

## MINIREVIEW

# SARS, MERS and COVID-19: clinical manifestations and organ-system complications: a mini review

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**One sentence summary:** This manuscript compares the effects of MERS, SARS and COVID-19 that may arise as damage to separate organ systems or as part of an immune mediated multi-organ failure.

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## ABSTRACT

Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and Coronavirus Disease 2019 (COVID-19) are caused by three distinct coronaviruses belonging to the same genus. COVID-19 and its two predecessors share many important features in their clinical presentations, and in their propensity for progression to severe disease which is marked by high rates of morbidity and mortality. However, comparison of the three viral illnesses also reveals a number of specific differences in clinical manifestations and complications, which suggest variability in the disease process. This narrative review delineates the pulmonary, cardiac, renal, gastrointestinal, hepatic, neurological and hematologic complications associated with these three respiratory coronaviruses. It further describes the mechanisms of immune hyperactivation—particularly cytokine release syndrome—implicated in the multi-organ system injury seen in severe cases of MERS, SARS and COVID-19.

**Keywords:** severe acute respiratory syndrome coronavirus 1; Middle East respiratory syndrome coronavirus; severe acute respiratory syndrome coronavirus 2; coronavirus disease 2019; cytokine release syndrome; pneumonia; acute respiratory distress syndrome; acute neurologic syndrome; central neurogenic respiratory failure; heart failure; acute kidney injury; acute hepatic injury

## INTRODUCTION

Coronaviruses have long been recognized as causative agents in self-limited upper respiratory tract infections affecting humans (Falsey *et al.* 1997), however three strains belonging to the Betacoronavirus (Viruses ICoTo and ICTV 2020) genus have been shown to cause more complications and worse patient outcomes than other strains overall (World Health Organization 2019, 2020, 2020). These three viruses are the Middle East

Respiratory Syndrome- related virus (MERS-CoV), Severe Acute Respiratory Syndrome- related virus (SARS CoV-1) and Severe Acute Respiratory Syndrome- related virus (SARS CoV-2), also known as Coronavirus Disease 2019- related virus (COVID-19 virus). MERS CoV was first identified in Jordan in 2012 (World Health Organization 2019), SARS CoV-1 was first described in Guangdong province, China in 2002, (World Health Organization 2020) and SARS CoV-2 was first detected in Hubei province,

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China in 2019 (World Health Organization 2020). SARS CoV-2/COVID-19 is an ongoing pandemic which to date has spread to more than 100 countries (World Health Organization 2020). In addition, MERS is still considered to be an ongoing epidemic but appears to be limited to its area of origin (Al-Tawfiq, Kattan and Memish 2016). On the other hand, according to the National Health Service (NHS) no new cases of SARS CoV-1 infection have been reported in humans since 2004 (National Health Service 2019). The estimated case fatality rates (CFR) for MERS and SARS were 20% and 6.4% respectively (Feng et al. 2009; Mizumoto et al. 2015), while the CFR for COVID-19 is estimated to be around 2.3% (Porcheddu et al. 2020). Nonetheless, despite its lower CFR, COVID-19 has thus far resulted in more deaths than both SARS and MERS combined (Mahase 2020). With regard to transmissibility, SARS CoV-2 has a reproduction number (R0) of 3.28 (Liu et al. 2020), whereas the R0 of SARS CoV-1 was approximately three according to estimates by the World Health Organization (WHO) (World Health Organization 2003). MERS CoV was found to have an R0 in the range of 2.0–2.8 during its initial outbreak in Riyadh, Saudi Arabia, versus an R0 in the range of 3.5–6.7 during a second outbreak occurring 11 days later in Jeddah, Saudi Arabia (Majumder et al. 2014). In addition to exhibiting some similarity in their levels of transmissibility, the diseases caused by these coronaviruses are characterized by similar presentations and complications—with notable variations—affecting different organ systems (Peeri et al. 2020).

## PULMONARY COMPLICATIONS

Pneumonia is an extremely common manifestation of these three viral diseases. It typically follows the initial presentation of a flu-like illness including fever, myalgia, cough and malaise, occurring in SARS (Sampathkumar et al. 2003), MERS (Banik, Khandaker and Rashid 2015) and COVID-19 (Jiang et al. 2020). In fact, up to 70% (Banik, Khandaker and Rashid 2015) or even 90% (Saad et al. 2014) of MERS patients eventually develop pneumonia, and all COVID-19 hospitalized patients in an early cohort from Wuhan developed pneumonia (Huang et al. 2020). In COVID-19, this pneumonia appears to predict poor outcome; 25.9% (72/278) of patients in a pooled cohort with pneumonia were admitted to an intensive care unit (ICU) (Lai et al. 2020).

Some clinical features are unique to each pandemic. While the presentation of COVID-19 can be variable, ranging from no symptoms to mild upper respiratory tract infection to respiratory failure (Zhou et al. 2020), upper respiratory symptoms appear infrequently in MERS (Arabi et al. 2014). Perhaps unique among the coronavirus pneumonias is SARS' bi- or triphasic presentation. A SARS patient may appear to recover from his/her initial illness before rapidly deteriorating (new fever, chest infiltrates, respiratory failure and watery diarrhea) a few days later (Sampathkumar et al. 2003). The first phase corresponds to viral replication and is marked by fever, myalgia and systemic symptoms, while the second phase reflects immune-mediated lung damage coinciding with a decrease in viral load (Hui, Wong and Wang 2003); this phased course may be explained by acute respiratory distress syndrome (ARDS)-like pathophysiology (discussed below).

ARDS is seen fairly often in the context of these diseases, and has been reported in up to 30% of SARS patients (Huang et al. 2005), 40% of MERS patients (Saad et al. 2014) and approximately 30% of hospitalized COVID-19 patients (Huang et al. 2020). Interestingly, a full 93% (50/54,  $P < 0.0001$ ) of patients who developed ARDS in a Chinese cohort were non-survivors (Zhou et al. 2020).

On autopsy, lung findings post-ARDS seem fairly uniform across the three diseases (Xu et al. 2020). Common features include epithelial desquamation and regeneration, and diffuse alveolar damage, possibly due to direct damage from the virus (Nicholls et al. 2006). One case report of a COVID-19 patient who succumbed to ARDS noted pathologic changes in the liver (microvascular steatosis), which may have been either due to the virus itself, or drug-induced (Xu et al. 2020).

The model of ARDS in these diseases is supported by radiographic and clinical data. SARS patients who suffer clinical deterioration in the phased manner typical of this disease often show bilateral lung involvement that resembles ARDS on radiologic imaging seen in other diseases (Tse et al. 2004). It is possible that an interferon-gamma (IFN- $\gamma$ ) mediated cytokine storm after SARS infection is the culprit (Huang et al. 2005). In fact, ARDS usually does not present until the third week of a SARS infection, whereas peak viral loads are observed around day 10 (Sampathkumar et al. 2003), leaving open the possibility that the host immune system is responsible for late-phase deterioration. MERS-associated ARDS shows typical signs on imaging (Ajlan et al. 2014), which resemble those of SARS-ARDS (acute hypoxic respiratory failure) (Arabi et al. 2014). Curiously, all 12 members of a cohort of MERS patients in Saudi Arabia who developed ARDS suffered from comorbidities (asthma, diabetes mellitus, renal failure and others), suggesting that ARDS tends to manifest more often in susceptible patients (Arabi et al. 2014).

## CARDIAC COMPLICATION

Heart problems have been reported fairly frequently, at least among MERS and COVID-19 patients. In a Saudi cohort of 70 MERS patients, for example, 11 of them (15.7%) developed arrhythmia, and 10 (14.3%) developed rhabdomyolysis (Saad et al. 2014) (it is unclear if the arrhythmia and rhabdomyolysis were related). Among COVID-19 patients, heart problems also seem fairly prevalent; acute cardiac injury or elevated cardiac enzymes were reported in five (12%) out of a cohort of 41 patients from Wuhan (Huang et al. 2020) and in 18 out of 80 patients (22.50%) of a cohort from Jiangsu province in China (Wu et al. 2020). One study found that levels of troponin I increased quickly in non-survivors of COVID-19 starting on day 16, whereas LDH levels initially increased in both survivors and non-survivors but started falling on day 14 in survivors (Zhou et al. 2020). In addition, heart failure was reported in 44 out of a group of 191 (23%) COVID-19 patients ( $P < 0.0001$ ); of the 44, 28 were non-survivors (Zhou et al. 2020).

## RENAL COMPLICATIONS

Kidney damage, especially acute kidney injury (AKI), appears to be frequent in the context of these diseases, especially MERS. In a Saudi cohort, 30 out of 70 MERS patients (42.9%) developed AKI during the course of their illness (Saad et al. 2014). Among critically ill MERS patients, the numbers are even higher—58% (7/12 patients) in one study required renal replacement therapy (Arabi et al. 2014). Arabi and coworkers have noted lower rates of AKI in the context of MERS in countries like Canada, where patients may not have as many comorbidities as those in Saudi Arabia; furthermore, the investigators suggested the possibility of direct renal involvement by the viral infection, as MERS can be isolated from the urine of affected patients.

In COVID-19, kidney damage is reported in as few as in 2.5% of hospitalized patients (2/80 individuals, a cohort in Jiangsu,

China; Wu et al. 2020). Another group reported AKI in 28/191 (15%;  $P < 0.001$ ) of Wuhan patients, although 27 (50%) of their non-survivors suffered AKI (Zhou et al. 2020).

## GASTROINTESTINAL COMPLICATIONS

Nonspecific gastrointestinal symptoms are commonly reported. Diarrhea, nausea and a variety of related complaints were documented in up to 10% of COVID-19 patients in one cohort (Jiang et al. 2020), in 30.0% of MERS patients (Saad et al. 2014) and in 20.3% of SARS patients (Leung et al. 2003). Among SARS patients, watery diarrhea was most often reported in the first week of illness, and the diarrhea did not correlate with mortality or subsequent requirement for supplemental oxygen (Leung et al. 2003); furthermore, Leung and coworkers detected viral particles on biopsy of the small intestine and colon (Leung et al. 2003).

## HEPATIC COMPLICATIONS

Acute hepatic injury has been reported, most often in MERS. In one Saudi cohort, 22/70 patients (31.4%) suffered from liver dysfunction during their illness (Saad et al. 2014). In a separate MERS cohort of critically ill patients, as many as half of these patients exhibited elevated aminotransferases during their ICU stay (Arabi et al. 2014). Although liver dysfunction has been reported in COVID-19 patients, its prevalence seems much lower; only 3/80 (3.75%) of patients in a Chinese cohort showed abnormal liver enzymes, and it should be further noted that this proportion was even lower than that in Wuhan (Wu et al. 2020).

## NEUROLOGIC COMPLICATIONS

Acute neurologic syndromes have been reported in both SARS and MERS; this phenomenon seems less common in COVID-19, although the latter pandemic is still evolving. An early report described a SARS patient who developed respiratory failure and status epilepticus several days after mounting a fever; SARS-CoV RNA was detected in her cerebrospinal fluid (CSF), suggesting a demyelinating disease process (Hung et al. 2003). Another case described a pregnant woman who suffered from generalized tonic-clonic seizures on day 22 of a SARS infection; RT-PCR for SARS-CoV in CSF was positive, even though CSF parameters were normal, and no focal neurologic deficits were observed (Lau et al. 2004).

MERS patients appear to have some risk of developing neurologic symptoms, although the presentation and pathophysiology seem to differ from those associated with SARS. Seizures were reported in 6/70 patients (8.6%) in a Saudi cohort (Saad et al. 2014). Another group described three MERS patients with severe neurologic symptoms. These patients presented with altered consciousness, coma, ataxia and focal motor deficits. On magnetic resonance imaging (MRI), T2-weighted images showed non-enhancing bilateral hyperintense lesions in white matter and in subcortical regions of the frontal, temporal, parietal lobes. Arabi et al did not report virus detection in brain tissue or CSF but noted that the disease process resembled acute disseminated encephalomyelitis, or non-occlusive stroke via MERS vasculopathy (Arabi et al. 2015).

The possibility of central neurogenic respiratory failure in the setting of coronavirus infection is supported by some evidence from animal models (Li et al. 2020). Netland et al. (2008) used transgenic mice with humanized Angiotensin converting

enzyme-2 (ACE2) receptors that could efficiently bind SARS-CoV-1 viral particles, to establish that SARS-CoV-1 particles could enter the brain via intranasal inoculation. The infection propagated from the sinuses to the olfactory bulb. Once the infection of the olfactory bulb was established, the infection spread throughout the brain to reach the medullary respiratory center; consequently, these mice died from central respiratory failure. Interestingly, the lungs of the mice showed minimal pathological changes, and the initial concentration of ACE2 receptors in brain tissue was only 1% of their concentration in lung tissue. In this experiment, establishing an infection of the sinuses may have been essential because hematogenous spread to the brain is unlikely (Ding et al. 2004). Similarly, Li et al. used transgenic mice positive for human dipeptidyl peptidase 4 (DPP-4) to show that a similar brain-infection mechanism of SARS-CoV-1 could occur once mice were inoculated with MERS-CoV intranasally; the infection showed a predilection for the thalamus and brainstem (the latter containing the respiratory center; Li et al. 2016). Until now, there have been no studies demonstrating SARS-CoV-2 involvement in damage to the respiratory centers. However, presentation with such an entity would merit thorough investigation, due to its complex involvement of both the peripheral components and the central neurologic components of the respiratory system.

Furthermore, several multicentric cohort studies demonstrated associations between anosmia and COVID-19 (Gane, Kelly and Hopkins 2020; Lechien et al. 2020). Of note, the pathogenesis of anosmia is not related to olfactory bulb damage demonstrated in SARS-CoV-1-positive mice or to any direct insult to the central nervous system. Instead it has been attributed to non-neural cell expression of SARS-CoV-2 entry genes in the respiratory epithelium (Brann et al. 2020), a finding which has been confirmed in both human and murine models.

Gustatory dysfunction seems to accompany olfactory dysfunction and may occur independently from nasal symptoms of COVID-19<sup>41</sup>. As with anosmia, dysgeusia was more prevalent among female patients with COVID-19 than male patients, in a multi-center European study by Leichen et al (2020). This finding was attributed to 'gender-related differences in the inflammatory reaction process' (Lechien et al. 2020), however further investigation of the pathogenesis of dysgeusia in the setting of COVID-19 is warranted.

## HEMATOLOGIC COMPLICATIONS

Sepsis and hypercoagulation are constant concerns in respiratory-infection patients, and these problems are particularly relevant in COVID-19. Sepsis was noted in 54/54 (100%) of non-survivors in one cohort, and septic shock in 38/54 (70%) of non-survivors ( $P < 0.0001$ ) (Zhou et al. 2020). In the same study, investigators correlated elevated D-dimer ( $> 1$  microg/mL) with fatal outcome (Zhou et al. 2020), yet current data do not support the use of prophylactic anti-coagulation in the setting of COVID-19 patients with no clinical indication for anti-coagulant use (Connors and Levy 2020). Indeed, COVID-19 coagulopathy is likely to present with elevated D-dimer and fibrin/fibrinogen products in the setting of normal prothrombin time, partial thromboplastin time and platelet counts (Connors and Levy 2020); these findings may appear in early COVID-19 infection even when there is no clinically identifiable bleeding. Interestingly, the pathophysiology of SARS-CoV-2-induced coagulopathy may be linked to the receptor of viral adhesion, the ACE2 receptor, which is abundant on vascular endothelial cells – and thus may facilitate endothelial dysfunction and



further coagulopathy in COVID-19 infections (Varga et al. 2020). Reports of SARS-CoV-2 viral inclusions in endothelial cells in postmortem studies (Varga et al. 2020) further support this mechanism for SARS-CoV-2 related coagulopathy.

In addition to the proposed mechanism of viral-mediated direct endothelial insult, inflammatory mediators of COVID-19 infection may have a pivotal role in the pathogenesis of coagulopathy (Jose and Manuel 2020). This interplay between the inflammatory and thrombotic processes is further delineated in the passage below.

## CYTOKINE RELEASE SYNDROME: AN IMMUNE ETIOLOGY FOR MULTIPLE ORGAN FAILURE

Cytokine-release syndrome (CRS) also known as cytokine storm, is the excessive proliferation of immune cells and increased release of inflammatory cytokines resulting in multi-organ system failure and tissue damage (Shimabukuro-Vornhagen et al. 2018). The trigger for this phenomenon is either a pathogen such as a virus (Fig. 1), or an iatrogenic intervention such as chimeric antigen receptor (CAR)-T cell therapy or anti-PD-1 (Programmed cell death protein 1) agents used to target specific malignancies (Rotz et al. 2017). Elevated Interleukin-6 (IL-6) and Interleukin-10 (IL-10) values have been described in patients with CRS (Tanaka, Narazaki and Kishimoto 2014; Shimabukuro-Vornhagen et al. 2018). IL-6 and IL-10 in addition to other cytokines such as Interferon-gamma (IFN- $\gamma$ ), Interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF- $\alpha$ ) were also found to be elevated in patients with COVID-19, in a number of cohort studies (Chen et al. 2020; Qin et al. 2020; Wan et al. 2020; Zeng et al. 2020). Moreover one report disclosed a positive correlation between higher values of IL-6 and IL-10 and increased severity of the disease (Qin et al. 2020; Wan et al. 2020). While relatively few studies (Tang et al. 2005; Baas et al. 2006; Hong et al. 2018) have described CRS in SARS and MERS, in comparison with COVID-19, this might be explained by the great discrepancy in case numbers between the current pandemic and previous epidemics.

Those cytokines observed at elevated levels in association with CRS – especially TNF, IL-6 and IL-1 $\beta$  – are inhibitors of tissue-factor, protein-C-system and antithrombin-mediated inhibition of thrombin (José, Williams and Chambers 2014). Consequently, CRS may be an inflammatory etiology for increased risk of coagulopathy in COVID-19 patients. CRS prerogative state is also characterized by disseminated intravascular coagulopathy leading to multi-organ failure (figure 1) (Tang et al. 2020). Such coagulopathies have been linked to cardiac injury in COVID-19 patients (Varga et al. 2020).

The high surge of IL-6 and IL-1 $\beta$  may also contribute to neurological manifestations such as dizziness and confusion (figure 1) (Descotes and Vial 2007), which might account for the neurological manifestations previously discussed.

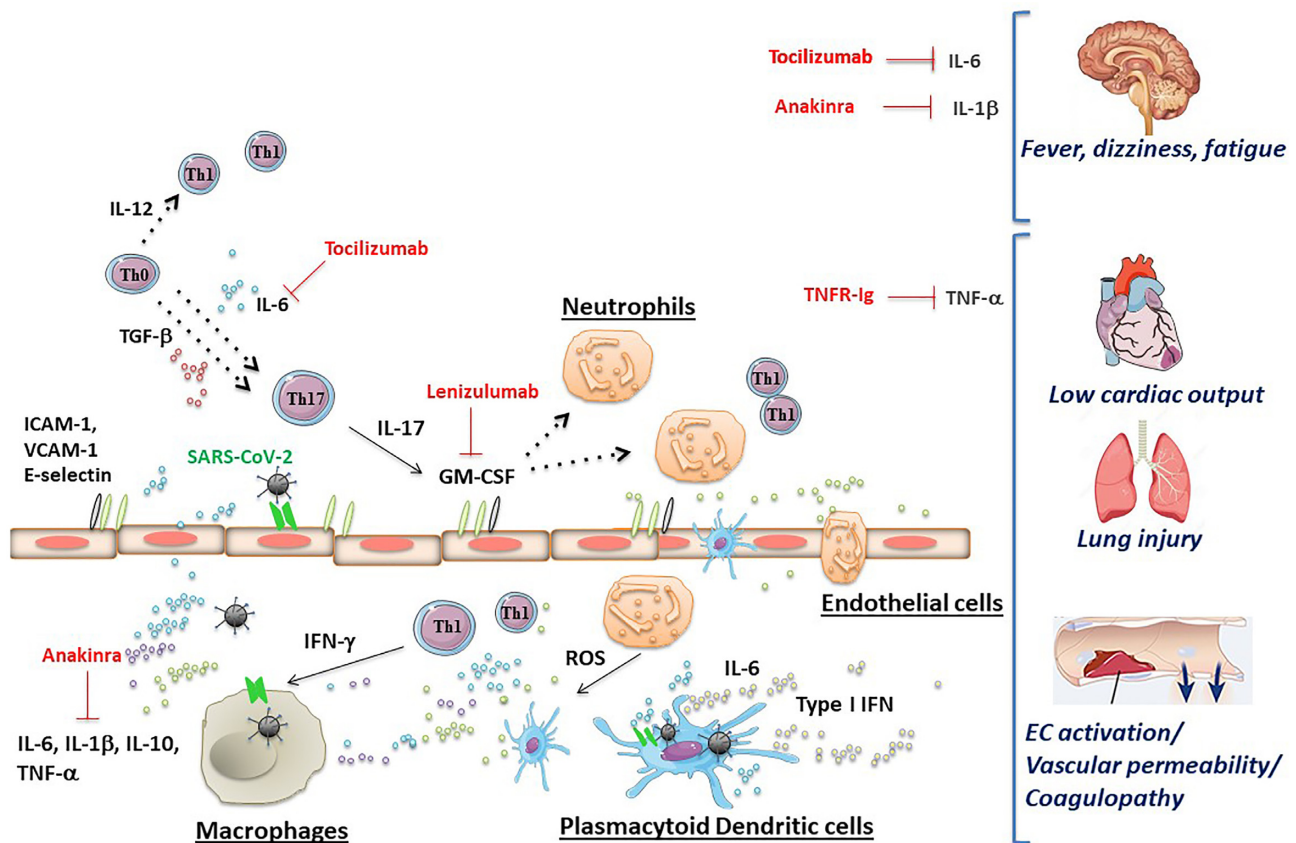
Another recognized immune hyperactivation mechanism is secondary hemophagocytic lymphohistiocytosis (sHLH). The pathophysiology of sHLH is conceived as a positive feedback loop between cytokines and immune cells that eventually escapes regulation, thus leading to tissue damage and multi-organ failure. sHLH has commonly been described in the setting of underlying disease states such as malignancies, autoimmune conditions and viral infections (Ramos-Casals et al. 2014). Of note, the cytokine profile of this condition has been correlated with the cytokine profile of severe COVID-19 cases (Huang et al. 2020).

The altered status of T cells in patients with COVID-19 is also proposed to play a role in the pathophysiology of the disease. Decreased levels of peripheral CD4 and CD8 T cells have been observed, yet the same cells were found to be hyperactivated. The activation of these cells was characterized by a high concentration of CCR6 + Th17 (figure 1), which is associated with a hyperinflammatory response (Wan et al. 2020; Wu et al. 2020; Xu et al. 2020). Similarly, several studies described elevated levels of TH17 and activation of IL-17-related pathways in MERS-CoV and SARS-CoV patients (Josset et al. 2013; Faure et al. 2014). Moreover, patients with elevated IL-17 experienced more severe disease (Faure et al. 2014).

CRS, sHLH and T-cell dysregulation all have been reported to cause interstitial pulmonary inflammation and ARDS, among other types of organ-system dysfunction (Seguin et al. 2016; Huang et al. 2020; Qin et al. 2020). In addition, lung damage related to COVID-19 infection has been associated with lymphocytic infiltrates, thus providing evidence for the role of CRS in induction of ARDS (Xu et al. 2020). Similar reports on the cytokine profile of MERS patients might help confirm the importance of CRS in the pathogenesis of MERS-associated ARDS: A higher concentration of IL-6, among other cytokines, was described in non-survivors versus survivors among MERS patients (Hong et al. 2018). However, other reports stop short of endorsing a definitive role for CRS in disease severity, since no studies have described a direct link between CRS and death of the patient (Josset et al. 2013). Still, the proposed mechanisms of CRS morbidity involve syndromes of organ-system failure such as ARDS, which indeed are themselves associated with increased mortality. Hence, it may be advisable to screen all COVID-19 patients with severe disease for hyper-inflammatory responses, using laboratory trends such as increasing ferritin, decreasing platelet counts and/or increasing erythrocyte sedimentation rate (Fardet et al. 2014), which are similar to trends associated with COVID-19 coagulopathy (Connors and Levy 2020).

Radiological findings from different cohort studies that included COVID-19 patients (Huang et al. 2020; Zhao et al. 2020) were similar to those characterizing lung damage caused by autoimmune and autoinflammatory diseases (Saper et al. 2019). This similarity might suggest that at least part of the damage caused by COVID-19 is due to a dysregulated immune response. Moreover, it might explain the efficacy of certain immune modulator drugs in the treatment of severe COVID-19 cases. Since the outset of the current pandemic, several drugs targeting general immune-system function were proposed for their potential role in alleviating symptoms. Corticosteroids were found to exacerbate lung injury in COVID-19 patients, as in the previous epidemics (SARS and MERS), and thus are not recommended (Russell, Millar and Baillie 2020). On the other hand, Tocilizumab (Interleukin-6 Receptor Antagonist) which was noted to have some efficacy in decreasing the symptoms of immune-related toxicity from anti-PD-1 agents in cancer patients including CRS (Horisberger et al. 2018; Stroud et al. 2019), might have promising results in the treatment of COVID-19. Currently, clinical trials of Tocilizumab (Chinese Clinical Trials Registration number: ChiCTR2000029765) are being conducted in China. Finally HCQ, CQ, IL-1 blockade (anakinra) and JAK2 inhibitors are among the immune modulators under consideration for the management of severe cases of COVID-19 (Ruiz-Irastorza et al. 2010; Shakoory et al. 2016; Wu et al. 2020).

Other immune-modulating medications were also considered in the treatment of COVID-19, after evidence of immune-mediated damage emerged. Hydroxychloroquine, which has held the attention of the media for some time, was among



**Figure 1.** Proposed model of pathophysiological mechanisms underlying cytokine release syndrome (CRS) and possible therapeutic interventions. CRS begins with binding of SARS-CoV-2 or SARS-CoV-2-immune complex (if coated with an antibody) to its receptor on immune cells and endothelial cells in the vicinity of alveoli. (a) This leads to activation of resident phagocytes, mainly macrophages which ingest the virus and initiate cytokine release; namely TNF- $\alpha$  and IL-1 $\beta$ . (b) The latter act on the endothelium to become activated, upregulate the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin), increase vascular permeability and induce leukocyte recruitment. (c) Plasmacytoid dendritic cells (pDCs), on the other hand, secrete Type I interferon, to inhibit viral replication and synthesis of viral proteins and educate naive T cells (Th0) in the lymph nodes to differentiate into effector cells, but these pDCs also secrete IL-6 which adds to the cytokine storm. (d) T cells become engaged, differentiate into Th1 subset, which secretes IFN- $\gamma$  that licenses macrophages to increase their phagocytic activity and cytokine production. (e) In addition, the simultaneous presence of TGF- $\beta$  and IL-6 drives the differentiation of Th0 to Th-17 subset which secretes IL-17 and GM-CSF, the latter stimulates neutrophil production by the bone marrow and its recruitment to the site of tissue injury. (f) Neutrophils discharge their granule contents and increase the production of intracellular reactive oxygen species (ROS); thereby, exacerbating inflammation. (g) Licensed macrophages, in turn, produce excessive amounts of additional cytokines: IL-6, IL-1 $\beta$  and TNF- $\alpha$  further contributing to systemic toxicity. (h) IL-6 and IL-1 $\beta$  act on the hypothalamus to induce fever, dizziness and fatigue. TNF- $\alpha$  leads to decreased cardiac output, cardiomyopathy, lung injury and coagulopathy. These processes represent potential targets for immunotherapy, some of which are still under clinical investigation. Tocilizumab (anti-IL-6 receptor antagonist) remains the current mainstay for management of CRS, although other drugs including anti-IL-1 $\beta$  antagonists (Anakinra), TNFR-antagonists (TNFR-Ig), or GM-CSF antagonists (Lenizulumab) act as potential therapeutics. Hydroxychloroquine (HCQ) can interfere with viral entry and replication; and can also inhibit immune cell overactivation and cytokine production. Key: IL-12, interleukin 12; IL-6, interleukin 6; IL-17, interleukin 17; IL-10, interleukin 10; IL-1 $\beta$ , interleukin 1beta; TNF- $\alpha$ , tumor necrosis factor alpha; TGF- $\beta$ , transforming growth factor beta; IFN- $\gamma$ , interferon gamma; Type I IFN, Type I interferon; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule; VCAM-1, vascular cellular adhesion molecules; GM-CSF, granulocyte monocyte colony stimulating factor; Th1, T helper subset 1; Th17, T helper subset 17; Th0, naive T cells; TNFR-Ig, tumor necrosis factor alpha receptor-immunoglobulin fusion protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HCQ, Hydroxychloroquine.

them. This malaria-prophylaxis drug, previously proven effective in the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE; PAGE 1951; Ben-Zvi et al. 2012) was tested in several randomized clinical trials. The resulting evidence for its efficacy in the treatment of COVID-19 infection was contradictory: Results from some trials suggested that hydroxychloroquine is effective in facilitating viral elimination and decreasing time to recovery (Chen et al. 2020; Gautret et al. 2020). However, these trials included a limited number of patients, most of whom were mildly symptomatic. One trial found no significant efficacy of hydroxychloroquine in combination with azithromycin in severe cases of COVID-19 and was discontinued due to severe side effects (Molina et al. 2020). The efficacy of hydroxychloroquine is still a matter of controversy, suggesting

the need for more evidence to support its use in COVID-19, along with continued close monitoring for potential adverse effects.

## CONCLUSION

MERS, SARS AND COVID-19 are all identified as respiratory viruses. Nevertheless, they exhibit systemic complications and complications specific to other organ systems, especially in the setting of severe disease. Analysis of their common and distinct features is instructive, vital for appropriate patient management, and suggestive of various disease mechanisms that may be targeted through the development of new therapies. The role of hyperactive immune states in severe disease, as supported by mounting evidence, should be urgently addressed in order to

reduce morbidity and mortality among individual patients and populations.

**Conflicts of interest.** None

## REFERENCES

- Ajlan AM, Ahyad RA, Jamjoom LG et al. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: chest CT findings. *AJR Am J Roentgenol* 2014;**203**:782–7.
- Al-Tawfiq JA, Kattan RF, Memish ZA. Middle East respiratory syndrome coronavirus disease is rare in children: an update from Saudi Arabia. *World Journal of Clinical Pediatrics* 2016;**5**:391–6.
- Arabi YM, Arifi AA, Balkhy HH et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;**160**:389–97.
- Arabi YM, Harthi A, Hussein J et al. Severe neurologic syndrome associated with Middle East respiratory syndrome coronavirus (MERS-CoV). *Infection* 2015;**43**:495–501.
- Baas T, Taubenberger JK, Chong PY et al. SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues. *J Interferon Cytokine Res* 2006;**26**:309–17.
- Banik GR, Khandaker G, Rashid H. Middle East respiratory syndrome coronavirus “MERS-CoV”: current knowledge gaps. *Paediatr Respir Rev* 2015;**16**:197–202.
- Ben-Zvi I, Kivity S, Langevitz P et al. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allergy Immunol* 2012;**42**:145–53.
- Brann DH, Tsukahara T, Weinreb C et al. Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. *bioRxiv* 2020, <https://doi.org/10.1101/2020.03.25.009084>.
- Chen C, Zhang XR, Ju ZY et al. (Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies). *Zhonghua Shao Shang Za Zhi* 2020;**36**:E005.
- Chen Z, Hu J, Zhang Z et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv* 2020, <https://doi.org/10.1101/2020.03.22.20040758>.
- Connors J, Levy J. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;**135**:2033–40.
- Descotes J, Vial T. Flu-like syndrome and cytokines. *Cytokines in Human Health*. Totowa, New Jersey: Springer; 2007, 193–204.
- Ding Y, He L, Zhang Q et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004;**203**:622–30.
- Falsey AR, McCann RM, Hall WJ et al. The “common cold” in frail older persons: impact of rhinovirus and coronavirus in a senior daycare center. *J Am Geriatr Soc* 1997;**45**:706–11.
- Fardet L, Galicier L, Lambotte O et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–20.
- Faure E, Poissy J, Goffard A et al. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside? *PLoS One* 2014;**9**:e88716.
- Feng D, de Vlas SJ, Fang LQ et al. The SARS epidemic in mainland China: bringing together all epidemiological data. *Trop Med Int Health* 2009;**14**(Suppl 1):4–13.
- Gane S, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinol* 2020;**58**:3–0.
- Gautret P, Lagier J, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;**048**:105949.
- Hong KH, Choi JP, Hong SH et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax* 2018;**73**:286–9.
- Horisberger A, La Rosa S, Zurcher JP et al. A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab therapy. *J Immunother Cancer* 2018;**6**:156.
- Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497–506.
- Huang KJ, Su IJ, Theron M et al. An interferon-gamma-related cytokine storm in SARS patients. *J Med Virol* 2005;**75**:185–94.
- Hui DS, Wong PC, Wang C. SARS: clinical features and diagnosis. *Respirology* 2003;**8** Suppl:S20–4.
- Hung EC, Chim SS, Chan PK et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 2003;**49**:2108–9.
- Jiang F, Deng L, Zhang L et al. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med* 2020;**35**:1545–9.
- Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;**8**.
- Josset L, Menachery VD, Gralinski LE et al. Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus. *mBio* 2013;**4**:e00165–13.
- José R, Williams A, Chambers R. Proteinase-activated receptors in fibroproliferative lung disease. *Thorax* 2014;**69**:190–2.
- Lai C-C, Shih T-P, Ko W-C et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;**55**:105924.
- Lau KK, Yu WC, Chu CM et al. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis* 2004;**10**:342–4.
- Lechien J, Chiesa-Estomba C, De Siati D et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;**277**:2251–61.
- Leung WK, To KF, Chan PK et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology* 2003;**125**:1011–7.
- Li K, Wohlford-Lenane C, Perlman S et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis* 2016;**213**:712–22.
- Liu Y, Gayle AA, Wilder-Smith A et al. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020;**27**:1–4.
- Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020;**92**:552–5.
- Mahase E. Coronavirus: covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ* 2020;**368**:m641.



- Majumder MS, Rivers C, Lofgren E et al. Estimation of MERS-coronavirus reproductive number and case fatality rate for the Spring 2014 Saudi Arabia outbreak: insights from publicly available data. *PLoS Curr* 2014;**6**.
- Mizumoto K, Saitoh M, Chowell G et al. Estimating the risk of Middle East respiratory syndrome (MERS) death during the course of the outbreak in the Republic of Korea, 2015. *Int J Infect Dis* 2015;**39**:7–9.
- Molina J, Delaugerre C, Goff J et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect* 2020;**50**:384.
- National Health Service. SARS (severe acute respiratory syndrome), National Health Service. 2019, October 24.
- Netland J, Meyerholz DK, Moore S et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008;**82**:7264–75.
- Nicholls JM, Butany J, Poon LL et al. Time course and cellular localization of SARS-CoV nucleoprotein and RNA in lungs from fatal cases of SARS. *PLoS Med* 2006;**3**:e27.
- PAGE F. Treatment of lupus erythematosus with mepacrine. *Lancet* 1951;**2**:755–8.
- Peeri NC, Shrestha N, Rahman MS et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol* 2020;**0**:1–4.
- Porcheddu R, Serra C, Kelvin D et al. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries* 2020;**14**:125–8.
- Qin C, Zhou L, Hu Z et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020.
- Ramos-Casals M, Brito-Zerón P, López-Guillermo A et al. Adult haemophagocytic syndrome. *Lancet* 2014;**383**:1503–16.
- Rotz SJ, Leino D, Szabo S et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr Blood Cancer* 2017;**64**.
- Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;**69**:20–8.
- Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;**395**:473–5.
- Saad M, Omrani AS, Baig K et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *J Glob Infect Dis* 2014;**29**:301–6.
- Sampathkumar P, Temesgen Z, Smith TF et al. SARS: epidemiology, clinical presentation, management, and infection control measures. *Mayo Clin Proc* 2003;**78**:882–90.
- Saper VE, Chen G, Deutsch GH et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis* 2019;**78**:1722–31.
- Seguin A, Galicier L, Boutboul D et al. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016;**149**:1294–301.
- Shakoory B, Carcillo JA, Chatham WW et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med* 2016;**44**:275–81.
- Shimabukuro-Vornhagen A, Gödel P, Subklewe M et al. Cytokine release syndrome. *J Immunother Cancer* 2018;**6**:56.
- Stroud CR, Hegde A, Cherry C et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract* 2019;**25**:551–7.
- Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014;**6**:a016295.
- Tang N, Li D, Wang X et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;**18**:844–7.
- Tang NL, Chan PK, Wong CK et al. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. *Clin Chem* 2005;**51**:2333–40.
- Tse GM, To KF, Chan PK et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). *J Clin Pathol* 2004;**57**:260–5.
- Varga Z, Flammer A, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;**395**:1417–8.
- Viruses ICoTo and ICTV. *Virus Taxonomy: 2019 Release*. 2020, March.
- Wan S, Yi Q, Fan S et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv* 2020, <https://doi.org/10.1101/2020.02.10.20021832>.
- World Health Organization. *Consensus Document on the Epidemiology of Severe acute Respiratory Syndrome (SARS)*. 2003.
- World Health Organization. *Coronavirus disease (COVID-19) Pandemic*. 2020, April 22.
- World Health Organization. *Middle East Respiratory Syndrome Coronavirus (MERS-CoV)*. 2019, March 11.
- World Health Organization. *Q&A on coronaviruses (COVID-19)*. 2020, April 17.
- World Health Organization. *SARS (Severe Acute Respiratory Syndrome)*. 2020.
- Wu J, Liu J, Zhao X et al. Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study. *Clin Infect Dis* 2020, DOI: 10.1093/cid/ciaa199.
- Xu Z, Shi L, Wang Y et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;**8**:420–2.
- Zeng H, Xu C, Fan J et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA* 2020;**323**:1848–9.
- Zhao W, Zhong Z, Xie X et al. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. *AJR Am J Roentgenol* 2020;**214**:1072–7.
- Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–62.