Preparing for the storm: mitigating the effect of SARS-CoV-2 induced hypercytokinemia

Adekunle B. Rowaiye¹,², Okiemute Ajiroghene Okpalefe², Olukemi Adejoke Onuh¹, Joyce Oloaigbe Ogidigo³, Oluwakemi Hannah Oladipo⁴, Ogu Amoge Chidinma¹, Angus Nnamdi Oli⁵, Samson Ayodeji Olofinase³, Onyekachi Onyekwere⁶

¹Department of Medical Biotechnology, National Biotechnology Development Agency, Abuja, Nigeria
²Department of Genetics, Genomics, and Bioinformatics, National Biotechnology Development Agency, Abuja, Nigeria
³Bioresources Development Centre, Abuja, National Biotechnology Development Agency, Abuja, Nigeria.
⁴Bioresources Development Centre, Ilorin, National Biotechnology Development Agency, Abuja, Nigeria.
⁵Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka
⁶Bioresources Development Centre, Ubulu Uku, National Biotechnology Development Agency, Abuja, Nigeria.

*Email of corresponding author: a.n.oli@live.com

Abstract

With increasing fatalities, the COVID-19 pandemic constitutes a formidable global health challenge. The causative agent, SARS-CoV-2 constantly tests the efficacy of the immune system of its victims. The protective ability of the innate immune system as the first responder largely determines the progression of disease and its clinical prognosis. Evidence suggests that mortalities associated with COVID-19 are largely due to hyperinflammation and a dysregulated immune response. Consequently, the degree of the release of pro-inflammatory cytokines such as IL1, IL-6, and TNF alpha remarkably distinguishes between mild and severe cases of COVID-19. The early prediction of a cytokine storm is made possible by several serum chemistry and hematological markers. The prompt use of these markers for laboratory tests, and the aggressive prevention and management of a cytokine release syndrome is critical in determining the level of morbidity and fatality associated with COVID-19. The early prediction of a cytokine storm is made possible by several serum chemistry and hematological markers. The prompt use of these markers for laboratory tests, and the aggressive prevention and management of a cytokine release syndrome is critical in determining the level of morbidity and fatality associated with COVID-19. With respect to the SARS-CoV-2 and the host cell, this literature review focuses on the dynamics of the COVID-19 disease highlighting on the pathogenesis, and the markers of Cytokine Storm. It also proffers solutions by critically looking at the current and potential pharmacological agents that are or can be used to mitigate and manage cytokine storms.

Keywords: COVID-19; SARS-CoV-2; Cytokine Storm; Hyperinflammation; hypercytokinemia

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of the Coronavirus disease 2019 (also known as COVID-19) which broke out in Wuhan, China in December 2019 and spread to almost all the entire globe [1]. On March 11th, 2020, the World Health Organization (WHO) pronounced the disease a pandemic. Over 43 million cases and 1,157,202 deaths have been reported in 217 countries and territories as of the 25th of October 2020 [2]. COVID-19 is characterized by pathologies of the lower respiratory system which includes pneumonia and the clinical presentations of the disease range from asymptomatic, mild, moderate, to severe forms. Immunocompromise, senility, and comorbidities are factors that complicate the COVID-19 disease [3,4].
SARS-CoV-2 is a single stranded RNA virus belonging to Beta-coronavirus genus and Coronaviridae family. The genome of coronavirus encodes four predominant proteins which are the Spike (S), Nucleocapsid (N), Membrane (M), and Envelope (E) proteins. Interestingly, the S protein is responsible for viral access into respiratory tissue through the Angiotensin-Converting Enzyme 2 (ACE-2) expressing epithelial cells. Being the first major point of contact with the host cell, the S protein is known to have strong immunogenic properties [5].

There are three main clinical stages of COVID-19. Stage one is the viral response phase which is the period of early infection. It lasts for about 4 days and it is typically characterized by non-specific symptoms such as fever, cough, and diarrhoea [6]. Stage two is the pulmonary phase which usually lasts between days 5 to 13. At this phase, the pulmonary symptoms are first without hypoxia, and later hypoxia develops [6]. Stage three is the systemic hyperinflammation phase which is usually from day 14 [6]. Most times, patients report at the hospital at the end of stage 1 or the beginning of Stage 2. At this time, the potentials of the innate immune system to combat the infection have been tested [7].

Evidence suggests that mortalities associated with COVID-19 are largely due to hyperinflammation and a dysregulated immune response. The SARS-CoV-2 infection induces a cytokine storm characterized by potentially life-threatening pathologies such as hyperinflammation, septic shock complications, coagulation dysfunction, and multiple organ failure [8]. Hypercytokinemia in COVID-19 patients is characterized by the speedy proliferation and hyperactivation of T-cells, macrophages, NK cells, and the excessive production of a host of pro-inflammatory cytokines and chemical mediators released by immune or non-immune cells [8,9,10].

The early prediction, aggressive prevention, and management of a cytokine release syndrome is critical in determining the level of morbidity and fatality associated with COVID-19. The development of hypercytokinemia is a strong indication of a disease escalation and immune suppression is a key therapeutic strategy in combating this complication [11]. Therefore, in the diagnosis and treatment of SARS-CoV-2 infected pneumonia, it is important to monitor cytokine levels and other markers to improve the rate of cure and in turn reduce the rate of human mortality from the burden of disease [12].

With respect to the SARS-CoV-2 and the host cell, this literature review focuses on the pathophysiological dynamics of the COVID-19 disease highlighting on the pathogenesis, and markers of cytokine storm. It also proffers solutions by critically looking at the current and potential pharmacological agents that are or can be used to mitigate and manage cytokine storms.

### 2. Pathogenesis of SARS-CoV-2 induced Cytokine Storm

Over the last decade, the term cytokine storm or cytokine release syndrome has been used to describe an abnormal release of soluble mediators, and the associated immunopathological event that occurs after severe bacterial and viral infections [13]. Cytokine storm syndrome is associated with an exacerbation of pro-inflammatory-mediated response along with an ineffective control mechanism by the anti-inflammatory system consequently leading to tissue damage [13,14].

The human immune system plays an essential role in the eradication of infectious agents such as influenza and coronaviruses through leucocyte recruitment, and the release of cytokines. An unconstrained and well harmonized stimulation of immune responses is usually the first mechanism of action that the body presents in trying to build a defense against any viral infection [15]. Nevertheless, unregulated as well as aggravated immune responses may alter immunological
function consequently leading to tissue damage and multiple organ failures [15,16]. The production of multiple cytokines which causes cytokine storms in SARS-CoV-2 patients results in immunopathogenic damages and therefore, the effective lowering of pro-inflammatory cytokine levels in severe COVID-19 patients is a crucial step in the prevention of the deterioration of health in infected persons [16,17,18].

The SARS-CoV-2 has been shown to infect epithelial cells of the human airway, THP-1 cells (a monocyte cell line), human peripheral blood monocyte-derived macrophages, dendritic cells, and lymphocytes. It also induces the stimulation of pro-inflammatory cytokines and chemokines [19]. The SARS-CoV-2 contains a receptor-binding domain (RBD) located in the S1 region that identifies a binding pocket in the Angiotensin-Converting Enzyme 2 (ACE2) and plays a role in the pathogenesis of COVID-19 [20]. ACE2 is expressed by epithelial cells of the lung, digestive tract, kidney, veins, terminal ileum, and colon [21]. Due to genetic similarity, polymorphisms of the ACE2 gene may affect the susceptibility to COVID-19 disease as it does affect the SARS CoV infection [20,22,23]. Mutations might also modify the expression level of ACE2 as shown in a murine model [24].

In infected cells, the nucleic acids of the invading virus are identified by Pattern Recognition Receptors (PPR) such as the Toll-Like Receptors (TLR3, TLR7, TLR8, and TLR9) [25,26,27]. The single nucleotide polymorphisms in gene coding for these TLR may lead to poor viral recognition and subsequently a susceptibility to cytokine storms [28]. The activated TLR release cytokines amongst which is Type 1 Interferon (IFN-1) made up of IFN-α and IFN-β which is key for antiviral immunity [29,30]. IFN-1 is produced in large quantities by activated plasmacytoid dendritic cells. Binding to the IFN-1 receptor, IFN-1 triggers the phosphorylation of transcription factors such as Signal transducer and activator of transcription 1 (STAT1) in a downstream signalling pathway that leads to the activation of hundreds of IFN-stimulated genes in the nucleus [13,31]. IFN-1 stimulates the NK cells through mechanisms that involve or do not involve class I major histocompatibility complex (MHC) protein [32]. Polymorphisms of class I MHC may also lead to increased susceptibility to COVID-19 [7]. Unfortunately, the SARS-CoV-2 evades the TLR8 and TLR9 receptors (Figure 1) through an intricate capping mechanism of its mRNA by its methyltranferases [33]. This suppresses IFN-I production and the downregulation of interferon-stimulated genes in COVID-19 patients [34]. However, independent of IFN-1, the NK cells can be triggered through other cytokines such as IL-2 and IL-15. These compensatory signalling mechanisms are important in the innate antiviral defence of most COVID-19 survivors [35].
The NK cells are responsible for the immunosurveillance of tumour and virally infected cells [36]. To effectively carry out this role, the NK cells are equipped with a set of pro-inflammatory cytokines (IFNγ and TNFα) and cytotoxic molecules (perforin and granzymes) [37]. Largely due to the presence of inhibitory receptors and regulatory cytokines such as IL-10, IL-3, and GM-CSF, NK cells also play an immunomodulatory role. They can control exaggerated immune responses as seen in autoinflammatory conditions and cytokine storms [38]. However, reduced activity, decreased number, and genetic deficiency of NK cells has been associated with the progression of cytokine storms [38,39].

Mutations in the genes of certain proteins expressed by NK cell affects the cytotoxic activities. For example, mutations in the PRF1 and GZMB genes lead to defective perforin and granzyme B expression respectively [39,40,41,42]. Perforinopathy and other deficiencies in expression of cytotoxic proteins could induce signals that trigger intense inflammatory response seen in cytokine storm syndrome [43,44]. Empirical evidence suggests that the failure of Granzyme/Perforin-induced apoptosis of target cells cause severe immune dysregulation. The prolonged survival of target cells causes IFN-γ secreted by the NK cells to directly trigger the activation of naive macrophages which consequently overproduce pro-inflammatory cytokines [39]. Therefore, though there is an absence of the death of virally infected cells due to decrease in NK cell cytotoxic activity, a flurry of cytokines is released by the resulting IL-6 cascade [44].
Figure 2: Defective NK cell signals the production of a flurry of cytokines

Upstream of the IL-6 signalling pathway, IL-1β and TNF alpha are two important pro-inflammatory cytokines in the pathogenesis of virus-induced cytokine storms. The TNFα and IL-1β trigger the Nuclear Factor kappa light chain enhancer of activated B cells (NF-κB) signalling pathway. On activation, the NF-κB, a DNA binding protein activates the transcription of various genes and thereby regulate inflammation [45]. The activation of NF-κB further activates IL-6, other pro-inflammatory cytokines, chemokines, enzymes, and adhesion molecules. Additionally, the NF-κB, regulates the proliferation, morphogenesis, and apoptosis of inflammatory cells [45,46,47].

IL-6 is a pleiotropic cytokine produced from multiple cell types including macrophages, dendritic cells, fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, B and T cells [48]. It not only has significant pro-inflammatory properties but can also trigger dual signalling pathways (cis or trans) based on their cellular distribution [49]. In the cis signalling pathway, IL-6 binds with the membrane-bound IL-6 receptor (mbIL-6R) which is expressed on neutrophils, naïve T cells, and monocytes/macrophages covering both the innate and acquired immune systems [49]. The IL-6/mbIL-6R complex binds with gp130 and triggers the Janus kinases (JAKs) and signal transducer and activator of transcription 3 (STAT3) proteins [49]. This signal cascade leads to multiple effects on the cells involved and culminates in a cytokine storm. Cytokines are elevated based on the level of inflammation. Activated T cells secrete cytokines such as IFNγ and Granulocyte macrophage colony stimulating factor (GM-CSF). The activated monocytes/macrophages secrete cytokines and chemokines such as Monocyte Chemoattractant Protein-1 (MCP1), Macrophage Inflammatory Protein 1-alpha (MIP1α), Macrophage Inflammatory Protein 1-beta (MIP1 β), Monokine induced by gamma interferon (MIG), IFNγ-induced protein 10 (IP-10), and CCL-5 The activated neutrophils also secrete pro-inflammatory cytokines such as TNF-α, IL-1-α, and IL-1-β [50,51,52,53,54,55].

In the trans signalling pathway, IL-6 binds to the soluble form of IL-6 receptor (sIL-6R) found on all somatic cells [49]. The IL-6/sIL-6R complex binds with gp130 and triggers the JAK-STAT3 signalling pathway. The cytokine storm is aggravated through the release of monocyte chemoattractant protein–1 (MCP-1), IL-8, vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein–1 (MCP-1) which are associated with tissue damage and inflammation. The vascular permeability and leakage associated with the hypotension and
pulmonary dysfunction in ARDS is due to reduced E-cadherin and increased VEGF expression [50,51,52,53].

The invasion of SARS-CoV-2 induces an alteration in T-cell responses leading to high serum levels of cytokines and chemokines in severe cases as compared with mild or moderate cases. For example, IL-6 was reported to be 76% higher than normal in severe cases as compared with 30% in mild cases [3, 56, 57, 58, 59, 60, 61]. As the cytokines and chemokines level increase, they tend to recruit many other inflammatory cells including neutrophils and monocytes, which results in the infiltration of the lung tissue causing acute respiratory distress syndrome (ARDS). The ARDS is characterized by apoptosis of the pulmonary epithelial and endothelial cells, damages of the lung microvascular and alveolar epithelial cell barrier, vascular leakage, alveolar oedema, hypoxia, and pulmonary fibrosis [8, 62].

Apart from the direct attack of SARS-CoV-2 on CD4 lymphocytes, IL-6 has also been shown to inhibit lymphopoiesis through lymphocyte trafficking and the direct suppression of progenitor cells [63, 64]. The uncommitted hematopoietic stem cells which contain precursors for both lymphoid and myeloid fates express the IL-6 receptor-α chain. These cells respond to IL-6 activation through the JAK/STAT3 pathway which causes the expression of the Id1 transcription factor. Consequently, lymphopoiesis is inhibited and myelopoiesis is elevated in a mitogen-activated protein kinase (MAPK)-dependent manner [65, 66].

The overall immunopathology of COVID-19 suggests remarkable lymphocytopenia, thrombocytopenia, basopenia, eosinopenia, monocytopenia, hyper-gamma-immunoglobulinemia, neutrophilia, T-cell activation, lymphocyte dysfunction, and increased pro-inflammatory cytokine production [67]. In terms of specific clinical symptoms, TNF-α causes flu-like symptom; IFN-γ causes fever, fatigue, chills, headaches, malaise, vascular leakage, cardiomyopathy, lung injury, and acute-phase protein synthesis [67]. IL-6 induces cardiomyopathy, vascular leakage, activation of complement and the coagulation cascade, and diffuses intravascular coagulation [68, 69, 70]. The excessive production of cytokines also leads to the generation of tissue factors which culminates in the over-coagulation of the blood. Tissue hypoxia and ischemia result from thrombosis and viscera embolization [58].

3. **Markers of SARS-CoV-2 induced Cytokine Storm**

The quick and early prediction of hypercytokinemia through specific biological markers would prevent many deaths. This would allow for closer clinical monitoring and aggressive supportive therapies to avoid poor prognosis [71]. The clinical markers (Table 1) that can be used to diagnose tissue damage in COVID-19 pathologies include serum chemistry and haematological parameters [72].

**Table 1: Markers of cytokine storm**

| Marker              | Type               | Association with cytokine storm                              | Normal range | COVID-19 Marker Cut-off | References |
|---------------------|--------------------|----------------------------------------------------------------|--------------|-------------------------|------------|
| Ferritin            | Serum Chemistry    | Cellular ferritin leaks from damaged cells                   | 18–350 ng/ml | ≥ 400 μg/L*              | [73]       |
| D-dimer             | Serum Chemistry    | Defective plasma coagulation                                 | 250 - 500 ng/ml | ≥ 1000 ng/ml*          | [78]       |
| Lactate dehydrogenase | Serum Chemistry | Lactic acidosis                                               | 140 -280 U/L | ≥ 450U/L *              | [71]       |
C-Reactive Protein asociated to IL-6 stimulation: 0.3 to 1.0 mg/dL ≥ 20 mg/dL* [86]

ALT Serum Chemistry: Damage of hepatocytes 19 to 33 IU/L 67 (47-100) IU/L* [90]

Cytokines Serum Chemistry: IL-1beta pro-inflammatory activity 0.10 pg/ml 0.67 pg/ml [103]
IL-6 pro-inflammatory activity 0.5 to 5 pg/mL <25 pg/mL* [101,102]
TNFα pro-inflammatory activity 0 to 8.1 pg/ml < 35 pg/ml* [104]

Neutrophil/Lymphocyte Ratio Increased neutrophil counts and lymphopenia. 1.0 - 3.0 6.6 (2.1–11.1)* [7,106]

Erythrocyte Sedimentation Rate Haematological Platelet destruction 0 to 29 mm/hr >100 mm/hr* [110]

* Marker levels suggest a remarkable increase from the normal range. They are not to be taken as fixed as they do vary as disease progresses and due to several other factors.

3.1 Ferritin:

The role of serum ferritin as a marker of inflammation and immune dysregulation is well established. While Ferritin is considered an acute phase reactant, it is not synthesized in the serum, but it is an intracellular iron storage protein [73]. Iron and inflammation are inescapably linked and the increase in production of cellular ferritin to bind it is a host defence mechanism to inhibit free radical production [74]. Serum ferritin originates from leakage from damage cells and therefore serves as an important disease marker. As ferritin exits the cells, it leaves an unbound Iron and consequently lacks most of the Iron it contains intracellularly. Though serum ferritin is benign, the unbound Iron further causes cellular damage through lipid oxidation [73,74]. Unliganded Iron catalyses hydroxyl radical formation and thus increases the production of markers such as malondialdehyde, 27-hydroxycholesterol, 8-hydroxydeoxyguanosine, 4-hydroxynonenal, and Isoprostanes [73,74]. Since the red blood cells contain the highest volume of ferritin, unbound Iron causes the distortion of their structure and function. Unbound Iron also causes pathological changes in fibrin morphology consequently making it to trap deformed erythrocytes [73,74].

Clinical data also suggests that increased ferritin levels are associated with the severity of COVID19, normal serum ferritin range being 18–350 ng/mL [75]. In severe cases, ferritin levels are > 400 μg/mL and could be between 1.5 and 5.3 times higher than moderate cases [76]. Where there is no liver disease or transfusion for anaemia, a disproportionately high and continuously increasing serum ferritin level is suggestive of a cytokine storm [77].

3.2 D-dimer (DD):

Soluble fibrin is generated during plasma coagulation. DD is released as a product of degeneration of cross-linked fibrin. Hence, it is a sensitive biomarker to rule out venous thromboembolism. However, increased DD levels are an indicator of the activation of coagulation [78]. There is a correlation between d-dimer (DD) and the progression of severe COVID-19. DD is directly associated with the activation of the proinflammatory cytokine cascade. On the contrary, it is not associated with anti-inflammatory cytokines (IL-10) [79].

There is a defective coagulation system in severe COVID-19 patients and DD can identify patients at increased risk of cytokine storm [78]. Beyond inflammation, coagulopathy plays an important role in the pathogenesis of severe COVID-19. Patients have multiple infarcts and ischemia of the extremities. DD is an important marker of the coagulopathy and elevated D-dimer levels is a
predictor of COVID-19 progression [79]. The normal plasma levels of D-dimer are below 250ng/mL for D-dimer units or below 500 ng/mL for fibrin equivalent units (www.clinlabnavigator.com/ddimer). DD levels higher than 1000 ng/ml show poor clinical prognosis and the need for anticoagulant therapy [80,81].

3.3 Lactate dehydrogenase (LDH):

This is an enzyme found in nearly all living cells. It is a major predictor of cytokine storm in COVID-19 disease because it is associated with metabolic acidosis [82]. In viral infections, conditions of tissue hypoxia prevail when pyruvate is converted to lactic acid and accumulates. Lactic acidosis induces the monocytes, and macrophages to produce IL-1β and trigger the inflammasome to activate inflammatory responses [83,84]. In homeostatic response to the acidosis, the LDH level is increased. Therefore, LDH is a marker of tissue damage caused by viraemia and dysregulated immune response because of tissue deterioration progresses, the LDH increases. It reflects the degree of various pathophysiological processes, and therefore it can predict the progression or regression of disease. There is significant difference in LDH levels between non-severe and severe groups of COVID-19 pneumonia patients [85]. Normal LDH levels range from 140 -280 units per liter (U/L), a cut off value of 450U/L is used as threshold for COVID 19 severity [71].

3.4 C-reactive protein (CRP):

In response to IL-6 stimulation, CRP is released from the Liver cells. CRP is an acute phase reactant which is markedly elevated in COVID-19 patients. CRP can be used as a marker to determine the severity of disease and a reliable predictor of cytokine release syndrome. Extremely high CRP levels are associated with poor prognosis. Based on the relationship between CRP levels and IL-6, it can be used as a surrogate marker. Daily monitoring is important to distinguish between whose fever would resolve and those whose symptoms would gravitate to a cytokine storm. The normal CRP range is 0.3 to 1.0 mg/dL but values greater than 20 mg/dL suggests hyperinflammation [86]. A patient whose CRP exceeds this threshold is at particularly high risk of cytokine storm [87]. LDH and CRP may also be related to respiratory function and be a predictor of respiratory failure in COVID-19 patients [86].

3.5 Alanine aminotransferase (ALT):

This is an enzyme found inside the hepatocytes and is released excessively into the blood stream during liver damage. Hepatic injury is a characteristic clinical feature of COVID-19 and it has been reported in at least one half of patients suffering from the disease [88,89]. Impaired liver function is characterized by elevations of ALT in multiples factors of the upper reference limit [90].

During SARS-CoV-2, the ACE-2 receptor acts as a target for cell entrance. This receptor plays a crucial role in the propagation of the virus as it is expressed on the endothelial cells of bile duct and liver therefore exposing the organ to possible infection [91]. A direct viral attack on the hepatocytes and the cholangiocytes elevates ALT levels. Other causes of liver injury in COVID-19 patients include drug-induced toxicity [89].

3.6 Blood Urea Nitrogen (BUN) to Creatinine Ratio:

BUN and creatinine are filtered by the glomerulus. While the tubular reabsorption of the creatinine is minimal, that of BUN can either be increased or decreased. The Normal BUN range is 7–20 mg/dL and that of creatinine is 0.7–1.2 mg/dL [92]. When the BUN to Cr ratio exceeds 20, this is predictive of acute kidney injury which makes BUN reabsorption increased due to hypoperfusion.
of the kidneys. BUN is generally increased during COVID-19 due to acute kidney injury, and other factors [93].

Gastrointestinal bleeding has been observed in patients with severe COVID-19. The SARS-CoV-2 attacks the epithelial cells of the gastrointestinal tract which highly expresses the ACE2 protein [94]. Consequently, there is histological degeneration, necrosis, and varying degrees of mucosal spillage as detected in the gastrointestinal mucosa of a deceased COVID-19 patient [94]. Gastrointestinal bleeding may also be due to an existing coagulopathy developed from multiple organ failure or the use of corticosteroid with heparin or salicylic acid in the treatment of intravascular thrombosis [95]. Gastrointestinal bleeding can cause an elevation in BUN to Cr ratio due to amino acid digestion. Haemoglobin is broken down into amino acids by the enzymes in the upper intestinal tract. The reabsorbed amino acids are broken down into urea and this increases BUN level [96,97]. High BUN levels are associated with mortality in COVID-19 patients [98].

3.7 Cytokines:

Though expensive to test, cytokines can be used to predict cytokine storm. The increase in the levels of pro-inflammatory cytokines such as IL-1beta, IL-6, and TNF alpha are predictors of disease progression and an impending cytokine storm [99,100]. These cytokines can also be used as prognostic markers to determine the clinical outcome of therapeutic agents administered to combat the SARS-CoV-2 infection. The normal range of IL-6 for healthy individuals is 0.5-5 pg/mL and it could exceed 25pg/mL during disease [101,102].

The normal range for IL-1beta is 0.10pg/mL, and it could exceed 0.67pg/ml during disease [103]. The normal range for TNF alpha is 0.0-8.1 pg/mL, and it could exceed 35pg/mL during disease [99,104]. Cytokine cut-offs are difficult to establish and may vary depending on several factors such as population genetics, pleiotropic nature, and health status of patient. Therefore, it is ideal to compare cytokine signatures with their baseline values to establish a diagnostic or prognostic decision [105].

3.8 The Neutrophil/Lymphocyte Ratio:

The NLR is potentially a predictive prognostic biomarker in patients infected with the SARS-CoV-2 [106]. Severe COVID-19 is characterized by high levels of circulating pro-inflammatory cytokines, increased neutrophil counts, and lymphopenia [107]. Lymphopenia as a reliable and effective predictor for COVID-19 disease state [108]. While the neutrophilia is due to prolonged neutrophil activation, the lymphocytopenia might be due to a direct attack of SARS-CoV on lymphocytes, sequestration of the lymphocyte in the lung, suppression of haematopoietic stem cells, or the cytokine-mediated disruption of lymphocyte Trafficking [109].

3.9 Erythrocyte Sedimentation Rate (ESR):

The ESR measures the rate at which red blood cells (RBC) settle in anti-coagulated whole blood. During inflammation the ESR is faster than normal because a high proportion of fibrinogen in the blood causes the RBC to stick together and increases its density [110].

In SARS-CoV-2 infection, the platelet destruction is by direct attack of the virus or the immune system on the bone marrow progenitor cells [111]. Platelets express specialized PRR and can activate thrombo-inflammatory responses against viruses. There exists a functional cross talk between the platelets and the innate immune system promotes thrombo-inflammation, and tissue damage [112]. Platelet activation potentiates the recruitment, activation, and transmigration of innate immune cells. The progression and resolution of the inflammation of platelets is promoted
in a disease-specific manner. Also, thrombo-inflammation is differentially regulated by platelet-leukocyte interactions [113].

As the severe COVID-19 diseases progresses, the platelet count decreases and consequently the erythrocyte sedimentation rate is lowered. This leads to an elevated production of red blood cells or white blood cells. The normal range for ESR is 0 to 22 mm/hr for men and 0 to 29 mm/hr for women [114]. However, in severe inflammation due to infection values higher than 100 mm/h, may be obtained [111].

4. Mitigation and Management of SARS-CoV-2 induced cytokine storm.

To effectively prevent or mitigate the effect of a cytokine storm, it is essential that the clinician eradicates all the predisposing factors. These include viraemia, cellular oxidation, immunosenescence, and comorbidities. The administration of immunomodulators would further strengthen the therapeutic strategy (Table 2). While WHO is yet to approve any cure for COVID-19, a lot of antiviral agents have been proposed. Some of these are natural compounds which can also serve as antioxidants to combat oxidative stress resulting from SARS-CoV-2 infection [7].

Immunosenescence is an age-related decline in immune function. This is a major contributory factor to the increased frequency of morbidity and mortality in the elderly. Immunosenescence is characterized by diminished activity of hematopoietic stem cells due to continuous oxidative damage to DNA [115], and the decreased number or activity of circulating phagocytes, dendritic cells, NK cells, and B-cells [116]. Patients from 65 years and above stand a high risk of COVID-19 fatality [117]. Immunosenescence can be combated through bone marrow transplantation and genetic reprogramming [118].

Comorbidities are major risk factor in COVID-19. Immunity in patients with SARS-CoV-2 infection is further weakened with conditions such as cardiovascular diseases, hypertension, diabetes, and lung diseases. These conditions reduce the resistance to the invading virus and therefore enhance the progression of disease. The clinician should take care of these comorbidities to prevent a cytokine storm [117].

Immunomodulators are therapeutic agents that can be used in regulating immune responses. In the case of COVID-19, the suppression of hypercytokinemia may be able to fully resolve ARDS. Immunomodulators are of different categories, and some are currently being developed or repurposed for use based on compassionate recommendations for the treatment of COVID-19 [119]. They are usually administered in combination with other drugs. They can be used prophylactically to prevent cytokine storm by promoting an effective innate immune response cascade through specific TLRs to bring about viral clearance [27]. Therapeutically, immunomodulators can also be used to activate an adaptive immune response. Immunomodulators range from synthetic drugs, natural compounds, to recombinant antibodies many of which are still undergoing clinical trials.
Table 2: Potential therapeutic agents for mitigating and managing COVID-19 cytokine storms

| Class            | Therapeutic Agent | Mechanism of action                                                                 | Stage of Development | References |
|------------------|-------------------|--------------------------------------------------------------------------------------|----------------------|------------|
| Micronutrients   | Zinc              | Decreased gene expression of pro-inflammatory cytokines, Regulates several enzymes within the apoptotic cascade, Recruitment of Lck to the TCR complex | Nutraceutical        | [119,123] |
| Fatty acids      | Omega-3 Fatty acid (PUFA) | Induce apoptosis in leucocytes                                                       | Nutraceutical        | [132]      |
|                  | Butyrate          | Suppress IL-12 expression, Enhance IL-10 expression                                   | Nutraceutical        | [135]      |
| Vitamins         | Vit. C            | Inhibit mRNA expression of pro-inflammatory cytokines, increased production of type 1 interferons | Nutraceutical        | [140]      |
| Phytochemicals   | Resveratrol       | Increased expression of IL-10                                                        | Nutraceutical        | [151]      |
|                  | Kaempferol        | Decreased expression of IL-6 and TNF-alpha                                           | Nutraceutical        | [151]      |
|                  | Apigenin          | Decreased expression of IL-6 and TNF-alpha                                           | Nutraceutical        | [151]      |
|                  | Quercetin         | Decreased expression of IL-6 and TNF-alpha                                           | Nutraceutical        | [151]      |
| Plant Extracts   | Echinacea purpurea | inhibit the release of TNF-α                                                         | Nutraceutical        | [147]      |
|                  | Camellia sinensis | promote γδ T lymphocyte functions                                                    | Nutraceutical        | [148]      |
|                  | Echium amoenum    | Decrease expression of IL-1β, IL-6, TNF-α, iNOS & COX2                              | Herbal Tea           | [149]      |
|                  | Ab Nelus esculentus | Activation of NK cells                                                                | Nutraceutical        | [150]      |
|                  | Androphoris paniculata | Activation of NK cells                                                                | Nutraceutical        | [37]       |
| Interferons      | IFN-λ             | Suppression of neutrophil infiltration and IL-1β production.                          | Clinical trial       | [159]      |
| Monoclonal       | Tocilizumab       | Blocks IL-6 receptors                                                                 | Approved             | [68]       |
| Antibodies       | Anakinra          | Interleukin-1 receptor antagonist                                                    | Approved             | [67]       |
|                  | Fingolimod        | Agonist of S1P1R, S1P3R, S1P4R and S1P5R receptors.                                  | Approved             | [176]      |
| JAK inhibitors   | Baricitinib       | JAK1, JAK2, JAK 3 and Tyrosine Kinase 2 inhibition                                     | Approved             | [185]      |
|                  | Pacritinin        | JAK2 and IRAK1 inhibition                                                            | Under investigation  | [189]      |
| Antimalarials    | Hydroxychloroquine | inhibits antigen processing                                                          | Approved             | [190]      |
| Macrolides       | Azithromycin      | inhibits bacterial protein synthesis and neutrophil activity                         | Approved             | [195]      |
| (Antibiotics)    | Clarithromycin    | inhibits bacterial protein synthesis and neutrophil activity                         | Approved             | [195,196] |
| Immune Supplements | Transfer Factor   | Activate NK cells, Reduce IL-6 and Increase IL-10                                    | Nutraceutical        | [200,202] |
| Corticosteroids  | Dexamethosone     | promote antiinflammatory activities                                                   | Approved             | [203,204] |
|                  | Methyldprednlsone | promote antiinflammatory activities                                                   | Approved             | [203,204] |
| Others           | Ulinastatin       | increases IL-10 level, reduces the levels of TNF-α, IL-6, and IFN-γ                   | Approved             | [205]      |
|                  | Eritoran          | TLR4 antagonist                                                                      |                      | [206,208] |

4.1 Micronutrients:

These include trace elements, polyunsaturated fatty acids (PUFAs) and vitamins. Zinc is an indispensable trace element involved in gene expression, protein folding, enzymatic reactions, and many physiological processes [120]. Indeed, the multifunctional effects of Zinc are cell specific and many proteins bind to zinc through their Zinc finger motifs [121]. In combating SARS-CoV-2
viremia and its associated cytokine storm, Zinc plays a major role in decreasing oxidative stress and optimizing immune function [122].

Zinc modulates the activities of immune cells. As a signalling molecule it triggers several cascades [122]. It is involved in the regulation of lipopolysaccharide (LPS) signalling through the TLR-4 receptor in monocytes/macrophages and dendritic cells (DCs) of the innate immune system. In the adaptive immune system, zinc is involved in the T Cell Receptor (TCR) signalling through the recruitment of lymphocyte-specific protein tyrosine kinase (Lck) to the TCR complex, and it is also a regulator of the activity of enzymes of apoptotic signal transduction of B cells function [122, 123]. Studies have shown that zinc modulates the response of B-cells (antibody production), monocytes, NK cells, neutrophils, and lymphocyte development including mediating the killing of viruses [124].

Zinc deficiency triggers the release of cytokines such as IL-1β, IL-2, IL-6, and TNF-α which in turn triggers the expression of cellular zinc transporters [122]. Conversely, zinc supplementation alters plasma cytokines in a dose-dependent manner [125]. It causes a down regulation of pro-inflammatory cytokines due to the decreased gene expression of TNF-α, IL-1β, and IL-8 [126].

In the treatment of COVID-19, zinc supplementation has proved to be important due to the direct antiviral and immunomodulatory properties of the micronutrient. It is beneficial for most of the population especially those with suboptimal zinc status [127]. Other trace elements that play an essential role in the management of cytokine storms include copper, iron, magnesium, and selenium [128,129,130].

4.2 Polyunsaturated fatty acids (PUFAs) and Butyrate:

PUFAs such as Omega-3 fatty acid can be found in fish, seafoods, and plant oils such as soybean, and canola oils. Omega-3 fatty acids are known to modulate monocyte and lymphocyte functions and modify host immunity during an inflammatory disease [131,132]. Omega-3 fatty acids consist of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) and they have direct effect on the immune response to viral infections [128,133].

The conversion of Omega-3 fatty acid by lipoxygenase to lipids mediators such as lipoxins, resolvins, and protectins facilitates a dual role of promoting pro-resolution of inflammation and antiinflammation. [134]. The programmed resolution of acute inflammation is by reducing the infiltration of neutrophil, increasing the recruitment of monocytes, and activating the macrophages to consume dead neutrophils [134,135]. Consequently, after a high dose Omega-3 fatty acids supplementation, there are decreased plasma levels of both IL-6 and IL-1β [103]. This anti-inflammatory property makes PUFAs useful in the prevention and treatment of COVID-19 cytokine storm [136].

Butyrate is a short chain fatty acid synthesized by intestinal microbiota as a product of lactic acid fermentation, and it serves as a source of energy for the intestinal epithelial cells. It also enhances the protection of the epithelium barrier through its anti-inflammatory activities [137]. By the inhibition of NFκB activation and the degradation of the I-kappa B alpha (IκBa) protein, butyrate suppresses the production of IL-12. It also suppressed the release of other pro-inflammatory cytokines such as IL-2 and IFN-γ in anti-CD3-stimulated peripheral blood mononuclear cells [138, 139]. Butyrate also enhances the production of anti-inflammatory cytokines, IL-10, and IL-4 [138]. Data from randomized control trials, suggests that the use of probiotic strains, holds good promise in the prevention of cytokine storms in COVID 19 patients [140].
4.3 Vitamins:

These are known to have immunomodulatory, anti-viral, and antioxidant properties [141]. Vitamin C is an essential micronutrient that modulates both innate and adaptive immune functions. Through the stimulation of p38 mitogen-activated protein kinase, vitamin C inhibits TNF-mediated activation of NFκB by the phosphorylation of IkBα [142].

A dietary supplementation of vitamin C significantly decreases the mRNA expression of pro-inflammatory cytokines and 70 kilodalton heat shock protein (HSP70) [143]. Also, the intravenous administration of vitamin C in high doses can ameliorate the neutrophil-related cytokine storm in the patients with COVID-19 [142,143]. Vitamin C also causes increased production of IFN-1 which SARS-CoV-2 suppresses [7,143]. Type I IFN activates the NK cell through both direct and indirect pathways [144,145].

Vitamin D has also been shown to suppress cytokine production in COVID-19 patients. Vitamin D binds with the vitamin D receptor (VDR) on Th17 cells and suppresses the production of IL-17 production by inducing C/EBP homologous protein (CHOP) expression. Consequently, the recruitment of neutrophil is impaired [144,146].

4.4 Phytochemicals and Plant extracts:

The extracts of a plethora of plants such as fruits, herbs, and spices can produce anti-inflammatory activities. For instance, the extract of *Echinacea purpurea* has been proven to stimulate phagocytosis in macrophages and inhibit the release of TNF-α. It also acts as an agonist against cannabinoid B2 receptor, trigger NK cells, and increase leucocyte circulation [147]. In a double-blind study, *Camellia sinensis* (green tea) extract reportedly reduced clinical symptoms of flu infection and promoted γδ T lymphocyte functions [148]. *Echium amoenum* (Boraginaceae) extract act on the macrophages to reduce iNOS and COX2 enzymes as well as IL-1β, IL-6, and TNF-α cytokine levels [149]. The extracts of plants such as *Abelmoschus esculentus* (Okra) and *Andrographis paniculata* have been predicted to be stimulators of the KIR2DS2 and KIR2DS4 receptors of NK cells respectively [37,150]. The stimulation of these activating receptors which engage the DAP12-ZAP 70/Syk ITAM-dependent signalling pathway would prevent cytokine storm by reducing the viral load [36].

Natural compounds such as resveratrol, kaempferol, diosmetin, naringenin, capsaiacin, apigenin, chrysin, quercetin, and luteolin can reduce the expression of IL-6, TNF-alpha, cyclooxygenase-2 (COX2), or inducible nitric oxide synthase (iNOS). They can also increase the expression of anti-inflammatory cytokines such as IL-10 [151]. Dietary polyphenolic compounds such as flavonoids have been shown to have beneficial effects on host defense reactions, and inhibit the transcription factor, NF-kB from producing pro-inflammatory cytokines [152,153]

4.5 Interferons:

Interferon Lambda (IFN-λ) is a type III interferon with an established antiviral activity in the epithelial cells of the respiratory tract [154]. In nature, Type III interferons act as a first line of defence against viruses. The production of IFN-λ is induced because of pathogen identification through the pattern recognition receptors (PRR) [155]. The receptors of type III interferon are expressed on all epithelial cells. Hence, they are found prominently in the respiratory, gastrointestinal, and reproductive tracts [156,157].

IFN-λ binds to IFN-λ receptor 1 (IFNLR1) with a high affinity and recruits its subunit, IL10Rb [158]. The complex formed transduces signals through the JAK-STAT pathway which culminates
in the expression of hundreds of IFN-stimulated genes (ISG) such as NF-κB [155]. Consequently, IFN-λ resolves inflammation through the suppression of neutrophil infiltration to the epithelial cells. IFN-λ also suppresses IL-1β production and reduces the activity of IFN-αβ thereby downplaying immune-response in inflammation [159].

With these anti-inflammatory properties, IFN-λ has the therapeutic potential to combat neutrophil-related cytokine storms [160]. The early administration of IFN-λ as an immunomodulator during the low viral titre stage of coronavirus infection recorded considerable success in clinical therapy. Similarly, some research work has indicated considerable success in the use of IFN-λ in combating the COVID 19. Due to the promise it has shown, IFN-λ has been approved by WHO for the management of COVID-19 patients [154].

4.6 Interleukin 6 Inhibitors:

They block the pro-inflammatory activity of IL-6 which is a key cytokine in severe COPVID-19. Sarilumab and Tocilizumab are human monoclonal antibodies that inhibit IL-6 signaling by binding to IL-6 receptor which is responsible for processes such as activation of T-cells, stimulation of immunoglobulin secretion, proliferation of hematopoietic cell, and differentiation stimulation [68].

Tocilizumab interacts with both transmembrane and soluble forms of IL-6 receptors, thereby blocking the transduction of signals that activate immune response [68]. Tocilizumab has been recommended for patients with severe COVID-19 conditions showing extensive bilateral lung lesions and high IL-6 levels [161,162]. A retrospective examination of 20 COVID-19 cases revealed that Tocilizumab decreased fever and lung lesion opacity and improved the percentage of lymphocyte in peripheral blood [163]. However, there are documented reports of Tocilizumab linked with increased chances of developing opportunistic infections such as tuberculosis, fungal, or other viral infections resulting from the use of IL-6 monoclonal antibodies for the treatment of rheumatoid arthritis [164].

4.7 Interleukin 1 Receptor antagonists:

These are blockers of IL-1 receptors. The pro-inflammatory properties of IL-1 dominate the innate immunity and are closely linked to damaging inflammation. A study revealed that the main inflammatory cells found in the bronchoalveolar fluids and lung tissues of COVID-19 patients are the highly inflammatory pro-fibrosing monocyte-derived macrophages [165]. This shows that IL-1α and IL-1β which are two major paracrine and juxtacrine stimulatory cytokines of monocyte-macrophagic cells are good targets for combating hypercytokinemia. The management of cytokine storm resulting from infection has been meticulously studied by testing the activities of agonists of IL-1 cytokines that are produced during infection. Inhibition of IL-1β, a cytokine of the IL-1 family produced alongside IL-33 and IL-18 during infection by Anakinra has considerably reduced cytokine storm [165]. It is a human recombinant monoclonal body antagonist that binds to IL-1R1 receptor is shown efficacy in the treatment of COVID-19 hypercytokinemia [166]. Investigation on some patients with moderate to severe COVID-19 pneumonia treated with Anakinra showed good clinical and biological outcomes [167,168].

4.8 TNF blocker:

These are agents that block the TNF signalling pathway and consequently suppress hyperinflammation. Anti-TNF therapies have been proven to suppress inflammation in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease [168]. Based
on the documented evidence of its effects, TNF-inhibitors could combat cytokine storm in COVID-19 [168,169,170].

Several natural compounds have also been shown to inhibit TNF production. They include curcumin from turmeric and catechins from green tea [171,172]. One major advantage TNF inhibitors have over cytokine blockers are that they downregulate the expression of several other pro-inflammatory mediators such as IL-1, IL-6, and Granulocyte-macrophage colony-stimulating factor (GM-CSF) as well as downregulate clotting markers such as DD and pro-thrombin fragments [173]. However, there are safety concerns about secondary bacterial infection following the administration of TNF inhibitors [174].

4.9 Sphingosine-1-phosphate receptor 1 (S1PR1) agonists:

Sphingosine-1-phosphate receptors, a group of G-protein-coupled receptors (GPCRs) to which the biologically active lipid called sphingosine 1-phosphate (S1P) have strong affinity, are sub-divided into: S1PR1, S1PR2, S1PR3, S1PR4 and S1PR5 [175]. S1P acts as signaling molecules for specific targets and their upregulation could serve as potential targets in combating hyperinflammation associated with SARS-CoV-2 infection [176,177]. Specifically, S1PR1 abundantly found on endothelial cells plays two important roles: (a) modulation of immune responses through the regulation of the maturation, migration, and trafficking of lymphocytes [178,179] (b) protection of the vascular endothelium against infection by regulating the vascular maturation, migration, cytoskeletal structure, and capillary-like network formation of endothelial cells [180,181]. The use of S1PR1 signaling can significantly reduce the immunopathologies associated with cytokine storm. This is because the treatment with S1PR1 ligands has a profound anti-inflammatory effect. Activated by phosphorylation, S1PR1 ligands bind to the S1P1 receptor inhibiting the release of certain lymphoid cells, suppress excessive cytokine production, and consequently reduce immune-mediated pulmonary injury [182,183].

Fingolimod is an approved agonist of S1P1, S1P3, S1P4 and S1P5 receptors. The oral administration of Fingolimod in COVID-19 patients stabilized the pulmonary endothelial barrier, decreased the inflammatory infiltrate, and reduced histopathologies associated with ARDS [176,184]. Also, CYM5442, a S1P1R analog significantly reduced hyperinflammation in H1N1 induced mice and improved survival. It has been suggested it is used as an adjunctive therapy in battling COVID-19 [176].

4.10 Janus kinase (JAK) inhibitors:

IL-1 and IL-6 signalling are critical to cytokine storms in COVID-19 patients. JAK inhibitors have dual therapeutic potential [185]. They have antiviral effect by blocking viral endocytosis, and they also block multiple pro-inflammatory cytokines activation [185]. A known example is Baricitinib which is a numb-associated kinase (NAK) inhibitor (a JAK1/2 inhibitor). It also inhibits other enzymes such as Tyrosine Kinase 2 and JAK3 [186].

Baricitinib has a high affinity for a clathrin-mediated viral endocytosis regulator, AP2-associated protein kinase - 1 (AAK1), which is expressed in lung AT2 alveolar epithelial cells [187]. The binding of Baricitinib to AAK1 prevent SARS-CoV-2 viral entry into the AT2 alveolar epithelial cells [188]. In an open-labeled investigation, patients administered Baricitinib along with existing therapies for 2 weeks significantly showed improvement in fever, oxygen saturation, partial pressure of arterial oxygen/percentage of inspired oxygen ratio, C-reactive protein, and early warning scores [188].
Another example of JAK inhibitors is Pacritinib which is under investigation. It is a JAK2 and Interleukin-1 receptor-associated kinase 1 (IRAK1) inhibitor that could mitigate the effects of IL-1 and IL-6, and macrophage activation syndrome [189].

4.11 Hydroxychloroquine:

This is used for the treatment of rheumatoid arthritis, malaria, and the autoimmune disease, Lupus [190]. Quinoline which is a component of HCQ is a potential immunomodulator that has the ability to reduce the generation of proinflammatory cytokines implicated in hypercytokinemia such as IL-1, IL-6, TNF-α and IFN-α by inhibiting the expression of MHC II, antigen processing, immune activation through TLR signaling, and the cyclic GMP–AMP synthase (cGAS) stimulation of interferon genes in T-cells [190]. HCQ increases endosomal pH inhibiting intracellular viral activity, and its presentation on the MHC 1 protein [7].

Hydroxychloroquine (HCQ) shows several potential effects against COVID-19 disease during the early stages, and its prompt administration is a key to the prevention of disease progression and severity [191].

4.12 Macrolides

These are antibiotics which have immunomodulatory properties such as neutrophil activation and clearance through apoptosis, prevention of pro-inflammatory cytokine released by immune cells, modulation of macrophage differentiation, inhibition of mucus, etc [192]. Macrolides have been suggested for use in controlling hypercytokinemia in influenza infections [193]. Chronic inflammation of the lung parenchyma is characterized by an elevation of alveolar macrophages, Th1 and Th17 T-cells, neutrophils, and innate lymphoid cells. There is also an elevation of pro-inflammatory cytokines elevated IL-1β, IL-4, IL-8, and TNF-α levels in their blood [194].

Azithromycin is a macrolide that has been used frequently in combination with other therapies for the treatment of COVID-19. Beyond treating bacterial infections, Azithromycin and Clarithromycin have been shown to decrease neutrophil count and reduce neutrophil elastase concentration, IL-4, IL-8, TNF-α, INF -γ, C- reactive protein, calprotectin, myeloperoxidase (MPO) and serum amyloid A in the blood, through various immunological mechanisms [195,196]. In a randomized clinical trial conducted in subjects with chronic obstructive pulmonary disease, (COPD) Azithromycin decreased white blood cell and platelet counts, the concentrations of C-reactive protein, IL-8, E-selectin, and lactoferrin in the blood [197]. Clarithromycin and Erythromycin have also been shown to significantly decrease total cell and neutrophil count, inhibit neutrophil chemotaxis, and decrease neutrophil elastase concentration [198,199].

4.13 Transfer Factors (TF)

These are low molecular weight polypeptides fractions obtained from natural sources such as colostrum, egg yolks, or porcine spleen [200]. Specifically, it is derived from T-lymphocytes and the immunomodulatory properties of TF have been well documented. It has been used to successfully combat viral infections [201]. TF increases innate defence by the activation of NK cells against viruses. TF can decrease IL-6 production and stimulate the release of IL-10. Thus, TF can potentially combat immune hyperresponsiveness and hyperinflammatory associated with COVID-19 [200,202].

4.14 Corticosteroids and other agents:

Corticosteroids such as Methylprednisolone and Dexamethasone have been shown to reduce the risk of death in COVID-19 patients with ARDS [203,24]. Methylprednisolone has been found to
decrease the risk of death in ARDS patients in a clinical study conducted in China [203]. Dexamethasone has also been shown to reduce the risk of hypercytokinemia-related deaths by one-third in ventilated COVID-19 patients [205]. Glucocorticosteroids have been used for lung inflammation during SARS and MERS epidemics but produced deleterious effects such as prolonged viral presence (due to immunosuppression) and induced diabetes [205]. The WHO has cautioned that routine use of corticosteroid for COVID-19 should be avoided due to exacerbation of problems such as asthma and cardiogenic shock. The WHO advised that the risk and benefit analysis should be done for individual patients before administering corticosteroids [205].

Unlike corticosteroids, Ulinastatin is not an immunosuppressant. Ulinastatin is a widely used clinical drug to combat inflammation. It increases IL-10 level (anti-inflammatory factor) and reduces the levels of TNF-α, IL-6, and IFN-γ, (proinflammatory factors). Therefore, it holds great prospects in the treatment of COVID-19 [206].

In infections with pathogenic human coronaviruses, there is an accumulation of oxidized phospholipids (OxPL) in the pulmonary tissues [207,208]. The OxPL stimulates the Toll-like receptor 4 (TLR4) which in turn increases the production of cytokines/chemokines in macrophages of the lungs. Eritoran is a Toll-like receptor 4 (TLR4) antagonist and consequently it decreases the secretion of OxPL, pro-inflammatory cytokines, and chemokines. Along with other OxPL inhibitors, Eritoran is a potential therapeutic candidate for COVID-19 disease [207,208].

**Conclusion**

The SARS COV-2 induced cytokine storm is characterized by immune dysregulation and hyperinflammation. It is also associated with tissue damage, multi-organ failure, and death. The early diagnosis and aggressive mitigation of cytokine storm is important to effectively reduce COVID-19 morbidities and mortalities. Clinical data suggests that certain markers of hyperinflammation have been proven to be accurate and reliable in distinguishing between mild and severe cases of COVID-19. Laboratory tests using these markers (on the first day of hospitalization and a few days after) would prove useful in the clinical evaluation of the status and the progression of the disease. For would be severe cases, a quick and aggressive administration of the potential therapeutic agents discussed would prevent or attenuate the effect of the advancing cytokine storm. A cocktail of these agents would directly or indirectly combat the surge of pro-inflammatory cytokines and ultimately avert the associated pathologies.

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REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733. doi: 10.1056/NEJMoa2001017.
2. Worldometer (2020). COVID-19 CORONAVIRUS PANDEMIC. Available at https://www.worldometers.info/coronavirus/ Accessed 27th October 2020
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, YU T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7.
4. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev. 2020 Jun;53:66-70. doi: 10.1016/j.cytogfr.2020.05.002.

5. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424-432. doi: 10.1002/jmv.25685

6. Ferreira AO, Polonini HC, Dijkers ECF. Postulated Adjuvant Therapeutic Strategies for COVID-19. J Pers Med. 2020 Aug 5;10(3):80. doi: 10.3390/jpm10030080.

7. Rowaiye AB, Onuh OA, Oli AN, Okpalefe OA, Oni S, Nwankwo EJ. The pandemic COVID-19: a tale of viremia, cellular oxidation and immune dysfunction. Pan Afr Med J. 2020 Jul 15;36:188. doi: 10.11604/pamj.2020.36.188.23476.

8. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, Zhi L, Wei H, Zhang Z, Qiu Y, Wang J, Wang A. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020 Jun;53:38-42. doi: 10.1016/j.cytogfr.2020.04.002.

9. Eccleston-Turner M, Phelan A, Katz R. Preparing for the Next Pandemic - The WHO's Global Influenza Strategy. N Engl J Med. 2019 Dec 5;381(23):2192-2194. doi: 10.1056/NEJMp1905224.

10. Teijaro JR, Walsh KB, Rice S, Rosen H, Oldstone MB. Mapping the innate signaling cascade essential for cytokine storm during influenza virus infection. Proc Natl Acad Sci U S A. 2014 Mar 11;111(10):3799-804. doi: 10.1073/pnas.1400593111.

11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0.

12. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH; , for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM). A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020 Feb 6;7(1):4. doi: 10.1186/s40779-020-0233-6.

13. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012 Mar;76(1):16-32. doi: 10.1128/MMBR.05015-11.

14. Ciavarella C, Motta I, Valente S, Pasquinelli G. Pharmacological (or Synthetic) and Nutritional Agonists of PPAR-γ as Candidates for Cytokine Storm Modulation in COVID-19 Disease. Molecules. 2020 Apr 29;25(9):2076. doi: 10.3390/molecules25092076.

15. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. J Infect. 2020 Jun;80(6):607-613. doi: 10.1016/j.jinf.2020.03.037.

16. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. Cell Host Microbe. 2016 Feb 10;19(2):181-93. doi: 10.1016/j.chom.2016.01.007.
17. Davidson S, Maini MK, Wack A. Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. J Interferon Cytokine Res. 2015 Apr;35(4):252-64. doi: 10.1089/jir.2014.0227.

18. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. Nat Rev Immunol. 2013 Dec;13(12):875-87. doi: 10.1038/nri3547.

19. Kim ES, Choe PG, Park WB, Oh HS, Kim EJ, Nam EY, Na SH, Kim M, Song KH, Bang JH, Park SW, Kim HB, Kim NJ, Oh MD. Clinical Progression and Cytokine Profiles of Middle East Respiratory Syndrome Coronavirus Infection. J Korean Med Sci. 2016 Nov;31(11):1717-1725. doi: 10.3346/jkms.2016.31.11.1717

20. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052. Epub 2020 Mar 5.

21. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett. 2002 Dec 4;532(1-2):107-10. doi: 10.1016/s0014-5793(02)03640-2. PMID: 12459472.

22. Niu W, Qi Y, Hou S, Zhou W, Qiu C. Correlation of angiotensin-converting enzyme 2 gene polymorphisms with stage 2 hypertension in Han Chinese. Transl Res. 2007 Dec;150(6):374-80. doi: 10.1016/j.trsl.2007.06.002.

23. Chen YY, Liu D, Zhang P, Zhong JC, Zhang CJ, Wu SL, Zhang YQ, Liu GZ, He M, Jin LJ, Yu HM. Impact of ACE2 gene polymorphism on antihypertensive efficacy of ACE inhibitors. J Hum Hypertens. 2016 Dec;30(12):766-771. doi: 10.1038/jhh.2016.24.

24. Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, Bernstein KE, Coffman TM, Chen S, Batlle D. ACE and ACE2 activity in diabetic mice. Diabetes. 2006 Jul;55(7):2132-9. doi: 10.2337/db06-0033.

25. Iwasaki A, Pillai PS. Innate immunity to influenza virus infection. Nat Rev Immunol. 2014 May;14(5):315-28. doi: 10.1038/nri3665.

26. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y. COVID-19: immunopathogenesis and Immunotherapeutics. Signal Transduct Target Ther. 2020 Jul 25;5(1):128. doi: 10.1038/s41392-020-00243-2.

27. Xagorari A, Chличилка К. Toll-like receptors and viruses: induction of innate antiviral immune responses. Open Microbiol J. 2008;2:49-59. doi: 10.2174/1874285800802010049.

28. Wurfel MM, Gordon AC, Holden TD, Radella F, Strout J, Kajikawa O, Ruzinski JT, Rona G, Black RA, Stratton S, Jarvik GP, Hajjar MA, Nickerson DA, Rieder M, Sevransky J, Maloney JP, Moss M, Martin G, Shanholtz C, Garcia JG, Gao L, Brower R, Barnes KC, Walley KR, Russell JA, Martin TR. Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. Am J Respir Crit Care Med. 2008 Oct 1;178(7):710-20. doi: 10.1164/rccm.200803-462OC.

29. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. Annu Rev Immunol. 2014;32:513-45. doi: 10.1146/annurev-immunol-032713-120231.

30. Kawai T, Akira S. Antiviral signaling through pattern recognition receptors. J Biochem. 2007 Feb;141(2):137-45. doi: 10.1093/jb/mvm032.

31. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smaja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020 Jun;178:104791. doi: 10.1016/j.antiviral.2020.104791.
32. Reiter Z. Interferon--a major regulator of natural killer cell-mediated cytotoxicity. J Interferon Res. 1993 Aug;13(4):247-57. doi: 10.1089/jir.1993.13.247.

33. Rowaiye AB, Onuh OA, Oladimeji-Salami JA, Bur D, Njoku M, Ifedilichukwu NH, John CO, Binuyo O, Pius FU. In silico identification of the potential natural inhibitors of SARS-CoV--2 Guanine-N7 methyltransferase. (Preprint). DOI: 10.26434/chemrxiv.12729044

34. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Pére H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Péne F, Marin N, Roche N, Szwebel TA, Merkling SH, Treluyer JM, Veyer D, Mouthon L, Blanc C, Tharaux PL, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kernéis S, Terrier B. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020 Aug 7;369(6504):718-724. doi: 10.1126/science.abc6027

35. Becknell B, Caligiuri MA. Interleukin-2, interleukin-15, and their roles in human natural killer cells. Adv Immunol. 2005;86:209-39. doi: 10.1016/S0065-2776(04)86006-1.

36. Rowaiye AB, Asala T, Oli AN, Uzochukwu IC, Akpa A, Esimone CO. The Activating Receptors of Natural Killer Cells and Their InterSwitching Potentials. Curr Drug Targets. 2020 Sep 10. doi: 10.2174/1389450121666200910160929. Epub ahead of print. PMID: 32914713.

37. Rowaiye AB, Oni S, Uzochukwu IC, Akpa A, Esimone CO. The Structure-Based Virtual Screening for Natural Compounds that Bind with the Activating Receptors of Natural Killer Cells. bioRxiv. 2020 Jan 1.(Preprint) https://www.biorxiv.org/content/10.1101/2020.06.19.160861v1

38. Vandenhoute J, Wouters CH, Matthys P. Natural Killer Cells in Systemic Autoinflammatory Diseases: A Focus on Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome. Front Immunol. 2020 Jan 15;10:3089. doi: 10.3389/fimmu.2019.03089.

39. Jenkins MR, Rudd-Schmidt JA, Lopez JA, Ramsbottom KM, Mannerling SI, Andrews DM, Voskoboinik I, Trapani JA. Failed CTL/NK cell killing and cytokine hypersecretion are directly linked through prolonged synapse time. J Exp Med. 2015 Mar 9;212(3):307-17. doi: 10.1084/jem.20140964.

40. Brisse E, Wouters CH, Matthys P. Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities. Br J Haematol. 2016 Jul;174(2):203-17. doi: 10.1111/bjh.14147.

41. Sepulveda FE, Debeurme F, Ménasché G, Kurowska M, Côte M, Pachlopni Schmid J, Fischer A, de Saint Basile G. Distinct severity of HLH in both human and murine mutants with complete loss of cytotoxic effector PRF1, RAB27A, and STX11. Blood. 2013 Jan 24;121(4):595-603. doi: 10.1182/blood-2012-07-440339.

42. Trapani JA, Voskoboinik I, Jenkins MR. Perforin-dependent cytotoxicity: 'Kiss of death' or prolonged embrace with darker elocation? Oncoimmunology. 2015 Apr 14;4(9):e1036215. doi: 10.1080/2162402X.2015.1036215.

43. Canna SW, Behrens EM. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am. 2012 Apr;59(2):329-44. doi: 10.1016/j.pcl.2012.03.002.

44. Voskoboinik I, Trapani JA. Perforinopathy: a spectrum of human immune disease caused by defective perforin delivery or function. Front Immunol. 2013 Dec 12;4:441. doi: 10.3389/fimmu.2013.00441.

45. Rex J, Lutz A, Faletti LE, Albrecht U, Thomas M, Bode JG, Borner C, Sawodny O, Merfort I. IL-1β and TNFα Differentially Influence NF-κB Activity and FasL-Induced
Apoptosis in Primary Murine Hepatocytes During LPS-Induced Inflammation. Front Physiol. 2019 Feb 20;10:117. doi: 10.3389/fphys.2019.00117.

46. Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer. 2013 Aug 2;12:86. doi: 10.1186/1476-4598-12-86. PMID: 23915189; PMCID: PMC3750319.

47. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Sig Transduct Target Ther 2, 17023 (2017). https://doi.org/10.1038/sigtrans.2017.23

48. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The Role of Interleukin 6 During Viral Infections. Front Microbiol. 2019 May 10;10:1057. doi: 10.3389/fmicb.2019.01057.

49. Lacroix M, Rousseau F, Guilhot F, Malinge P, Magistrelli G, Herren S, Jones SA, Jones GW, Scheller J, Lissilaa R, Kosco-Vilbois M, Johnson Z, Buatois V, Ferlin W. Novel Insights into Interleukin 6 (IL-6) Cis- and Trans-signaling Pathways by Differentially Manipulating the Assembly of the IL-6 Signaling Complex. J Biol Chem. 2015 Nov 6;290(45):26943-53. doi: 10.1074/jbc.M115.682138.

50. Tamura K, Kanazawa T, Tsukada S, Kobayashi T, Kawamura M, Morikawa A. Increased serum monocyte chemoattractant protein-1, macrophage inflammatory protein-1beta, and interleukin-8 concentrations in hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008 Nov;51(5):662-8. doi: 10.1002/pbc.21660.

51. Takada H, Takahata Y, Nomura A, Ohga S, Mizuno Y, Hara T. Increased serum levels of interferon-gamma-inducible protein 10 and monokine induced by gamma interferon in patients with haemophagocytic lymphohistiocytosis. Clin Exp Immunol. 2003 Sep;133(3):448-53. doi: 10.1046/j.1365-2249.2003.02237.x.

52. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, Ohta H, Fujisaki H, Kobayashi M, Sakata N, Kawa-Ha K, Okada S, Tawa A. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood. 1997 Jun 1;89(11):4100-3.

53. Briso EM, Dizen O, Rincon M. Cutting edge: soluble IL-6R is produced by IL-6R ectodomain shedding in activated CD4 T cells. J Immunol. 2008 Jun 1;180(11):7102-6. doi: 10.4049/jimmunol.180.11.7102.

54. Calabrese LH, Rose-John S. IL-6 biology: implications for clinical targeting in rheumatic disease. Nat Rev Rheumatol. 2014 Dec;10(12):720-7. doi: 10.1038/nrrheum.2014.127. Epub 2014 Aug 19. Erratum in: Nat Rev Rheumatol. 2014 Dec;10(12):i.

55. Ott LW, Resing KA, Sizemore AW, Heyen JW, Cocklin RR, Pedrick NM, Woods HC, Chen JY, Goebi MG, Witzmann FA, Harrington MA. Tumor Necrosis Factor-alpha- and interleukin-1-induced cellular responses: coupling proteomic and genomic information. J Proteome Res. 2007 Jun;6(6):2176-85. doi: 10.1021/pr060651l.

56. Tsang K, Zhong NS. SARS: pharmacotherapy. Respirology. 2003 Nov;8 Suppl:S25-30. doi: 10.1046/j.1440-1843.2003.00525.x.

57. Chien JY, Hsueh PR, Cheng WC, Yu CJ, Yang PC. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. Respirology. 2006 Nov;11(6):715-22. doi: 10.1111/j.1440-1843.2006.00942.x.

58. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
59. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: The anger of inflammation. Cytokine. 2020 Sep;133:155151. doi: 10.1016/j.cyto.2020.155151.

60. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, Sun R, Tian Z, Xu X, Wei H. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. National Science Review, 2020 June;7(6):998–1002. https://doi.org/10.1093/nsr/nwaa041

61. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, Wang F, Li G, Li Y, Xing L, Peng L, Yang M, Cao M, Zheng H, Wu W, Zou R, Li D, Xu Z, Wang H, Zhang M, Zhang Z, Gao GF, Jiang C, Liu L, Liu Y. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J Allergy Clin Immunol. 2020 Jul;146(1):119-127.e4. doi: 10.1016/j.jaci.2020.04.027.

62. Herrero R, Sanchez G, Lorente JA. New insights into the mechanisms of pulmonary edema in acute lung injury. Ann Transl Med. 2018 Jan;6(2):32. doi: 10.21037/atm.2017.12.18.

63. Wee JL, Greenwood DL, Han X, Scheerlinck JP. Inflammatory cytokines IL-6 and TNF-α regulate lymphocyte trafficking through the local lymph node. Vet Immunol Immunopathol. 2011 Nov 15;144(1-2):95-103. doi: 10.1016/j.vetimm.2011.07.007.

64. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, Su X, Cao B. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020 May 9;395(10235):1517-1520. doi: 10.1016/S0140-6736(20)30920-X.

65. Maeda K, Baba Y, Nagai Y, Miyazaki K, Malykhin A, Nakamura K, Kincade PW, Sakaguchi N, Coggeshall KM. IL-6 blocks a discrete early step in lymphopoiesis. Blood. 2005 Aug 1;106(3):879-85. doi: 10.1182/blood-2005-02-0456.

66. Maeda K, Malykhin A, Teague-Weber BN, Sun XH, Farris AD, Coggeshall KM. Interleukin-6 aborts lymphopoiesis and elevates production of myeloid cells in systemic lupus erythematosus-prone B6.Sle1.Yaa animals. Blood. 2009 May 7;113(19):4534-40. doi: 10.1182/blood-2008-12-192559.

67. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. J Immunother Cancer. 2018 Jun;6(1):56. doi: 10.1186/s40425-018-0343-9.

68. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016 Jul;8(8):959-70. doi: 10.2217/imt-2016-0020.

69. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015 May;16(5):448-57. doi: 10.1038/ni.3153.

70. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Orague EE, McCabe C, Welch SB, Whitney A, O’Gara P, Nadel S, Relman DA, Harding SE, Levin M. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004 Jan 17;363(9404):203-9. doi: 10.1016/S0140-6736(03)15326-3.

71. Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, Nuccetelli M, Vadacca GB, Guidetti D, Vercelli A, Magnacavallo A, Bernardini S, Terracciano C. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clin Chim Acta. 2020 Oct;509:135-138. doi: 10.1016/j.cca.2020.06.012.

72. Potempa LA, Rajab IM, Hart PC, Bordon J, Fernandez-Botran R. Insights into the Use of C-Reactive Protein as a Diagnostic Index of Disease Severity in COVID-19 Infections. Am J Trop Med Hyg. 2020 Aug;103(2):561-563. doi: 10.4269/ajtmh.20-0473.

73. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014 Apr;6(4):748-73. doi: 10.1039/c3mt00347g.
74. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017 Nov 1;29(9):401-409. doi: 10.1093/intimm/dxx031.

75. Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. Rev Panam Salud Publica. 2020 Jun 1;44:e72. doi: 10.26633/RPSP.2020.72.

76. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF, Zborowski M, Yazer M, Chalmers JJ. Hyperferritinemia in critically ill COVID-19 patients - Is ferritin the product of inflammation or a pathogenic mediator? Clin Chim Acta. 2020 Oct;509:249-251. doi: 10.1016/j.cca.2020.06.033.

77. Shaw TY, Schivo M. Weathering a Cytokine Storm: A Case of EBV-Induced Hemophagocytic Lymphohistiocytosis. J Investig Med High Impact Case Rep. 2016 May 2;4(2):2324709616647409. doi: 10.1177/2324709616647409.

78. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. Chest. 2002 Apr;121(4):1262-8. doi: 10.1378/chest.121.4.1262.

79. Magro G. Cytokine Storm: Is it the only major death factor in COVID-19 patients? Coagulation role. Med Hypotheses. 2020 Sep;142:109829. doi: 10.1016/j.mehy.2020.109829.

80. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Jun;18(6):1324-1329. doi: 10.1111/jth.14859.

81. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, Tang L, Luo Q, Xu M, Yang L, Huang G, Liu X, Tang J. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis. 2020 Oct;50(3):548-557. doi: 10.1007/s11239-020-02171-y.

82. Chhetri S, Khamis F, Pandak N, Al Khalili H, Said E, Petersen E. A fatal case of COVID-19 due to metabolic acidosis following dysregulate inflammatory response (cytokine storm). IDCases. 2020 May 19;21:e00829. doi: 10.1101/j.idcr.2020.e00829.

83. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci. 2019 Jul 6;20(13):3328. doi: 10.3390/ijms20133328.

84. Erra Díaz F, Dantas E, Geffner J. Unravelling the Interplay between Extracellular Acidosis and Immune Cells. Mediators Inflamm. 2018 Dec 30;2018:1218297. doi: 10.1155/2018/1218297.

85. Wu MY, Yao L, Wang Y, Zhu XY, Wang XF, Tang PJ, Chen C. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. Respir Res. 2020 Jul 6;21(1):171. doi: 10.1186/s12931-020-01427-8.

86. Nehring SM, Goyal A, Bansal P, et al. C Reactive Protein. [Updated 2020 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441843/ Accessed 4th Nov, 2020.

87. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020 Jun;18(7):1561-1566. doi: 10.1016/j.cgh.2020.04.002.

88. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. United European Gastroenterol J. 2020 Jun;8(5):509-519. doi: 10.1177/2050640620924157.
90. Bertolini A, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, Fiorotto R, Jonker JW, Strazzabosco M, Verkade HJ, Peserico G. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. Hepatology. 2020 Jul 23;10.1002/hep.31480. doi: 10.1002/hep.31480.

91. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020 May;40(5):998-1004. doi: 10.1111/liv.14435.

92. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. J Hepatol. 2020 Sep;73(3):566-574. doi: 10.1016/j.jhep.2020.04.006.

93. Morgan DB, Carver ME, Payne RB. Plasma creatinine and urea: creatinine ratio in patients with raised plasma urea. Br Med J. 1977 Oct 8;2(6092):929-32. doi: 10.1136/bmj.2.6092.929.

94. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020 May;5(5):428-430. doi: 10.1016/S2468-1253(20)30057-1.

95. Gulen M, Satar S. Uncommon presentation of COVID-19: Gastrointestinal bleeding. Clin Res Hepatol Gastroenterol. 2020 Sep;44(4):e72-e76. doi: 10.1016/j.clinre.2020.05.001.

96. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020 May;51(9):843-851. doi: 10.1111/apt.15731.

97. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5.

98. Cheng A, Hu L, Wang Y, Huang L, Zhao L, Zhang C, Liu X, Xu R, Liu F, Li J, Ye D, Wang T, Lv Y, Liu Q. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents. 2020 Sep;56(3):106110. doi: 10.1016/j.ijantimicag.2020.106110.

99. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Van Oekelen O, Rahman A, Kovatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnajtic S. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020 Oct;26(10):1636-1643. doi: 10.1038/s41591-020-1051-9.

100. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020 Dec;9(1):1123-1130. doi: 10.1080/22221751.2020.1770129.

101. O'Neill CM, Lu C, Corbin KL, Sharma PR, Dula SB, Carter JD, Ramadan JW, Xin W, Lee JK, Nunnemaker CS. Circulating levels of IL-1B+IL-6 cause ER stress and dysfunction in islets from prediabetic male mice. Endocrinology. 2013 Sep;154(9):3077-88. doi: 10.1210/en.2012-2138.

102. Grifoni E, Valoriannia A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, Vannucchi V, Moroni F, Pelagatti L, Tarquini R, Landini G, Vanni S, Masotti L. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020 Sep;81(3):452-482. doi: 10.1016/j.jinf.2020.06.008.

103. Mandel M, Harari G, Gurevich M, Achiron A. Cytokine prediction of mortality in COVID19 patients. Cytokine. 2020 Dec;134:155190. doi: 10.1016/j.cyto.2020.155190.
104. Li G, Wu W, Zhang X, Huang Y, Wen Y, Li X, Gao R. Serum levels of tumor necrosis factor alpha in patients with IgA nephropathy are closely associated with disease severity. BMC Nephrol. 2018 Nov 14;19(1):326. doi: 10.1186/s12882-018-1069-0.

105. Wu D, Dinh TL, Bausk BP, Walt DR. Long-Term Measurements of Human Inflammatory Cytokines Reveal Complex Baseline Variations between Individuals. Am J Pathol. 2017 Dec;187(12):2620-2626. doi: 10.1016/j.ajpath.2017.08.007.

106. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to-lymphocyte is associated with severe COVID-19. Epidemiol Infect. 2020 Jul 9;148:e139. doi: 10.1017/S0950268820001557.

107. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, Wei S, Deng Y, Liu J, Liu HG, Yang M, Hu Y. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020 May 5;133(9):1032-1038. doi: 10.1097/CMD.0000000000000775.

108. Tan A, Sullenbarger B, Prakash R, McDaniel JC. Supplementation with eicosapentaenoic acid and docosahexaenoic acid reduces high levels of circulating proinflammatory cytokines in aging adults: A randomized, controlled study. Prostaglandins Leukot Essent Fatty Acids. 2018 May;132:23-29. doi: 10.1016/j.plefa.2018.03.010.

109. He Z, Zhao C, Dong Q, Zhuang H, Song S, Peng G, Dwyer DE. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. Int J Infect Dis. 2005 Nov;9(6):323-30. doi: 10.1016/j.ijid.2004.07.014.

110. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020 Jun;99(6):1205-1208. doi: 10.1007/s00277-020-04019-0.

111. Hottz ED, Bozza FA, Bozza PT. Platelets in Immune Response to Virus and Immunopathology of Viral Infections. Front Med (Lausanne). 2018 Apr 30;5:121. doi: 10.3389/fmed.2018.00121.

112. Rayes J, Bourne JH, Brill A, Watson SP. The dual role of platelet-innate immune cell interactions in thrombo-inflammation. Res Pract Thromb Haemost. 2019 Oct 17;4(1):23-35. doi: 10.1002/rth2.12266.

113. Ito K, Hirao A, Arai F, Matsuoka S, Takubo K, Hamaguchi I, Nomiyama K, Hosokawa K, Sakurada K, Nakagata N, Ikeda Y, Mak TW, Suda T. Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. Nature. 2004 Oct 21;431(7011):997-1002. doi: 10.1038/nature02989.

114. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020 Aug;81(2):e16-e25. doi: 10.1016/j.jinf.2020.04.021.

115. Stahl EC, Brown BN. Cell Therapy Strategies to Combat Immunosenesence. Organogenesis. 2015;11(4):159-72. doi: 10.1080/15476278.2015.1120046.

116. Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, Gurram PR, Stevens RW, Razonable RR. Treatment Considerations for COVID-19: A Critical Review of the Evidence (or Lack Thereof). Mayo Clin Proc. 2020 Jul;95(7):1454-1466. doi: 10.1016/j.mayocp.2020.04.027.

117. Chasapis CT, Loutsidou AC, Spiliopoulou CA, Stefanidou ME. Zinc and human health: an update. Arch Toxicol. 2012 Apr;86(4):521-34. doi: 10.1007/s00204-011-0775-1.

118. Cassandri M, Smirnov A, Novelli F, Pitoli C, Agostini M, Malewicz M, Melino G, Raschellà G. Zinc-finger proteins in health and disease. Cell Death Discov. 2017 Nov 13;3:17071. doi: 10.1038/cddiscovery.2017.71.
119. Haase H, Rink L. Functional significance of zinc-related signaling pathways in immune cells. Annu Rev Nutr. 2009;29:133-52. doi: 10.1146/annurev-nutr-080508-141119.

120. Hojyo S, Fukada T. Roles of Zinc Signaling in the Immune System. J Immunol Res. 2016;2016:6762343. doi: 10.1155/2016/6762343.

121. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr. 2007 Oct;98 Suppl 1:S29-35. doi: 10.1017/S0007114507832971.

122. Foster M, Samman S. Zinc and regulation of inflammatory cytokines: implications for cardiometabolic disease. Nutrients. 2012 Jul;4(7):676-94. doi: 10.3390/nu4070676.

123. Prasad AS. Zinc in human health: effect of zinc on immune cells. Mol Med. 2008 May-Jun;14(5-6):353-7. doi: 10.2119/2008-00033.Prasad.

124. Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. Front Immunol. 2020 Jul 10;11:1712. doi: 10.3389/fimmu.2020.01712.

125. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Nutrients. 2020 Apr 23;12(4):1181. doi: 10.3390/nu12041181.

126. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020 Apr 2;12(4):988. doi: 10.3390/nu12040988.

127. Muscogiuri G, Barrea L, Savastano S, Colao A. Nutritional recommendations for CoVID-19 quarantine. Eur J Clin Nutr. 2020 Jun;74(6):850-851. doi: 10.1038/s41430-020-0635-2.

128. Samuchiwal SK, Boyce JA. Role of lipid mediators and control of lymphocyte responses in type 2 immunopathology. J Allergy Clin Immunol. 2018 Apr;141(4):1182-1190. doi: 10.1016/j.jaci.2018.02.006.

129. Innes JK, Calder PC. Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids. 2018 May;132:41-48. doi: 10.1016/j.plefa.2018.03.004.

130. Messina G, Polito R, Monda V, Cipolloni L, Di Nunno N, Di Mizio G, Murabito P, Carotenuto M, Messina A, Pisanelli D, Valenzano A, Cibelli G, Scarinci A, Monda M, Sessa F. Functional Role of Dietary Intervention to Improve the Outcome of COVID-19: A Hypothesis of Work. Int J Mol Sci. 2020 Apr 28;21(9):3104. doi: 10.3390/ijms21093104.

131. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008 May;8(5):349-61. doi: 10.1038/nri2294.

132. Weitzel LR, Mayles WJ, Sandoval PA, Wischmeyer PE. Effects of pharmaconutrients on cellular dysfunction and the microcirculation in critical illness. Curr Opin Anaesthesiol. 2009 Apr;22(2):177-83. doi: 10.1097/AOC.0b013e328328d32f.

133. Szabó Z, Marosvölgyi T, Szabó É, Bai P, Figler M, Verzár Z. The Potential Beneficial Effect of EPA and DHA Supplementation Managing Cytokine Storm in Coronavirus Disease. Front Physiol. 2020 Jun 19;11:752. doi: 10.3389/fphys.2020.00752.

134. Licciardi PV, Wong SS, Tang ML, Karagiannis TC. Epigenome targeting by probiotic metabolites. Gut Pathog. 2010 Dec 21;2(1):24. doi: 10.1186/1757-4749-2-24.

135. Säemann MD, Böhmg GA, Österreicher CH, Burtscher H, Parolini O, Diakos C, Stöckl J, Hörl WH, Zlabinger GJ. Anti-inflammatory effects of sodium butyrate on human...
monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. FASEB J. 2000 Dec;14(15):2380-2. doi: 10.1096/fj.00-0359fje.

136. Segain JP, Raingeard de la Blétière D, Bourreille A, Leray V, Gervois N, Rosales C, Ferrier L, Bonnet C, Blottière HM, Galmiche JP. Butyrate inhibits inflammatory responses through NFκB inhibition: implications for Crohn's disease. Gut. 2000 Sep;47(3):397-403. doi: 10.1136/gut.47.3.397.

137. Baud D, Dimopoulou Agri V, Gibson GR, Reid G, Giannoni E. Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. Front Public Health. 2020 May 8;8:186. doi: 10.3389/fpubh.2020.00186.

138. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. PharmaNutrition. 2020 Jun;12:100190. doi: 10.1016/j.phanu.2020.100190.

139. Bowie AG, O'Neill LA. Vitamin C inhibits NF-kappa B activation by TNF via the activation of p38 mitogen-activated protein kinase. J Immunol. 2000 Dec 15;165(12):7180-8. doi: 10.4049/jimmunol.165.12.7180.

140. Jang IS, Ko YH, Moon YS, Sohn SH. Effects of Vitamin C or E on the Pro-inflammatory Cytokines, Heat Shock Protein 70 and Antioxidant Status in Broiler Chicks under Summer Conditions. Asian-Australas J Anim Sci. 2014 May;27(5):749-56. doi: 10.5713/ajas.2013.13852.

141. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients. 2020 May 19;12(5):1466. doi: 10.3390/nu12051466.

142. Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. BMJ Open. 2020 Jul 8;10(7):e039519. doi: 10.1136/bmjopen-2020-039519.

143. de Melo AF, Homem-de-Mello M. High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection. Crit Care. 2020 Aug 13;24(1):500. doi: 10.1186/s13054-020-03228-3.

144. Stackaruk ML, Lee AJ, Ashkar AA. Type I interferon regulation of natural killer cell function in primary and secondary infections. Expert Rev Vaccines. 2013 Aug;12(8):875-84. doi: 10.1586/14760584.2013.814871.

145. Lee AJ, Mian F, Poznanski SM, Stackaruk M, Chan T, Chew MV, Ashkar AA. Type I Interferon Receptor on NK Cells Negatively Regulates Interferon-γ Production. Front Immunol. 2019 Jun 4;10:1261. doi: 10.3389/fimmu.2019.01261.

146. Chang SH, Chung Y, Dong C. Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression. J Biol Chem. 2010 Dec 10;285(50):38751-5. doi: 10.1074/jbc.C110.185777.

147. Chicca A, Raduner S, Pellati F, Strompen T, Altmann KH, Schoop R, Gertsch J. Synergistic immunomopharmacological effects of N-alkylamides in Echinacea purpurea herbal extracts. Int Immunopharmacol. 2009 Jul;9(7-8):850-8. doi: 10.1016/j.intimp.2009.03.006.

148. Rowe CA, Nantz MP, Bukowski JF, Percival SS. Specific formulation of Camellia sinensis prevents cold and flu symptoms and enhances gamma, delta T cell function: a randomized, double-blind, placebo-controlled study. J Am Coll Nutr. 2007 Oct;26(5):445-52. doi: 10.1080/07315724.2007.10719634.

149. Naseri N, Kalantar K, Amirghofran Z. Anti-inflammatory activity of Echium amoenum extract on macrophages mediated by inhibition of inflammatory mediators and
cytokines expression. Res Pharm Sci. 2018 Feb;13(1):73-81. doi: 10.4103/1735-5362.220970.

150. Rowaiye AB, Olubiyi OO, Bur D, Uzochukwu IC, Akpa A, Esimone CO. In silico screening and molecular dynamic simulation studies of potential small molecule immunomodulators of the KIR2DS2 receptor. bioRxiv. 2020 Jan 1. Preprint. https://www.biorxiv.org/content/10.1101/2020.05.10.087148v1 Accessed 4th Nov. 2020

151. Aravindaram K, Yang NS. Anti-inflammatory plant natural products for cancer therapy. Planta Med. 2010 Aug;76(11):1103-17. doi: 10.1055/s-0030-1249859.

152. Shapiro H, Lev S, Cohen J, Singer P. Polyphenols in the prevention and treatment of sepsis syndromes: rationale and pre-clinical evidence. Nutrition. 2009 Oct;25(10):981-97. doi: 10.1016/j.nut.2009.02.010.

153. Lewicka A, Szymański Ł, Rusiecka K, Kucza A, Jakubczyk A, Zdanowski R, Lewicki S. Supplementation of Plants with Immunomodulatory Properties during Pregnancy and Lactation-Maternal and Offspring Health Effects. Nutrients. 2019 Aug 20;11(8):1958. doi: 10.3390/nu11081958.

154. Broggi A, Ghosh S, Sposito B, Sprefico R, Balzarini F, Lo Cascio A, Clementi N, De Santis M, Mancini N, Granucci F, Zanoni I. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science. 2020 Aug 7;369(6504):706-712. doi: 10.1126/science.abc3545.

155. Syedbasha M, Egli A. Interferon Lambda: Modulating Immunity in Infectious Diseases. Front Immunol. 2017 Feb 28;8:119. doi: 10.3389/fimmu.2017.00119.

156. Kotenko SV, Durbin JE. Contribution of type III interferons to antiviral immunity: location, location, location. J Biol Chem. 2017 May 5;292(18):7295-7303. doi: 10.1074/jbc.R117.777102.

157. Lazear HM, Nice TJ, Diamond MS. Interferon-λ: Immune Functions at Barrier Surfaces and Beyond. Immunity. 2015 Jul 21;43(1):15-28. doi: 10.1016/j.immuni.2015.07.001.

158. Lazear HM, Schoggins JW, Diamond MS. Shared and Distinct Functions of Type I and Type III Interferons. Immunity. 2019 Apr 16;50(4):907-923. doi: 10.1016/j.immuni.2019.03.025.

159. Blazek K, Eames HL, Weiss M, Byrne AJ, Pervocheau D, Pease JE, Doyle S, McCann F, Williams RO, Udalova IA. IFN-λ resolves inflammation via suppression of neutrophil infiltration and IL-1β production. J Exp Med. 2015 Jun 1;212(6):845-53. doi: 10.1084/jem.20140995.

160. Rivera A. Interferon Lambda's New Role as Regulator of Neutrophil Function. J Interferon Cytokine Res. 2019 Oct;39(10):609-617. doi: 10.1089/jir.2019.0036.

161. Alattar R, Ibrahim T BH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, Khatib MY, Aboukamar M, Abukhattab M, Alsoub HA, Almaslamani MA, Omrani AS. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020 May 5:10.1002/jmv.25964. doi: 10.1002/jmv.25964.

162. (Released by National Health Commission & National Administration of Traditional Chinese Medicine on March 3, 2020). Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl). 2020 May 5;133(9):1087-1095. doi: 10.1097/CM9.0000000000000819.

163. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 May 19;117(20):10970-10975. doi: 10.1073/pnas.2005615117.
164. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2018 Jun;77(6):905-910. doi: 10.1136/annrheumdis-2017-2128

165. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, Justet A. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020 Oct;79(10):1381-1382. doi: 10.1136/annrheumdis-2020-217706.

166. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, Justet A. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020 Oct;79(10):1381-1382. doi: 10.1136/annrheumdis-2020-217706.

167. King A, Vail A, O'Leary C, Hannan C, Brough D, Patel H, Galea J, Ogungbenro K, Wright M, Pathmanaban O, Hulme S, Allan S. Anakinra in COVID-19: important considerations for clinical trials. Lancet Rheumatol. 2020 Jul;2(7):e379-e381. doi: 10.1016/S2665-9913(20)30160-0.

168. Robinson PC, Richards D, Tanner HL, Feldmann M. Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. The Lancet Rheumatol. 2020 2(11), E653-E655. DOI: https://doi.org/10.1016/S2665-9913(20)30309-X

169. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020 May;55(5):105954. doi: 10.1016/j.ijantimicag.2020.105954.

170. Heimfarth L, Serafini MR, Martins-Filho PR, Quintans JSS, Quintans-Júnior LJ. Drug repurposing and cytokine management in response to COVID-19: A review. Int Immunopharmacol. 2020 Aug 31;88:106947. doi: 10.1016/j.intimp.2020.106947.

171. Agnihotri R, Gaur S. Implications of tobacco smoking on the oral health of older adults. Geriatr Gerontol Int. 2014 Jul;14(3):526-40. doi: 10.1111/ggi.12285.

172. Starzonek J, Roscher K, Blüher M, Blaue D, Schedlbauer C, Hirz M, Raila J, Vervuert I. Effects of a blend of green tea and curcuma extract supplementation on lipopolysaccharide-induced inflammation in horses and ponies. PeerJ. 2019 Nov 12;7:e8053. doi: 10.7717/peerj.8053.

173. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. Int J Mol Sci. 2019 Nov 28;20(23):6008. doi: 10.3390/ijms20236008.

174. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, Fernández-Ruiz M, Torre-Cisneros J. ESCMID Study Group for Infections in Compromised Hosts (ESGICHI) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). Clin Microbiol Infect. 2018 Jun;24 Suppl 2:S10-S20. doi: 10.1016/j.cmi.2017.12.025.

175. Kunkel GT, Maceyka M, Milstien S, Spiegel S. Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. Nat Rev Drug Discov. 2013 Sep;12(9):688-702. doi: 10.1038/nrd4099.

176. Naz F, Arish M. Battling COVID-19 Pandemic: Sphingosine-1-Phosphate Analogs as an Adjunctive Therapy? Front Immunol. 2020 May 15;11:1102. doi: 10.3389/fimmu.2020.01102.
177. McGowan EM, Haddadi N, Nassif NT, Lin Y. Targeting the SphK-S1P-SIPR Pathway as a Potential Therapeutic Approach for COVID-19. Int J Mol Sci. 2020 Sep 29;21(19):7189. doi: 10.3390/ijms21197189.

178. Allende ML, Dreier JL, Mandala S, Proia RL. Expression of the sphingosine 1-phosphate receptor, S1P1, on T-cells controls thymic emigration. J Biol Chem. 2004 Apr 9;279(15):15396-401. doi: 10.1074/jbc.M314291200.

179. Du X, Zeng H, Liu S, Guy C, Dhungana Y, Neale G, Bergo MO, Chi H. Mevalonate metabolism-dependent protein geranylgeranylation regulates thymocyte egress. J Exp Med. 2020 Feb 3;217(2):e20190969. doi: 10.1084/jem.20190969.

180. Lee MJ, Van Brocklyn JR, Thangada S, Liu CH, Hand AR, Menzeleev R, Spiegel S, Hla T. Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. Science. 1998 Mar 6;279(5356):1552-5. doi: 10.1126/science.279.5356.1552.

181. Liu CH, Thangada S, Lee MJ, Van Brocklyn JR, Spiegel S, Hla T. Ligand-induced trafficking of the sphingosine-1-phosphate receptor EDG-1. Mol Biol Cell. 1999 Apr;10(4):1179-90. doi: 10.1091/mbc.10.4.1179.

182. Iwasaki A, Medzhitov R. A new shield for a cytokine storm. Cell. 2011 Sep 16;146(6):861-2. doi: 10.1016/j.cell.2011.08.027.

183. Subei AM, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis. CNS Drugs. 2015 Jul;29(7):565-75. doi: 10.1007/s40263-015-0261-z.

184. Foerch C, Friedauer L, Bauer B, Wolf T, Adam EH. Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. Mult Scler Relat Disord. 2020 Jul;42:102180. doi: 10.1016/j.msard.2020.102180.

185. Mehta P, Ciurtin C, Scully M, Levi M, Chambers RC. JAK inhibitors in COVID-19: the need for vigilance regarding increased inherent thrombotic risk. Eur Respir J. 2020 Sep 24;56(3):2001919. doi: 10.1183/13993003.01919-2020.

186. La Rosée P, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, Fellhauer M, Henkes M, Kumle B, Russo SG, La Rosée P. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia. 2020 Jul;34(7):1805-1815. doi: 10.1038/s41375-020-0891-0.

187. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. CTI Biopharma Announces Initiation of Phase 3 PRE-VENT Study Evaluating Pacritinib in Hospitalized Patients with Severe COVID-19. CTI Biopharma. 2020 Apr 27. Available at https://cbc.gcs-web.com/news-releases/news-release-details/cti-biopharma-announces-initiation-phase-3-pre-vent-study. Accessed 4th Nov 2020.

188. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020 Mar;16(3):155-166. doi: 10.1038/s41584-020-0372-x.

189. Li X, Wang Y, Agostinis P, Rabson A, Melino G, Carafoli E, Shi Y, Sun E. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis. 2020 Jul 8;11(7):512. doi: 10.1038/s41419-020-2721-8.

190. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev. 2010 Jul;23(3):590-615. doi: 10.1128/CMR.00078-09.
193. Bermejo-Martin JF, Kelvin DJ, Eiros JM, Castropheza J, Ortiz de Lejarazu R. Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. J Infect Dev Ctries. 2009 Apr 30;3(3):159-61. doi: 10.3855/jidc.18.

194. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The Immunomodulatory Effects of Macrolides-A Systematic Review of the Underlying Mechanisms. Front Immunol. 2018 Mar 13;9:302. doi: 10.3389/fimmu.2018.00302. PMID: 29593707; PMCID: PMC5859047.

195. Ratjen F, Saiman L, Mayer-Hamblett N, Lands LC, Kloster M, Thompson V, Emmett P, Marshall B, Accurso F, Sagel S, Anstead M. Effect of azithromycin on systemic markers of inflammation in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa. Chest. 2012 Nov;142(5):1259-1266. doi: 10.1378/chest.12-0628. PMID: 22595153; PMCID: PMC3610595.

196. Pukhalsky AL, Shmarina GV, Kapranov NI, Kokoarovtseva SN, Pukhalskaya D, Kashirskaja NJ. Anti-inflammatory and immunomodulating effects of clarithromycin in patients with cystic fibrosis lung disease. Mediators Inflamm. 2004 Apr;13(2):111-7. doi: 10.1080/09629350410001688495. PMID: 15203552; PMCID: PMC1781547.

197. Parnham MJ, Ćulić O, Eraković V, Munić V, Popović-Grle S, Barisić K, Bosnar M, Brajsa K, Cepelak I, Cuzić S, Glojnarić I, Manojlović Z, Novak-Mircetić R, Oresković K, Pavčić-Beljak V, Radosević S, Sucić M. Modulation of neutrophil and inflammation markers in chronic obstructive pulmonary disease by short-term azithromycin treatment. Eur J Pharmacol. 2005 Jul 4;517(1-2):132-43. doi: 10.1016/j.ejphar.2005.05.023.

198. He ZY, Ou LM, Zhang JQ, Bai J, Liu GN, Li MH, Deng JM, MacNee W, Zhong XN. Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. Respiration. 2010;80(6):445-52. doi: 10.1159/000321374.

199. Banerjee D, Honeybourne D, Khair OA. The effect of oral clarithromycin on bronchial airway inflammation in moderate-to-severe stable COPD: a randomized controlled trial. Treat Respir Med. 2004;3(1):59-65. doi: 10.2165/00151829-200403010-00007.

200. Krishnaveni, M. A review on transfer factor an immune modulator. Drug Invent. Today 2013, 5, 153–156.

201. Li C, Huang L, Wang Y, Li X, Liang S, Zheng Y. Preparation and properties of the specific anti-influenza virus transfer factor. Head Face Med. 2010 Sep 13;6:22. doi: 10.1186/1746-160X-6-22.

202. Castrejón Vázquez MI, Reséndiz-Albor AA, Ynga-Durand MA, Arciniega Martínez IM, Orellana-Villazon VI, García López CA, Laue Noguera ML, Vargas Camaño ME. Dialyzable Leukocyte Extract (Transferon™) Administration in Sepsis: Experience from a Single Referral Pediatric Intensive Care Unit. Biomed Res Int. 2019 Jun 23;2019:8980506. doi: 10.1155/2019/8980506.

203. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents. 2020 Jun;55(6):105982. doi: 10.1016/j.ijantimicag.2020.105982.

204. Mahase E. Covid-19: Low dose steroid cuts death in ventilated patients by one third, trial finds. BMJ. 2020 Jun 16;369:m2422. doi: 10.1136/bmj.m2422.

205. Wang H, Liu B, Tang Y, Chang P, Yao L, Huang B, Lodato RF, Liu Z. Improvement of Sepsis Prognosis by Ulinastatin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2019 Nov 26;10:1370. doi: 10.3389/fphar.2019.01370.
206. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607-613. doi: 10.1016/j.jinf.2020.03.037.

207. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020 Jul;39(7):2085-2094. doi: 10.1007/s10067-020-05190-5.

208. Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell. 2008 Apr 18;133(2):235-49. doi: 10.1016/j.cell.2008.02.043.