# Hazards of the cytokine storm and cytokine-targeted therapy in COVID-19 patients: A Review

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# Hazards of the cytokine storm and cytokine-targeted therapy in COVID-19 patients: A Review

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## *Abstract*

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged medicine and healthcare on a global scale. Its impact and frightening mortality rate are in large part attributable to the fact that there is a lack of available treatments. It has been shown that in severely-ill patients, SARS-CoV-2 can lead to an inflammatory response known as cytokine storm, which involves activation and release of inflammatory cytokines in a positive feedback loop of pathogen-triggered inflammation. Currently, cytokine storm is one of the leading causes of morbidity and mortality in SARS-CoV-2, but there is no proven treatment to combat this systemic response.

**Objective:** To study the cytokine storm response in SARS-CoV-2 and to explore the available treatment options for critically-ill coronavirus disease 2019 (COVID-19) patients in the early stages of the pandemic by reviewing literature.

**Methods:** A literature review was performed from December 1, 2000 to April 4, 2020, to explore and compare different treatments that have been proposed to manage cytokine storm among COVID-19 patients. Thirty-eight eligible studies including 24 systematic reviews, 5 meta-analysis, 5 experimental model studies, 7 cohort studies, and 4 case reports matched criteria.

**Results:** Severity of the cytokine storm, measured by elevated levels of IL1B, IFN?, IP10, and MCP1, was associated with the COVID-19 disease severity. Tocilizumab, an IL-6 monoclonal antibody, showed improvement in lung lesions, oxygenation, and lymphocytopenia. One of earliest proposed treatments, chloroquine and hydroxychloroquine demonstrated efficacy in viral load reduction but have not been studied extensively among critically-ill COVID-19 patients. The anti-oxidative properties of melatonin and Vitamin C showed decreased mortality rate among patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19. Glucocorticoids, on the other hand, delayed clearance of the COVID-19 viral RNA from respiratory tract secretions. Plasma therapy in treatment-resistant patients who required mechanical ventilation showed improvement in viral load, inflammatory markers, and ventilation needs.

**Conclusions:** Many treatment options with different targets have been proposed from the early stages of the COVID-19 pandemic, ranging from targeting the virus itself to managing the systemic inflammation caused by the virus. Among the different agents to manage cytokine storm in COVID-19 patients, there is developing support for convalescent plasma therapy particularly for critically-ill and mechanically ventilated patients who are resistant to antivirals and supportive care. Treatment options that were proposed in the beginning phases of the pandemic were multi-dimensional, and further research is needed to establish treatment guidelines.

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# Original Manuscript

Hazards of the cytokine storm and cytokine-targeted therapy in COVID-19 patients: A Review

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## Introduction

In December 2019, a novel coronavirus emerged from Wuhan, China. Since then, it has rapidly spread around the world. Termed coronavirus disease 2019, COVID-19 ranges from a self-limiting upper respiratory tract illness to severe pneumonia, multiorgan failure, and death. It has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1, 2, 35]. Despite its impact, there is still much uncertainty regarding the frontline treatment of choice for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Current research indicates that cytokine storm is one of the leading causes of morbidity and mortality in COVID-19 patients. This evidence is based on elevated levels of interleukins (IL) and other cytokine signaling pathways that are implicated in inflammatory cascades. Chen et al explored risk factors among COVID-19 patients who are at higher risk of adverse events, such as admission to an intensive care unit (ICU), mechanical ventilation dependence, or death among three hospitals in Wuhan, China from January 13, 2020 to February 26, 2020. As part of their analysis, 28 cancer patients with COVID-19 were included. Lung cancer was the most frequent type of cancer involved with 7 of 28 patients (25%). 8 of 28 patients (29%) were suspected to have received COVID-19 from hospital-associated transmission. 15 of 28 patients (54%) had a severe event with an overall mortality rate of 29% [3]. Receiving antineoplastic therapy within two weeks of analysis significantly increased the risk of developing severe events with a hazard ratio of 4.079 ($P$=.03) [3].

Convalescent plasma therapy is one of the proposed treatments for critically-ill COVID-19 patients with exaggerated inflammatory response to the virus. Plasma therapy has been used in prior viral pandemics such as pandemic Influenza A (H1N1), SARS, Middle East Respiratory Syndrome (MERS), and Ebola with moderate success. Here, we present a literature review regarding current and potential pharmacologic treatments that specifically aim to target the cytokine storm in the battle against COVID-19.

## Methods

We searched PubMed and EMBASE databases. We specifically screened studies that were published between December 1, 2000 and April 4, 2020. The following research terms were used: coronavirus, COVID-19, SARS, SARS-CoV-2, cytokine storm, inflammatory response, cytokines, interleukins, immunomodulatory, anti-inflammation treatment, and immunocompromised. Exclusions included studies without detailed methodological reporting. Search was limited to only studies published in English. PRISMA criteria were applied.

Screening of titles and abstracts was performed by the authors. The full texts were reviewed in a second screening. Papers were considered if the study design was a case report, cohort study, series of cases, ecological studies, systematic reviews, meta-analysis, and clinical trials related to the cytokine storm effect and treatment of coronavirus infection.

## Search Results

Our literature search identified 2616 abstracts, from which 89 potential studies were selected for detailed full-text review. After excluding the studies that were focused on direct antiviral therapy, 41 studies remained.  The studies focused on management of coronavirus infection and cytokine storm. Zero non-peer reviewed publications were excluded from the study. Studies that were not available

in full text were excluded. 38 studies were included in the final analysis. Of these, 24 systematic reviews, 5 meta-analysis, 5 experimental model studies, 7 cohort studies, and 4 case reports were selected. Some studies contributed to more than one section in this review (Figure 1).

**Figure 1.** Flow Diagram of Search Results.
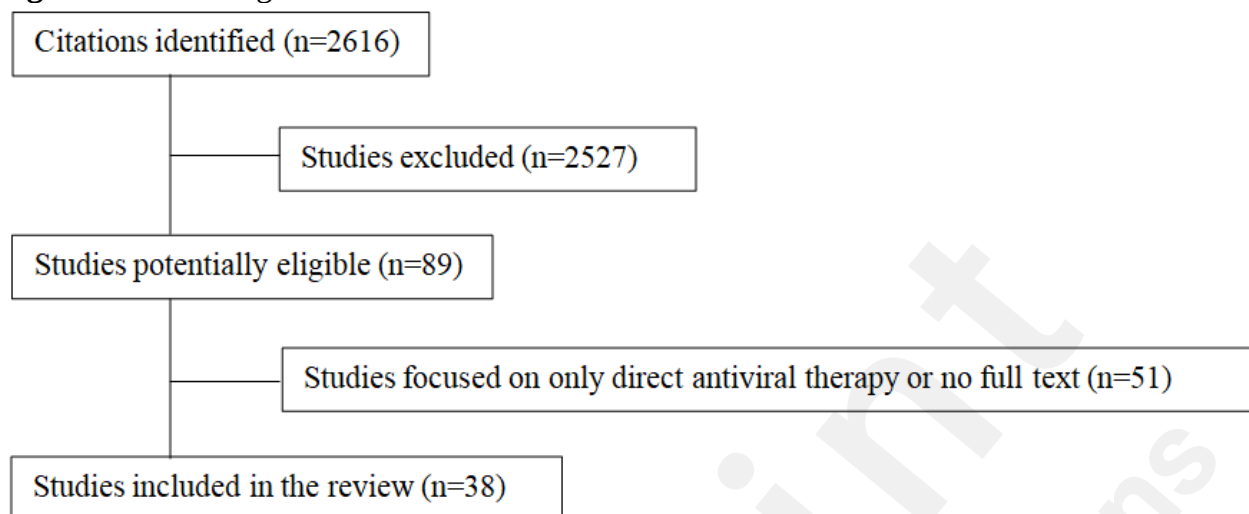


## Discussion

The pathogenesis of cytokine storm in critically-ill COVID-19 patients involves a dysregulation of the immune response. Excessive release of cytokines causes damage on a local and systemic level. Elevated cytokine responses have been associated with a high rate of morbidity and mortality. Our study explored multiple treatment strategies ranging from direct antiviral therapy to glucocorticoids to those that specifically target the cytokine storm effect, such as immunomodulators and plasmapheresis (Figure 2). While there are currently no well-established treatment guidelines, further research in targeting the cytokine storm is crucial in order to benefit critically-ill patients at the earliest stage possible.

**Figure 2.** Clinical Management Studies in Viral Outbreaks

| | SARS-CoV-2 | MERS | H1N1 | SARS |
|---|---|---|---|---|
| Glucocorticoids | Wang et al. 2020.[a] [11] WHO. 2020. [13] | Russell et al. 2020.[c] [12] | WHO. 2020. [13] | Russell et al. 2020.[c] [12] |
| IL-6 Antibody | Xu et al. 2020.[b] [14] Sanofi. 2020. [15] Gritti. 2020.[b] [16] | | | |
| IL-1 Antibody | Nicastri et al. 2020.[b] [17] Sobi. 2020. [40] | | | |
| CQ/HCQ | Zhang et al. 2020.[b] [19] Dong et al. 2020.[c] [20] Gautret et al. 2020.[b] [21] | | | Zhang et al. 2020.[c] [18] |
| JAK2 Inhibitors | Wu et al. 2020.[b] [41] | Wu et al. 2020.[b] [41] | Wu et al. 2020.[b] [41] | |
| Antioxidants | Zhang et al. 2020.[c] [31] Peng. 2020.[b] [32] | Zhang et al. 2020.[c] [31] | | Zhang et al. 2020.[c] [31] |
| Plasma Therapy | Tanne, J H. 2020. [22] Roback et al. 2020. [30] Shen et al. 2020.[b] [27] | Chun et al. 2016.[a] [28] | Hung et al. 2011.[b] [26] | Cheng et al. 2004.[b] [25] |

[a]Case Report
[b]Series of Cases/Observational Studies
[c]Review

# 1. Cytokine storm and the impaired immune system

Coronavirus pneumonia, such as SARS and MERS, have demonstrated that a combination of severe inflammation, oxidation stress, and an exaggerated immune response contributes to the COVID-19 pathology. This uncontrolled and excessive load of pro-inflammatory cytokines, referred to as a cytokine storm, can lead to acute lung injury, acute respiratory distress syndrome (ARDS), and even death. Huang et al reported that critically-ill COVID-19 patients have an elevated cytokine profile that resembles that of cytokine storms reported in SARS and MERS [4]. The prospective cohort study from Wuhan, China measured the cytokine levels in 41 patients. 13 of 41 patients (32%) were admitted to the ICU for high-flow nasal cannula or higher-level oxygen support requirements. The majority of the patients in this cohort presented with fever, dry cough, and dyspnea. Chest CT scans showed bilateral ground-glass opacities, and some patients even progressed to ARDS in just two days.

The pathophysiology of critically-ill COVID-19 patients is attributed to the diffuse alveolar damage that SARS-CoV-2 causes, similar to what was reported in prior SARS patients. While the viral infection targets the alveolar epithelial cells, coronavirus is known for a long incubation period. During this time, the virus can cause multi-organ damage, specifically affecting the spleen, lymph nodes, small blood vessels, heart, liver, and kidney. Consequently, the impaired organs that make up the immune system lead to lymphocytopenia which interferes with clearance of the virus. Autopsy from COVID-19 patients and pathology from those who had pneumonectomy for lung cancer have

shown varying degrees of diffuse alveolar damage, including type II epithelial cell hyperplasia, alveolar cavity fibrosis, and microvascular thrombus [5].

In addition to the virus itself causing alveolar damage, an immunocompromised system poses further challenge to treating critically-ill COVID-19 patients that have elevated levels of IL-1β, IFN-γ, IP-10, and MCP-1, which activate T-helper-1 (Th1) cell responses. Patients who required ICU admission had higher concentrations of G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α than did those not requiring ICU admission. Overall, Huang suggested that the cytokine storm was associated with disease severity. Despite supportive treatment, mortality was as high as 6 of the 41 patients (15%) in this cohort [4].

Early studies with SARS patients showed that elevation of proinflammatory cytokines, such as IL-1β, IL-6, IL-12, IFN-γ, IP-10, and MCP-1, is associated with pulmonary inflammation and extensive lung damage [4]. A prospective cohort study by Wong et al found that SARS patients exhibited a significant increase in the antiviral cytokine IFN-γ and proinflammatory cytokines (IL-1β, IL-6 and IL-12) during a cytokine storm, with a moderate increase in anti-inflammatory IL-10 in only some patients [6]. This selective IL-10 response was not further analyzed. The early elevation of inflammatory cytokines was attributed to the SARS-induced activation of Th-1 cells and NK cells, resulting in pulmonary inflammation. In a former clinical study by Wong et al, 128 of 157 SARS patients (82%) developed neutrophilia associated with ICU admission and mortality from pneumonia [34]. Therefore, studies indicate that polymorphonuclear leukocyte (PMN)-induced acute pneumonitis in the early stages of SARS-CoV-2 infection contributes to the later development of ARDS and ultimately the pulmonary destruction in SARS patients.

A similar elevation of inflammatory cytokines has been reported among MERS patients, although the theory of cytokine storm has been much less studied during the MERS outbreak. A study by Mahallawi et al compared the profile of cytokine responses in plasma samples from MERS patients (n=7) versus those of the healthy controls (n=13) [36]. A strong proinflammatory Th-1 and Th-17 response was seen in MERS patients, with markedly increased concentrations of proinflammatory cytokines (IFN-γ, TNF-α, IL-15, and IL-17), that elicited a type II interferon response with innate and acquired immunity interfering with viral replication [5, 7]. MERS patients also had a marked increase in IFN-α2 concentration compared to the healthy controls (*P*<.01). Infected patients had a significant increase in IFN-α2 ranging from 26 to 71-fold increase when compared to healthy controls, indicating a type I interferon response as first line defense against the viral infection [5].

## 2. Lymphocytopenia and Inflammatory Response

Lymphocytopenia is a prominent marker of COVID-19 that is a diagnostic criteria for COVID-19 in China. Both T cell and NK cell counts are depressed in COVID-19 patients with pronounced reduction noted among the more severe cases [8]. A study by Zhang et al examined COVID-19 patients in Wuhan, China. Patients were categorized as mild versus severe. Severe patients were those with extra-pulmonary systemic hyperinflammation syndrome and required ICU care [9]. Among these patients, CD8+ T cells were reported to be reduced by 28.43% and 61.9% in mild and severe groups respectively, while NK cells were reduced by 34.31% and 47.62% in mild and severe groups respectively [9]. According to prior studies, the more severe cases of COVID-19 were associated with acute lymphocytopenia with destruction of lymphoid tissues including the spleen and lymph node. Immunohistochemical staining showed that CD4+ T cells and CD8+ T cells were decreased, which was associated with an overexpression of proinflammatory cytokines and chemokines. While the mechanism is not conclusive, studies attribute lymphocytopenia in critically-ill COVID-19 patients ultimately to a dysregulation of the immune system [10].

The overall mechanism that leads to rapid respiratory failure in the setting of excessive inflammatory response remains unclear. Prominent theories propose a direct invasion via angiotensin converting enzyme 2 (ACE 2) versus a systemic inflammatory response via the cytokine storm effect. Given that there have been no findings of ACE 2 expression on lymphocytes, it is largely theorized that the

lymphocyte destruction is due to cytokine storm alone. A study by Zhang et al showed that in type II alveolar epithelia and macrophages, virus inclusion bodies were detected, indicating a primary cytokine storm effect [9]. Regardless of the underlying mechanism, anti-inflammatory treatment specifically targeting the cytokine storm effect seems vital to the survival of critically-ill COVID-19 patients, though there is a lack of evidence at this time supporting effective treatments.

## 3. Glucocorticoid Therapy

The effect of glucocorticoids has been extensively studied with SARS and MERS in the past. During the SARS outbreak in 2003, it became the primary immunomodulatory therapy with mixed results. While glucocorticoids improved fever and oxygenation in many cases, other studies showed adverse reactions, including delayed virus clearance or even further worsening of the disease. Currently, glucocorticoids are used to suppress cytokine storm symptoms and improve ARDS.

A retrospective review of 138 patients in Wuhan, China by Wang et al examined characteristics of hospital-related transmission of the illness [11]. The review also analyzed a variety of treatments, including antivirals, antibiotics, and glucocorticoids. While it did not control for any variables, the study found significant treatment differences between ICU patients and non-ICU patients, with a trend toward non-ICU patients receiving some form of treatment. 62 of 138 patients (44.9%) received glucocorticoids. Of the 36 patients admitted to the hospital and transferred to the ICU, 26 patients (72%) were receiving glucocorticoids.

Russel et al reported in a literature review that patients during SARS and MERS outbreaks who received glucocorticoids were more likely to require mechanical ventilation, vasopressor support, and renal replacement therapy. It also did not improve 90-day mortality (adjusted odds ratio 0.8, 95% CI 0.5–1.1; $P$=.12). Rather, the results indicated delayed clearance of viral RNA from respiratory tract secretions (adjusted hazard ratio 0.4, 95% CI 0.2–0.7; $P$<.001) [12]. Because of overall poor clinical support for glucocorticoid therapy, the current WHO guideline does not support glucocorticoid use for treatment of viral pneumonia and ARDS for COVID-19 cases without concurrent conditions such as COPD or asthma that would independently require glucocorticoid use [13].

## 4. IL-6 Antibodies

### 4.1 Tocilizumab (TCZ)

Tocilizumab (TCZ) is a recombinant human interleukin 6 (IL-6) monoclonal antibody that inhibits IL-6 signaling and mediation of inflammatory response. Xu et al conducted a retrospective study to determine the efficacy of TCZ in addition to the typical treatment with Lopinavir, Methylprednisolone, and supplemental oxygen to treat severely-ill COVID-19 patients [14]. Severity was defined by the Diagnosis and Treatment Protocol for Novel Coronavirus Criteria sponsored by the National Health Commission of the People's Republic of China and was defined if one of the following conditions were met: respiratory rate ≥30 breaths/minute, SpO2 ≤93% while breathing room air, or PaO2/FiO2 ratio ≤300mmHg. TCZ 400mg once intravenously was administered to 21 patients. Prior to treatment with TCZ, inflammatory markers, including CRP and IL-6 were measured, with a mean CRP value of 75.06mg/L and mean IL-6 level of 132.38pg/ml [14]. Patients' fevers improved within a few days, and 15 of 20 (75%) patients that required oxygen had improved oxygenation with opacity of lung lesions on CT scans showing improvement in 19 of 21 (91%) of patients. The percentage of peripheral lymphocytes returned to normal in 10 of 19 (53%) of patients with measured levels. Additionally, CRP levels returned to normal in 16 of 19 (84%) of patients by the fifth day of treatment. IL-6 levels, unfortunately, were not measured after treatment [14]. Overall, the data suggested that TCZ may be an effective treatment in severe COVID-19 cases. Based on promising results from the Xu study, Sanofi and Regeneron pharmaceuticals received approval to open a clinical trial on Sarilumab, another anti-IL-6 monoclonal antibody in mid-March [15].

## 4.2 Siltuximab

Siltuximab is an IL-6 targeted monoclonal antibody that has been approved by numerous regulatory bodies including the FDA in the treatment of Castleman's disease who are negative for human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8). Gritti et al began enrollment into the Siltuximab In Serious COVID-19 (SISCO) study at the Papa Giovanni XXIII hospital in Bergamo, Italy in March of 2020 as a retrospective cohort study examining patients receiving Siltuximab versus matched controls [16]. Their primary endpoints were need for invasive ventilation, time spent in ICU, and 30-day mortality. Preliminary results included 21 patients that received a dose of 11mg/kg Siltuximab given over one hour with a second dose per investigator discretion. Five patients received the second dose 48-72 hours after the initial infusion. Clinical improvement was observed in 7 of the 21 patients (33%), 9 patients (43%) stabilized clinically (no change or worsening in condition), and 5 patients (24%) experienced worsening in condition. Of the five that worsened, one died, and one experienced a stroke. Sixteen patients had CRP levels measured with improvement in the days after administration. The study is currently ongoing, and the currently released data is promising in that it offers a potential therapy for COVID-19.

## 4.3 Sarilumab

Sarilumab is an additional IL-6 targeted monoclonal antibody that has been approved in the treatment of rheumatoid arthritis [15].  There is currently no data for the use of Sarilumab in the viral syndromes such as cytokine storm. Given available data for TCZ, additional IL-6 therapies are being investigated. There is currently a phase II/III randomized, double-blind, placebo-controlled trial to evaluate response in severely-ill COVID-19 patients. The primary endpoint is reduction of fever, and the secondary endpoint is decreased demand for supplemental oxygen.

## 5. IL-1 Antibodies

Anakinra is a targeted monoclonal antibody interleukin 1 (IL-1) receptor antagonist that is being investigated. Due to promising current data on TCZ, Anakinra is being investigated in a phase II/III open label, controlled, parallel, three arm study versus Emapalumab or standard of care [17]. Emapalumab is a monoclonal antibody against interferon gamma (IFN-γ), which is currently being used in the treatment of hemophagocytic lymphohistiocytosis, a life-threatening disease caused by excessive immune activation [40].

## 6. Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for decades as the primary choice for prophylaxis and treatment of malaria but also have had effect on the Marburg virus, Zika virus, dengue virus, Ebola virus, and SARS.  CQ blocks viral infection by altering the endosomal pH that is required for viral particles to bind to the cell surface receptor. CQ also interferes with the glycosylation of cellular receptors of SARS, specifically ACE 2. Its immunomodulatory, anti-inflammatory, and antiviral mechanism works synergistically, making it a choice for their efficacy and side-effect profile [18].

An early clinical trial conducted in COVID-19 patients in China showed better clinical outcome and earlier viral clearance in patients treated with CQ compared to control groups [19, 20]. Based on these positive findings, Chinese experts recommended that patients with mild, moderate, and severe cases of COVID-19 pneumonia be treated with 500mg CQ twice per day for 10 days [20].

A clinical trial by Guatret et al studied the effect of HCQ in SARS-CoV-2 patients from hospitals in South France [21]. A total of 26 patients received oral HCQ 200mg three times per day for ten days, and 16 were control patients. Among the HCQ-treated patients, 6 patients also received azithromycin (500mg on day 1, followed by 250mg per day for the next four days) to prevent bacterial superinfection. Each day, patients received a standardized clinical examination along with a

nasopharyngeal sample collection. Additionally, six patients treated with hydroxychloroquine were lost in follow-up by survey due to early cessation of treatment. Despite a small sample size, the study showed that the HCQ treatment was associated with clinical improvement, faster viral load reduction, and effect reinforcement with azithromycin [19]. At day 6 post-inclusion, 14 of 20 of HCQ-treated patients (70%) were virologically cured compared with the 2 of 16 (13%) in the control group ($P$=.001). All patients treated with HCQ and azithromycin combination were virologically cured compared to the 8 of 14 (57.1%) in patients treated with HCQ and 2 of 16 (13%) in the control group ($P$<.001). One patient who was still polymerase chain reaction (PCR) positive on day six post-inclusion under HCQ treatment only received azithromycin in addition to the HCQ on day eight post-inclusion; the viral load was cleared on day nine post-infection. The clearing of viral nasopharyngeal carriage of SARS-CoV-2 is critical as studies have shown that the mean duration of viral shedding in patients with COVID-19 in China was 20 days [19]. Given the prolonged viral shedding period, transmissibility is a critical issue, and further investigation and trials are needed to determine the efficacy of these agents.

## 7. JAK2 Inhibitors

Patients with severe COVID-19 syndrome have elevated counts of Th-17 cells contributing to the development of cytokine storm. Wu and Yang proposed the use of the JAK2 inhibitor Fedratinib for the suppression of Th-17 cytokine production. JAK2 works through STAT3 to mediate IL-6 and IL-23 signals for Th-17 cells. JAK1 and TYK2 receptors work through STAT1 and STAT2, which are important to the function of anti-viral immunity. Wu and Yang thus proposed selective targeting of JAK2 inhibition to mitigate or even prevent the cytokine storm in COVID-19. In their previous testing in vitro, they found that Fedratinib decreased expression of IL-17 and IL-22 expression [41]. Fedratinib is currently approved by the FDA for use in myeloproliferative neoplasms that take advantage of the JAK2 pathway such as polycythemia vera, however, it has not been tested in the setting of viral syndromes yet.

## 8. Targeting the Antioxidant Effect

Other therapies, such as melatonin and Vitamin C, have been implicated in anti-inflammatory and antioxidant effects and could potentially prove beneficial in the COVID-19 setting. There is currently a clinical trial underway for Vitamin C, however, melatonin has not been examined yet at this time.

## 8.1 Melatonin

While many therapies have been proposed based on previous use in viral pandemics, others are proposed simply due to beneficial effects seen in other non-viral conditions. Melatonin, a drug typically used for insomnia, has been found to have beneficial effects in other diseases such as atherosclerosis and respiratory distress. Zhang et al discuss that in contrast to other SARS viruses, CoV-2 infection leads to increased levels of IL-1$\beta$, IFN-$\gamma$, IP-10, and MCP-1, in addition to IL-4 and IL-10, which was diminished in many SARS patients [31]. The study suggested that melatonin mediates anti-inflammatory effects through Sirtuin-1 (SIRT1) which inhibits proteins, down-regulates macrophages toward pro-inflammation, and  attenuates lung injury and inflammation. It has also been shown to suppress pro-inflammatory cytokines and regulate NOD-like receptor 3 (NLRP3) in radiation-induced lung injury.

Melatonin may also have anti-oxidative effects in the setting of ARDS.  Previous studies by Gitto et al used melatonin in newborns with respiratory distress with success due to antioxidant and anti-inflammatory effects [37]. In a study of multiple sclerosis patients, melatonin has been shown to reduce serum concentrations of TNF-a, IL-6, IL-1B, and lipoperoxides, further leading to evidence that it may reduce inflammatory cytokines [38]. Testing melatonin in ICU patients in the past has not shown significant adverse events. Given the high safety profile, Zhang et al proposed the use of

melatonin for study in patients with COVID-19 [31, 39].

## 8.2 Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin that aids in the synthesis of collagen in connective tissue and may also work as an antioxidant. Studies in chicken embryo cultures demonstrated that Vitamin C provided resistance to coronavirus infection. Furthermore, there have been human trials that are suggestive of a lower incidence of pneumonia in groups on Vitamin C treatment [32, 33].

Given previous data on Vitamin C, there is currently an ongoing prospective randomized clinical trial in Wuhan, China examining seven days of high dose intravenous Vitamin C therapy versus placebo with endpoints being ventilator requirements, vasopressor requirements, ICU length of stay, and 28-day mortality. Full results of the study will be expected to release by September [32].

## 9. Convalescent Plasma Therapy

The search for COVID-19 treatment has extended to plasma therapy which has been used in previous viral outbreaks such as SARS, Ebola, and H1N1. Convalescent plasma therapy relies on the purified plasma obtained usually by apheresis from patients that have recovered from the particular infection and subsequently transfused to ABO compatible patients with the active disease. Given previous success, this therapy is currently being proposed in critically-ill patients who have failed more conservative management. In fact, as of March 2020, the FDA approved the use of convalescent plasma therapy to treat critically-ill COVID-19 patients, provided that the treating physicians apply via the process for an investigational new drug (IND) application [22]. Here, we aim to discuss plasma therapy in critically-ill patients as it has been used in prior respiratory viral outbreaks and potential applications in the current pandemic, including efficacy in inflammatory syndromes.

## 9.1 SARS treatment in Hong Kong in 2003

During the height of the SARS epidemic in 2003, Cheng et al explored the efficacy of convalescent plasma therapy. The study included 339 patients that were admitted at the Prince of Wales Hospital in Hong Kong between March 20 and May 26 of 2003 for SARS. Initial treatment was with Cefotaxime and Levofloxacin (or clarithromycin) to treat community-acquired pneumonia. If fever persisted, patients were treated with Ribavirin at 1200mg PO TID or IV 400mg q8h and Prednisolone (0.5-1mg/kg) on day three. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone 500mg I.V. daily for 2-3 doses. For patients that continued to deteriorate per SaO2<90% on 0.5 FiO2, 200-400ml (4-5ml/kg) of ABO-compatible convalescent plasma obtained from recovered SARS patients was administered. 80 of 339 (24%) received convalescent plasma treatment [25].

Of the 80 patients selected for convalescent plasma treatment, 33 (41%) had good outcomes (discharge by day 22), and 47 (59%) had poor outcomes (hospitalization beyond 22 days or death). The median age of patients with good outcomes was 37.9 and the median age of patients with poor outcomes was 50.2 (*P*<.001). The median day of plasma infusion was 11.7 for good outcome patients and 16 for poor outcome patients (*P*<.001). Patients given convalescent plasma before day 14 tended toward a better outcome, with a mortality of 6.3% (3/48) versus 22% (7/32) in before or after day 14 groups (*P*=.08). 20 of 33 (61%) of patients with good outcome were PCR positive and seronegative for coronavirus compared to 10 of 47 (21%) with poor outcome (*P*<.001). The 30 patients that were PCR positive and seronegative at the time of convalescent plasma therapy had better outcomes than patients already seropositive 67% (20 of 30) vs 20% (10 of 50) (*P*=.001). There were no reported adverse effects after administration of plasma infusions, however, the primary limitation of plasma convalescent therapy was availability. Mortality rate recorded in the study was 13% (10 of 80) while the SARS mortality rate in Hong Kong during that same time period was 17% (299 of 1755) from

March 6 to May 24 of 2003 [25].

## 9.2 H1N1 Treatment in Hong Kong in 2009

During the H1N1 virus pandemic of 2009, Hung et al examined the effects of convalescent plasma treatment in critically-ill patients in Hong Kong via a prospective cohort study. From September 1, 2009 to June 30, 2010, patients above the age of 18 with H1N1 infection requiring intensive care were offered treatment with convalescent plasma harvested via apheresis from suitable donors [26]. 93 patients were recruited with 20 patients receiving plasma therapy. The remaining patients declined plasma treatment and were included as untreated controls. Donors were selected by reverse transcriptase-polymerase chain reaction (RT-PCR) positive influenza A virus M and pandemic H1 genes and negative RT-PCR testing of seasonal influenza A virus H1 and H3 genes with clinical recovery from infection at least 2 weeks in addition to meeting standard plasma donation criteria. All patients received treatment with oseltamivir and inhaled zanamivir for Influenza.

Of the patients that received convalescent plasma therapy versus untreated patients, mortality was found to be 20% (4 of 20) versus 55% (40 of 73) with $P$=.01 [26]. Overall mortality was 47% (44 of 93). Other measured factors included viral load, IL-6, IL-10, and TNF-α which were all found to be significantly lower in the treatment group on subsequent measurements. No reported adverse events were recorded from plasma therapy.

## 9.3 SARS-CoV-2 Treatment in Shenzhen, China in 2020

One of the earliest studies of convalescent plasma therapy for SARS-CoV-2 was done by Shen et al in Shenzhen, China. From January 20, 2020 through March 25, 2020 at Shenzhen Third People's Hospital, five critically-ill COVID-19 patients were treated with convalescent plasma transfusion [27]. Selection criteria included COVID-19 diagnosis via RT-PCR, severe pneumonia with rapid progression ($P_aO_2/F_iO_2$ of < 300 with mechanical ventilatory support), and continuously high viral load despite antiviral treatment.

Treatment prior to plasma therapy included methylprednisolone, lopinavir/ritonavir, interferon alfa-1b, arbidol, and favipiravir. One day prior to receiving treatment, the patient's blood was collected and enzyme-linked immunosorbent assay (ELISA) and neutralizing antibody titers were tested. On the day of treatment, ABO blood type and compatibility with convalescent plasma donors were measured. Patients were then treated with two consecutive transfusions of 200-250mL ABO-compatible convalescent plasma for 400mL in total with ongoing treatment with antiviral agents until SARS-CoV-2 viral loads were negative [27].

Convalescent donors were between 18 and 60 years of age and had recovered from SARS-CoV-2 infection. They were previously diagnosed with COVID-19 by qRT-PCR and tested negative for SARS-CoV-2, respiratory viruses, hepatitis B, hepatitis C, HIV, and syphilis. They were also required to be asymptomatic for at least 10 days and have SARS-CoV-2 specific ELISA antibody titer higher than 1:1000 and a neutralizing antibody titer greater than 40. Donation of 400mL of convalescent plasma was then obtained by apheresis and immediately transfused to recipients [27].

Administration of plasma was between 10 to 22 days with the median being day 20. Patients were between 30 and 70 years of age. Of the five patients, only one had pre-existing conditions of hypertension and mitral insufficiency, and none had a history of smoking. Measured characteristics before and after transfusion included body temperature, cycle threshold value, procalcitonin, CRP, and IL-6 levels [27].

Results noted improvement of cycle threshold value one day post transfusion, with negative testing achieved between days 1 to 12 post transfusion. IL-6, CRP, and procalcitonin trended downward. Of the five patients, three were able to be weaned from ventilation, and one was able to be weaned from ECMO to mechanical ventilation. Donor's plasma receptor binding domain IgG and IgM and neutralizing antibody titers were measured via a cell culture in order to determine inhibition activity

against SARS-CoV-2 [27].

## 9.4 Risks and Challenges to Plasma Therapy

Convalescent plasma therapy involves strict quality control to ensure that there is adequate neutralizing antibody present in the obtained plasma. However, even with quality control, it is not without risk. The risks of convalescent plasma include the same risks as those with transfusion of any blood products: anaphylactic shock, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI).

During the MERS outbreak in May 2015, convalescent plasma therapy was utilized in many patients. Chun et al described one such patient that experienced an unfortunate complication from this therapy [28]. The patient was a 32-year-old male who was admitted and diagnosed with MERS and subsequently treated with ribavirin and lopinavir/ritonavir, as well as a single dose of interferon α-2a. ABO/RhD compatible convalescent plasma was then obtained from a patient who had previously recovered from MERS. Within two hours of transfusion, the patient developed respiratory distress that was concerning for TRALI despite apparent compatibility. Viral load was found to be reduced in the patient, and retrospective analysis was not able to trace anti-HLA or anti-HNA antibodies.

Investigation into these issues has shown that the additive risk of HLA in female donors with one childbirth can be as high as 14.5%, arguing for a preference toward male donors to reduce this risk [23, 24, 29]. Since then, many studies and authors have suggested the use of only male donors citing a previous review [24].

In addition to the limitations in the case series published by Shen, Roback and Guarner in their editorial to JAMA reported difficulties in finding standard antibody doses from donors of convalescent plasma [27, 30]. Therefore, they proposed combining convalescent plasma with hyperimmune globulin (H-Ig). Unlike convalescent plasma, H-Ig has standardized antibody doses from collecting plasma samples from patients with high antibody titers and filtering out IgM antibodies. H-Ig and convalescent plasma may both be stored for years. Monitoring patient response in comparison to objective lab values such as antibody titers and neutralizing activity could help identify which patients can be donors or recipients [30].

## Conclusion

SARS-CoV-2 is a global pandemic that has challenged the world of medicine, research, and healthcare. The purpose of this paper is to highlight the important current and developing therapies in the management of severe COVID-19, in particular, therapies that can aid in the syndrome known as cytokine storm.

Immunomodulators such as Siltuximab, Anakinra, Sarilumab, Fedratinib, and Tocilizumab target different components of the inflammatory cascade involved in cytokine storm and are in clinical trials. Data is currently strongest for Tocilizumab, however, results of these studies are not all ready, and investigators may wish to evaluate if patients could be candidates for any one of these trials.

While convalescent plasma therapy works by using passively produced antibodies from patients recovered from the illness to treat patients in active disease states, a preliminary case series from China has found that there may also be activity that reduces the markers of cytokine storm such as interleukin 6. Further use of this therapy is underway in multiple nations around the world in various clinical trials, and it is a promising avenue of treatment for critically-ill patients.

The treatment for COVID-19 has been met with dire need and urgency during this global pandemic. Current treatments are essentially limited to supportive care and treatment of secondary infections without directly targeted therapies to either the virus or the hypothesized cytokine storm. While there are a number of clinical trials underway with constantly new therapies being proposed for critically-ill patients, further study and concrete data are needed to establish treatment guidelines.

## Conflicts of Interests

None declared.

## Abbreviations

ACE 2: angiotensin converting enzyme 2

ARDS: acute respiratory distress syndrome

COVID-19: coronavirus disease 2019

CQ: chloroquine

CRP: C-reactive protein

ECMO: extracorporeal membrane oxygenation

ELISA: enzyme-linked immunosorbent assay

GCSF: granulocyte colony-stimulating factor

H-Ig: hyperimmune globulin

H1N1: pandemic Influenza A

HCQ: hydroxychloroquine

HHV-8: human herpesvirus-8

HIV: human immunodeficiency virus

HLA: human leukocyte antigen

HLH: hemophagocytic lymphohistiocytosis

HNA: human neutrophil antigen

ICU: intensive care unit

IFN: interferon

Ig: immunoglobulin

IL: interleukin

IND: investigational new drug

IP-10: interferon-inducible protein 10

IV: intravenous

JAK2: Janus kinase 2

MERS: Middle East Respiratory Syndrome

MCP-1: monocyte chemoattractant protein 1

MIP1A: macrophage inflammatory protein 1A

NK: natural killer

NLRP3: NOD-like receptor protein-3

PMN: polymorphonuclear leukocyte

PO: per os

RT-PCR: reverse transcriptase-polymerase chain reaction

SARS: severe acute respiratory syndrome

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SIRT1: Sirtuin-1

SISCO: Siltuximab in serious COVID-19

STAT: signal transducer and activator of transcription

TACO: transfusion-associated circulatory overload

TCZ: Tocilizumab

Th: T helper

TID: ter in die

TNFα: tumor necrosis factor alpha

TRALI: transfusion-related acute lung injury

WHO: World Health Organization

## References

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. (2020, March 11). Retrieved March 30, 2020, from https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

2. Wilson N, Kvalsvig A, Barnard L, et al. Case-Fatality Risk Estimates for COVID-19 Calculated by Using a Lag Time for Fatality. *Emerging Infectious Diseases*. 2020;26(6):1339-1441. doi:10.3201/eid2606.200320

3. Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu SY, Zhao JP, Zhou M, Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China, Annals of Oncology (2020), doi: 10.1016/j.annonc.2020.03.296

4. C Huang, Y Wang, X Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395 (2020), pp. 497-506. doi:https://doi.org/10.1016/S0140-6736(20)30183-5

5. Zhang Ting, Sun Luxi, Feng Rui'e. Clinical and pathological manifestations and comparative analysis of severe acute respiratory syndrome and new coronavirus pneumonia [J / OL]. Chinese Journal of Tuberculosis and Respiratory Diseases, 2020,43 (2020-04-03). : //rs.yiigle.com/yufabiao/1186974.htm. DOI: 10.3760 / cma.j.cn112147-20200311-00312. [Pre-published online].

6. Wong RSM, Wu AKL, To KF, et al. Haematological changes in patients with severe acute respiratory syndrome. Br Med J. 2003;326:1358–62. doi: 10.1136/bmj.326.7403.1358

7. A. Gattoni, A. Parlato, B. Vangieri, M. Bresciani, R. Derna, Interferon-gamma:biologic functions and HCV therapy (type I/II) (2 of 2 parts), La Clinica terapeutica157 (2006) 457–468.PMID: 17147054

8. National Health Commission of the People's Republic of China, The Diagnosis and Treatment Plan for 2019-nCoV (The Seventh Trial Edition), http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml (accessed 4 March 2020).

9. Zhang, W, Zhao, Y, Zhang, F, Wang, Q, Li, T, Liu, Z, Zhang, S (2020). The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clinical Immunology, 214, 108393. doi: 10.1016/j.clim.2020.108393

10. C Qin, L Zhou, Z Hu, S Zhang, S Yang, Y Tao, et al, Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa248.

11. Wang, D, Hu, B, Hu, C, Zhu, F, Liu, X, Zhang, J, Peng, Z (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. Jama, 323(11), 1061. doi: 10.1001/jama.2020.1585

12. Russell, C D, Millar, J E, & Baillie, J K (2020). Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. The Lancet, 395(10223), 473–475. doi: 10.1016/s0140-6736(20)30317-2

13. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed 2020 Mar 19.

14. X Xu, M. Han, T Li, W Sun, D Wang, B Fu, et al. Effective treatment for severe COVID-19 patients with tocilizumab. ChinaXiv:20200300026 (2020) doi: 10.1073/pnas.2005615117

15. Sanofi and Regeneron begin global Kevzara® (sarilumab) clinical trial program in patients with severe COVID-19 [press release]. Cambridge, Mass and Tarrytown, NY; Sano-fi: March 16, 2020. http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19. Accessed 2020 Mar 19.

16. Gritti, G, Raimondi, F, Ripamonti, D, Riva, I, Landi, F, Alborghetti, L, Rambaldi, A (2020). Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. doi: 10.1101/2020.04.01.20048561

17. Nicastri, Emanuele et al. Swedish Orphan Biovitrum. Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients with COVID-19 Infection. ClinicalTrials.gov. National Library of Medicine (U.S.). NLM identifier: NCT04324021. Accessed 2020 Mar 30. Available from https://clinicaltrials.gov/ct2/show/study/NCT04324021

18. Zhang, W, Zhao, Y, Zhang, F, Wang, Q, Li, T, Liu, Z, Zhang, S (2020). The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clinical Immunology, 214, 108393. doi: 10.1016/j.clim.2020.108393

19. Q Zhang, Y Wang, C Qi L Shen, J Li, Clinical trial analysis of 2019-nCoV therapy registered in China, J. Med. Virol, (2020), doi:10.1002/jmv.25733

20. L Dong, S Hu, J Gao. Discovering drugs to create coronavirus disease 2019 (COVID-19), Drug

Discov. Ther. 14 (2020) 58-60. doi: 10.5582/ddt.2020.01012

21. Gautret, Philippe, et al. "Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Preliminary Results of an Open-Label Non-Randomized Clinical Trial." 2020. doi:10.1101/2020.03.16.20037135

22. Tanne, J H (2020). Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. Bmj, m1256. doi: 10.1136/bmj.m1256

23. Maclennan, S, & Barbara, J A (2006). Risks and side effects of therapy with plasma and plasma fractions. Best Practice & Research Clinical Haematology, 19(1), 169–189. doi: 10.1016/j.beha.2005.01.033

24. Schmickl, C N, Mastrobuoni, S, Filippidis, F T, Shah, S, Radic, J, Murad, M H, Gajic, O (2015). Male-Predominant Plasma Transfusion Strategy for Preventing Transfusion-Related Acute Lung Injury. Critical Care Medicine, 43(1), 205–225. doi: 10.1097/ccm.0000000000000675

25. Cheng, Y, Wong, R, Soo, Y O Y, Wong, W S, Lee, C K, Ng, M H L, Cheng, G (2004). Use of convalescent plasma therapy in SARS patients in Hong Kong. European Journal of Clinical Microbiology & Infectious Diseases, 24(1), 44–46. doi: 10.1007/s10096-004-1271-9

26. Hung, I F, To, K K, Lee, C-K, Lee, K-L, Chan, K, Yan, W-W, Yuen, K-Y (2011). Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection. Clinical Infectious Diseases, 52(4), 447–456. doi: 10.1093/cid/ciq106

27. Shen, C, Wang, Z, Zhao, F, Yang, Y, Li, J, Yuan, J, Liu, L (2020). Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. Jama. doi: 10.1001/jama.2020.4783

28. Chun, S, Chung, C R, Ha, Y E, Han, T H, Ki, C-S, Kang, E-S, Cho, D (2016). Possible Transfusion-Related Acute Lung Injury Following Convalescent Plasma Transfusion in a Patient With Middle East Respiratory Syndrome. Annals of Laboratory Medicine, 36(4), 393. doi: 10.3343/alm.2016.36.4.393

29. *Handbook of Transfusion Medicine*. Norwich: The Stationery Office; 2001.

30. Roback, J D, & Guarner, J (2020). Convalescent Plasma to Treat COVID-19. Jama. doi: 10.1001/jama.2020.4940

31. R Zhang, X Wang, L Ni, et al. COVID-19: Melatonin as a potential adjuvant treatment, Life Sciences (2020), https://doi.org/10.1016/j.lfs.2020.117583

32. Peng, ZhiYong. Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia. ClinicalTrials.gov. National Library of Medicine (U.S.). NLM Identifier NCT04264533. Accessed 2020 April 3. Available from: https://clinicaltrials.gov/ct2/show/NCT04264533.

33. Kashiouris MG, L'Heureux M, Cable CA et al. The emerging role of vitamin C as a treatment for sepsis. Nutrients. 2020; 12 pii: E292. DOI: 10.3390/nu12020292. PMID: 31978969

34. CK Wong, CWK Lam, AKL Wu, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol, 136 (2004), pp. 95-103. doi: 10.1111/j.1365-2249.2004.02415.x

35. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-346. doi: http://dx.doi.org/10.15585/mmwr.mm6912e2

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

37. E Gitto, RJ Reiter, G Sabatino, G Buonocore, C Romeo, P Gitto, C Buggé, G Trimarchi, I Barberi. Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: improvement with melatonin treatment, J. Pineal Res. 39 (2005) 287–293. doi: 10.1111/j.1600-079X.2005.00251.x

38. AL Sanchez-Lopez, GG Ortiz, FP Pacheco-Moises, MA Mireles-Ramirez, OK Bitzer-Quintero, DLC Delgado-Lara, LJ Ramirez-Jirano, IE Velazquez-Brizuela. Efficacy of melatonin on serum pro-inflammatory cytokines and oxidative stress markers in relapsing remitting multiple sclerosis, Arch.

Med. Res. 49 (2018) 391–398. doi: 10.1016/j.arcmed.2018.12.004

39. G Mistraletti, M Umbrello, G Sabbatini, S Miori, M Taverna, B Cerri, ES Mantovani, P Formenti, P Spanu, A D'Agostino, S Salini, A Morabito, F Fraschini, RJ Reiter, G Iapichino. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial, Minerva Anestesiologica. 81 (2015). PMID: 25969139

40. Sobi to initiate a clinical study to evaluate whether anakinra and emapalumab may relieve complications associated with severe COVID-19 disease [press release]. Stock-holm, Sweden; Swedish Orphan Biovitrum AB (publ): March 18, 2020. https://www.sobi.com/sites/default/files/pr/202003183346-1.pdf. Accessed 2020 Mar 30.

41. Wu, D, & Yang, X O (2020). TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *Journal of Microbiology, Immunology and Infection*. doi: 10.1016/j.jmii.2020.03.005

# **Supplementary Files**

# Figures

Flow Diagram of Search Results.



Figure 1. Flow Diagram of Search Results.
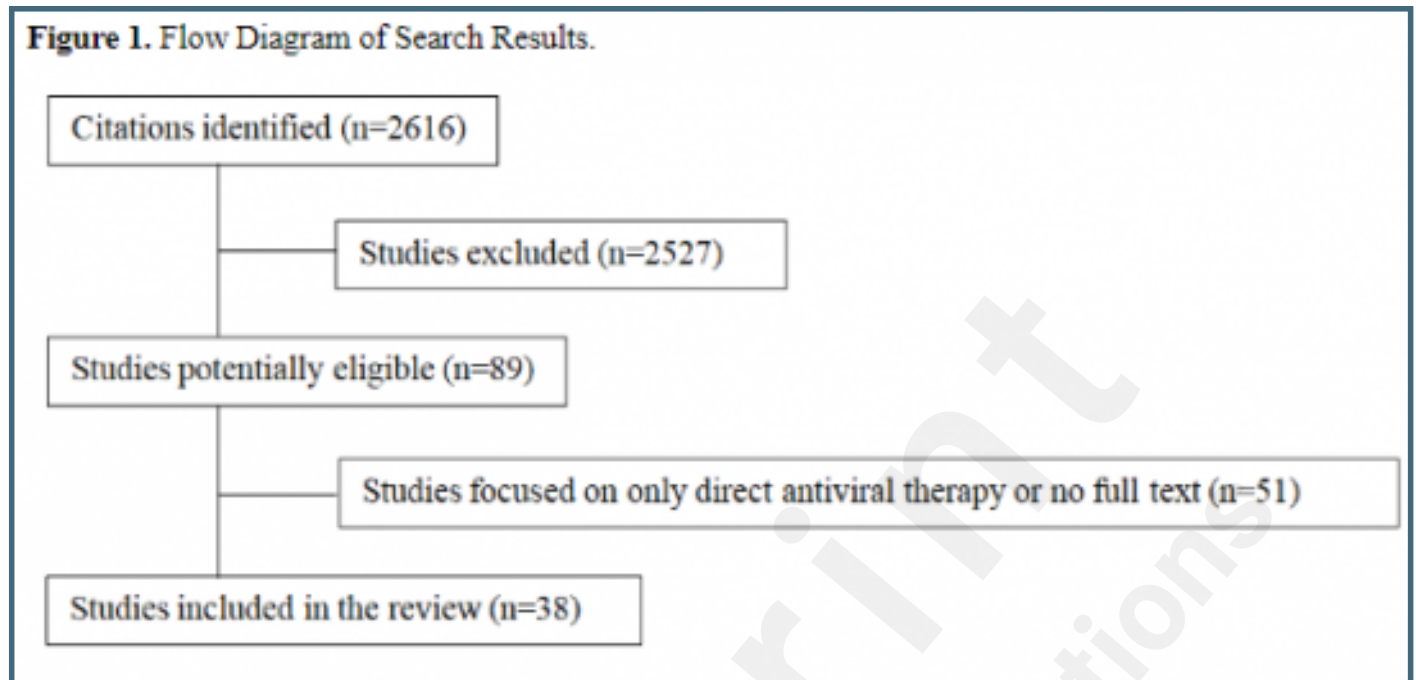
Clinical Management Studies in Viral Outbreaks.

**Figure 2.** Clinical Management Studies in Viral Outbreaks

|  | SARS-CoV-2 | MERS | H1N1 | SARS |
|---|---|---|---|---|
| Glucocorticoids | Wang et al. 2020.[a] [11] WHO. 2020. [13] | Russell et al. 2020. [c] [12] | WHO. 2020. [13] | Russell et al. 2020. [c] [12] |
| IL-6 Antibody | Xu et al. 2020.[b] [14] Sanofi. 2020. [15] Gritti. 2020.[b] [16] |  |  |  |
| IL-1 Antibody | Nicastri et al. 2020. [b][17] Sobi. 2020. [40] |  |  |  |
| CQ/HCQ | Zhang et al. 2020. [b] [19] Dong et al. 2020. [c] [20] Gautret et al. 2020. [b] [21] |  |  | Zhang et al. 2020. [c] [18] |
| JAK2 Inhibitors | Wu et al. 2020. [b] [41] | Wu et al. 2020. [b] [41] | Wu et al. 2020. [b] [41] |  |
| Antioxidants | Zhang et al. 2020. [c] [31] Peng. 2020. [b] [32] | Zhang et al. 2020. [c] [31] |  | Zhang et al. 2020. [c] [31] |
| Plasma Therapy | Tanne, J H. 2020. [22] Roback et al. 2020. [30] Shen et al. 2020. [b] [27] | Chun et al. 2016. [a] [28] | Hung et al. 2011. [b] [26] | Cheng et al. 2004. [b] [25] |

[a]Case Report
[b]Series of Cases/Observational Studies
[c]Review