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## Review article

# Pharmacological management of COVID-19 patients with ARDS (CARDS): A narrative review



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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is highly infectious. It has been highlighted that if not expertly and individually managed with consideration of the vasocentric features, a COVID-19 patient with an acute respiratory distress syndrome (CARDS) may eventually develop multiorgan failure. Unfortunately, there is still no definite drug for CARDS that is capable of reducing either short-term or long-term mortality and no specific treatments for COVID-19 exist right now. In this narrative review, based on a selective literature search in EMBASE, MEDLINE, Scopus, The Cochrane Library, Web of Science, and Google Scholar and [ClinicalTrials.gov](https://www.clinicaltrials.gov), we have examined the emerging evidence on the possible treatment of CARDS. Although numerous pharmacologic therapies to improve clinical outcomes in CARDS have been studied also in clinical trials, none have shown efficacy and there is great uncertainty about their effectiveness. There is still no recommendation for the therapeutic use of any specific agent to treat CARDS because no drugs are validated to have significant efficacy in clinical treatment of COVID-19 patients in large-scale trials. However, there exist a number of drugs that may be useful at least in some patients. The real challenge now is to link the right patient to the right treatment.

## 1. Introduction

Corticosteroids, inhaled vasodilators such as inhaled NO (iNO) or prostacyclin,  $\beta_2$ -agonists, surfactant therapy, agents that accelerate lung water resolution and ion transports, and anti-infective (antibacterial and/or antiviral) agents are suggested as pharmacological treatment of adult acute respiratory distress syndrome (ARDS) [1]. However, a recent systematic review with meta-analysis found insufficient evidence to determine confidently whether any type of drug was effective at reducing deaths in people with ARDS, or the length of time that they needed mechanical ventilation [2]. In particular, no studies reported fitness to return to work at 12 months and in any case, most of the findings were supported by low- or very low-certainty evidence.

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) was identified in Wuhan, China. The World Health Organization declared this outbreak a significant threat to international health. COVID-19 is highly infectious and presents itself with impressive non-uniformity. Some patients develop severe lung failure [3] with a respiratory distress that appears to include an important vascular insult [4]. COVID-19 pneumonia presents particularly distinctive features such as

severe hypoxemia often associated with normal to high pulmonary compliance, low lung elastance, low lung weight and low lung recruitability with variable degrees of severity [5]. Impaired blood flow and hypoxic pulmonary vasoconstriction likely cause hypoxemia [5]. It has been highlighted that if not expertly and individually managed with consideration of the vasocentric features, a COVID-19 patient with ARDS ("CARDS") may eventually develop multiorgan failure [4]. Conversely, Ziehr et al. described a series of 66 intubated patients with COVID-19 that exhibited gas exchange values, respiratory system mechanics, and responses to prone ventilation similar to those observed in patients with "typical" ARDS [6]. Therefore, Navas-Blanco and Dudaryk were right when they pointed out that further research is required to determine the description of CARDS as an "atypical" presentation of ARDS [7].

In any case, a controlled graduated method of escalating oxygen therapy, based on individual clinical judgment, in otherwise non-distressed patients [8], the application of a continuous positive airway pressure by means of a helmet [9], noninvasive ventilation often applied outside the intensive care unit (ICU), in emergency rooms or in other medicine wards, and endotracheal intubation when respiratory distress

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is present [10] represent the pivotal therapeutic approach to these patients.

This approach should, however, be complemented by pharmacological treatments aimed on mitigating the morphological changes in CARDS, thus improving lung function through reduction of inflammation and lung oedema and improvement in repair mechanisms. However, no specific pharmacological treatments for COVID-19 exist right now.

We aim to verify what is the evidence existing in the literature on the possible pharmacological treatment of CARDS. Specific therapies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are beyond the scope of this review.

## 2. Methods

We searched EMBASE, MEDLINE, Scopus, The Cochrane Library, Web of Science, and Google Scholar through July 28, 2020. Search terms included *acute respiratory distress syndrome*, *coronavirus*, *severe acute respiratory syndrome coronavirus 2*, *2019-nCoV*, *SARS-CoV-2*, *SARS-CoV*, *MERS-CoV* and *COVID-19* in combination with *treatment* and *pharmacology*. We supplemented the bibliographic database searches with backward citation tracking of relevant publications. We also searched <http://www.clinicaltrials.gov> for ongoing studies. The information thought to be more significant has been selected.

## 3. Current challenges in pharmacological management of CARDS

Although numerous pharmacologic therapies to improve clinical outcomes in ARDS have been studied in clinical trials, none have shown efficacy and there is great uncertainty about their effectiveness. This uncertainty is even greater when examining the therapeutic responses in patients with COVID-19. However, interesting possibilities are emerging thanks to the use of drugs that were originally developed for other clinical indications, but whose pharmacological profile suggests an impact on some of the multiple pathophysiological aspects of CARDS.

## 4. Corticosteroids

According to 2017 guidelines of the Society of Critical Care Medicine and European Society of Intensive Care Medicine, corticosteroids should be used in patients with early moderate to severe ARDS ( $\text{PaO}_2/\text{FiO}_2$  of  $<200$  and within 14 days of onset) [11]. However, this recommendation was of moderate quality of evidence. Methylprednisolone should be preferred for its best ability to penetrate the lung and longer residence time. The dose to be used should be 1 mg/kg/day in patients with early (up to day 7 of onset) and 2 mg/kg/day in those with late (after day 6 of onset) persistent ARDS followed by slow tapering over 13 days. In effect, a systematic review and meta-analysis of seven randomized controlled trials (RCTs) showed that the early administration of systemic corticosteroids in patients with ARDS might reduce mortality and ventilator duration, and increase the number of ventilator-free days [12]. It can also induce hyperglycaemia, while the effect on neuromuscular weakness is unclear. However, the overall evidence scenery, which was mainly influenced by weaker non-randomized observational type studies, was very conflicted. Anyway, a very recent systemic review and meta-analysis on the use of corticosteroids in patients with influenza-related ARDS and severe pneumonia found an association between corticosteroid therapy and increased mortality and incidence of nosocomial infection [13].

These findings support the view that corticosteroid treatment should not be used for the treatment of Sars-CoV-2-induced lung injury or shock outside of a clinical trial [14]. No unique reason exists to expect that patients with Sars-CoV-2 infection will benefit from corticosteroids, and they might be more likely to be harmed with such treatment.

Nevertheless, according to the expert consensus statement from the

Chinese Thoracic Society, the following basic principles should be followed when using corticosteroids: the benefits and harms should be carefully weighed before using corticosteroids; corticosteroids should be used prudently in critically ill patients with COVID-19 pneumonia; for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be cautious; the dosage should be low-to-moderate ( $\leq 0.5\text{--}1$  mg/kg per day methylprednisolone or equivalent) and the duration should be short ( $\leq 7$  days) [15]. These suggestions contrast with the findings of a recent systematic review with meta-analysis of the effect of corticosteroid treatment on patients with COVID-19 that found that corticosteroids could lead to higher mortality, longer length of stay, a higher rate of bacterial infection and hypokalemia [16]. Another recent meta-analysis has shown that corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing, did not convincingly improve survival, and did not even reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation [17]. Furthermore, there were several adverse effects.

In any case, patients with severe conditions were more likely to require corticosteroids. A late meta-analysis concluded that corticosteroids might reduce mortality for patients with COVID-19 and ARDS, while for patients with severe COVID-19 but without ARDS, evidence regarding benefit from different bodies of evidence is inconsistent and of very low quality [18]. These findings fit well with the preliminary report of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial has documented that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [19].

Noteworthy is the documentation that patients with asthma and COPD who are stable while using inhaled corticosteroids should continue on their treatment [20].

## 5. Heparin, anti-coagulant and anti-platelet therapies

Histologic analysis of pulmonary vessels in patients with COVID-19 showed severe endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes, widespread thrombosis with microangiopathy and occlusion of alveolar capillaries, and significant new vessel growth [21]. It is therefore not a surprise that there is evidence suggesting that preventing platelet activation and expression of surface adhesion proteins that lead to microvascular thrombus formation and tissue injury could mitigate lung damage [22], although pre-hospital antiplatelet therapy is associated with a reduced rate of ARDS but has no effect on the mortality in the subjects at high risk [23]. Conversely, a meta-analysis of 9 trials concluded that adding low-molecular-weight heparin within the initial 7-day-onset of disease seems to reduce 7-day and 28-day mortality and to improve the oxygenation index in ARDS patients [24].

Patients with severe COVID-19 are at greater risk of disseminated intravascular coagulation, which may be further complicated by the effects of the extracorporeal membrane oxygenation (ECMO) circuit and the combination may increase thrombo-hemorrhagic morbidity [25]. Abnormal coagulation parameters (prolonged prothrombin time and increased D-dimer) are predictors of a poor prognosis and may be important therapeutic targets. Apparently, patients with COVID-19 meeting sepsis-induced coagulopathy (SIC) criteria ( $\text{SIC} \geq 4$ ) or with markedly elevated D-dimer ( $>3.0$  mg/mL) may benefit from anticoagulant therapy mainly with low-molecular-weight heparin for 7 days or longer [26].

There are several ways by which heparin can prove beneficial in patients with COVID-19 [27]. It can cause anticoagulant and anti-inflammatory effects, induce endothelial protection and elicit an antiviral activity, although it is not clear whether anti-inflammatory functions, endothelial protection, and viral inhibition should be

considered independently of anticoagulant properties in the COVID scenario. In any case, it is well known that SARS-CoV-2 entry into a cell via the angiotensin-converting enzyme 2 (ACE-2) receptor leads to shedding of this receptor [28], and it has been documented that SARS-CoV-2 Spike S1 protein receptor-binding domain attaches to unfractionated heparin and undergoes conformational change that may prevent it from binding ACE-2 as a result [29].

The correct dose of low-molecular-weight heparin is a matter of immediate interest as a drug can only be effective if administered in an efficient dose [27]. Although a prophylactic dose may be adequate in most patients, it would be important to consider a higher dose in individuals with high body mass index. In any case, it has yet to be established whether low molecular weight heparin can be administered at a higher than prophylactic dose in those with extremely high D-dimers (e.g., six to eight fold) at admission and at higher doses in patients who may need higher levels of ventilation (oxygen requirements) or develop CARDS.

Interestingly, it has been shown that mechanically ventilated patients hospitalized with COVID-19 who received systemic anticoagulation (including oral, subcutaneous, or intravenous [IV] forms) during their hospital course had lower hospital mortality [30]. This difference was not seen in all COVID-19 patients, suggesting that the beneficial effects may be more pronounced in patients with severe disease although bleeding events were more common among intubated patients than among nonintubated patients.

A small proof of concept, case control, phase IIb study concluded that enhanced platelet inhibition plus anticoagulation, with tirofiban and fondaparinux in association with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) might be effective in improving the ventilation/perfusion ratio in COVID-19 patients with severe respiratory failure [31].

According to the Journal of the American College of Cardiology state-of-the-art review [32], in patients with SARS-CoV-2 and critical illness, unfractionated heparin can be used in the setting of anticipated procedures, or in patients with deteriorating renal function to reduce the risk of venous thromboembolism, but if there is no urgent procedure, low-molecular-weight heparins are a reasonable alternative. In patients requiring ECMO, anticoagulation is frequently required to maintain circuit patency, especially at lower flow settings. Low-molecular-weight heparin prophylaxis may decrease thrombin generation and modify the course of disseminated intravascular coagulation, but long-acting antiplatelet agents should be generally discontinued in most patients with disseminated intravascular coagulation, unless in the presence of an absolute indication as in the case of acute coronary syndrome or stent implantation. In this case it is suggested to continue dual antiplatelet therapy if platelet count is  $\geq 50,000/\mu\text{L}$ , reduce to single antiplatelet therapy if platelet count is  $\geq 25,000/\mu\text{L}$  and  $< 50,000/\mu\text{L}$ , and discontinue if platelets are  $< 25,000/\mu\text{L}$ .

## 6. Statins

Statins probably make little or no difference to early mortality or to ventilator-free days in patients with ARDS [2]. However, a secondary analysis of the Acute Lung Injury to Reduce Pulmonary Dysfunction-2 Study cohort, a study that tested the hypothesis that treatment with simvastatin would improve clinical outcomes in patients with ARDS [33], identified two subphenotypes of ARDS, the hypoinflammatory and the hyperinflammatory subphenotypes. The hyperinflammatory subphenotype had improved survival with simvastatin compared with placebo [34].

It has been suggested that adjuvant treatment and continuation of pre-existing statin therapy could improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage [35]. In experimental models, statins inhibit the myeloid differentiation factor 88–nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) proinflammatory pathway and promote ACE2 up-regulation. Through

these mechanisms, statins may prove beneficial in COVID-19 patients. Statins may also counteract hyperlipidaemia caused by some antiviral and immunosuppressive treatments currently used for COVID-19. In effect, a large retrospective study on hospitalized patients with COVID-19 found the use of statins was associated with a lower risk of all-cause mortality (the risk for 28-day all-cause mortality was 5.2% and 9.4% in the matched statin and non-statin groups, respectively) and a favourable recovery profile [36].

However, there is evidence, always from experimental models, that statins increase ACE2 expression in the heart via epigenetic histone modifications [37], a finding that raises concerns about the safety of statins in the current COVID-19 pandemic [38]. Nevertheless, it has been suggested that people with COVID-19, who are already on a statin for an underlying co-morbid condition, should continue on it because cardiovascular complications, including myocarditis, myocardial infarction and venous thromboembolic events are common in people with COVID-19 [39].

## 7. Thiol-based drugs

Thiol-based drugs are mucolytic agents, but they can also act as antioxidant drugs directly through free sulfhydryl groups that serve as a source of reducing equivalents, as well as indirectly through the replenishment of intracellular glutathione levels, interfere with inflammatory pathways and modulate human bronchial tone, reduce bacterial adhesion to the respiratory epithelial cell surface and inhibit biofilm formation, causing biofilm disruption and thereby improving the efficacy of antibiotic therapy, and influence viral replication and infectivity [40]. Increased oxidative stress is a major insult in ARDS, but in adults with ARDS, N-acetylcysteine (NAC) does not lower mortality but is beneficial for ICU stay [41]. Nevertheless, it has been suggested that oral and IV glutathione as well as glutathione precursors (NAC, alpha-lipoic acid) may represent a novel treatment approach for blocking NF- $\kappa\text{B}$  and addressing “cytokine storm syndrome” and respiratory distress in patients suffering with COVID 19 pneumonia [42]. A remarkable benefit of IV NAC in severe COVID-19 infection has been described, with a significant overall reduction in inflammatory markers (C-reactive protein and ferritin) during IV NAC administration, although a rebound of inflammation was noted in some patients following discontinuation of NAC [43].

## 8. Inhaled vasodilators

In ARDS, shunting and increased ventilation-perfusion mismatch are the main mechanisms leading to hypoxemia [44]. Given systemically, vasodilators can decrease pulmonary vascular resistance but also blunt hypoxic vasoconstriction, leading to increased shunting and worsening hypoxemia. In contrast, inhaled vasodilators, such as iNO or prostacyclin, act preferentially in well-ventilated areas and can decrease ventilation-perfusion mismatch.

Evidence is insufficient to support iNO in any category of critically ill patients with ARDS [45]. In effect, iNO induces a transient improvement in oxygenation and reduces the rate of severe respiratory failure, but it does not reduce mortality or the length of stay in ICU or hospital [45]. However, it has been suggested to use iNO in cases of ARDS with deep hypoxemia despite the implementation of a protective ventilation strategy and prone positioning, and before envisaging use of veno-venous ECMO [46]. In COVID-19, the oxygenation response to iNO is variable [10]. It has been suggested that iNO should not work in fully vasoplegic patients and apparently the COVID-19 pneumonia appears to interfere with the vascular regulation up to complete loss of vascular tone to vasoconstricting or vasodilating agents, but possibly works in patients in which pulmonary hypertension is more likely. Furthermore, both endogenous and exogenous NO were shown to inhibit SARS-CoV viral replication [47].

A systematic review of the literature that included 25 studies

published until 2014 showed that inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures and may be associated with hypotension [48]. The current opinion is that inhaled prostacyclin should not be used routinely in patients with ARDS [44]. Their use should be reserved to decrease right ventricular afterload in the context of hemodynamically significant right ventricular failure complicating ARDS and in patients with refractory life-threatening hypoxemia who may be treated with other advanced intervention (eg, ECMO) to induce a transitory improvement in oxygenation that could allow time for assessment, transport, and initiation of ECMO at a referral centre. A small study that examined 39 spontaneously breathing patients with COVID-19 who underwent therapy with iNO showed that more than half did not require mechanical ventilation after treatment [49]. However, in another small study, the use of NO or almitrine bismesylate, or both did not improve oxygenation in moderate to severe CARDS [50].

According to Australian and New Zealand Intensive Care Society COVID-19 Guidelines, there is no evidence for routine use of iNO, prostacyclin or other selective pulmonary vasodilators in acute respiratory failure [51]. However, during emerging infectious disease outbreaks when resources are exhausted, iNO and prostacyclin may be considered as a temporising measure if patients develop refractory hypoxemia despite prone ventilation, or in the presence of contraindications to prone ventilation or ECMO.

## 9. $\beta_2$ -agonists

Several in vitro and in vivo animal or human studies suggest a potential role for  $\beta_2$ -agonists in the treatment of ARDS [52]. These agents have been shown to reduce pulmonary neutrophil sequestration and activation, accelerate alveolar fluid clearance, enhance surfactant secretion, and modulate the inflammatory and coagulation cascades.

In patients with ARDS,  $\beta_2$ -agonists probably slightly increase early mortality by 40 per 1000 patients, whereas there is some uncertainty whether they increase ventilator-free days [2].

It has been suggested to avoid their use in patients with COVID-19 because of the presence of a hypothetical vicious loop consist of adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) in COVID-19 condition [53]. Inhaled  $\beta_2$ -agonists or IV noradrenaline for treating the septic shock condition in COVID-19 patients might hyperactivate the ARAS loop and worsen the condition.

Nonetheless, COVID-19 patients that also suffer from COPD, asthma or other pulmonary disorders need bronchodilators. When nebulisers are required, ideally they should be provided in isolation within negative pressure rooms with providers wearing N95 masks, goggles/face shield, and other personal protective equipment required for droplet particle protection [54]. Alternatively, it is likely safer to use metered-dose inhalers with spacers in lieu of nebulisers [54]. In any case, it is advisable to avoid the opening of the ventilator circuit and to use a closed system that requires minimal staff handling and no circuit opening, thereby reducing workload and increasing safety [55].

## 10. Exogenous surfactant therapy

Several pathways can contribute to surfactant dysfunction in acute inflammatory pulmonary injury [56]. Initiators of lung injury can act either from the alveolar side (direct lung injury) or from the vascular side (indirect or extra-pulmonary lung injury). Restoration of a proper pulmonary surfactant function can therefore pose a crucial need to improve the outcome of ARDS patients. However, the administration of an exogenous surfactant material in enough amounts to replace the inactivated complexes of the injured lungs is much more difficult than supplementing the immature but healthy lungs of preterm neonates [56]. The inactivating environment of injured and inflamed lungs also leads to a rapid inactivation of the exogenous surfactant. Current clinical surfactants are often more susceptible to inactivation than the endogenous native complexes.

A meta-analysis that included 11 RCTs with 3038 patients indicated that surfactant administration does not improve mortality but improves oxygenation in adult ARDS patients [57]. However, some data suggest that the transcription of the surfactant genes, production of active surfactant proteins, and their turnover might be deregulated in the lung of the COVID-19 patient [58]. Furthermore, lung surfactant is considered as a physiological barrier to viral infections, with the lipid portion is mainly responsible for the antiviral activity [59]. The lung surfactant protein has also the ability for selective recognition of SARS coronavirus spike glycoprotein and subsequent macrophage activation [59]. Consequently, a trial is investigating administering exogenous surfactant to treat ARDS in mechanically ventilated COVID-19 patients, with the overall goal to reduce their mortality (ClinicalTrials.gov Identifier: NCT04375735).

## 11. New directions in pharmacological management of CARDS

There are several pharmacological candidates for treating CARDS that are currently under investigation in clinical trials, although initial data are not always promising.

## 12. Vitamin D

In subjects at highly risk of ARDS there is a deficiency of vitamin D, with a correlation between the severity of this deficiency and increased epithelial damage, development of ARDS and survival [60]. Vitamin D induces cathelicidins and defensins that can lower viral replication rates. Furthermore, it reduces concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, and increases concentrations of anti-inflammatory cytokines [60]. It also enhances the expression of genes related to antioxidant (glutathione reductase and glutamate-cysteine ligase modifier subunit) [61].

A meta-analysis that included 7 studies published between 2011 and 2016 with a total of 716 patients, suggested that the administration of vitamin D could reduce mortality in critically ill patients although no statistically significant differences in length of ICU and hospital stay were found [62]. However, early administration of high-dose enteral vitamin D<sub>3</sub> did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D-deficient patients [63]. The severity of vitamin D deficiency at baseline did not affect the association between the treatment assignment and mortality. Nonetheless, a recent review suggested using vitamin D loading doses of 200,000–300,000 IU in 50,000-IU capsules to reduce the risk and severity of COVID-19 [64]. Therefore, it has been proposed that during the COVID-19 epidemic, all people in the hospital, including patients and staff, should take vitamin D supplements to raise 25(OH)D concentrations as an important step in preventing infection and spread [60].

## 13. Vitamin C

Several pharmacological properties of vitamin C, which can play a role as an antioxidant agent, are potentially useful for the treatment of ARDS [65]. In particular, early use of large dose of vitamin C may become an effective treatment of ARDS because of its antioxidant effects [66].

IV vitamin C reduces the duration of vasopressor support and mechanical ventilation [67]. Three to 10 g vitamin C results in lower overall mortality rates. In patients with sepsis and severe acute respiratory failure, a 96-h infusion of vitamin C (50 mg/kg in dextrose 5% in water), showed a 16.5% lower mortality compared with placebo but it did not significantly improve organ dysfunction scores or alter plasma biomarkers of inflammation (C-reactive protein levels) and vascular injury (thrombomodulin levels) [68].

It has been suggested that a moderate amount of vitamin C



supplementation may be a way to prevent COVID-19 [69]. An observational study that reviewed the feasibility of using vitamin C in the setting of COVID-19 in a series of patients who were requiring at least 30% of FiO<sub>2</sub> or more noted a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO<sub>2</sub> requirements, after vitamin C administration [70].

A clinical trial to investigate vitamin C infusion for the treatment of severe SARS-CoV-2 infected pneumonia has begun ([ClinicalTrials.gov Identifier: NCT04264533](https://clinicaltrials.gov/ct2/show/study/NCT04264533)).

#### 14. Anti-interleukin-6

It is a long time since it was shown that a plasma interleukin-6 (IL-6) level >400 pg/mL on any day in the first week of ARDS is associated with a low likelihood of survival [71]. The SARS-CoV-2 binds to alveolar epithelial cells, and then the virus activates innate and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6 [72]. IL-6 plays a central role in cytokine storm. IL-6 is a multi-effective cytokine with anti-inflammatory and pro-inflammatory effects.

Some experimental models of viral pulmonary infection triggering ARDS show that IL-6 may have contextual protective or exacerbating roles including severity of infection, survival and tissue remodeling [73]. Bacterial, rather than viral infections, originating outside the lung that also trigger ARDS but in this setting IL-6 blockade may be beneficial. The SARS-CoV-2 suppression of first line interferon responses and abrogation of T-cell responses suggests a role for type 2 pneumocyte gp130 receptor expression and IL-6 in pulmonary pathology.

It is presently unclear if elevated IL-6 levels are detrimental or beneficial in COVID-19 pneumonia [73], although a systematic review and meta-analysis demonstrated the association of elevated IL-6 with severe COVID-19 [74]. In experimental model systems, IL-6 can either suppress or facilitate viral replication, so studies on COVID-19 are urgently needed [73]. Timing of anti-IL-6 receptor (IL-6R), if too early might adversely affect viral clearance, which needs to be assessed in trials. If it emerges that blocking IL-6R early in the course of COVID pneumonia macrophage activation syndrome-like disease has a detrimental impact on type-2 pneumocyte anti-viral immunity, then local augmentation of IL-6 could be considered [73]. However, it has been reported that registry data from over 16,000 cases of rheumatoid arthritis treated with tocilizumab, a IL-6R antagonist, showed an increased risk of bacterial infection but no evidence for an increased risk of viral infection in humans, suggesting that IL-6 reduction is not linked to the emergence of previously known common viral infections [75].

In hospitalized adult patients with severe COVID-19, tocilizumab could be a safe option. An improvement in respiratory and laboratory parameters was observed in several small trials [76,77]. Two large trials are currently ongoing in patients with COVID-19 pneumonia in China and Italy, respectively [78]. However, it has been reported that the phase III COVACTA study of tocilizumab did not meet its primary endpoint of improved clinical status in hospitalized adult patients with severe COVID-19 associated pneumonia [79]. Also the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge.

A retrospective study of patients with COVID-19 induced pneumonia/ARDS analyzed patients who received treatment with siltuximab [80]. Results suggested that siltuximab administered at the onset of ventilatory support reduces mortality associated with COVID-19 and respiratory failure compared with best supportive care. A trial that is investigating efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID-19 pneumonia is ongoing ([ClinicalTrials.gov Identifier: NCT04329650](https://clinicaltrials.gov/ct2/show/study/NCT04329650)).

Also sarilumab, another IL-6R antagonist mAb approved for rheumatoid arthritis, is under investigation in a multicentre, double-blind, phase II/III trial for hospitalized patients with severe COVID-19 that is

active, but not recruiting ([ClinicalTrials.gov Identifier: NCT04315298](https://clinicaltrials.gov/ct2/show/study/NCT04315298)).

#### 15. Mesenchymal stromal cell therapies

Mesenchymal stromal cell therapies are potentially useful in the treatment of ARDS [81]. Mesenchymal stromal cells exert cell-contact dependent effects on macrophages, reprogramming them to an M2 reparative phenotype, and on the injured lung epithelial cells, via direct transfer of mitochondria, DNA and RNA [82]. Key paracrine effects include secretion of soluble growth factors (e.g., keratinocyte growth factor, vascular endothelial growth factor and angiopoietin-1), antimicrobial peptides (e.g., LL-37, LCN-2) and matrix metalloproteinases and their inhibitors. The effects of mesenchymal stromal cells include reduced inflammation, reduced bacterial growth and increased clearance, enhanced membrane integrity and alveolar fluid clearance, and enhanced lung repair with reduced lung fibrosis [52].

In patients with moderate to severe ARDS based on prespecified haemodynamic and respiratory parameters, intravenous bone-marrow-derived mesenchymal stromal cells therapy was well tolerated [83]. Clinical outcomes did not differ significantly between groups, but post-hoc analyses showed a trend for improvement in oxygenation index in the MSC group. Post-thaw viability of mesenchymal stromal cells emerged as a potentially important factor in the biological and clinical effects of this treatment for ARDS.

In COVID-19, autologous or allogenic mesenchymal stromal cells are a therapeutic option to regulate inflammatory response, maintain functional alveoli microenvironment, promote endogenous regeneration and repair, and natural resistance against it with no or minimal side-effects [84]. Mesenchymal stromal cells through their anti-inflammatory and immunomodulatory potential inhibit the overactivation of immune system and play a vital role in regeneration of the affected tissues, thus enhancing recovery.

One study of ACE2 negative mesenchymal stromal cells has reported results in seven patients with COVID-19, showing improvement in both clinical and inflammatory outcome compared with three control patients treated with saline [85]. The serum levels of pro-inflammatory cytokines and chemokines were reduced dramatically and those of IL-10 and Vascular-Endothelial Growth Factor increased. Furthermore, a treatment with IV administration of adipose tissue-derived MSCs in 13 patients with severe COVID-19 pneumonia under mechanical ventilation did not induce significant adverse events and was followed by clinical and biological improvement in most subjects [86].

#### 16. Keratinocyte growth factor

Keratinocyte growth factor possesses many attributes required of a molecule that plays an important, if not crucial, role in mediating epithelial tissue repair following injury [87]. It is up-regulated following tissue injury, and it acts to strengthen the integrity of the epithelial barrier via multiple mechanisms, including the stimulation of cell proliferation, migration, differentiation, survival, DNA repair and the induction of enzymes involved in the detoxification of reactive oxygen species. Subsequent pre-clinical studies have shown that palifermin, a recombinant truncated keratinocyte growth factor, has a remarkable ability to protect many different epithelial tissues from a variety of toxic insults [87].

In the Keratinocyte growth factor for the treatment of the acute respiratory distress syndrome (KARE) study, twenty-nine patients with ARDS received palifermin and 31 placebo. All were intubated and mechanically ventilated and had a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of ≤300 mm Hg, and bilateral pulmonary infiltrates consistent with pulmonary oedema [88]. There was no improvement in physiological or clinical outcomes in ARDS patients that received palifermin. Oxygenation metrics did not improve, ventilator-free days were fewer, and 28-day mortality was increased. Apparently, no trial is exploring the effects of palifermin in COVID-19 patients.

## 17. Neutrophil elastase inhibitors

There are multiple potential mechanisms whereby neutrophil elastase may contribute to the pathogenesis of lung injury, such as direct cytotoxicity to endothelial and epithelial cells, degradation of endothelial and epithelial intercellular adhesion molecules, including (V- and E-cadherin), direct modulation of the inflammatory response by effects on neutrophil adhesion molecules and cytokines, and modulation of the repair phase by effects on growth factors and cytokines such as transforming growth factor  $\beta$  [89].

A meta-analysis of 6 RCTs reporting data on 804 patients with ARDS showed that sivelestat might increase the PaO<sub>2</sub>/FiO<sub>2</sub> level, but with little or no effect on 28–30 days mortality, ventilation days, and ICU stays [90].

In autopsy samples from the lungs COVID-19 patients, neutrophil infiltration in pulmonary capillaries, acute capillaritis with fibrin deposition, extravasation of neutrophils into the alveolar space, and neutrophilic mucositis were observed [91]. Fortunately, there are several approaches to targeting neutrophil extracellular traps [91]. Neutrophil elastase, peptidyl arginine deiminase type 4, and gasdermin D inhibitors can prevent neutrophil extracellular trap formation. Deoxyribonuclease has been used safely to digest neutrophil extracellular traps in the mucous secretions of the airways of cystic fibrosis patients. Colchicine inhibits neutrophil migration and infiltration into sites of inflammation. IL-1 $\beta$  blockers have the potential to prevent an inflammatory loop between neutrophil extracellular traps and IL-1 $\beta$ . It was reported the favourable outcome of 9 domiciliary consecutive COVID-19 patients treated with a loading dose of 1 mg oral colchicine 12 h apart followed by 1 mg daily colchicine until third day of axillary temperature <37.5 °C [92]. Colchicine was started after a median of 8 days from COVID-19 onset and after 3–5 days of spiking fever despite acetaminophen or antibiotic treatment. Trials to treat COVID-19 with colchicine are already ongoing or being launched.

## 18. Other potential therapies

There are also therapies that are under development for other clinical indications but have a pharmacological profile suggesting their use in CARDS, and candidates with biological plausibility that have been tested successfully in preclinical phases, but then not clinically developed.

Studies that focus on the inhibition of IL-1 $\beta$  to reduce the cytokine storm have attracted most attention. In fact, re-analysis of data from a phase III RCT of IL-1 blockade (anakinra) in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events [93]. A retrospective cohort study of patients with CARDS managed with non-invasive ventilation outside of the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients [94].

A therapeutic anti-inflammatory strategy against complement has the potential to stem the downstream inflammatory response and capillary leak, and, consequently, lung damage and CARDS, assuming adequate tissue penetration of drug to the site of complement activation [95]. A number of clinically ready potential therapeutic agents are available. Eculizumab a humanized mAb directed against the complement C5a component that is currently being used in renal transplantation, inhibits the terminal complement protein C5 and prevents its cleavage into C5a, which is proinflammatory, and C5b, which coordinates the formation of membrane attack complex [96].

At present, TNF blockers have not been suggested in the treatment of patients with COVID-19, but the efficacy of TNF blockers in treatment of patients with COVID-19 deserves further exploration because in mice, neutralization of TNF activity or loss of TNF receptor provides protection against SARS-CoV-induced morbidity and mortality [97,98].

Experimental evidence suggests that an early interferon (IFN) response has a protective effect on mice infected with SARS-CoV but delayed IFN- $\alpha\beta$  signaling causes an imbalance of the anti-SARS-CoV

immune responses in humans [98]. Therefore, IFN- $\alpha\beta$  receptor blockers or antagonists should be administered in the later stages of severe disease to prevent excessive inflammatory responses [98]. However, IV IFN- $\beta$ -1a administered for 6 days to patients with moderate or severe ARDS was similar to placebo when its activity was evaluated by a composite score that included death and number of ventilator-free days over 28 days [99].

In recent years, the JAK/STAT pathway has been described to play a key role in various conditions of excessive inflammation [100]. Baricitinib, a potent and selective JAK inhibitor approved for rheumatoid arthritis and myelofibrosis, concentration-dependently suppresses the production of type-I IFN by dendritic cells, and inhibits the production of IL-6 from B cells and also the IL-6-induced phosphorylation of STAT1 and STAT3 [101]. Therefore, it has been suggested to test this JAK inhibitor in CARDS in order to verify if it is able to reduce both the viral entry and the inflammation [102]. The cases of 3 patients with hyper-inflammatory response linked to COVID-19, who had a rapid favourable outcome after the use of ruxolitinib, a JAK1/JAK2 kinase inhibitor designed for the treatment of myelofibrosis [100].

## 19. Conclusions

It is still impossible to make recommendations for the use of any specific agent in the treatment of CARDS because no drug has been validated to have demonstrated significant efficacy in COVID-19 patients in large-scale trials. However, these patients must also be treated pharmacologically. Promisingly, there exist a number of drugs that may be useful at least in some subjects. The real challenge now is to link the right patient to the right available treatment.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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