

## COVID-19 pathology and therapeutics

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**Key words:**

SARS-CoV-2, COVID-19, ARDS, Pathology, Inflammation, therapy.

**Abbreviations:**

SARS-CoV-2: Severe Acute Respiratory Syndrome-Corona Virus-2

ARDS: Acute Respiratory Distress Syndrome

SIRS: Systemic Inflammatory Response Syndrome

CARS: Compensatory Anti-inflammatory Response Syndrome

CT: Computed Tomography

DAD: Diffuse Alveolar Damage

PE: Pulmonary Embolism

LMWH: Low Molecular Weight Heparin

PMNL: Polymorphonuclear Lymphocytes

APPT: Activated Partial Thromboplastin Time

DVT: Deep Venous Thrombosis

ESR: Erythrocyte Sedimentation Rate

ICU: Intensive Care Unit

COPD: Chronic Obstructive Pulmonary Disorder

PEEP: Positive End Expiratory Pressure

AKI: Acute Kidney Injury

PT: Prothrombin Time

LDH: Lactate Dehydrogenase

ACE-2: Angiotensin Converting Enzyme-2

ALI: Acute Lung Injury

BAL: Bronchoalveolar Lavage

FIO<sub>2</sub>: Fractional Inspired Oxygen

**Abstract:**

The SARS-CoV-2 pandemic has hit the world by surprise since its first outbreak in Wuhan, China resulting in millions of cases and thousands of deaths around the globe. The current situation is challenged by the lack of knowledge about the COVID-19 pathogenesis. Experts are not sure about the primary driver for mortality, is it the virus or the host immune response. The highly noted difference in outcomes reflects that individuals could react uniquely in response to infection where the inflammatory processes appear to impact the course and outcome of infection. Moreover, findings that came from COVID-19 autopsies suggest that SARS-CoV-2 pneumonia could transform to a severe form of ARDS. This paper aims at addressing briefly various complications observed in COVID-19 patients and providing a list of drugs that could be incorporated as a part of standard care for patients that are most severely affected by SARS-CoV-2 infection.

## **Introduction:**

The clinical presentation and histopathological studies of COVID-19 patients are consistent with those observed in ARDS. This includes persistent hypoxemia that requires assisted oxygenation and unilateral or bilateral pulmonary consolidation (ground glass opacity) on chest CT scans (Gurka and Balk 2008) (Tian, Hu et al. 2020). Evidence for alveolar and endothelial dysfunction is also noted. Macroscopic findings revealed heavy and wet lungs secondary to pulmonary edema, hyaline membrane disposition combined with profound inflammation and pulmonary infiltration by PMNL (Luca Carsana, Aurelio Sonzogni et al. 2020) (Gurka and Balk 2008) (Fox, Akmatbekov et al. 2020). Diffuse alveolar damage (DAD) is the most abundant manifestation observed in deceased COVID-19 patients (Fox, Akmatbekov et al. 2020, Luca Carsana, Aurelio Sonzogni et al. 2020, Wichmann, Sperhake et al. 2020). DAD could contribute to impaired gaseous exchange that is refractory to mechanical ventilation and defective formation of surfactants. ACE-2 is predominantly found in type-2 alveolar cells responsible for surfactant production and has recently been identified as the target receptor for SARS-CoV-2 (C.Mossel, JieruWang et al. 2008, Uhal, Dang et al. 2013).

Among the highly noted alterations in COVID-19 patients' biochemistries are the coagulation profile. This includes increased activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen and D-dimer tests (Min Cao, Dandan Zhang et al. 2020). Patients admitted to ICU tend to experience extensive elevations of these parameters than non-ICU patients (Min Cao, Dandan Zhang et al. 2020). A concern for deep venous thrombosis (DVT) and pulmonary embolism (PE) is highly encountered in critically ill COVID-19 patients (Leonard-Lorant, Delabranche et al. 2020, Poissy, Goutay et al. 2020, Wichmann, Sperhake et al. 2020). Autopsies from deceased patients also demonstrated the presence of microthrombi consisting of fibrin and platelet aggregates in the small blood vessels within the lungs that could contribute to persistent hypoxemia observed in some of COVID-19 patients (Fox, Akmatbekov et al. 2020, Luca Carsana, Aurelio Sonzogni et al. 2020). Other findings revealed heart congestion, right ventricular dilation with individual cellular necrosis, pulmonary hypertension, sinus tachycardia, ST-segment elevation and conduction abnormalities (Bangalore, Sharma et al. 2020, Fox, Akmatbekov et al. 2020, Inciardi, Lupi et al. 2020, Lakkireddy, Chung et al. 2020, Oxley, Mocco et al. 2020). Consistent with these findings an elevation of cardiac troponin-I and lactate dehydrogenase (LDH) has been recorded (Min Cao, Dandan Zhang et al. 2020). Alterations of serum electrolytes in addition to kidney and liver function tests are also noted (Min Cao, Dandan Zhang et al. 2020).

The main drive for these complications appears to be the unbalanced immune response. Moreover, the highly noted difference in outcomes reflects that individuals could react uniquely in response to infection. Previous studies showed that the pathophysiology of ARDS is typically a consequence of the dysregulation between anti-inflammatory and pro-inflammatory mediators leading to both immunosuppression and more predisposition to infections (excessive CARS) or organ dysfunction (excessive SIRS) (Gurka and Balk 2008). Critical COVID-19 cases demonstrated high circulating levels of inflammatory cytokines most specifically TNF-alpha, IL-6 and IL-1 (Tufan, Avanoglu Guler et al. 2020). Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein were elevated in almost all COVID-19 patients admitted to ICU in a study from China (100% and 78.6% respectively) (Min Cao, Dandan Zhang et al. 2020). Other markers included dramatically increased ferritin levels which suggested a potential role for cytokine storm

and anti-phospholipid syndrome (Shoenfeld 2020). Secondary infections or sepsis may also augment these complications (Koehler, Cornely et al. 2020).

Several trials have been conducted to test the efficacy of some therapies for the management of ARDS. Despite an initial improvement, the effects on mortality rate were mild (Gurka and Balk 2008). That's why, it appears that a combination therapy and close monitoring of pre-existing conditions and vital parameters such as serum electrolytes, blood glucose, renal and cardiac functions as well as the adoption of a healthy diet that's rich in antioxidants and immunomodulatory agents are necessary for COVID-19 patients to efficiently reverse these devastating effects. Early diagnosis and intervention are also crucial to reduce disease morbidity and mortality (Min Cao, Dandan Zhang et al. 2020). The following lines include a list of drugs that could be incorporated as a part of standard care in severely affected COVID-19 patients.

### **Anti-inflammatory drugs:**

The elevated levels of inflammatory markers in critically ill COVID-19 patients suggest a correlation between increased inflammation and poor prognosis (Min Cao, Dandan Zhang et al. 2020). The high mortality rate in male gender than females has later been explained by the potential anti-inflammatory effects of endogenous estrogen (Robinson, Lorenzo et al. 2011, Jin, Bai et al. 2020) (Vermillion, Ursin et al. 2018). NSAID use could contribute to a hierarchy of beneficial actions that include reduced inflammation, attenuation of pulmonary fibrosis and augmented anti-viral activity.

Few studies showed that the anti-viral therapy tend to be more efficacious in the presence of anti-inflammatory drugs (Jennifer R. Tisoncik, Marcus J. Korth et al. 2012). A combination therapy of mesalazine, celecoxib and zanamivir improved survival and reduced mortality in mice infected with a highly pathogenic strain of H5N1 (Zheng, Chan et al. 2008, Carey, Bradbury et al. 2010). It was also reported that pre-treatment with Meloxicam (a selective COX-2 inhibitor) attenuated pulmonary fibrosis associated with bleomycin- induced lung injury in mice model combined with an increase in the reduced form of glutathione (Arafa, Abdel-Wahab et al. 2007). This is consistent with the observed increase in glutathione reductase levels in critically ill COVID-19 patients (66.7%) (Min Cao, Dandan Zhang et al. 2020).

In context, a recent study demonstrated a potent anti-viral activity of indomethacin against SARS-CoV-2 in vitro and canine coronavirus in vivo (Tianhong Xu, Xuejuan Gao et al. 2020). The treatment of SARS-CoV-2 infected Vero E6 cells with indomethacin resulted in diminishing of viral infectivity 48h post infection as evidenced by luciferase activity (**Zero**) without inducing toxicity (Tianhong Xu, Xuejuan Gao et al. 2020). Moreover, all dogs received indomethacin and supportive treatment survived (9 dogs) compared to those treated with ribavirin plus supportive therapy (3 died out of 8) (Tianhong Xu, Xuejuan Gao et al. 2020). The treatment with indomethacin was approximately equivalent to a combination that included anti-canine coronavirus serum, hemoglobin, immunoglobulins and interferon (1 died out of 9) (Tianhong Xu, Xuejuan Gao et al. 2020). The proposed mechanism for these anti-viral activities is still investigational, but it's thought to act by interfering with viral RNA polymerase and impairing replication (Tianhong Xu, Xuejuan Gao et al. 2020). The IC<sub>50</sub> was (1 µM) which is nearly 10 times following oral administration of 50 mg (7-11 µM) (Tianhong Xu, Xuejuan Gao et al. 2020).

Among these beneficial effects, indomethacin could also reduce the levels of circulating IL-6 which have been reported to be high in critically ill COVID-19 patients in addition to reducing the incidence of dyspnea and the production of sputum as shown in patients with COPD and bronchoalveolar carcinoma (Tianhong Xu, Xuejuan Gao et al. 2020).

### **Anticoagulants:**

The use of anti-thrombotic therapy has been strongly recommended in COVID-19 patients (Thachil, Tang et al. 2020). A recent study showed that LMWH use was associated with a significant decrease in fatality rate in patients who experienced extensive elevation of D-dimer (6-fold increase above upper limit) than non-users (64.2% and 40% respectively) (Tang, Bai et al. 2020). A prophylactic anti-coagulation should be initiated as soon as D-dimer test shows 4-fold increase above normal upper limit and altered coagulation profile unless contraindicated. The recommended dose of LMWH is 100U/kg/12h for 3-5 days (Lin, Lu et al. 2020). Patients that are refractory to LMWH or experiencing anti-thrombin-3 deficiency could be anti-coagulated with bivalirudin. Moreover, the use of unfractionated heparin could be considered in COVID-19 patients with evidence of acute kidney injury (AKI).

Patients who experience extreme elevation of D-dimer (more than 6-fold increase above normal upper limit) that have been refractory to LMWH therapy and are hemodynamically unstable with persistent hypoxemia and didn't meet the exclusion criteria are eligible for fibrinolytic therapy. A proposed approach was to administer 25 mg of tPA over 2 hours followed by another dose infusion over the next 22 hours with a dose not exceeding 0.9 mg/kg (Moore, Barrett et al. 2020). In all COVID-19 patients on anticoagulant therapy, PT, APTT, fibrinogen and D-dimer tests should be frequently monitored and stoppage of therapy is assigned once returned to normal. It's also noteworthy that thrombocytopenia frequently reported with SARS-CoV-2 infection may prompt the discontinuation of the anti-coagulant therapy and initiation of platelet transfusion (Zulfiqar, Lorenzo-Villalba et al. 2020) (Min Cao, Dandan Zhang et al. 2020).

### **4-methylumbelliferone (hymecromone):**

The disposition of hyaline membranes is highly encountered in ARDS & COVID-19 patients (Hallgren, Samuelsson et al. 1989, Juul, Kinsella et al. 1994, Gurka and Balk 2008) (Tian, Hu et al. 2020). The increased production of hyalourinan was also reported to be associated with multiple organ dysfunction (MOD) in ARDS patients (Esposito et al. 2017). Samples obtained by bronchoalveolar lavage (BAL) from ARDS patients showed a high concentration of hyalourinan (353-515Mg/ml) which is nearly 20 times higher than normal concentrations (20Mg/ml) (LeBlanc and Stern 2017). Moreover, a recent study highlighted the potential role of excessive hyalourinan on increased morbidity and mortality in COVID-19 patients (Michael A Mong, Jacob A Awkal et al. 2020). The inhibition of hyalourinan production could be achieved through the use of 4-methylumbelliferone (hymecromone) (Nagy, Kuipers et al. 2015). In context, oral administration of 4-methylumbelliferone to mice models with acute lung injury (ALI) has resulted in reduced inflammation (McKallip, Hagele et al. 2013, McKallip, Ban et al. 2015). The approved dose of 4-methylumbelliferone for adults is 300-800mg PO TID (Nagy, Kuipers et al. 2015).

Hymecromone could be also found naturally in Cinnamon Cassia while its derivative umbelliferone is found in chamomile flowers which are known to possess anti-inflammatory and immunomodulatory actions (Drummond, Harbourne et al. 2013, K.Kamalakaran, Rayar et al. 2016, Mazimba 2017, Yahfoufi, Alsadi et al. 2018). Daily administration of chamomile or Chinese cinnamon tea could be considered in COVID-19 patients as a part of their treatment regimen unless contraindicated. The patient's coagulation profile should be closely monitored during the intake of all indomethacin, anticoagulants and chamomile.

### **Fluid & electrolyte management:**

Most of COVID-19 patients showed alterations in their serum electrolytes (Min Cao, Dandan Zhang et al. 2020). In a study, all patients admitted to the ICU experienced hypocalcemia (Min Cao, Dandan Zhang et al. 2020). ORS use could be considered to provide an immediate supply of necessary salts. Conservative fluid therapy is superior to liberal fluid therapy in patients with ARDS and resulted in improved oxygenation (Gurka and Balk 2008). In addition, patients with profound pulmonary edema, could consider the use of furosemide while Hypoalbuminemia may mandate albumin transfusion to maintain fluid balance especially in those with hepatic decompensation (Gurka and Balk 2008).

### **Maintaining oxygenation:**

Persistent hypoxemia that is irresponsive to mechanical ventilation is seen in severe cases of COVID-19 most probably due to impaired gas exchange secondary to DAD or thrombus formation. Patients should be closely monitored for their oxygen saturation levels. Alterations in breathing rate or oxygen saturation less than 93 should mandate oxygen therapy since rapid deterioration and dropping of oxygen levels is observed in COVID-19. Humidified high flow oxygen therapy could be considered and is superior to mechanical ventilation (Shike Geng, Qing Mei et al. 2020). Mechanical ventilation should be a last resort as its use has been associated with worsening lymphopenia, ventilator-associated lung injury (VLI) and ventilator-associated pneumonia (Plötz, Vreugdenhil et al. 2002, Vreugdenhil, Heijnen et al. 2004, Bates and Smith 2018). In case of mechanical ventilation, a lung protective protocol should be adopted with low tidal volumes (6ml/kg of measured body weight) and the application of positive end expiratory pressure (PEEP) less than or equal to (30cm H<sub>2</sub>O) based on the fraction of inspired oxygen (FIO<sub>2</sub>) (Gurka and Balk 2008). Higher benefits could be seen by turning patients into the prone position to allow efficient recruitment of alveoli (Gurka and Balk 2008).

### **Other therapies:**

Antibiotic use should be considered to prevent nosocomial or secondary bacterial infections in COVID-19 patients. In addition, maintaining a healthy diet that's rich in anti-oxidants and immunomodulatory agents is generally beneficial for patients during viral infections. Enteric route is highly encouraged to prevent bacterial translocation or stress-induced ulcer whenever accessible (Gurka and Balk 2008). Nigella Sativa could be of great benefit for COVID-19 patients due to the anti-inflammatory and protective effects of thymoquinone on the lungs and the brain (Khader and Eckl 2014, Shao, Li et al. 2017, Noorbakhsh, Shaterzadeh-Yazdi et al. 2018). In context, Nigella Sativa and Anthemis Hyalina demonstrated a reasonable efficacy against coronaviruses in vitro

(Ulasli, Gurses et al. 2014). Moreover, the extra virgin olive oil has also been known for its anti-inflammatory and immunomodulatory actions (Puertollano, Puertollano et al. 2010, Aparicio-Soto, Sanchez-Hidalgo et al. 2017, Santangelo C, Vari R et al. 2018). A diet that includes legumes could provide additional healing properties by reducing oxidative stress (Mirmiran, Hosseinpour-Niazi et al. 2018). Furthermore, the potential effects of bee's honey on SARS-CoV-2 have not been excluded and now is being evaluated in clinical trials (NCT04323345), however it could be also incorporated due to its proven inhibitory effects on various bacteria and viruses such as Varicella-Zoster (VZV) (Shahzad and Cohrs 2012, Hashem 2020). The best thing of all these natural remedies is that they are widely available and notably non-toxic.

**Conclusion:**

Researchers are enriching the literature by new findings about COVID-19 pathology and related therapeutic protocols in a speedy manner. We need to take into consideration all of these proposed pathologies and to apply well to each patient individually. Until a vaccine of SARS-CoV-2 is made available, the treatment of COVID-19 would not be that easy that a personalized therapy is necessary. Health care professionals should monitor any alterations of vital signs or biochemical parameters and act accordingly. Symptomatic treatment of COVID-19 would mean a concise clinical approach that aims basically at counteracting the devastating effects of the disease as being observed. Moreover, a healthy diet that includes protective herbs and vitamin supplements may also play a vital role in patient re-nourishment and recovery.

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The authors declare no conflicts of interest.

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