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PATHOPHYSIOLOGICAL EFFECT OF NOVEL HUMAN CORONAVIRUS (SARS-COV-2) ASSOCIATED CYTOKINE STORM ON VITAL ORGANS: A REVIEW

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ABSTRACT

As Novel human coronavirus (SARS-CoV-2) cases fill the hospitals, among the sickest and most likely to die are those whose bodies react in a signature, catastrophic way. Immune cells flood and attack the lungs, which they should be protecting. Blood vessels leak; the blood itself clots. Blood pressure plummets and organs start to fail. Such cases, doctors and scientists increasingly believe, are due to an immune system gone overboard so that it harms instead of helping. Though there are tests and treatments that could help to identify and tamp down this insurrection, it's too early to be sure of the best course of therapy for those who are suffering a storm, Cytokine Storm due to Novel human coronavirus (SARS-CoV-2). The common idea of an over the top or uncontrolled releases of pro-inflammatory cytokines are well known. In this article, we center on the cytokine storm within the setting of Novel human coronavirus (SARS-CoV-2); we moreover address prove for the part of the cytokine storm within the pathology of clinical and infectious illness and talk about its mechanism included together with therapies to move forward the clinical results for patients with severe acute Novel human coronavirus (SARS-CoV-2).

KEYWORD: Cytokine, Novel human coronavirus (SARS-CoV-2), Cytokine storm, inflammation.

INTRODUCTION

The numbers of patients suffering from active Novel human coronavirus (SARS-CoV-2) infection are rising drastically across the world; scientists are close to deciding on some promising drug, vaccine candidates and clinical trials are on at multiple centers to test the safety and efficacy of the available alternatives.[1] The ongoing Novel human coronavirus (SARS-CoV-2) pandemic holds many mysteries;[2] among the more baffling has been the Cytokine storm. Whereas most people stay asymptomatic or create as it were gentle indications, up to 15–20% require hospitalization and less than 5% create a critical sickness characterized by an intense acute respiratory distress syndrome (ARDS) and multiple-organ failure (MOF).[3] The excess cytokine discharge in reaction to viral disease, a condition known as cytokine discharge disorder (CRS) or cytokine storm is rising as one of the mechanisms driving to ARDS and MOF in Novel human coronavirus (SARS-CoV-2).[4] Cytokines secreted by specific cells of the immune system, interact with cells of the immune system in order to regulate the body's response to disease and infection, as well as mediate normal cellular processes in the body.[3] Pro-inflammatory cytokines, a general term for those immunoregulatory cytokines that favor inflammation, they are secreted from the immune cells like helper T-cells and macrophages, and certain other cell types that promote inflammation.[4] The net impact of an inflammatory reaction is decided by the balance between pro-inflammatory and anti-inflammatory cytokines.[3] They are delivered by activated macrophages and are included within the up-regulation of inflammatory responses.[5] There's an inexhaustible proof that certain pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are included within the process of pathological pain. Cytokines related with the Cytokine Storm incorporate the following-

Interleukins (ILs): Anti-inflammatory interleukins, IL-β, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12 are cytokines that play a great role in counterbalancing the pro-inflammatory response in Novel human coronavirus (SARS-CoV-2) specific cytokine storm. Interleukins are responsible for regulating motility, cell growth and differentiation, particularly important in stimulating immune responses, for example inflammation.

Interferons (IFNs): IFN-gamma plays a major role in inflammation in Novel human coronavirus (SARS-CoV-2) patients; it has long been recognized as a pro-

inflammatory cytokine. There's presently rising proofs showing that IFN-gamma possesses unexpected properties in the regulation of immune responses and inflammation.

Chemokines: Inflammatory chemokines work basically as chemo-attractants for leukocytes, selecting monocytes, neutrophils and other effector cells from the blood to the locales of infection or tissue damage. Certain inflammatory chemokines enact cells to start an immune reaction or advance wound recuperation.

Tumor necrosis factor (TNF): Tumor necrosis factor alpha is one of the cytokines that make up the acute phase reaction in cytokine storm. It is also involved in systemic inflammation as a cell signaling protein.

The first hints that severe Novel human coronavirus (SARS-CoV-2) cases included a cytokine storm came out of Chinese hospitals near the outbreak's epicenter.[6] Physicians in Wuhan, in a study of 29 patients, reported that higher levels of the cytokines IL-2R and IL-6 were found in more severe Novel human coronavirus (SARS-CoV-2) infections.[6] The cytokine storm is best exemplified by serious lung contaminations, in which neighborhood inflammation spills over into the systemic circulation, creating systemic sepsis, as characterized by persistent hypotension, hyper- or hypothermia, leukocytosis or leukopenia, and frequently thrombocytopenia.[7-9] In a few cases, persistent tissue damage without extreme microbial disease within the lungs too is related to a cytokine storm and clinical signs that mirror sepsis disorder.[10] In expansion to lung infections, the cytokine storm could be a result of extreme diseases within the gastrointestinal tract, urinary tract, central apprehensive framework, skin, joint spaces, and other locales.[11-13] Besides, ACE-2 utilization by viral passage interrupts angiotensin II (AngII) digestion system, coming about in an introductory increment in nearby Ang II concentrations which will improve pro-inflammatory cytokine discharge.[12] As this writing advances, it is imperative that cytokine estimations are standardized to permit comparison.[14]

PATHOPHYSIOLOGY

Cytokines are a fundamental component of the inflammatory process. Cytokines are delivered by immune cells, counting the innate macrophages, dendritic cells, natural killer cells and the T and B lymphocytes.[12] Amid an immune response to a viral disease, Pattern recognition receptors (PRRs) recognize diverse molecular structures that are characteristic of the attacking virus.[10] These atomic structures are alluded to as pathogen associated molecular designs (PAMPs).[12] Authoritative of PAMPs to PRRs triggers the begin of the inflammatory reaction against the attacking infection coming about within the actuation of few signaling pathways and in this way transcription variables which initiate the expression of genes responsible for generation of several items included within the host's resistant reaction to the infection, among which are the genes encoding several pro-inflammatory cytokines.[12-14] The major transcription variables that are enacted by PRRs are nuclear figure kB, activation protein 1, interferon reaction variables three and seven. These transcription components initiate the expression of genes encoding inflammatory cytokines, chemokines and adhesion molecules.[15] This grouping of occasions comes about within the recruitment of leukocytes and plasma proteins to the location of disease where they perform different effector capacities that serve to combat the activating disease.[15]

Three of the foremost critical pro-inflammatory cytokines of the innate immune reaction are IL-1, TNF-α, and IL-6. Tissue macrophages, mast cells, endothelial, and epithelial cells are the major source of these cytokines amid the innate immune reaction.[16] The "cytokine storm" comes about from a sudden intense increment in circulating levels of diverse pro-inflammatory cytokines, counting IL-6, IL-1, TNF- α, and interferon.[13] This increment in cytokines comes about in deluge of different safe cells such as macrophages, neutrophils, and T cells from the circulation into the location of disease with dangerous impacts on human tissue coming about from destabilization of endothelial cell to cell intuitive, harm of vascular obstruction, capillary harm, diffuse alveolar harm, multi-organ disappointment, and eventually passing.[15,16] Lung damage is one result of the cytokine storm that can advance into intense lung damage or its most serious form ARDS.[16] ARDS driving to low oxygen immersion levels may be a major cause of mortality in Novel human coronavirus (SARS-CoV-2). In spite of the fact that the precise mechanism of ARDS in Novel human coronavirus (SARS-CoV-2) patients isn't completely caught on, the intemperate generation of pro-inflammatory cytokines is considered to be one of the major contributing variables.[17]

HOW OTHER ORGANS ARE AFFECTED

LUNGS: The SARS-CoV-2 S protein ties to angiotensin converting enzyme 2 (ACE2) to enter into the host cells. Most Novel human coronavirus (SARS-CoV-2) patients show with respiratory indications since ACE2 receptors are communicated in vascular endothelial cells of the lower respiratory tract. In extreme Novel human coronavirus (SARS-CoV-2) cases, hyper-cytokinemia within the lungs leads to diffuse alveolar harm, hyaline membrane arrangement, thrombus formation [affirmed in small vessels at post-mortem examination], fibrin exudates, and fibrotic mending. These pathologic changes result in intense lung harm and show clinically as intense acute respiratory distress syndrome (ARDS).[18]

HEART: ACE2 receptors are too displayed in cardiac tissue and within the gastrointestinal tract, ostensibly clarifying the cardiac and gastrointestinal clinical signs in a few Novel human coronavirus (SARS-CoV-2)

patients. Accessible information propose that those with basic cardiovascular malady, hypertension, extreme dyslipidemia, weight, and diabetes are at high hazard for extreme Novel human coronavirus (SARS-CoV-2) illness, while other information show that SARS-CoV-2 infects the heart, bringing about myocarditis and myocardial areas of localized necrosis. Patients with basic cardiovascular illness are at expanded hazard of cytokine storm and destitute results.[19] Novel human coronavirus (SARS-CoV-2) patients with fundamental cardiovascular malady are too at higher chance of myocardial damage [with cardiac troponin (TnT) increment], as well as both atherosclerosis-related and thromboembolic occasions.[20]

KIDNEY: Novel human coronavirus (SARS-CoV-2)-related kidney damage happens because ACE2 receptors are found in the kidneys within the brush border of proximal tubular cells. In spite of the fact that the kidneys of Novel human coronavirus (SARS-CoV-2) patients inspected autopsy uncover SARS-CoV 2 antigens within the proximal tubules, the part of cytokine storm in causing kidney harm isn't however clear.[21]

BRAIN: The foremost question for numerous neuroscientists, in any case, is why the brain is affected at all despite the presence of the blood brain barrier. The fact that the pattern of disorders is decently reliable, the basic components are not however clear. Several people who have recovered from a mild illness of the disease later noted trouble with concentration, confused thoughts and memory issues as well. As of now, clear links have been established that the virus does cause problems in the brain including confusion, loss of consciousness, stroke, seizures, loss of smell and taste (anosmia), trouble focusing etc. There have been several speculations pertaining to COVID-19's effect on the brain, including a decline in cognition leading to worsening of pre-existing neurological conditions like dementia. When a blood clot is formed in the arteries supplying blood to the brain, it cuts off the oxygen and blood supply to the brain, leading to a stroke. In fact, many COVID patients with severe illness develop blood clots in intensive care, even after they are put on blood thinner drugs.

DIGESTIVE SYSTEM (STOMACH and INTESTINES): Although the virus spreads through respiratory droplets and secretions, the gastrointestinal (GI) tract can also be a potential route of viral transmission. Diarrhea, nausea and vomiting, and abdominal discomfort have been described in COVID-19 patients. Angiotensin converting enzyme II (ACE2) acts as the potential target site transmitting SARS-CoV-2 to humans. ACE2 was found not only highly expressed in the lung alveolar type 2 cells, but also found in esophagus, absorptive enterocytes from ileum (small intestine) and colon large intestine). It is also found in the liver and biliary system. Loss of appetite is the most common symptom. Nausea, vomiting, diarrhea and abdominal pain are the other GI symptoms.

PANCREAS: At this time, there have been no studies regarding pancreatitis and COVID-19. Depending on the pancreatitis patient, the levels of a compromised immune system can vary. Patients that have chronic pancreatitis with complications of diabetes are at a higher risk as diabetes is a risk factor in COVID-19, but there has been no research shown for those that have pancreatitis being at-risk. The virus can cause multisystem involvement, and although COVID-19 induced acute pancreatitis is rare, it can cause severe damage to the patient as the target organ of both COVID-19 and pancreatitis is the same.

Mechanism of Action and its effect

When the cytokines that raise immune activity become too abundant, the immune system may not be able to stop it. Immune cells spread beyond infected body parts and start attacking healthy tissues, gobbling up red and white blood cells and damaging the liver.[22] Blood vessel walls open up to let immune cells into surrounding tissues, but the vessels get so leaky that the lungs may fill with fluid, and blood pressure drops. Blood clots throughout the body, further choking blood flow.[23] When organs don't get enough blood, a person can go into shock, risking permanent organ damage or death. Most patients experiencing a storm will have a fever, and about half will have some sort of nervous system symptoms, such as headache, seizures or even coma.[24]

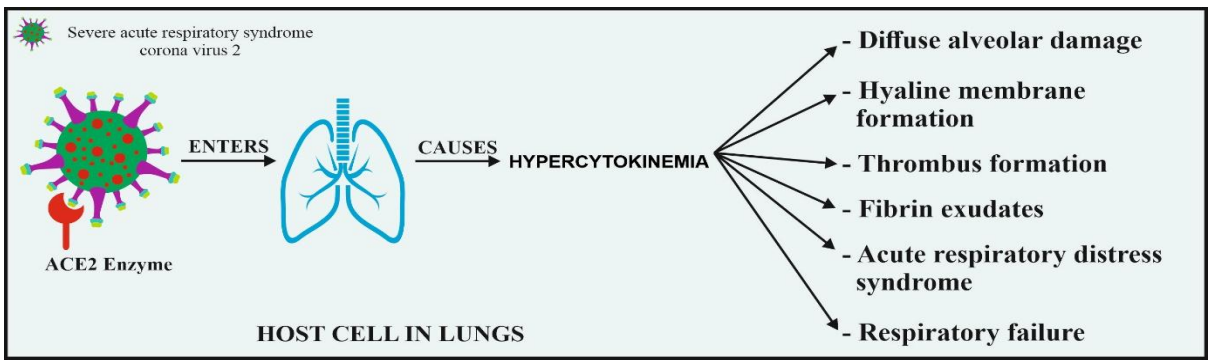

Figure 1: Pathophysiology of cytokine storm, the SAR-CoV-2 attaches itself to the ACE2 to enter into the host cell causing Hypercytokinemia.

TREATMENT

Given the potential for cytokines to cause tissue harm, it's necessary to relieve the impacts of high levels of cytokines and advance the move into the resolution stage of an immune reaction.

CONVALESCENT PLASMA THERAPY: Convalescent plasma treatment (CPT) is based on the transfusion of plasma collected from patients who have recouped from SARS-CoV2 malady, and created antibodies, for individuals enduring from the same in arrange to offer them speedy resistance.[25] Plasma from healthy donors gives neutralizing antibodies, obliging viral improvement and immunomodulatory impacts through the blend of anti-inflammatory cytokines and antibodies that piece complement, inflammatory cytokines, and autoantibodies. Of note, the CPT advantage is more unmistakable when it is utilized in a helpful way inside the early viremic arrange as its transcendent action is through direct neutralization of the contamination.[26]

BLOOD PURIFICATION TREATMENT: The blood decontamination medications right now utilized in clinical practice can evacuate inflammatory components to a certain degree.[27] Blood filtration framework counting plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can expel inflammatory components and piece the "cytokine storm", to diminish the harm of inflammatory reaction within the body.[27] This treatment can be utilized for severe and basic patients within the early and center stages of the infection. Early renal substitution treatment, which is comparative to the treatment guideline of manufactured liver innovation, appears to be a compelling strategy to control cytokine storm.[28]

CORTICOSTEROIDS: Corticosteroids are a class of steroid hormones that have anti-inflammatory capacities. Corticosteroids are commonly utilized to smother inflammation. Amid the 2003 SARS epidemic, corticosteroids were the essential implies of immune-modulation.[29] Opportune organization of corticosteroids regularly leads to early advancements such as diminishing fever, soothing radiation invasion of the lung, and progressing oxygenation. Corticosteroids and NSAIDs can successfully smother hyper-inflammatory reactions; in any case, postponed viral clearance might lead to encourage complications conjointly increment the hazard of transmission.[29] Although corticosteroids may well be utilized intensely to target cytokine storm, their utilization in respiratory viral contamination is related with expanded mortality, expanded hazard of auxiliary bacterial or parasitic contaminations, and delayed ICU confirmation.[30]

STEM CELL THERAPY: As a vital part of the stem cell family, mesenchymal stem cells (MSC) has got potential of self-renewal and multidirectional separation, but to have solid anti-inflammatory and resistant administrative capacities.[31] MSC can hinder the unusual enactment of T lymphocytes and macrophages, and initiate their separation into the administrative T cell (Treg) subsets and anti-inflammatory macrophages, separately. It can too restrain the discharge of pro-inflammatory cytokines, such as, IL-1, TNF-α, IL-6, IL-12, and IFN-γ, in this manner decreasing the event of cytokine storms.[26] Hence, numerous capacities of the MSC are anticipated to form a compelling strategy for the treatment of Novel human coronavirus (SARS-CoV-2).[26]

CONCLUSION

Cytokine storm (CS) could be a basic life-threatening condition requiring serious care, affirmation and having a very high mortality. CS is characterized by a clinical introduction of overpowering systemic inflammation, hyper-ferritinemia, hemodynamic instability, and multi-organ failure, and on the off chance that cleared out untreated, it leads to passing.[30] In expansion to anti-viral treatments that can specifically target the infection, anti-inflammatory treatments that reduce the cytokine reactions are recommended to diminish both the morbidity and mortality in Novel human coronavirus (SARS-CoV-2) patients.[32] The Cytokine storm shows up to be one of the common causes of mortality within the as of late announced widespread of Novel human coronavirus (SARS-CoV-2). Helpful approaches to oversee the Novel human coronavirus (SARS-CoV-2) cytokine storm might give a road to diminish the Novel human coronavirus (SARS-CoV-2) related morbidity and mortality and is the center of upcoming studies. Studies so far haven't been peer-reviewed. Its part of an effort to get scientific findings out more quickly in the midst of a pandemic, more research will be needed to find out if this approach will help keep Novel human coronavirus (SARS-CoV-2) patients out of the hospital, or off ventilators, in the real world. The identification of mutation present in protein structure and cis acting untranslated region is important for studying the virulence. This mutational divergence is important for further studies with inclusion of metabolic pathway intraviral and virus host interaction for the prognosis of this newly emerged strain of coronavirus.[33]

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