D, another fat-soluble vitamin, plays a vital role in modulating both innate and adaptive immune responses. Vitamin C is known as an antioxidant and essential enzyme cofactor for many

physiological reactions in the body, such as hormone production, collagen synthesis and immune boosting.

KEYWORDS: Covid -19, Antivirals, Glucocorticoids, Zinc, Vitamin D, Vitamin C.

INTRODUCTION

Severe acute respiratory syndrome corona virus (SARS - CoV) -2, a novel RNA corona virus, was identified in early January 2020 as the cause of pneumonia epidemic. Affecting the city of Wuhan, from where it spread rapidly throughout China, infecting and killing thousands of people in China, and later on affected most of the countries.[1]

The World Health Organization named corona virus disease 2019 (COVID-19) and subsequently declared it a pandemic due to widespread infectivity and high contamination rate. Human corona viruses commonly cause respiratory and enteric infections.

The current spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which causes COVID-19 disease, is progressing rapidly, posing an urgent challenge to healthcare systems around the world. In the absence of curative treatment and an effective and safe vaccine at this time, there is an urgent focus on identifying and correcting deficits in immune function. Furthermore, nutritional, immunological and clinical data suggest that zinc status may play a vital role in the prevention and control of COVID-19 disease. This opens up possibilities for specific nutritional and preventive dietary intervention measures to enhance the antiviral immune response. Considering the current COVID-19 pandemic, where not effective preventive and curative medicine is available, the immune system is one of the most important weapons to exist. Various vitamins and trace elements are essential for the normal functioning of the immune system. Supplementing with Vitamin C and D has increased humoral immunity of pediatric patients after influenza vaccination. High dosage zinc Supplementation showed immune enhancement in patients. Finally, practical recommendations were developed on both preventive and therapeutic nutritional interventions for COVID-19.[2]

ETIOLOGY

Corona viruses (CoVs) are positive stranded Ribo nucleic acid viruses (+ ssRNA) that appear as corona under the electron microscope due to the presence of spike glycoproteins in the

envelope. The Orthocoronavirinae taxonomic group of the Coronaviridae family (order Nidovirales) is classified into four genera of CoVs:

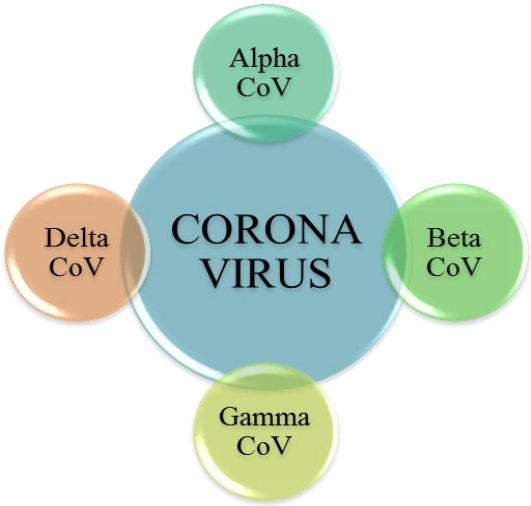

Figure 1: Classification of corona virus.

The Beta CoV genus is split into five subgenera or lineages. Genomic characterization has shown that bats and rodents are the doubtful sources of genes for alpha CoV and beta CoV. In contrast, bird species seems to be the gene sources for delta CoV and gamma CoV. CoVs become major pathogens in rising respiratory disease epidemics. Members of this huge family of viruses can cause respiratory, enteric, liver and neurological diseases in several animal species, together with camels, cattle, cats and bats.[2]

PATHOGENESIS

Asymptomatic Phase

SARS-CoV-2 which is received through respiratory aerosols binds to nasal epithelial cells in the upper respiratory tract. The main host receptor for virus entry into cells is ACE-2, which is highly expressed in adult nasal epithelial cells. The virus undergoes local replication and spread, along with infection of the hair cells in the pathways and conductive areas. This phase lasts a couple of days and the immune response generated during this phase is limited. Despite having a low viral load at this time, individuals are highly infectious and the virus can be detected by a nasal swab test.[3]

Invasion and Infection of The High Respiratory Tract

At this stage, there is a migration of the virus from the nasal epithelium to the upper respiratory tract through the conductive airways. Due to the involvement of the upper

respiratory tract, the disease manifests itself with symptoms of fever, malaise and dry cough. There is an increased immune response during this phase involving the release of the CXC motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and IFN-λ) from virus infected cells. This phase as the mounted immune response is sufficient to contain the spread of the infection.

Involvement of The Lower Respiratory Tract And Progression Of Acute Respiratory Difficulty Syndrome

About one fifth of all infected patients progress to this stage of the disease and develop severe symptoms. The virus invades and enters type 2 alveolar epithelial cells via the host's ACE-2 receptor and begins to replicate to produce more viral nucleocapsids. Virus-laden pneumocytes now release many different inflammatory markers and cytokines, such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemotactic protein-1 (MCP-1) and inflammatory macrophage protein-1α (MIP-1α). This "cytokine storm" acts as a chemofactor for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to sequester in lung tissue. These cells are responsible for fighting the virus, but in doing so they are responsible for subsequent lung inflammation and injury. The host cell undergoes apoptosis with the release of new viral particles, which then similarly infect adjacent type 2 alveolar epithelial cells. Due to persistent injury caused by sequestered inflammatory cells and viral replication leading to loss of pneumocytes in both type 1 and type 2, there is diffuse alveolar damage that eventually culminates in acute respiratory distress syndrome.[3]

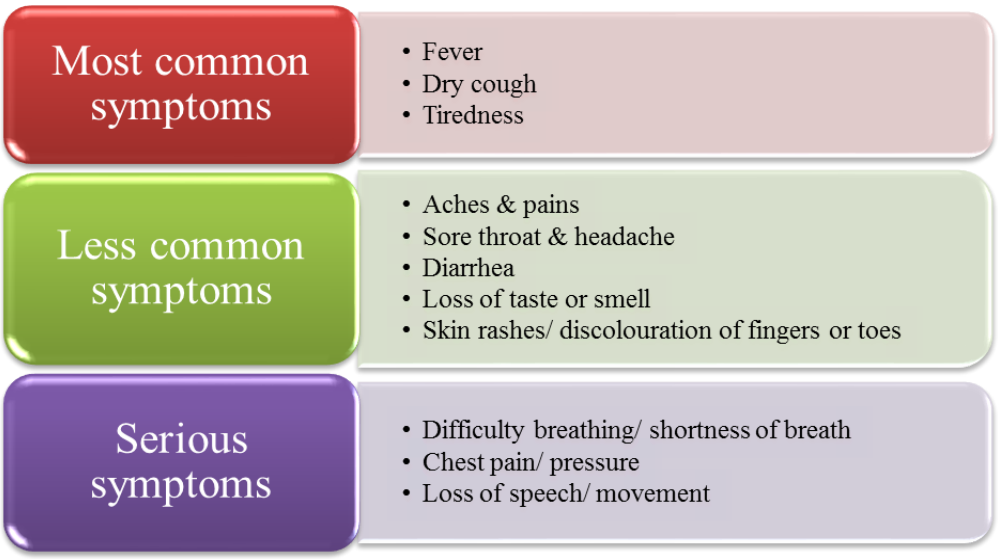

Figure 2: Symptoms of Covid-19.

DIAGNOSIS

Molecular tests (RTPCR)

The standard diagnostic test modality is to analyze a SARS-CoV-2 nasopharyngeal swab for nucleic acid using a real-time PCR test. SARS-CoV-2 antigen tests are less sensitive but have a faster response time than molecular PCR tests.

Serological tests

An antibody test can evaluate the presence of antibodies produced as a result of an infection. Antibody tests play an important role in extensive surveillance for COVID-19, and many commercially produced antibody test kits are available to test for antibodies to SARS-CoV-2. Antibody testing may be critical in broad surveillance for COVID-19 and in assessing immunity conferred by infection or vaccination.

Other laboratory evaluation

A complete blood count (CBC), a complete metabolic panel (CMP) including kidney and liver function tests, and a coagulation panel should be performed in all hospitalized patients.

Additional tests may be considered in hospitalized patients, such as tests for inflammatory markers such as ESR, C-reactive protein (CRP), ferritin, lactate dehydrogenase, D-dimer, and procalcitonin.

CHEST X - RAY AND CT are also done to check whether pneumonia had occured.[3]

MANAGEMENT

Effects of Various Available Antivirals

Remdesivir is a broad spectrum antiviral agent that has previously demonstrated antiviral activity against SARS-CoV-2 in vitro. Remdesivir was superior in shortening recovery times in adults who were hospitalized with mild to severe COVID-19. The Food and Drug Administration US (FDA) has approved remdesivir for clinical use in adult and pediatric patients (12 years of age and older and weighing 40 kilograms or more) for the treatment of hospitalized patients with COVID-19.

Hydroxychloroquine and chloroquine were initially proposed as antiviral treatments for COVID-19 during the pandemic. However, data from randomized controlled trials evaluating the use of hydroxychloroquine with or without azithromycin in hospitalized patients did not improve clinical status or overall mortality compared to placebo. Data from randomized

controlled trials of hydroxychloroquine used as post-exposure prophylaxis did not prevent SARS-CoV-2 infection or symptomatic COVID-19 disease. Lopinavir / ritonavir is an FDA-approved combination therapy for the treatment of HIV and has been proposed as an antiviral therapy against COVID-19 during the early onset of the pandemic. Currently, lopinavir / ritonavir is not indicated for the treatment of COVID-19 in inpatients and outpatients.[4]

Effect of Glucocorticoids

In COVID-19, a variety of protocols that employ complementary treatments [i.e. antiviral, antimalarial and antirheumatic agents, serine protease IL inhibitors, blockers and low molecular weight heparin (LMWH)] have been developed in several countries, some of which use Glucocorticoids (GC) for treatment of hospitalized patients with phase IIb-III COVID-19. The essence here is that GC can be useful in preventing cytokine-induced alveolar / pulmonary damage and chemokine storm. Although GCs are used in this situation as immunosuppressants (i.e. they lead to an inhibition of cytokine production), they can cause a delay in the elimination of the virus and impair the proliferation of lymphocytes. However, in the past, GCs have been used in the treatment of ARDS caused by Middle East Respiratory Syndrome (MERS) and SARS-CoV, both characterized by histological and pulmonary inflammation for diffuse alveolar damage. The efficacy of GC treatment in the management of COVID-19 was not clear in several literatures, considering the potential delay in the elimination of virus and increased risk of secondary infections and adverse effects (e.g. hyperglycemia, psychosis, and avascular necrosis). Recently, the results of a randomized trials were publicly announced, revealing that low doses dexamethasone (DX) has helped save the lives of seriously ill patients with COVID-19 , which reduces the risk of death by a third for patients with respirators and by a fifth for those receiving oxygen (O2).[5]

Effect of Zinc In Covid-19 Patients

Zinc participates in the generation of both innate and acquired antiviral immune responses. It is essential for the barrier function of the mucosal epithelium due to its antioxidant and anti-inflammatory activity. It also regulates tight junction proteins, which are important for maintaining mucosal integrity. In COVID-19, there are strong indications of down regulation of the innate immune response along with an elevated inflammatory condition, characteristics similar to those found in SARS and Middle Eastern respiratory syndrome. This may explain why the elderly are at a higher risk of contracting COVID-19 than young children who benefit from a highly effective innate immune response. In addition to its role in immune

functions, zinc has also shown direct antiviral activity for various RNA viruses. Zinc has been shown to effectively inhibit SARS-CoV replication in cell culture, demonstrating the crucial role of intracellular zinc in inhibiting virus replication. Zinc pyrithione ionophore, carries Zinc ions in large quantities from the extracellular matrix to the cell, in order to increase intracellular zinc levels. Without zinc, the ionophore could not effectively inhibit viral replication. The pharmaceuticals chloroquine and hydroxychloroquine, also known to function as zinc ionophores, are now being tested in several clinical trials for the treatment of COVID-19, without simultaneous zinc supplementation. The antiviral properties of these drugs or other zinc ionophores may depend on the availability of zinc, demonstrating that the combination with zinc supplements could be useful in enhancing their therapeutic effect in COVID-19 patients.[6]

Effect of Vitamin D

Vitamin D, another fat-soluble vitamin, plays a vital role in modulating both innate and adaptive immune responses. Vitamin D plays an important modulatory role in innate immune responses and respiratory viral infections, such as influenza A and B, para-influenza 1 and 2 and respiratory syncytial virus (RSV). A systematic review on the role of vitamin D in the prevention of acute respiratory infections, reports higher plasma TGFb levels without improving antibody production, and suggested that supplementation appears to direct the lymphocyte polarization towards a tolerogenic immune response.

Similarly, in another RCT, a high monthly dose (100,000 IU / month) Vitamin D supplementation reduced the incidence of acute respiratory infections in older long-term care residents, compared to a standard dose group (12,000 IU / month). It is evident that the role of vitamin D supplementation in antiviral immunity against respiratory infections probably depends on vitamin D state of the individual. Additionally, vitamin D has been proven a beneficial effect on other viral infections, for example by adding Vitamin D to conventional therapy with Peg-a-2b / ribavirin for treatment-naïve patients with chronic HCV genotype 1 infection significantly improved viral response and a similar effect has also been observed in patients with genotype 2e3 HCV.[7]

Effect of Vitamin C

Vitamin C is known as an antioxidant and essential enzyme, cofactor for many physiological reactions in the body, such as hormone production, collagen synthesis and immune boosting. In vivo animal studies in mice have shown that it is an essential factor for antiviral immune

responses against influenza A virus (H3N2) by increasing the production of interferon-a / b, especially in the early stages of infection.

However, the use of vitamin C for the treatment of specific viral infections is effective. Additionally, a systematic review and meta-analysis on the role of vitamin C in the prevention and treatment of the common cold, found no conclusive evidence to indicate the existence of an advantage the use of megadose prophylaxis of vitamin C in the community to reduce the incidence of common cold.[8]

CONCLUSION

The global health and economic consequences of the SARS - CoV - 2 pandemic are severe. Although many therapies have been suggested, there are currently no specific options that can treat COVID-19 disease or prevent SARS CoV - 2. The only currently viable intervention that has been shown to reduce the infection rate appears to be the strict quarantine measures for the general population. Specially designed randomized clinical trials are urgently needed to determine the most appropriate evidence-based treatment modality to reduce the spread of this disease and prevent the burden of any future outbreaks.[9]

Patients and families should be educated and encouraged to adhere to social distancing guidelines, mask use and travel guidelines according to CDC guidelines and state and local authority social distancing protocols on social distancing. Patients should be instructed on frequent hand washing for a minimum of 20 seconds with soap and water when they come into contact with contaminated surfaces. They should be educated and encouraged to seek emergency care when needed. Patients should be educated and have the option of receiving telemedicine services instead of outpatient visits, if applicable. High-risk patients should be encouraged to seek early treatment and be educated about new treatment options such as monoclonal antibodies. Patients require education on the efficacy of available vaccines and the benefits of vaccination.

Epidemiological research and observational studies provide indications for zinc depletion in high-risk groups for COVID-19. Correcting low zinc levels in risk groups could play a vital role in the prevention and control of COVID-19 disease.

Large-scale studies are urgently needed to investigate the role of micronutrients in antiviral immunity, in particular the interaction between drug and micronutrient immunity. In addition

to treating malnutrition, weight reduction in obese subjects, highlighted the potential preventive and therapeutic application of few vitamins and trace elements.

Synthetic Glucocorticoids are a known, inexpensive, widely available solution. It works in limiting an exaggerated immune response that begins in the lung. GCs have been used in clinical practice for management of hospitalized patients for COVID-19. In fact, in a health emergency situation of this type, doctors used GC as an "accepted" therapy, for its reasonable expectation of success in the treatment of individual patients. Therefore, the GCs were administered at the physician's discretion, based on the best interest of the patient. Prevention is better than cure hence following the guidelines of WHO and getting vaccinated along with social distancing and mask usage can help reduce the risk of Covid 19.[10]

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