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CYTOKINE STORM IN VIRAL RESPIRATORY SARS-COVID-2: MECHANISMS AND IMPLICATIONS

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Abstract: The concentrations of trace metals (mg/kg) in three eroded environments (A, B, C) and a control site (U) in Yelwan Tudu Bauchi, Bauchi State Nigeria were analyzed. The levels of metals, including Na, Ca, Mg, K, N, P Mg, Fe, Mn, Cu, Zn in both eroded and uneroded soil Samples were measured using Atomic Absorption Spectrophotometry.

The soil samples were obtained at a depth of 0-30 cm and were thoroughly homogenized to obtain a composite sample for each site and was analyzed using standard procedure. Significant differences in metal concentrations were found across the sites A, B, C and control site, as shown by one-way ANOVA and least significant difference (LSD) tests.

Keywords: IL-6, IFN-γ, TNF-α, SARS, coronavirus COVID-19.

1. Introduction

Wuhan, Hubei Province, China reported numerous pneumonia cases for unclear reasons in December 2019. As most pneumonia patients had attended the Wuhan wet animal market in the month preceding their diagnosis, the pneumonia was linked to it. Scientists immediately identified and named the infectious cause, SARS-Cov-2, a novel member of the Coronaviridae family. This is similar to what they did with SARS in 2002 and MERS in 2012. The estimated global mortality rate due to coronavirus 2019 (COVID-19) as of March 12, 2020 was 3.7% [1]. It remains much the same. A further 5% of the infected population is predicted to suffer catastrophic diseases requiring intensive care, with extracorporeal organ support therapy being a common necessity. This severely unwell group has a high mortality rate of 40–50% [2]. Molecular diagnostics, most commonly reverse-transcriptase polymerase chain reaction (RT-PCR), are increasingly being used to detect SARS-Cov-2, and these patients may show no symptoms at all (termed asymptomatic or presymptomatic infection). Contrarily, the most common symptoms of COVID-19 are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%), are all possible symptoms. A patient with infectious pneumonia who stays in the hospital might develop acute respiratory distress syndrome (ARDS) [4, 5], sudden cardiac damage [6, 7], and future infections [8]. In the worst cases, COVID19 can cause ARDS, which affects 20–41% of hospitalized patients [4,8]. Multiple organ failure, including heart failure, kidney failure, liver damage, shock, and multi-organ failure, has also been described. The severity of a disease is rated according to its symptoms [9]. Adult COVID-19 instances are classified as [10-13]:

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1. Mild illness: patients who exhibit any of the COVID-19 symptoms (such as a high temperature, cough, sore throat, malaise, headache, or muscular pain) but who do not have dyspnea, shortness of breath, or abnormal chest imaging.
2. Moderate illness: people with lower respiratory illness and a peripheral oxygen saturation (SpO2) of 94% (room air at sea level).
3. Serious sickness is defined as breathing rates of 30 breaths per minute, SpO2 of 94% (room air at sea level), a PaO2/FiO2 ratio of less than 300 mmHg, or lung infiltrates of more than 50%.

Critical illnesses are defined as those that have respiratory failure (requiring mechanical ventilation), septic shock, and/or multiple organ dysfunctions [9].

Overexpression of the gene for angiotensin-converting enzyme-2 (ACE2) is associated with many organ dysfunctions. RNA expression has been found in a number of human organs [14]. High levels of ACE2, the SARS-Cov-2 entrance receptor, cause the most damage to cells, tissues, and organs. Nevertheless, earlier research has demonstrated that ACE2 is strongly expressed in human lung and small intestine epithelia, indicating that these tissues may serve as entryways for SARSCov-2 [15]. Nevertheless, recent studies show that lung surface expression is undetectable [16]. According to information available from the Human Protein Atlasn, the pathophysiology of COVID-19 illness is not causally related to ACE2 cell-surface protein expression [16]. Nevertheless, it is possible that the discrepancy is caused by the selective, transitory expression of ACE2 in some tissues, as was seen in the heart and kidneys [17,18].

2. The Cytokine Storm

The term "cytokine storm" (CS) was first used in 1993 in relation to graft-versus-host disease (GVHD) [24,25]. Despite the fact that the concept of an uncontrolled, cytokine-mediated response was originally investigated in the 1980s in connection to malaria and sepsis [19,20], it wasn't applied to pancreatitis [21], variola virus [22], and influenza virus H5N1 [23] until the 2000s. Some medications and a variety of conditions may directly cause this =. In the latter case, the condition is known as cytokine release syndrome or infusion reaction. Adoptive T-cell treatments, such as CAR-T-cell therapy [26], monoclonal antibody drug regimens [27,28], and immune checkpoint blockade drugs [29–31] have all been linked to CS. Stressed or infected cells activate B cells, T cells, natural killer cells, macrophages, dendritic cells, and monocytes through receptor ligand interactions. In a positive feedback loop, inflammatory cytokines are generated, stimulating additional white blood cells. After an initial infection, CS travels through the bloodstream and infects other parts of the body. Inflammation symptoms include heat, discomfort, redness, swelling, and loss of function. Localized reactions first eliminate the trigger. The release of leukocytes and the transport of plasma proteins to the injury site are both aided by an increase in blood flow. Both discomfort and an elevated core temperature serve as defensive mechanisms against bacterial infections (notifying the host of the impending challenge). Yet, the occurrence of a pathologic trigger initiates the healing process. There are two possible results from these operations.

(1) Organ function gradually returns; (2) fibrosis develops, which may result in irreversible organ dysfunction.

Despite this, SARS-Cov-2 does not stand alone when it comes to the CS symptoms seen; similar results have been reported in SARS-Cov-1 and MERS-Cov cohorts [32,33]. A new study found that COVID-19 CS is characterized by abnormal immune activation and hyper inflammation. According to Ruan et al. [6], critically

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sick patients admitted to the ICU had increased levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, IP-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), and tumor necrosis factor- (TNF-) [6]. Uncontrolled severe inflammation has been linked to death, and data from recovered individuals contradicts that seen in critically sick patients. Key immunological components of the inflammatory environment form the basis of CS. In this article, we will examine the relationship between cytokines and intensive care unit (ICU) admission. TNF, interleukin family members, and interferon-related antiviral cytokines are among them. Lastly, we will talk about IL-6 and how we now perceive it to have contributed to the present COVID-19 epidemic.

3. Interferons (IFN)

IFN cytokines I, II, and III aid pathogen defense. Virus-infected leucocytes and fibroblasts produce type I and III interferons. Macrophages and NK cells create type II interferon to fight viral and intracellular bacterial infections (IFN-). In antigen-specific immunity, T helper (TH) CD4 [34] and CD8 CTL effector T cells produce IFN- [35]. Interferons activate a complex downstream signaling network when they connect to their receptors (IFNAR1/IFNAR2 for Type I, IFN-γR1/IFN-γR2 for Type II, and the receptor complex IL-28R/IL-10Rβ for Type III, also known as lambda interferons). Therefore, transcription factors are activated and numerous IFN-stimulated antiviral, antiproliferative, and immunomodulatory genes are expressed. It has been demonstrated that influenza defense is provided by lambda interferons (type III). an infection in a mouse model [36]. With viral load, COVID-19's IFN- levels rose [3]. The patient's condition and the delayed peak, which occurred at a time when lymphocyte numbers were down, both enhanced the amount of neutrophil infiltration in the lung's alveoli [3,37,38]. IFN- has been linked to the severity of illness in the past. Increased IFN- γ was linked to inflammation in the lungs and serious lung damage in SARS-Cov-1 and MERS-Cov [39,40], which are both signs of getting worse. IFN-, like IL-6, predicts COVID-19 worsening and ICU admission [37,38,41]. It is widely acknowledged that CD4 T cells directly produce IFN-, which enhances CD8 T cell proliferation and cytotoxicity. Supporting the development of monocytes (CD16+ CD14+ CD45+) and releasing IFN-, CD4 T cells secrete granulocyte and colony-stimulating substances into the blood.

4. TNF (tumor **necrosis factor)**

There are 19 members of the TNF superfamily, all of which are type II transmembrane proteins that, after being cleaved by an extracellular proteolytic enzyme, are secreted as cytokines. TNF- is secreted by many different cell types including "macrophages, monocytes, endothelial cells, neutrophils, smooth muscle cells, activated lymphocytes, astrocytes, and adipocytes". One of TNF's various roles is to control the expression of genes that encode for other proteins, including receptors, transcription factors, cytokines, and growth factors. This cytokine's widespread effects can be attributed to the presence of TNF-'s major receptor, TNFR1, on all cell types. Proteins such as "growth factors, cytokines, transcription factors, and receptors" can all have their gene expression controlled by TNF-. The impact of TNF- on CS is substantial. In COVID-19, patient deterioration was significantly influenced by TNF-, which was elevated in ICU patients compared to non-ICU patients [38,42]. TNF- levels rise early in the infection and remain high throughout, much like IL-6 and the soluble IL-2 receptor [3,38]. TNF- also increases HA-synthase-2 (HAS2) in EpCAM+ lung alveolar epithelium, CD31+ lung alveolar endothelium, and fibroblasts in the lungs of COVID19 patients [43]. The fluid inflow caused by HA (hyaluronan)

in the lung alveoli is a major contributor to hypoxia and the need for mechanical ventilation. Lung epithelial cells do not produce TNF- in a highly pathogenic H5N1 influenza model. ARDS lung epithelium produces TNF-. The rise of TNF- is caused by soluble substances made by macrophages interacting with lung epithelial cells [45]. CS's pro-inflammatory cascade emphasizes its ability to cross-talk with injured mucosal tissue and self-amplify, causing systemic CS escalation. It would be interesting to determine whether SARS-Cov-2 infection also induces CS-induced TNF- generation in lung epithelial cells.

5. Interleukins

Interleukins (ILs) control immune cell development and inflammation. Many cells generate interleukin, which transmits leucocytes. IL-1 induces IL-2, which is necessary for T-cell homeostasis and T-cell-derived immunity [46] and IL-2 receptor expression [47,48]. Acute-phase signaling, immune cell trafficking to infection sites, epithelial cell activation, and the production of secondary cytokines are all enhanced by IL-1 and IL-1. Infection causes a wide range of proinflammatory local and systemic consequences, including an increase in particular cytokine synthesis, which may help eliminate viruses. While IL-1 does have some effect on TH1 cells, it is primarily a costimulatory factor for TH2 cells [48]. TH2 cells have the abundant expression of the high-affinity IL-1RI receptor [49]. Animal models of hypersensitivity showed that IL-1/animals had reduced IL-4 and IL-5 levels compared to controls, resulting in milder allergy responses [50]. In mouse trichuriasis muris infection, IL-1 created a TH2 immune milieu that was crucial for parasite defense [51]. Moreover, IL-1 is essential for the induction and operation of TH17. Fewer TH17 cells were generated by IL-1RI/ mice compared to wild-type controls [52]. In contrast, experimental autoimmune encephalomyelitis had no effect in IL1RI/ animals [52]. Notably, IL-1, which is made by dead, inactive Mycobacterium tuberculosis, is needed for TH17 to develop in experimental models of autoimmune diseases [53]. Mice infected with the influenza virus that have their IL-1 receptors activated in the respiratory tract have improved acute lung immunopathology and survival. This is because IL-1 receptor activation attracts CD4 T cells and boosts IgM antibody responses [54]. A rise in IL-1, IL-7, IL-8, and IL-9 levels in the initial plasma concentration is associated with a CT lung scan for COVID-19 in a patient with multiple bilateral lobular pneumonia [3]. This elevation was consistent in both ICU and non-ICU patients, indicating that COVID-19 immunopathology is important [3]. Additionally, ICU patients had greater levels of IL-2 and IL-7 than non-ICU patients [3,55]. Also, the growth of IL-10 is like that of IL-2 and IL-7 [3]. Antigen-presenting cells that activate CD8 T and TH cells may produce IL-10 in response to IFN- and IL-6. IL-10, a potent immunoregulator, may suggest COVID-19 immune insufficiency. While increased IL-10 levels are not linked to a compromised immune system, they do signal a failed attempt by the immune system to suppress the CS in the past [38]. Late immune regulation enhances IL-4, a TH2 cytokine, and inflammatory suppressor, in ICU patients [3]. ILs affect CS morbidity, even though they are not IFNs.

IL6: in the hurricane's eye

The gene for human IL-6 is on chromosome 7p21 and encodes a protein of 212 amino acids and a signal peptide of 28 amino acids. Although the core protein is 20 kDa, glycosylation accounts for the normal IL-6 size of 21-26 kDa. IL-6 has a variety of key tasks in the immune system, including aiding in the development of anti-viral immunity. The pro-inflammatory cytokine IL-6 is widely recognized for its several roles in the inflammatory process. Many different cell types can be affected by the interleukin 6 (IL-6) that is produced. A pleiotropic

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cytokine, that functions both pro- and anti-inflammatory (a kind of cytokine produced by muscle cells in response to muscle contraction). As soon as IL-6 is produced, it immediately binds to its soluble receptor, creating the IL6/IL6R complex. Many immune cells and tissues have a place where they can get IL-6. The IL6 receptor-signaling complex (gp130) is made up of two transmembrane-IL-6 binding chains, soluble IL-6 receptors, and cytoplasmic signaling molecules. Leukemia inhibitory factors, IL-22, IL-27, and IL-25 share the cytoplasmic signaling molecule IL-6R. Hence, receptor co-sharing may explain IL-22, IL-27, IL-25, and IL-6 redundancy and pleiotropy. Soluble IL-6 and its ligand increase gp130. IL-6/IL-6R complex creation initiates the cell's IL-6 signaling pathway. The intracellular cascade that occurs following the creation of a complex activates both the Janus kinase (JAK)-STAT3 pathway and the JAK-SHP-2-MAP kinase pathway. Through stimulating the Suppressor of cytokine signaling 1 (SOCS1) and Suppressor of cytokine signaling 3 (SOCS3), STAT3 is able to control the IL-6 response by inhibiting intracellular feedback loops and IL-6 signaling. In addition to macrophages, neutrophils, dendritic cells, and lymphocytes, there are many more immune cells that produce IL-6. In an inflammatory setting, IL-6 is produced by a broad variety of cells, not just those of the immune system. They include mesenchymal cells, endothelial cells, and fibroblasts. These findings underscore IL-6's prevalence and deep potential in inflammatory conditions. IL-6 enters the liver via the bloodstream and immediately stimulates hepatocytes, causing them to generate C-reactive proteins, serum amyloid A, and fibrinogen. In addition, a decrease in albumin levels after hyperinflammation may point to liver injury and, more significantly, systemic illness. Central differentiation of naive CD4 T cells into effector and helper cells is promoted by IL-6 [56]. IL-6 promotes TH7 production [57] and the activation and development of cytotoxic CD8 T cells [58] by linking innate immunity with adaptive immunological responses. In addition, IL-6 prevents the maturation of T Regulatory T CD4+ CD25+ FOXP3 cells [59], which promotes the onset of autoimmune conditions. Via promoting the expansion of T-follicular helper cells, B cells, plasma cells, and IL-21, IL-6 has a secondary effect on immunoglobulin production. Apart from that, some viruses have the ability to alter the intracellular cascade of events involved in inflammation and the production of IL-6. HIV-1, for example, increases the ability of NFkB and NF-IL-6 to bind to DNA. This increases IL-6 RNA transcription, which causes too much IL-6 to be released. In human airway epithelial cell cultures, when the SARS-Cov-1 structural protein N (nucleocapsid) bound to the NFkB regulatory region on the IL-6 promoter, it significantly turned on the promoter. This was not the case for the SARSCov-1 structural proteins S (spike), E (envelope), or M. (membrane) [60]. This might counteract IL-6 control mechanisms, ending IL-6-mediated activation once the risk is gone. COVID-19's long-term effects must be examined in light of environmental factors and temporary autoimmune illnesses that follow viral infections. COVID-19 has focused on IL-6 [61]. Early on in the pandemic, IL-6 levels were a great indicator of how bad the disease was and how much help was needed for breathing [6, 62, 63]. Pedersen and his colleagues show that high levels of IL-6 (along with TNF- and IL10) are linked to a lower chance of getting better and the need to stay in the ICU [38]. Researchers found a statistically significant correlation between low to moderate IL-6 and other levels, and mild to moderate occurrences. Prompetchara et al. found a 52% rise in IL-6 levels between ICU and non-ICU patients [41]. The elevated CRP levels decreased lymphocyte count, and increased neutrophil count were all linked to this. According to the research of Zhao et al., GM-CSF production by CD4 TH cells is responsible for the indirect upregulation of IL-6 and IFN [64]. IL-6 is released into the pulmonary environment after GM-CS

stimulates the generation and recruitment of CD14+CD16+ monocytes. Upon viral protein identification, innate, MyD88dependent immunological receptors activate to generate IL-6 early in SARS-Cov-1 and MERS. Data showing enhanced IL-6 production in SARS-Cov-1 pathogenesis [60] lend credence to the idea that the two members of the Coronaviridae family may have identical physio pathological mechanisms.

7. Antigen-independent, cytokine-dependent inflammatory loop amplification

Innate and adaptive immune responses are frequently started off by viral antigens [66]. HLA class I and II predicted peptide'mega pools showed 100% and 70% of COVID-19 convalescent patients have SARS-Cov-2-specific CD4 and CD8 T cells, respectively. These reactions were connected to anti-SARS-Cov-2 IgG and IgA levels in every case. The spike protein elicited the majority of CD8 T-cell responses. The M (membrane) protein was discovered as the second most prevalent antigen [66]. The findings from this study provide credence to the ongoing efforts to create a vaccination against the SARS-CoV-2 Spike protein [67]. Naive T cells acquire a wide variety of phenotypic and functional characteristics and effector activities after being activated and differentiated in response to TCR recognition of HLA/peptide-epitope complexes [68-70]. Modeling T-cell responses in COVID-19 suggests that naïve T-cell cytokine programming may have an effect on disease severity [71]. Interferons I and III, IL-2, and mild sickness are all linked. During T-cell priming, severe illness is associated with IL-6, IL-10, IL-1, TNF, CXCL8, and other CXCLs. Antigen exposure and viral persistence alter clinical outcome [72]. Furthermore, proinflammatory cytokines impact viral load [73,74]. In spite of this, antigen-independent, cytokinedependent immune amplification may maintain COVID-19 hyperinflammation. In Lescure et alcase .'s series, late respiratory worsening in the absence of nasopharyngeal viral RNA supports immunologically driven late, severe symptoms [75]. As healthy donors have cross-reactive Cov memory T cells, memory T cells may play a role in COVID-19 illness [66]. Memory that is homeostatic and antigen-independent IL-7 and IL-15 have been demonstrated to enhance the proliferation of T-cells and bystander T-cells [77–80]. Furthermore, IL-2 produced by activated T cells may promote bystander activation [79-81]. According to Lucas et al. [73], COVID-19 contains high quantities of IL-7, IL-15, and IL-2, all of which have been shown to trigger IFN production in an antigen-independent way [82]. With cytokine combinations such as IL-12 + IL18, it is feasible to activate CD8 T cells specific for naive and memory viruses without an antigen [83]. During infections with intracellular pathogens, these cytokines could trigger fast anti-gennonspecific IFN secretion [84]. Considering the high levels of numerous cytokines during COVID19, the synergistic potential of cytokine "cocktails" must be noted. In comparison to IL-12 alone, subthreshold TNF coupled with IL-12 leads to a more than 20-fold increase in IFN-producing CD8 T cells [83]. There was a TCR-independent IL-12-dependent mechanism for IFN- production by CD4 and CD8 T cells in a dengue virus model [85]. Chronic viral infections present antigens for a long time, generating CD8 T cells that react to cytokines without TCR activation [83]. COVID19 IL-1 elevations may reflect inflammasome activity [86,87]. Nonetheless, it has been shown that cognate interactions between effector CD4 T cells and myeloid cells increase IL-1 production via the TNF/TNFr axis [88]. An immature form of natural killer cells, those responsible for producing IL-22, are given a boost by IL-1 and are maintained throughout the body. When bacteria and fungi infect the exterior of cells, IL-22 is involved in the development of Type 3 immune responses. Type 3 responses, such as elevated IL-17 and IL-22 levels, are more common in patients with severe cases of COVID-19 [73]. In some cases, cytokines can stimulate

both antigen-specific and antigen-independent immune responses. Cytokine storms can occur without regulating systems.

8. Discussion

Secondary haemophagocytic lymphohistiocytosis (HLH) is similar to the hyperinflammatory condition [89]. Some people think COVID-19 should be categorized with other hyperinflammatory diseases [90]. Hepatomegaly and splenomegaly are associated in the clinic with HLH. A risk algorithm based on recognized diagnostic criteria can be used to evaluate the probability of HLH in COVID-19 [91-93]. Regarding biochemistry, COVID-19 has been linked to hypertriglyceridemia [94], an additional characteristic that overlaps with hyperinflammatory illnesses such as HLH. Hyperferritinemia is another resemblance to HLH. Ferritin levels in persons with severe COVID-19 are greatly elevated [6]. It is outside the scope of this investigation to examine ferritin's function in cell biology during infection. However, Kernan et al. [95] give a more in-depth look. COVID-19's uncontrolled immune response is significantly connected to the aforementioned clinical symptoms. COVID-19 causes two-stage immune responses. The adaptive immune response destroys infected epithelial cells and stops viral multiplication in the early (asymptomatic, pre-incubation) phase [43]. As SARS-Cov-2 was able to spread during the second phase, this suggests that adaptive immunity was unable to eradicate the virus. During budding, viruses are demonstrated to induce immunogenic cell death [87] and to activate the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome [86]. Zhou et. al., and Hoffmann et. al., discovered SARSCov-2 cell entrance mechanisms [96, 97]. Both investigations demonstrated that SARS-Cov-2 employs ACE2 as an entry receptor and, more importantly, that viral spike (S) protein binding to cellular receptors requires priming by the serine protease TMPRSS2. The scientists showed that a widely available TMPRSS2 inhibitor can block the viral entrance, speeding up COVID-19 clinical trials [98]. Virus entry and replication can activate many TLRs and signaling pathways. TLR sensing study aims to boost antiviral immunity [99-101]. Van der Made et al. showed that X-chromosomal TLR7 loss-of-function variants reduce type I and II IFN responses and lower IRF7 mRNA expression, which affects COVID-19 disease severity (figure 4). Increasing anti-viral immunity with the TLR7 agonist imiquimod has been suggested as a therapeutic because of TLR7's significance [102]. Customized nanoparticle vaccines [103] might be used to investigate the efficient in vivo distribution of vaccines to dendritic cells and the induction of a robust adaptive immune response [104]. Both the apoptotic cascade and widespread death of infected tissues cause inflammation that is reminiscent of the body's innate immune response [100,105,106]. Early in the infection, endogenous viral proteins activate immune receptors through the innate, MyD88-dependent pathway, leading to the production of IL-6 [107]. SARS-Cov-2 infection activated the respiratory system's IL-6 amplifier (IL-6 Amp) via NFB and STAT3. IL-6 amplification may cause COVID-19 hyperinflammation in several inflammatory and autoimmune disorders [61,108]. A variety of immune cells, such as activated CD4 T cells [66], monocytes, and macrophages [110], are drawn to the local inflammatory milieu [109], which may enhance IL-6 Amp in a potentially harmful positive feedback loop. Infectious epithelial cells generate IL-6, which allows activated pro-inflammatory immune cells to invade and increase local cytokine levels. Lung inflammation causes ARDS The link between COVID-19 and lung illness is well-established; however, recent research suggests that other organ abnormalities, including acute kidney injury (AKI), may also be present. [111,112]. Despite this, COVID-19-induced AKI etiology and pathogenesis are still poorly understood

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[113,114]. Several studies [115-117] have linked IL-6/IL-6r to AKI pathogenesis. Additionally, IL-6 levels in kidney damage patients have a substantial concentration-dependent correlation with mortality [118]. Many ideas have been proposed to explain how IL-6 contributes to renal impairment. For example, IL-6 may cause renal illness by elevating tubular epithelial cell sensitivity to pro-fibrotic cytokines like TGF-. Moreover, IL-6 has been demonstrated to worsen mesangial proliferative glomerulonephritis by increasing the proliferation of mesangial cells [117,119]. Moreover, prolonged cytokine stimulation of the liver results in the liver manufacturing more clotting factors, which leads to COVID-19-induced coagulopathy [120,121], which has been associated with hyperinflammation [122]. Moreover, thromboembolic symptoms are evident in post-mortem reports [123]. We [124] and others [125] found that hospitalized COVID-19 patients had highly elevated levels of D-dimers (more than 500 ng ml1) and fibrinogen (greater than 5.5 g l1). Some extremely unwell people have D-dimers more than 20,000, indicating a severe hypercoagulable condition.

COVID-19 for possible treatments

COVID-19 treatments are not FDA-approved [126]. Many studies and observations have shown that lowering SARS-Cov-2-induced hyperinflammation in COVID-19 patients may decrease disease development [6]. Modern COVID-19 therapy emphasizes respiratory support. We advocate immune-modifying medication research based on cytokine data and clinical findings of COVID-19's immunological genesis. In fact, immunomodulatory are the most rapidly investigated treatments thus far [126]. Tocilizumab, a recombinant humanized anti-IL-6 receptor (IL-6r) mAb, and siltuximab, a recombinant human-mouse chimeric monoclonal antibody that binds IL-6, may lessen CS [127,128] and prevent renal function deterioration [129]. One such treatment option for IL-1 inhibition is anakinra. Interleukin-1 receptor (IL-1r) antibodies are often used to treat hyperinflammatory diseases, and their use has a favorable safety profile even at large doses, indicating potential as a treatment option for COVID-19 [130]. Anakinra is used to counteract the negative effects of IL-1 and IL-1. Two cohort studies [131-133] looked at clinical efficacy and found it to be effective. Without randomized studies, the FDA encourages clinicians to exercise cautious [134]. Preventing systemic inflammation with antibody-mediated neutralization of particular cytokines has given mixed outcomes in clinical settings [135-138] or success in limited subgroups. Hence, blood purification by filtration, dialysis (diffusion), and adsorption have been key study areas for non-specific inflammatory mediator sequestration [139-142]. The ultimate goal of blood purification is to reduce potentially harmful concentrations of pro-inflammatory mediators. By reducing IL-6 levels [116], which restores immunological homeostasis, we hope to reduce the prevalence of COVID-19-induced acute kidney injury and improve patient outcomes and survival. Recent research suggests that cytokine adsorption, blood purification, and IL-6 reduction in advanced COVID-19 illness can diminish hyperinflammation [124,130,143]. To evaluate the effectiveness of blood purification techniques in fostering clinical recovery in COVID-19 patients, randomized controlled studies are nonetheless required.

10. Conclusions

In this work, we identify the most prominent targets in the deadly cytokine response in severe COVID-19 patients by a thorough analysis of the rapidly growing data. Several therapeutic drugs were being examined in clinical trials at the time of writing; surprise, IL-6 blocking was the primary focus [144-146]. TNF blockade, on the other

hand, should be investigated [147,148]. While clinical trials are still in their early stages, they hold great promise for alleviating the pain of COVID-19 sufferers.

References

Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020 Mar 19;91(1):157-160. doi: 10.23750/abm. v91i1.9397. PMID: 32191675; PMCID: PMC7569573.

Ronco C, Reis T, De Rosa S. 2020 Coronavirus epidemic and extracorporeal therapies in intensive care: si vis pacem para bellum. Blood Purification 49, 255–258. (doi:10.1159/000507039)

Huang C et al. 2020 Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 395, 497–506. (doi:10.1016/ S0140-6736(20)30183-5)

Zhou F et al. 2020 Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–1062. (doi:10.1016/S0140-6736(20) 30566-3)

Hu H, Ma F, Wei X, Fang Y. 2020 Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur. Heart J. 16, ehaa190.

(doi:10.1093/eurheartj/ehaa190)

Ruan Q, Yang K, Wang W, Jiang L, Song J. 2020 Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 46, 846–848. (doi:10.1007/s00134-020-05991-x)

Bikdeli B Madhavan MV Jimenez D Chuich T Dreyfus I COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. Journal of the American College of Cardiology. 2020; 75:2950–2973. [PMC free article] [PubMed] [Google Scholar]

Wu C et al. 2020 Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Med. 180, 934–943. (doi:10.1001/jamainternmed.2020.0994)

World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020.

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed April 9, 2020.

Peng PWH, Ho P-L, Hota SS. 2020 Outbreak of a new coronavirus: what anaesthetists should know. Br. J. Anaesth. 124, 497–501. (doi: 10.1016/j.bja. 2020.02.008)

Original Article

Centers for Disease Control and Prevention. People Who Are at Higher Risk for Severe Illness. 2020; https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-athigher-risk.html. Accessed April 8,2020.

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. PMID: 32358325; PMCID: PMC7213636.

Poston JT, Patel BK, Davis AM. 2020 Management of critically ill adults with COVID-19. JAMA. 323, 1839–1841. (doi:10.1001/jama.2020.4914)

Li M.-Y., Li L, Zhang Y, Wang X.-S. 2020 Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious Dis. Poverty 9, 45. (doi:10.1186/s40249- 020-00662-x)

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. 2004 Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J. Pathol. 203, 631–637. (doi:10. 1002/path.1570)

Uhlen M et al. 2015 Proteomics. Tissue-based map of the human proteome. Science 347, 1260419. (doi:10.1126/science.1260419)

Goulter AB, Goddard MJ, Allen JC, Clark KL. 2004 ACE2 gene expression is up-regulated in the human failing heart. BMC Med. 2, 19. (doi:10.1186/1741- 7015-2-19)

Danilczyk U, Penninger JM. 2006 Angiotensinconverting enzyme II in the heart and the kidney. Circul. Res. 98, 463–471. (doi: 10.1161/01.RES. 0000205761.22353.5f)

Clark IA, Virelizier JL, Carswell EA, Wood PR. 1981 Possible importance of macrophage- derived mediators in acute malaria. Infect Immun. 32, 1058–1066. (doi:10.1128/IAI.32.3.1058- 1066.1981)

Clark IA. 1982 Suggested importance of monokines in pathophysiology of endotoxin shock and malaria. Klin Wochenschr. 60, 756–758. (doi:10.1007/ BF01716573)

Makhija R, Kingsnorth AN. 2002 Cytokine storm in acute pancreatitis. J. Hepatobiliary Pancreat. Surg. 9, 401–410. (doi:10.1007/s005340200049)

Jahrling PB, Hensley LE, Martinez MJ, Leduc JW, Rubins KH, Relman DA, Huggins JW. 2004 Exploring the potential of variola virus infection of cynomolgus macaques as a model for human smallpox. Proc. Natl Acad. Sci. USA 101, 15 196– 15 200. (doi:10.1073/pnas.0405954101)

Original Article

Yuen KY, Wong SS. 2005 Human infection by avian influenza A H5N1. Hong Kong Med. J. 11, 189–199.

Ferrara JL, Abhyankar S, Gilliland DG. 1993 Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant Proc. 25, 1216–1217. (doi:10.1097/00007890-199312000-00045)

Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. 2012 Into the eye of the cytokine storm. Microbiol. Mol. Biol. Rev. 76, 16–32. (doi:10. 1128/MMBR.05015-11)

Zhao L, Cao YJ. 2019 Engineered T cell therapy for cancer in the clinic. Front. Immunol. 10, 2250–2250. (doi:10.3389/fimmu.2019.02250)

Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. 2006 Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. New Engl. J. Med. 355, 1018–1028. (doi:10.1056/NEJMoa063842)

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. 2010 The safety and side effects of monoclonal antibodies. Nat. Rev. Drug Discov. 9, 325–338. (doi:10.1038/nrd3003)

Honjo O, Kubo T, Sugaya F, Nishizaka T, Kato K, Hirohashi Y, Takahashi H, Torigoe T. 2019 Severe cytokine release syndrome resulting in purpura fulminans despite successful response to nivolumab therapy in a patient with pleomorphic carcinoma of the lung: a case report. J. ImmunoTherapy Cancer 7, 97. (doi:10.1186/s40425-019-0582-4)

Ceschi A, Noseda R, Palin K, Verhamme K. 2020 Immune checkpoint inhibitor-related cytokine release syndrome: analysis of WHO global pharmacovigilance database. Front. Pharmacol. 11, 557. (doi:10.3389/fphar.2020.00557)

Bakacs T, Mehrishi JN, Moss RW. 2012 Ipilimumab (Yervoy) and the TGN1412 catastrophe. Immunobiology 217, 583–589. (doi:10.1016/j.imbio. 2011.07.005)

Zhang Y et al. 2004 Analysis of serum cytokines in patients with severe acute respiratory syndrome. Infect. Immun. 72, 4410–4415. (doi:10.1128/IAI.72. 8.4410-4415.2004)

Min CK et al. 2016 Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Sci. Rep. 6, 25359. (doi:10.1038/ srep25359)

Rosalia RA et al. 2013 Administration of anti-CD25 mAb leads to impaired αgalactosylceramidemediated induction of IFN-γ production in a murine model. Immunobiology 218, 851–859. (doi:10. 1016/j.imbio.2012.10.012)

Original Article

Parkin J, Cohen B. 2001 An overview of the immune system. Lancet 357, 1777–1789. (doi:10.1016/ S0140-6736(00)04904-7)

Mordstein M, Kochs G, Dumoutier L, Renauld JC, Paludan SR, Klucher K, Staeheli P. 2008 Interferonlambda contributes to innate immunity of mice against influenza A virus but not against hepatotropic viruses. PLoS Pathog. 4, e1000151.

(doi: 10.1371/journal.ppat.1000151)

Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. 2020 Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol. Immunol. 17, 533–535. (doi:10.1038/s41423-020- 0402-2)

Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020 May 1;130(5):2202-2205. doi: 10.1172/JCI137647. PMID: 32217834; PMCID: PMC7190904.

Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. 2018 MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 104, 8–13. (doi:10.1016/j.cyto.2018.01.025)

Wong CK et al. 2004 Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 136, 95–103. (doi:10. 1111/j.13652249.2004.02415.x)

Prompetchara E, Ketloy C, Palaga T. 2020 Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac. J. Allergy Immunol. 38, 1–9. (doi:10. 12932/AP-200220-0772)

Chen G et al. 2020 Clinical and immunological features of severe and moderate coronavirus disease 2019. J. Clin. Invest. 130, 2620–2629. (doi:10.1172/ JCI137244)

Shi Y et al. 2020 COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 27, 1451–1454. (doi:10.1038/s41418-020-0530-3)

Chan MC et al. 2005 Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. Respir. Res. 6, 135. (doi:10.1186/1465-9921-6-135)

Lee SM et al. 2008 Hyperinduction of cyclooxygenase-2-mediated proinflammatory cascade: a mechanism for the pathogenesis of avian influenza H5N1 infection. J. Infect. Dis. 198, 525–535. (doi:10.1086/590499)

Original Article

Rosalia RA, Arenas-Ramirez N, Bouchaud G, Raeber ME, Boyman O. 2014 Use of enhanced interleukin-2 formulations for improved immunotherapy against cancer. Curr. Opin. Chem. Biol. 23, 39–46. (doi:10. 1016/j.cbpa.2014.09.006)

Herrmann F, Oster W, Meuer SC, Lindemann A, Mertelsmann RH. 1988 Interleukin 1 stimulates T lymphocytes to produce granulocyte-monocyte colony-stimulating factor. J. Clin. Invest. 81, 1415–1418. (doi:10.1172/JCI113471)

Lichtman AH, Chin J, Schmidt JA, Abbas AK. 1988 Role of interleukin 1 in the activation of T lymphocytes. Proc. Natl Acad. Sci. USA 85, 9699–9703. (doi:10.1073/pnas.85.24.9699)

Taylor-Robinson AW, Phillips RS. 1994 Expression of the IL-1 receptor discriminates Th2 from Th1 cloned CD4+ T cells specific for Plasmodium chabaudi. Immunology 81, 216–221.

Nakae S et al. 2003 IL-1 is required for allergenspecific Th2 cell activation and the development of airway hypersensitivity response. Int. Immunol. 15, 483–490. (doi:10.1093/intimm/dxg054)

Helmby H, Grencis RK. 2004 Interleukin 1 plays a major role in the development of Th2mediated immunity. Eur. J. Immunol. 34, 3674–3681. (doi:10. 1002/eji.200425452)

Sutton C, Brereton C, Keogh B, Mills KH, Lavelle EC. 2006 A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. J. Exp. Med. 203, 1685–1691. (doi:10.1084/jem.20060285)

van de Veerdonk FL, Teirlinck AC, Kleinnijenhuis J, Kullberg BJ, van Crevel R, van der Meer JW, Joosten LA, Netea MG. 2010 Mycobacterium tuberculosis induces IL17A responses through TLR4 and dectin-1 and is critically dependent on endogenous IL-1. J. Leukoc. Biol. 88, 227–232. (doi:10.1189/jlb.0809550)

Schmitz N, Kurrer M, Bachmann MF, Kopf M. 2005 Interleukin-1 is responsible for acute lung immunopathology but increases survival of respiratory influenza virus infection. J. Virol. 79, 6441–6448. (doi:10.1128/JVI.79.10.6441- 6448.2005)

Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, Dong XQ, Zheng YT. 2020 Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol. Immunol. 17, 541–543. (doi:10.1038/s41423-020-0401-3)

Dienz O, Rincon M. 2009 The effects of IL-6 on CD4 T cell responses. Clin. Immunol. 130, 27–33. (doi:10.1016/j.clim.2008.08.018)

Original Article

Ivanov, II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR. 2006 The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126, 1121–1133. (doi:10.1016/j. cell.2006.07.035)

Yang R, Masters AR, Fortner KA, Champagne DP, Yanguas-Casas N, Silberger DJ, Weaver CT, Haynes L, Rincon M. 2016 IL-6 promotes the differentiation of a subset of naive CD8+ T cells into IL-21-producing B helper CD8+ T cells. J. Exp. Med. 213, 2281–2291. (doi:10.1084/jem.20160417)

Dominitzki S et al. 2007 Cutting edge: transsignaling via the soluble IL-6R abrogates the induction of FoxP3 in naive CD4+CD25 T cells. J. Immunol. 179, 2041–2045. (doi:10.4049/ jimmunol.179.4.2041)

Zhang X, Wu K, Wang D, Yue X, Song D, Zhu Y, Wu J. 2007 Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NFkappaB. Virology 365, 324–335. (doi: 10.1016/j.virol.2007.04.009)

Gubernatorova EO, Gorshkova EA, Polinova AI, Drutskaya MS. 2020 IL-6: relevance for immunopathology of SARSCoV-2. Cytokine Growth Factor Rev. 53, 13–24. (doi:10. 1016/j.cytogfr.2020.05.009)

Lin L, Lu L, Cao W, Li T. 2020 Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg. Microbes Infect. 9, 727–732. (doi:10.1080/22221751.2020.1746199)

Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, Bergwelt-Baildon MV, Klein M, Weinberger T. 2020 Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J. Allergy Clin. Immunol. 146, 128–136.

(doi: 10.1016/j.jaci.2020.05.008)

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. Natl Sci Rev. 2020 Jun;7(6):998-1002. doi: 10.1093/nsr/nwaa041. Epub 2020 Mar 13. PMID: 34676125; PMCID: PMC7108005.

Magro G. 2020 SARS-CoV-2 and COVID-19: is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides Tocilizumab? SGP130Fc. Cytokine X. 100029. (doi:10.1016/j.cytox. 2020.100029) royalsocietypublishing.org/journal/rsob Open Biol. 10: 200160 10 Downloaded from https://royalsocietypublishing.org/ on 22 February 2023

Grifoni A et al. 2020 Targets of T Cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 181, 1489–1501. (doi: 10.1016/j.cell.2020.05.015)

Original Article

Salvatori G, Luberto L, Maffei M, Aurisicchio L, Roscilli G, Palombo F, Marra E. 2020 SARS-CoV-2 SPIKE PROTEIN: an optimal immunological target for vaccines. J. Transl. Med. 18, 222. (doi:10.1186/ s12967-020-02392-y)

Barberis M, Helikar T, Verbruggen P. 2018 Simulation of stimulation: cytokine dosage and cell cycle crosstalk driving timing-dependent T cell differentiation. Front. Physiol. 9, 879. (doi:10.3389/ fphys.2018.00879)

Cox MA, Harrington LE, Zajac AJ. 2011 Cytokines and the inception of CD8 T cell responses. Trends Immunol. 32, 180–186. (doi:10.1016/j.it.2011.01.004)

Condotta SA, Richer MJ. 2017 The immune battlefield: the impact of inflammatory cytokines on CD8+ T-cell immunity. PLoS Pathog. 13, e1006618. (doi: 10.1371/journal.ppat.1006618)

Chen Z, John Wherry E. 2020 T cell responses in patients with COVID-19. Nat. Rev. Immunol. 20, 529. (doi:10.1038/s41577-020-0402-6)

Chang D et al. 2020 Persistent viral presence determines the clinical course of the disease in COVID19. J. Allergy Clin. Immunol. Pract. S2213–2198(2220) 30614–30610. (doi:10.1016/j.jaip.2020.06.015)

Lucas C et al. 2020 Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 584, 463–469. (doi:10.1038/s41586- 020-2588-y)

Perlman S. 2020 COVID-19 poses a riddle for the immune system. Nature 584, 345–346. (doi:10. 1038/d41586-020-02379-1)

Lescure F-X et al. 2020 Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect. Dis. 20, 697–706. (doi:10. 1016/S1473-3099(20)30200-0)

Raeber ME, Zurbuchen Y, Impellizzieri D, Boyman O. 2018 The role of cytokines in Tcell memory in health and disease. Immunol. Rev. 283, 176–193. (doi:10.1111/imr.12644)

Boyman O, Létourneau S, Krieg C, Sprent J. 2009 Homeostatic proliferation and survival of naïve and memory T cells. Eur. J. Immunol. 39, 2088–2094. (doi:10.1002/eji.200939444)

Boyman O, Purton JF, Surh CD, Sprent J. 2007 Cytokines and T-cell homeostasis. Curr. Opin. Immunol. 19, 320–326. (doi: 10.1016/j.coi.2007.04.015)

David F. Tough et al., Induction of Bystander T Cell Proliferation by Viruses and Type I Interferon in Vivo.Science272,1947-1950(1996). DOI:10.1126/science.272.5270.1947

Original Article

Zhang X, Sun S, Hwang I, Tough DF, Sprent J. 1998 Potent and selective stimulation of memoryphenotype CD8+ T cells in vivo by IL-15. Immunity 8, 591–599. (doi:10.1016/s10747613(00)80564-6)

Kim J, Lee JY, Cho K, Hong S.-W., Kim KS, Sprent J, Im S.-H., Surh CD, Cho J.-H. 2018 Spontaneous proliferation of CD4+ T cells in RAG-deficient hosts promotes antigenindependent but IL-2-dependent strong proliferative response of naïve CD8+ T cells. Front. Immunol. 9, 1907. (doi:10.3389/fimmu.2018.01907)

Arenas-Ramirez N et al. 2016 Improved cancer immunotherapy by a CD25-mimobody conferring selectivity to human interleukin-2. Sci. Transl. Med. 8, 367ra166. (doi:10.1126/scitranslmed.aag3187)

Freeman BE, Hammarlund E, Raué H-P, Slifka MK. 2012 Regulation of innate CD8+ Tcell activation mediated by cytokines. Proc. Natl Acad. Sci. USA 109, 9971–9976. (doi:10.1073/pnas.1203543109)

Berg RE, Crossley E, Murray S, Forman J. 2003 Memory CD8+ T cells provide innate immune protection against Listeria monocytogenes in the absence of cognate antigen. J. Exp. Med. 198, 1583–1593. (doi:10.1084/jem.20031051)

Suwannasaen D, Romphruk A, Leelayuwat C, Lertmemongkolchai G. 2010 Bystander T cells in human immune responses to dengue antigens. BMC Immunol. 11, 47. (doi:10.1186/1471-2172-11-47)

Zhao C, Zhao W. 2020 NLRP3 inflammasome-a key player in antiviral responses. Front. Immunol. 11, 211. (doi:10.3389/fimmu.2020.00211)

Li G et al. 2020 Coronavirus infections and immune responses. J. Med. Virol. 92, 424– 432. (doi:10.1002/jmv.25685)

Jain A, Irizarry-Caro RA, McDaniel MM, Chawla AS, Carroll KR, Overcast GR, Philip NH, Oberst A, Chervonsky AV, Katz JD, Pasare C. T cells instruct myeloid cells to produce inflammasome-independent IL-1β and cause autoimmunity. Nat Immunol. 2020 Jan;21(1):6574. doi: 10.1038/s41590-019-0559-y. Epub 2019 Dec 17. PMID: 31848486; PMCID: PMC6927526.

Prilutskiy A et al. 2020 SARS-CoV-2 infectionassociated hemophagocytic lymphohistiocytosis. Amer. J. Clin. Pathol. (doi:10.1093/ajcp/aqaa124)

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/S01406736(20)30628-0. Epub 2020 Mar 16. PMID: 32192578; PMCID: PMC7270045.

Original Article

Henter JI et al. 2007 HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric Blood Cancer 48, 124–131. (doi:10.1002/pbc.21039)

Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. 2014 Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthr. Rheumatol. 66, 2613–2620. (doi:10.1002/art.38690)

Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, Corazza F. 2016 Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. Amer. J. Clin. Pathol. 145, 862–870. (doi:10.1093/ ajcp/aqw076)

Gadiparthi C, Bassi M, Yegneswaran B, Ho S, Pitchumoni CS. 2020 Hyperglycemia, hypertriglyceridemia, and acute pancreatitis in COVID-19 infection: clinical implications. Pancreas 49, e62–e63. (doi:10.1097/mpa.0000000 000001595)

Kernan KF, Carcillo JA. 2017 Hyperferritinemia and inflammation. Int. Immunol. 29, 401–

409. (doi:10. 1093/intimm/dxx031)

Zhou P et al. 2020 A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273. (doi:10.1038/s41586- 020-2012-7)

Hoffmann M et al. 2020 SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280. (doi: 10.1016/j.cell.2020.02.052)

McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. 2020 Candidate drugs against SARSCoV-2 and COVID-19. Pharmacol Res. 157, 104859. (doi: 10.1016/j.phrs.2020.104859)

Mazaleuskaya L, Veltrop R, Ikpeze N, Martin-Garcia J, Navas-Martin S. 2012 Protective role of Toll-like Receptor 3-induced type I interferon in murine coronavirus infection of macrophages. Viruses 4, 901–923. (doi:10.3390/v4050901)

Totura AL, Whitmore A, Agnihothram S, Schäfer A, Katze MG, Heise MT, Baric RS. 2015 Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio 6, e00638-15. (doi:10.1128/mBio.00638-15)

Astuti IY. 2020 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab. Syndr. 14, 407–412. (doi: 10.1016/j.dsx.2020.04.020)

Original Article

Angelopoulou A, Alexandris N, Konstantinou E, Mesiakaris K, Zanidis C, Farsalinos K, Poulas K. 2020 Imiquimod—a toll like receptor 7 agonist—is an ideal option for management of COVID 19. Environ. Res. 188, 109858. (doi: 10.1016/j.envres.2020. 109858)

Cruz LJ, Rosalia RA, Kleinovink JW, Rueda F, Löwik CW, Ossendorp F. 2014 Targeting nanoparticles to CD40, DEC-205 or CD11c molecules on dendritic cells for efficient CD8(+) T cell response: a comparative study. J. Control. Release 192, 209–218. (doi: 10.1016/j.jconrel.2014.07.040)

Shin MD et al. 2020 COVID-19 vaccine development and a potential nanomaterial path forward. Nat. Nanotechnol. (doi:10.1038/s41565-020-0737-y)

Choudhury A, Mukherjee S. 2020 In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. J Med. Virol. (doi:10.1002/jmv.25987)

Moreno-Eutimio MA, López-Macías C, PastelinPalacios R. 2020 Bioinformatic analysis and identification of single-stranded RNA sequences recognized by TLR7/8 in the SARSCoV-2, SARS-CoV, and MERS-CoV genomes. Microbes Infect. 22, 226–229.

(doi: 10.1016/j.micinf.2020.04.009)

De Wit E, Van Doremalen N, Falzarano D, Munster VJ. 2016 SARS and MERS: recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 14, 523.

(doi:10.1038/nrmicro.2016.81)

Murakami M, Kamimura D, Hirano T. 2019 Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. Immunity 50, 812–831. (doi: 10.1016/j.immuni.2019.03.027) 109. Wong JJM, Leong JY, Lee JH, Albani S, Yeo JG. 2019 Insights into the immunopathogenesis of acute royalsocietypublishing.org/journal/rsob Open Biol. 10: 200160 11 Downloaded from https://royalsocietypublishing.org/ on 22 February 2023 respiratory distress syndrome. Ann. Transl. Med. 7, 504. (doi:10.21037/atm.2019.09.28)

Merad M, Martin JC. 2020 Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat. Rev. Immunol. 20, 355–362. (doi:10.1038/s41577020- 0331-4)

Ronco C, Reis T, Husain-Syed F. 2020 Management of acute kidney injury in patients with COVID-19. Lancet Respir. Med. 8, 738–742. (doi:10.1016/ S2213-2600(20)30229-0)

Original Article

Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, Swaminathan S, Covid, Ace2 in Cardiovascular L, Kidney Working G. 2020 Acute kidney injury in COVID19: emerging evidence of a distinct pathophysiology. J. Am. Soc. Nephrol. 31, 1380–1383. (doi:10.1681/ASN.2020040419)

Hirsch JS et al. 2020 Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 98, 209–218. (doi: 10.1016/j.kint.2020.05.006)

Ng JJ, Luo Y, Phua K, Choong A. 2020 Acute kidney injury in hospitalized patients with coronavirus disease 2019 (COVID-19): a meta-analysis. J. Infect. (doi: 10.1016/j.jinf.2020.05.009)

Nechemia-Arbely Y, Barkan D, Pizov G, Shriki A, Rose-John S, Galun E, Axelrod JH. 2008 IL-6/IL-6R axis plays a critical role in acute kidney injury. J. Am. Soc. Nephrol. 19, 1106–1115. (doi:10.1681/ ASN.2007070744)

Su H, Lei CT, Zhang C. 2017 Interleukin-6 signaling pathway and its role in kidney disease: an update.Front. Immunol. 8, 405. (doi:10.3389/fimmu.2017.00405)

Jones SA, Fraser DJ, Fielding CA, Jones GW. 2015 Interleukin-6 in renal disease and therapy. Nephrol. Dial. Transplant. 30, 564–574. (doi:10.1093/ndt/gfu233)

Simmons EM et al. 2004 Plasma cytokine levels predict mortality in patients with acute renal failure. Kidney Int. 65, 1357–1365. (doi:10.1111/j. 1523-1755.2004. 00512.x)

Horii Y et al. 1989 Involvement of IL-6 in mesangial proliferative glomerulonephritis. J. Immunol. 143, 3949–3955.

The Lancet Haematology. COVID-19 coagulopathy: an evolving story. Lancet Haematol. 2020 Jun;7(6):e425. doi: 10.1016/S2352-3026(20)30151-4. PMID: 32470428; PMCID: PMC7250563.

Connors JM, Levy JH. 2020 COVID-19 and its implications for thrombosis and anticoagulation. Blood 135, 2033–2040. (doi:10.1182/blood. 2020006000)

Bester J, Pretorius E. 2016 Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity. Scient. Rep. 6, 32188. (doi:10.1038/ srep32188)

Menter T et al. 2020 Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 77, 198–209. (doi:10.1111/his.14134)

Ugurov P, Popevski D, Gramosli T, Neziri D, Vuckova D, Gjorgon M, Stoicovski E, Marinkovic S, Veljanovska-Kiridjievska L, Ignevska K, Mehandziska S, Ambarkova E, Mitrev Z, Rosalia RA. Early Initiation of Extracorporeal Blood Purification Using the AN69ST (oXiris®) Hemofilter as a Treatment Modality for

Original Article

COVID-19 Patients: a Single-Centre Case Series. Braz J Cardiovasc Surg. 2022 Mar 10;37(1):35-47. doi: 10.21470/1678-9741-20200403. PMID: 33113325; PMCID: PMC8973137.

Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. 2020 Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J. Thromb. Haemost. 18, 1738–1742. (doi:10.1111/jth.14850)

Nainwal LM, Suman. FDA Coronavirus Treatment Acceleration Program: approved drugs and those in clinical trials. Coronavirus Drug Discovery. 2022:249–64. doi: 10.1016/B978-0-323-85156-5.00013-4. Epub 2022 Jun 10. PMCID: PMC9217692.

Atal S, Fatima Z. IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy? Pharmaceut Med. 2020 Aug;34(4):223-231. doi: 10.1007/s40290-020-00342-z. PMID: 32535732; PMCID: PMC7292936.

Michot JM et al. 2020 Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann. Oncol. 31, 961–964. (doi:10.1016/j.annonc.2020.03.300)

Maeshima A, Nakasatomi M, Henmi D, Yamashita S, Kaneko Y, Kuroiwa T, Hiromura K, Nojima Y. 2012 Efficacy of tocilizumab, a humanized neutralizing antibody against interleukin-6 receptor, in progressive renal injury associated with Castleman's disease. CEN Case Rep. 1, 7–11. (doi:10.1007/ s13730-012-0004-7)

van de Veerdonk FL, Netea MG. 2020 Blocking IL-1 to prevent respiratory failure in COVID-19. Crit. Care 24, 445. (doi:10.1186/s13054-020-03166-0)

Filocamo G, Mangioni D, Tagliabue P, Aliberti S, Costantino G, Minoia F, Bandera A. 2020 Use of anakinra in severe COVID-19: a case report. Int. J. Infect. Dis. 96, 607–609. (doi:10.1016/j.ijid.2020.05.026)

Cavalli G et al. 2020 Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2, e325–e331. (doi:10.1016/ S2665-9913(20)30127-2)

Huet T et al. 2020 Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2, e393-e400. (doi:10.1016/S2665-9913(20)30164-8)

Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol. 2020 Sep;10(9):200160. doi: 10.1098/rsob.200160. Epub 2020 Sep 23. PMID: 32961074; PMCID: PMC7536084.

Siegler BH, Brenner T, Uhle F, Weiterer S, Weigand MA, Hofer S. 2016 Why a second look might be worth it: immuno-modulatory therapies in the critically ill patient. J. Thor. Dis. 8, E424–E430. (doi:10.21037/jtd.2016.04.37)

Zeni F, Freeman B, Natanson C.1997 Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit. Care Med. 25, 1095–1100. (doi:10. 1097/00003246199707000-00001)

Original Article

Cohen J, Carlet J. 1996 INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. Crit. Care Med. 24, 1431–1440. (doi:10.1097/00003246-199609000-00002)

Schulte W, Bernhagen J, Bucala R. 2013 Cytokines in sepsis: potent immunoregulators and potential therapeutic targets–an updated view. Mediators Inflamm. 2013, 165974. (doi:10.1155/ 2013/165974)

Datzmann T, Trager K. 2018 Extracorporeal membrane oxygenation and cytokine adsorption. J. Thoracic Dis. 10, S653–S660. (doi:10.21037/jtd.2017.10.128)

Rimmele T, Kellum JA. 2011 Clinical review: blood purification for sepsis. Crit. Care 15, 205. (doi:10. 1186/cc9411)

Bonavia A, Groff A, Karamchandani K, Singbartl K. 2018 Clinical utility of extracorporeal cytokine hemoadsorption therapy: a literature review. Blood Purif. 46, 337– 349. (doi:10.1159/000492379)

Shum HP, Yan WW, Chan TM. 2016 Extracorporeal blood purification for sepsis. Hong Kong Med. J. 22, 478–485. (doi:10.12809/hkmj164876)

Zhou P, et al. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273. (10.1038/s41586-020-2012-7) [PMC free article] [PubMed] [CrossRef] [Google Scholar]

Liu B, Li M, Zhou Z, Guan X, Xiang Y. 2020 Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. 111, 102452. (doi: 10.1016/j.jaut.2020.102452)

Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and metaanalysis. Rev Med Virol. 2020 Nov;30(6):1-9. doi: 10.1002/rmv.2141. Epub 2020 Aug 26. PMID: 32845568; PMCID: PMC7460877.

Zhang Y, Zhong Y, Pan L, Dong J. 2020 Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: are we already that far? Drug Disc. Therapeut. 14, 100–102. (doi:10.5582/ddt.2020.03006)

Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T. 2020 Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet. 395, 1407–1409. (doi:10.1016/s0140-6736(20)30858-8)

Duret PM, Sebbag E, Mallick A, Gravier S, Spielmann L, Messer L. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. Ann Rheum Dis. 2020 Sep;79(9):1251-1252. doi: 10.1136/annrheumdis-2020-217362. Epub 2020 Apr 30. PMID: 32354772; PMCID: PMC7456545.