Emerging pharmacological therapies for ARDS COVID-19 and beyond

Horie, S., McNicholas, B., Rezoagli, E., Pham, T., Curley, G., McAuley, D., O'Kane, C., Nichol, A., Dos Santos, C., Rocco, P. R. M., Bellani, G., & Laffey, J. G. (2020). Emerging pharmacological therapies for ARDS COVID-19 and beyond. *Intensive Care Medicine*. Advance online publication. https://doi.org/10.1007/s00134-020-06141-z

Published in:
Intensive Care Medicine

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Title: Emerging pharmacologic therapies for ARDS: COVID-19 and beyond

Authors: *Shahd Horie, MSc, PhD[1]

*Bairbre McNicholas, MB, PhD[2]

Emanuele Rezoagli, MD, PhD[1,3]

Tài Pham, MD, PhD[4]

Ger Curley, MB, PhD[5]

Danny McAuley, MB, PhD[6]

Cecilia O'Kane, MB, PhD[6]

Alistair Nichol, MB, PhD[7,8,9]

Claudia dos Santos, MD, MSc[10]

Patricia R. M. Rocco, MD, PhD[3]

Giacomo Bellani, MD, PhD[12]

John G. Laffey, MD, MA FCAI[1,2]

*Joint First Authors

Institution:

[1]Lung Biology Group, Regenerative Medicine Institute (REMEDI) at CÚRAM Centre for Research in Medical Devices, Biomedical Sciences Building, National University of Ireland, Galway, Ireland.

[2]Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Galway, Ireland.

[3]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy and Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy;

[4] Service de médecine intensive-réanimation, AP-HP, Hôpital de Bicêtre, Hôpitaux Universitaires Paris-Saclay, Le Kremlin-Bicêtre, France

[5]Department of Anaesthesiology, Beaumont Hospital and Royal College of Surgeons in Ireland, Dublin, Ireland.

[6]Welcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, and Royal Victoria Hospital, Belfast, Northern Ireland.

[7]University College Dublin- Clinical Research Centre at St Vincent's University Hospital, Dublin, Ireland.

[8]Australian and New Zealand Intensive Care Research Centre, Monash University, Australia

[9]Alfred Hospital Intensive Care Unit, Australia

[10] Keenan Research Centre and Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada

[11]Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Address for correspondence: John G. Laffey, Lung Biology Group, Regenerative Medicine Institute (REMEDI) at CÚRAM Centre for Research in Medical Devices, Biomedical Sciences Building, National University of Ireland Galway, Galway. E-mail: john.laffey@nuigalway.ie. Phone: +353 91 495438

Take home message: Several ARDS therapies show promise in clinical studies, while a growing pipeline of therapies are in preclinical testing. The history of unsuccessful clinical trials of promising therapies underlines the challenges to successful translation. Attention is now focussed on identifying biologically homogenous subtypes within ARDS, to enable us to identify more specific "precision medicines" for this severe syndrome.

140 Character Summary: Multiple ARDS therapies show promise in earlier and later phase clinical trials, while a pipeline of therapies are in preclinical testing.

Conflicts of Interest: The authors report no conflicts of Interest.

Author Contributions

Drafting of the manuscript: SH, BM and JL wrote the first and subsequent drafts of the manuscript.

Critical revision of the manuscript for important intellectual content: All authors.

Abstract

ARDS, first described in 1967, is the commonest form of acute severe hypoxemic respiratory failure. Despite considerable advances in our knowledge regarding the pathophysiology of ARDS, insights into the biologic mechanisms of lung injury and repair, and advances in supportive care, particularly ventilatory management, there remains no effective pharmacological therapy for this syndrome. Hospital mortality at 40% remains unacceptably high underlining the need to continue to develop and test therapies for this devastating clinical condition.

This review discusses the current status of promising emerging pharmacological therapies for patients with ARDS, and potential impact of these and other emerging therapies for COVID-19 induced ARDS. We focus on drugs that: 1) modulate the immune response, both via pleiotropic mechanisms and via specific pathway blockade effects, 2) modify epithelial and channel function, 3) target endothelial and vascular dysfunction, 4) have anti-coagulant effects, and 5) enhance ARDS resolution. We also critically assess drugs that demonstrate potential in emerging reports from clinical studies in patients with COVID-19 induced ARDS.

Several therapies show promise in earlier and later phase clinical testing, while a growing pipeline of therapies is in preclinical testing. The history of unsuccessful clinical trials of promising therapies underlines the challenges to successful translation. Given this, attention has focused on the potential to identify biologically homogenous subtypes within ARDS, to enable us to target more specific therapies “precision medicines”. It is hoped that the substantial number of studies globally investigating potential therapies for COVID-19 will lead to the rapid identification of effective therapies to reduce the mortality and morbidity of this devastating form of ARDS.

Background

Acute Respiratory distress syndrome is the commonest form of acute severe hypoxemic respiratory failure in the critically ill. First described in 1967, the management of ARDS remains supportive [1]. Despite considerable advances in our knowledge regarding the pathophysiology of ARDS, insights into the biologic mechanisms of injury and lung repair, and advances in supportive care, particularly ventilatory management, there remains no effective direct therapy for ARDS. Mortality and morbidity remain unacceptably high [2], underlining the need to continue to develop and test therapies for this devastating clinical condition. The lack of effective ARDS therapies has been further highlighted in the evolving COVID-19 pandemic, which causes severe acute respiratory failure and ARDS in 3-5% of infected patients.

In this review, we assess the current status of promising emerging therapies for patients with ARDS We focus on drugs that: 1) modulate the immune response, both via pleiotropic mechanisms and via specific pathway blockade effects, 2) modify epithelial and channel function, 3) target endothelial and vascular dysfunction, 4) have anti-coagulant effects, and 5) enhance ARDS resolution. We also critically assess drugs that demonstrate potential in emerging reports from clinical studies in patients with COVID-19 induced ARDS.

Therapies in Clinical Trials for ARDS

Immunomodulatory Therapies

A number of medications with a broad base of 'pleiotropic' immunomodulatory effects are in clinical trials for the treatment of ARDS [***Table 1, Figure 1***].

Steroids: Steroids have long been studied as a potential therapy for both early and late phase ARDS, with some studies suggesting potential benefit, via suppression of the pro-inflammatory cytokine response, while other studies demonstrating potential risks due to immune suppression. A recent interesting open label multi-centre study examined the efficacy of high dose dexamethasone regimen in patients with established moderate to severe ARDS (i.e. P/F ratio < 200mmHg at 24hrs following ARDS diagnosis). Although terminated early for low recruitment, it found that the mean number of ventilator free days was 4.8 days higher and the number of patient deaths lower (21% versus 50%) following early treatment with dexamethasone [3]. The authors highlight the dosing regimen and time of administration as key to the use of corticosteroid therapy in ARDS. Additional studies, focused on this specific moderate to severe ARDS population (diagnosed within 24 hours), will be required to confirm and extend these interesting findings.

Ulinastatin: Ulinastatin is a urinary glycoprotein and protease inhibitor with potent anti-oxidant and anti-inflammatory effects [4]. In a small phase 2 trial, patients (n= 40 per group) with ARDS treated with ulinastatin injection (12 hourly for 14 days) demonstrated improved lung oxygenation and function and reduced duration of mechanical ventilation and reduced hospital stays compared to standard care [4]. Ulinastatin therapy also significantly lowered inflammatory cytokines and increased anti-oxidant activities [4]. Another phase 2 trial of ulinastatin is currently enrolling and a number of other protease inhibitors are in the preclinical stages of testing.

Vitamin C: Vitamin C is recognised for its anti-oxidant and reparative properties. In a phase 2 study of patients with sepsis induced ARDS, vitamin C did not reduce SOFA scores, which was the primary outcome, nor did it have an effect on biomarkers, even at high doses [5]. Of the secondary outcomes, vitamin C did reduce 28 day mortality. The time delay between onset of shock and development of ARDS delayed the administration of Vitamin C infusion when compared to other studies in sepsis [5]. A phase 2 trial is currently recruiting SARS-CoV-2 patients for treatment with Vitamin C (NCT04254533).

Vitamin D: Vitamin D deficiency is prevalent in critically ill patients, and may have important immunomodulatory properties. A large scale phase 3 Vitamin D study recently used point-of-care testing to identify critically ill patients at risk of death with low vitamin D3 levels at ICU admission. Vitamin D therapy did not result in any improvement in outcomes compared to placebo [6]. However, only a minority (<10%) developed ARDS in this study.

Carbon Monoxide: Carbon monoxide (CO) is a gas produced endogenously by hemeoxygenase, which protects against oxidative stress, cell death and suppresses inflammation [7]. Preclinical lung injury studies have shown safety and promising efficacy of low dose inhaled carbon monoxide [8]. In an exploratory phase 1 study, 8 patients with ARDS were treated with inhaled low dose carbon monoxide (100-200 parts per million), which was well tolerated with trends towards a difference in lung injury severity score and a trend towards improved SOFA scores in the treatment group [9]. A phase 2 efficacy study of carbon monoxide in ARDS is currently recruiting.

Mesenchymal Stromal Cell (MSC) Therapies: MSCs have immunomodulatory and pro-reparative effects and show efficacy in pre-clinical models of ARDS [10, 11]. A single IV infusion of allogeneic, bone marrow-derived human MSCs was well tolerated in nine patients with moderate to severe ARDS in a 2015 phase 1 dose escalation trial [12]. However, in the subsequent phase 2a study in 60 participants, MSC treatment did not improve outcomes [13]. MSC viability was variable and may have altered their efficacy, while the patient group that had received MSC therapy was more severely ill at baseline [13]. A phase 1 study of an umbilical cord derived MSC in moderate-severe

ARDS showed safety and potentially interesting immunomodulatory effects [14]. A preliminary report from an unpublished phase 1/2 trial of MultiStem® (bone-marrow derived human MSCs), suggested that MultiStem® therapy enhanced the number of ventilator-free days (VFDs) and ICU-free days and lowered mortality [15]. Another MSC trial using umbilical cord derived cells is currently recruiting (NCT03042143) and two others are ongoing (NCT02444455, NCT03608592).

Pathway Specific Immunomodulators

Dalimapimod: The p38 mitogen-activated protein kinase (MAPK) pathway is activated during cellular stress and drives downstream production of inflammatory cytokines [16]. Dalimapimod is a specific p38MAPK inhibitor and potent anti-inflammatory. In a small dose response study in trauma patients at risk for ARDS development, a 24hr Dalimapimod infusion was well tolerated and reduced concentrations of the pro-inflammatory cytokines IL-6, IL-8 and soluble tumour necrosis factor receptor 1 (TNFR1) [16]. The incidence of ARDS was low overall and not different between the groups [16].

Anti-TNFR1: An anti-TNFR1 antibody selectively antagonises TNF-α signalling through TNF receptor-1 (TNFR1), but not through TNFR2. In a volunteer study in 37 healthy humans challenged with a low dose of inhaled LPS, anti-TNFR1 attenuated pulmonary neutrophil infiltration, inflammatory cytokine release and reduced evidence of endothelial injury [17]. Targeting TNFR1 may have potential in ARDS and requires further investigation.

Therapies Targeting Epithelial/ Endothelial Dysfunction

ARDS is a disorder involving injury and dysfunction of the pulmonary epithelium and endothelium, with resultant dysfunction of the alveolar-capillary barrier leading to lung oedema. Consequently, targeting epithelial ion channels/channel dysfunction and endothelial/vascular dysfunction in ARDS constitute an important therapeutic target.

AP-301: AP-301 (also termed Solnatide) is an activator of alveolar epithelial sodium channel. Nebulized AP-301 every 12 hours for 7 days was recently shown to decrease extravascular lung water and reduce ventilation pressures in a small phase 2 (n = 20 per group) randomized blinded exploratory study in patients with early ARDS (<48hrs of diagnosis) stratified based on SOFA score (SOFA score ≥ 11) [18].

Levosimendan: Right ventricular dysfunction may be under-recognised in ARDS and may worsen outcome in patients with ARDS. Levosimendan is an inotrope, vasodilator and calcium sensitizer, and was shown to improved right ventricular performance through pulmonary vasodilation in a pilot study of 35 patients with ARDS associated with septic shock [19]. A phase 3 study is currently recruiting.

Citrulline: This non-essential amino acid is a substrate for nitric oxide synthase (NOS) in the formation of nitric oxide (NO). Low levels of citrulline are seen in patients with ARDS [20]. Citrulline deficiency may cause NOS to produce harmful nitrites, while a drop in NO can induce vasodilation, leukocyte adhesion and other important aspects of endothelial function [20]. A recently completed, small phase 2 study of lower (n = 26) versus higher (n = 24) dose citrulline for patients with sepsis induced ARDS showed no effect over placebo (n = 22) on the primary outcome measure (vasopressor dependency index), but a full report has not been published (NCT01474863).

ACE2: Angiotensin II is a vasoconstrictor, which has been implicated in lung inflammation and pulmonary oedema, and is inactivated by angiotensin converting enzyme 2 (ACE2). Angiotensin (1-7), the product of ACE2, attenuates ventilator- or acid aspiration-induced lung injury and inflammation [21] and reduces post-injury lung fibrosis [22]. Recombinant ACE2 administration was well tolerated in a phase 1 dose escalation study, while in the subsequent phase 2a study of 39 ARDS patients with concomitant infection/sepsis, there were no differences in lung or SOFA scores between the treatment and placebo groups [23].

Anti-coagulants and Thrombolytic Therapies

Dysfunction of coagulation in ARDS plays a key role in ARDS pathogenesis. Consequently, anti-coagulants and thrombolytics have also received attention as therapies for ARDS.

ALT-836: Tissue factor (TF) is a glycoprotein that is upregulated in the lung during inflammation and leads to fibrin deposition which incites further inflammatory effects [24]. Studies have observed that increased TF in the serum of ARDS patients correlates with higher mortality [24]. The anti-TF drug, ALT-836 was found to be safe when administered to ARDS patients in a phase 1, randomized, placebo-controlled, dose-escalation study [25]. A phase 2 efficacy study of ALT-836 in 150 septic patients with ARDS, was completed in 2013, but these results have not been published.

Heparin: Heparin has been investigated in ARDS for potential anti-inflammatory effects. Nebulised heparin, which avoids the systemic anti-coagulant effects, reduced the need for mechanical

ventilation in a small phase 2 study of 50 critically ill patients [26]. Prophylactic nebulized heparin enhanced alveolar perfusion and CO_2 elimination in patients following cardiac surgery [27].

Streptokinase: Streptokinase binds plasminogen to form plasmin. Nebulized streptokinase improved oxygenation and lung compliance in a phase 3 trial in 60 patients with late phase (>10 days) severe ARDS, suggesting promise as a rescue therapy for ARDS patients [28].

Potential Therapies in Preclinical ARDS Studies

There are a substantial number of potential therapies in preclinical testing. We will concentrate on those demonstrating particular promise in each of the key therapeutic target areas [***Table 2, Figure 2***].

Pleiotropic Immunomodulators

Elafin: Elafin is an endogenous and immunomodulatory protease inhibitor produced by lung epithelial cells among others. Low levels of elafin, due to dysregulated cleavage, is associated with high mortality in ARDS [29-31]. One study showed that a functional variant of elafin that was more resistant to degradation, had enhanced therapeutic benefit in a mouse model of LPS induced ALI [30]. Specifically, it dampened immune cell infiltration into the lung and lowered monocyte chemoattractant protein (MCP)-1 levels [30].

Alpha 1-antitrypsin: Alpha 1-antitrypsin (AAT) is an endogenous protease inhibitor of several pro-inflammatory cytokines associated with ARDS including interleukin-6, IL-1β and TNF-α. AAT inactivation has been demonstrated in infected lung lobes in community acquired pneumonia [32]. AAT significantly improved oxygenation, decreased pulmonary oedema and BAL protein levels and inflammatory cytokines, and inhibited cell apoptosis in a dual hit mechanical ventilation and LPS induced ALI rodent model [33]. Another study using the same dual hit injury model in the rat (and a single hit murine model), found no therapeutic benefit with AAT treatment [34], suggesting that additional studies are needed to further understand its therapeutic potential.

Pathway Specific Immunomodulators

Imatinib: The tyrosine kinase inhibitor imatinib has potent anti-oxidant and anti-inflammatory effects *in vivo* and has been shown to ameliorate lung injury and mortality in single and dual hit

ARDS pre-clinical models [35, 36]. There is also an ongoing "first in human study" examining the effects of imatinib in healthy volunteers exposed to LPS with no results available yet (NCT03328117).

Bevacizumab: Bevacizumab, a human monoclonal antibody against vascular endothelial growth factor (VEGF), has been investigated in a model of high-permeability pulmonary oedema in mice, which was induced by VEGF overexpression [37]. Bevacizumab was shown to reduce lung fluid and BAL protein levels [37]. Currently, there is a phase 2/3 trial recruiting patients with SARS-CoV-2 pneumonia for treatment with Bevacizumab (NCT04275414).

Anti-IFN-γ: Interferons appear to play a complex role in ARDS, with variable effects reported depending on the specific interferon, whether type I, II or III, and ARDS aetiologic agent. Interferon-β1α (Type I interferon), which has anti-viral, anti-inflammatory and anti-fibrotic functions demonstrated promise in a phase 2a study, but the subsequent phase 3 study did not show efficacy in ARDS [38]. In contrast, certain interferons may worsen influenza induced ARDS, as evidenced by the finding that a monoclonal antibody to IFN-γ (Type II interferon) reduced the severity of murine H1N1 influenza induced ARDS, reduced inflammation and improved mortality [39].

NLRP3 Inflammasome Inhibitors: The NLRP3 inflammasome is important in innate immunity, and causes caspase 1 activation and the release of pro-inflammatory cytokines such as IL-1β [40]. Pirfenidone, another, NLRP3 inflammasome inhibitor, was shown to suppresses oxidative stress and apoptosis *in vitro* [41]. In a LPS-induced ALI mouse model, pirfenidone, reduced lung injury scores, lung cell infiltration and lung permeability, while also limiting caspase activation, inflammatory IL-1β release and profibrotic, TGF-β release [41]. In a recently published abstract, tetracycline, an NLRP3 inflammasome inhibitor, was shown to reduce mortality, vascular leakage and neutrophil infiltration in a murine LPS ALI model [42]. Caspase activation and pro-inflammatory cytokine release were also diminished [42]. Currently, Pirfenidone is under phase 3 clinical investigation in the treatment of SARS-CoV-2 (NCT04282902).

Targeting Epithelial/ Endothelial Dysfunction

TRPV4 Inhibitors: The transient receptor potential vanilloid 4 (TRPV4) channel is a mechano-sensitive and immuno-sensitive calcium transport channel which functions to maintain pulmonary epithelial cell homeostasis. Increased TRPV4 channel activity has been implicated in ARDS pathology particularly in the context of lung stiffness [43, 44], leading to alveolar epithelial and endothelial barrier dysfunction, activation of innate immune cells and potentiation of pro-inflammatory cytokine release, oxidative stress and extracellular matrix deposition [44, 45]. TRPV4 -/- mice are protected

against VILI [46] and chemically induced ALI [43], while TRPV4 channel inhibitors GSK2220691 and GSK2337429A also reduced ALI [43]. The TRPV4 inhibitors, GSK634775 and GSK1016790 attenuated acid instillation or chlorine gas induced lung injury, decreasing lung oedema, improving oxygenation, and attenuating immune cell infiltration and pro-inflammatory cytokine release [47]. However, a recent first in human study of TRPV4 inhibitor, GSK2798745, in volunteers receiving inhaled LPS was terminated early for inefficacy (NCT03511105). The effect of TRPV4 appears cell and injury specific, affecting its utility as a therapeutic target, as recently, macrophage TRPV4 activity has been shown to enhance macrophage phagocytosis and to confer protection against Pseudomonas aeruginosa infection in mice [48].

Adenosine A2A Receptor Agonists: Adenosine A2A receptors which are expressed on many cell types have been shown to regulate fluid transport as well as inflammation in the lung [49]. The adenosine A2A receptor agonist GW328267C enhanced alveolar fluid clearance in models of acid instillation, LPS and live E.coli induced lung injury [49]. Another adenosine A2A receptor agonist, CGS-21680, improved lung compliance, reduced neutrophil infiltration and pro-inflammatory cytokine release in a rat VILI model [50].

RAGE Inhibitors: The receptor for advanced glycation end-products (RAGE) is expressed primarily in alveolar type-1 epithelial cells and is a regulator of epithelial barrier transport. Plasma soluble RAGE concentrations constitute a maker of epithelial lung injury, are increased in ARDS patients and can predict ARDS development in 'at risk' patients [51]. RAGE appears to drive lung injury also, as evidence by the finding that blockade of RAGE (using peptides, monoclonal antibodies or soluble RAGE decoy receptors) reduced acid-induced lung injury in mice [52] and piglets [53].

Haptoglobin: Plasma free hemoglobin causes the formation of reactive oxygen species and is elevated in clinical pneumonia or sepsis. Scavengers of plasma free hemoglobin such as haptoglobin reduced iron availability, oxidative injury and lung injury, and increase survival in a preclinical model of S. aureus pneumonia [54]. Transgenic mice overexpressing haptoglobin were also protected from hemoglobin included lung injury [55].

Pro-Resolution Effects

Lipoxin A4: Lipoxin A4, which is an endogenous pro-resolving lipid mediator, enhanced alveolar epithelial wound repair, promoted differentiation of alveolar type II (ATII) cells to type I cells, and promoted ATII proliferation and limit apoptosis *in vitro* [56]. In a murine LPS induced ALI model, Lipoxin A4 enhanced alveolar epithelial type II cell proliferation, thus decreasing apoptosis by limiting caspase 3 activation and limiting epithelial-mesenchymal transition as evidenced by

immunofluorescent staining [57]. Lipoxin A4 warrants further investigation in other pre-clinical ARDS models.

Emerging Therapies for COVID-19 Induced ARDS

The lack of proven therapies for COVID-19 ARDS has prompted a vast research effort to identify new targets or re-purpose existing drugs to treat COVID-19 induced ARDS [***Table 3***]. A positive effect of this global focus on severe COVID-19 disease is the acceleration of multiple potential therapies into clinical testing. Given the rapidly evolving nature of COVID-19 research, we indicate where have cited unpublished and/or un-reviewed reports in this section.

Antiviral Therapies/Strategies

Remdesivir: Remdesivir, a broad spectrum antiviral originally investigated as an anti-Ebola drug [58], is an analogue of adenosine that disrupts viral RNA polymerase and viral replication [59]. Remdesivir inhibits MERS-CoV and SARS-CoV *in vitro* and *in vivo* [59]. A recent study showed that Remdesivir was particularly effective against SARS-CoV-2 infection *in vitro* [60]. A study of compassionate Remdesivir use in 61 patients with SARS-CoV-2 infection observed clinical improvement in 68% of cases with improved oxygenation and a decrease in patients requiring mechanical ventilation [61]. An unpublished recent report suggesting that Remdesivir shortened recovery times, but did not impact mortality rates has led to the drug being licensed for use in COVID-19 patients in the US. The results of several phase 2/3 Remdesivir clinical trials are awaited [***Table 3***].

Favipiravir: Favipiravir is a broad-spectrum antiviral RNA polymerase inhibitor, already approved for use in influenza A and B [62]. A recent, open-label, control study, showed that Favipiravir exhibited significant improvements in chest CT scans and viral clearance in COVID-19 patients [63]. Several other clinical studies are underway with one examining the potential of Favipiravir in combination with Tocilizumab.

Lopinavir/ritonavir: Lopinavir/ritonavir are HIV protease inhibitors, and are generally used as part of combinations therapies. A recently concluded, open label trial of Lopinavir/ritonavir in 199 severe COVID-19 patients unfortunately, showed no clinical improvement, although the mortality rate was slightly lower in the treatment group (19.2% vs. 25%) [64]. Potential explanations include lopinavir/ritonavir use in late COVID-19 infection, its use as a single agent, and in relatively lower doses, which should be addressed in ongoing studies [64].

Arbidol: Arbidol, an antiviral approved for influenza that can affect viral interaction and binding via ACE2, was recently shown to enhance viral clearance in comparison to Lopinavir/ritonavir treatment, in a retrospective study of 50 COVID-19 patients [65]. Arbidol co-therapy with lopinavir/ritonavir, and Shufeng Jiedu capsule (traditional Chinese medicine), in 4 patients in a case study improved outcome [66]. An un-reviewed preprint reporting an open label, multicenter trial comparing Arbidol with Favipiravir in 240 COVID-19 patients, with recovery at day 7 as the primary outcome measure and found no differences between these two treatments [67]. A number of studies are currently examining the safety and efficacy of Arbidol in patients with COVID-19.

Chloroquine and Hydroxychloroquine: The antimalarial' drugs, chloroquine and it hydroxylated version, hydroxychloroquine, disrupt ACE2 binding and hence viral entry and also affect endosomal and lysosomal pH, which can inhibit the virus from merging with host cells [68]. These drugs also suppress pro-inflammatory cytokine release [69] and chloroquine has specifically been shown to inhibit influenza A H5N1 virus induced lung injury in preclinical models [70]. A recent study also showed that chloroquine inhibited SARS-CoV-2 infection *in vitro* [60]. A small clinical study recently showed that hydroxychloroquine in combination with azithromycin reduced viral load in 20 patients with SARS-CoV-2 infection [71]. Conversely, concerns have been raised regarding potential adverse effects (e.g. cardiotoxicity) with hydroxychloroquine, particularly when used in combination with azithromycin, in COVID-19 patients [72]. A number of other and larger clinical investigations of chloroquine and hydroxychloroquine are underway, including one looking at the combination of antimalarials with antivirals (***Table 3***).

TMPRSS2 Inhibitor: SARS-CoV-2 viral entry into lung epithelial cells is dependent on the ACE2 receptor while priming of the viral spike protein is dependent on the host serine protease TMPRSS2 [73]. A protease inhibitor of TMPRSS2 blocked viral entry *in vitro* and may be a promising therapeutic option [73]. Clinical studies investigating the efficacy of TMPRSS2 inhibitor, camostat mesilate are currently recruiting.

Baricitinib: Another drug which may inhibit viral entry via ACE2 receptor mediated endocytosis is Baricitinib, a JAK inhibitor, that also disrupts the cytokine cascade and dampens inflammation [74] and is an approved drug for rheumatoid arthritis. Baricitinib with its anti-inflammatory and antiviral potential was identified using a data search with the BenevolentAI drug discovery platform. A recent study of 12 patients with moderate COVID-19, observed that Baricitinib administered at 4 mg/day for 14 days was well tolerated and improved outcome in these patients when compared to patients receiving standard care [75]. Other trials evaluating Baricitinib for COVID-19 are underway.

Convalescent Plasma: Hoffmann et al. showed that SARS-CoV-1 serum from convalescent patients offered protection from SARS-CoV-2 infection and this option may perhaps be effective if used prophylactically [73]. Convalescent plasma has also been shown to reduce viral load and mortality in critically ill H1N1 patients [76] and most recently has been shown to reduce viral load and improve outcome in a series of 5 cases of critically ill SARS-CoV-2 patients [77]. Another study that included 10 patients with severe SARS-CoV-2 infection, observed that one dose of 200 mL of convalescent plasma was well tolerated, increased oxyhemoglobin and reduced vial load in 7 of these patients [78]. Another trial is currently recruiting patients for treatment with anti-SARS-CoV-2 inactivated convalescent plasma (NCT04292340).

Angiotensin/ACE: In addition, SARS-CoV-2 binds to the ACE receptor on lung epithelial cells, which is a key step in virus infection of these cells. Losartan, which is an angiotensin II receptor antagonist, is currently under investigation in SARS-CoV-2 patients (NCT04328012).

Immunomodulatory – Pleiotropic Effects

Methylprednisolone: The effects of steroids in COVID-19 appear to depend on the dose and the degree of 'hyperinflammation' present, the stage of infection, and the presence of ARDS. A recent single center, retrospective study of 46 patients with COVID-19 published as an un-reviewed preprint, showed that early, low dose and short term administration of methylprednisolone improved chest CT and clinical outcome in the treatment group [79]. Another, larger retrospective study of 201 SAR-CoV-2 patients, showed that methylprednisolone treatment in those with ARDS, reduced risk of death [80]. Of potential relevance, there is evidence that corticosteroid use may hinder viral clearance in MERS coronavirus infection [81]. Currently, there are a number of phase 2/3 clinical trials investigating the efficacy and safety of methylprednisolone in patients with COVID-19 ARDS.

Thalidomide: Thalidomide, an immunomodulatory drug that acts to enhance apoptosis, inhibit IL-6 and promote T cell responses and has been shown to lead beneficial effects in preclinical bacterial and viral induced ARDS [82, 83]. A single case report, published as an un-reviewed preprint, suggested that thalidomide and low dose glucocorticoid dampened hyperinflammation in a patient with SARS-CoV-2 pneumonia [84]. The case study also showed that thalidomide maintained T cell homeostasis suggesting that it can avoid secondary infections [84]. Thalidomide is currently under clinical phase 2 investigation for therapy against SARS-CoV-2 (NCT04273581).

Interferons: As discussed earlier, type I interferon, interferon-β1α, was ineffective as a sole agent in a recent phase 3 ARDS trial ARDS [38]. However, type I interferons have been shown to respond with different inhibitory potencies towards MERS and SARS [85] and, as such, interferons have been investigated, as an adjunct to antivirals, in these viral infections [86]. A recent study published as an un-reviewed preprint, has observed that SARS-CoV-2 infection is potentially sensitive to type I interferons [87] and currently, there are a number of phase 2/3 clinical trials investigating the efficacy of both type I or type III interferons (including REMAP-CAP and SOLIDARITY), either as sole agents or as a co-therapies in patients with SARS-CoV-2.

Mesenchymal Stromal Cell (MSC) Therapies: The immunomodulatory effects of MSCs have immunomodulatory has generated considerable interest as a potential therapeutic for COVID-19 ARDS. A recent study of 7 COVID-19 patients, observed that a single dose of ACE2-/- MSCs (10 million cells/kg), was well tolerated, and improved pulmonary function, reduced TNF-α release while enhancing IL-10 release in comparison to the placebo [88]. A number of other trials are investigating the effects of MSCs and MSC derived exosomes in patients with SARS-CoV-2 infection (***Table 3***).

Immunomodulatory – Pathway Specific

A subgroup of severely ill COVID-19 patients develop a 'cytokine storm' profile with rapid and sustained elevations in cytokines such as IL-6, and fulminant organ failure with features in common with secondary haemophagocytic lymphohistiocytosis (HLH) [89]. This has led to interest in specific anti-cytokine therapies

Tocilizumab and Sarilumab: Tocilizumab and Sarilumab, which are human monoclonal antibodies that block the IL-6 receptor. IL-6 inhibition has been shown to be therapeutic in patients with adult-onset Still's disease complicated with SIRS and ARDS [90, 91]. One recent non-controlled retrospective study of 21 patient with COVID-19, published as an un-reviewed preprint, suggested that Tocilizumab treatment may have decreased white cell counts, improved CT lung opacity and lung oxygenation [92]. There are currently several, phase 2/3 trials investigating Tocilizumab and/or Sarilumab for COVID-19 patients, with reports expected imminently.

Anakinra: Anakinra is a recombinant IL-1 receptor antagonist that neutralizes the biologic activity of IL-1a and IL-1b by competitively inhibiting their binding to interleukin-1 type I receptor, and is widely used in rheumatic diseases. Anakinra did not improve mortality in patients with sepsis and septic shock in large phase 3 studies [93-95]. However, in a post-hoc analysis anakinra improved survival in the subgroup of sepsis patients with features of HLH (ferritin elevation in excess of 2,000 ng/ml,

coagulopathy, and liver enzyme elevations) [96]. Anakinra is being trialled in the 'COVID domain' of the REMAP-CAP study (NCT02735707).

Other Potential Therapies

Heparin: Disordered coagulation, specifically, pulmonary microvascular thrombosis is increasingly implicated in the pathogenesis of severe COVID-19 respiratory failure. Other thrombotic complications including deep venous thrombosis are also reported. Anti-coagulant therapy, mainly with low molecular weight heparin, has been associated with better prognosis in severe COVID-19 patients with evidence of coagulation activation such as markedly elevated D-dimers [97]. Consequently heparin has been recommended by some expert consensus groups, however its efficacy remains to be proven. Intravenous heparin is being trialled in the REMAP-CAP study (NCT02735707). Studies of nebulized heparin, such as the CHARTER study, are also in progress [98].

Finding ARDS therapies - Future Directions

Improved preclinical models: Understanding, and where relevant, addressing limitations to current preclinical models that may help reduce future 'translational failures' of potential therapies for ARDS. Preclinical models are designed to be reliable and reproducible, but in achieving this, may poorly model the complexity of ARDS. More preclinical models can provide initial proof-of principle, it allows ineffective strategies to be rapidly discarded.

Issues such as multiple or sequential insults, the timing of insults, the role host factors such as age, sex and premorbid conditions, and the usually prolonged duration of ARDS, are not well reflected in current preclinical models. Testing promising therapies in more complex and diverse animal models, of varying age and species, employing multiple hits, and modelling longer durations of ARDS, while challenging, may be a useful step prior to embarking on clinical studies. Multi-center trials, incorporating randomization and blinding for preclinical studies, may minimize bias and improve robustness by increasing heterogeneity.

Other useful 'intermediate' steps for promising therapies prior to trials in ARDS patients may be the use of human models such as endotoxin inhalation in volunteers or testing in surgical populations, such as those undergoing one lung ventilation. Testing promising therapies in the ex vivo human lung perfusion model may provide proof of concept that the intervention can work in an acutely injured human lung.

Improved Clinical Trials: Improving our approach to clinical trial design and patient selection [99] may enhance the likelihood of finding effective therapies. One key issue relates to the heterogeneity of ARDS and the non-specific nature of the ARDS clinical criteria, which may result in recruitment of patients who do not possess the underlying injury processes and biologic pathways characteristic of ARDS. 'Practical enrichment' involves careful selection of candidates who are likely to complete the intervention and survive the study period. 'Prognostic enrichment' aims to reduce the numbers required to detect a significant difference by enrolling patients who are most likely to experience the primary endpoint. 'Predictive enrichment' involves selecting patients based on pathobiological factors that will predispose them to a treatment response. This latter approach may offer most promise, by selecting for patients who have a strong likelihood for a response to the intervention (and by the same token, select 'out' those who are unlikely to respond). This would reduce study noise, sample size, and study-associated harm. In ARDS this approach has already borne fruit: an important -positive- study of prone positioning randomized only patients who demonstrated an initial positive response to prone positioning.

Targeting ARDS subtypes: Identifying patients more likely to respond to a specific pharmacologic intervention should increase chances of trial success. A key recent advance in our understanding of the pathobiology of ARDS has been the ability to divide ARDS into subgroups or sub-phenotypes. Latent class analysis identifies one third of ARDS patients with a 'hyper-inflammatory' phenotype, and reanalysis of a large negative RCT of Simvastatin in ARDS using this approach suggested benefit in the 'hyperinflammatory' group [100]. ARDS phenotyping based on the focal versus diffuse distribution of lung infiltrates is also potentially feasible [101], as are transcriptomics-based approaches [102]. While prospective trials are required to validate phenotyping approaches, and subsequently to test therapies in specific phenotypes, this approach offers considerable hope for the repurposing of drugs previously deemed to have 'failed' clinical translation.

Conclusions

There are a host of potential drug therapies demonstrating promise for ARDS, from drugs that modulate the immune response, specific inflammatory pathway blockers, epithelial and channel function modulators, endothelial and vascular dysfunction therapies, anti-coagulant drugs, and therapies that aid resolution of ARDS. A promising pipeline of therapies is also progressing through preclinical testing. An important area of investigation is the potential for advances in our understanding of the pathobiology of ARDS, and specifically the potential to identify biologically homogenous subtypes within ARDS, to enable us to target more specific therapies. It is hoped that

the substantial number of studies globally investigating potential therapies for severe COVID-19 patients will help the identification of effective therapies for ARDS.

FIGURE LEGENDS

Figure 1: Pharmacological therapies and their targets, in clinical testing for ARDS therapy.

Figure 2: Pharmacological therapies and their targets, in preclinical testing for ARDS therapy.

Table 1: Classification of Therapies in Clinical Studies Classified by Biologic Target

Proposed Therapy	Mechanism of Action	Stage in Translation Pathway	Key Recent Studies
Immunomodulatory – Pleiotropic Effects			
1. Dexamethasone	Corticosteroid, anti-inflammatory	Phase 2/3 – Completed	DEXA-ARDS – Study of Dexamethasone for Established Moderate-Severe ARDS [3] - Patients recruited with P/F ≤ 200mmHg 24hrs following ARDS diagnosis - 277 patients enrolled (139 received Dex 20mg/day on D1-D5, then 10mg/day D6-D10) - Stopped early for poor recruitment at 88% target - VFD 4.8 days higher with Dex; Day 28 Mortality 21% versus 50% in Placebo
2. Ulinastatin	Urinary protease inhibitor	Phase 2	Study of Ulinastatin Efficacy and Mechanical Ventilation in ARDS [4] - 80 patients enrolled; 40 patients received standard care alone, while 40 patients also received ulinastatin (200,000 units in 100 ml normal saline, IV infusion once every 12 hrs, for 14 days) - Arterial blood lactate lower, oxygen uptake rate, arterial oxygen content higher with ulinastatin - FEV_1 and FEV_1/FVC levels smaller with ulinastatin - Shorter duration mechanical ventilation and hospital stays with ulinastatin - TNF-α, IL-6, CRP, adrenaline and norepinephrine lower with ulinastatin Malondialdehyde, super oxide dismutase and total antioxidant capacity higher in with ulinastatin The Safety and Dose Response of Ulinastatin for ARDS – Enrolling by invitation – NCT02895191
3. Vitamin C	Anti-oxidant, reparative properties	Phase 2 – Completed	CITRIS-ALI – Study of Vitamin C Infusion for Treatment in Sepsis Induced ALI [5] - Patients recruited with P/F ≤ 300mmhg, with sepsis and ARDS present for less than 24 hrs - 167 patients enrolled (84 received Vitamin C (50mg/kg) every 6 hrs for 96 hrs) - No effect observed on SOFA score, C-reactive protein or thrombomodulin levels
4. Vitamin D	Regulator of immune functions, maintains epithelial surface integrity	Phase 3 – Completed	VIOLET – Study of Early Vitamin D Administration for Critically Ill Patients [6] - Vitamin D deficient patients were recruited within 12 hrs of admission to the ICU - 1059 patients enrolled (531 received a single dose of 540,000 IU of Vitamin D3) - No effect on primary outcome measure (90 day mortality) or secondary outcome measures (ventilator days, 28 day mortality or length of hospital stay)
5. Carbon Monoxide	Anti-inflammatory, reduces oxygen induced damage	Phase 1 – Completed Phase 2 – Recruiting	Study of Low Dose Inhaled Carbon Monoxide for Sepsis Induced ARDS [9] - Patients recruited with P/F ≤ 300mmhg and SOFA score of ≥ 2 - 12 patients enrolled (cohort 1 = 4 patients received 100 ppm CO, 2 patients received placebo; cohort 2 = 4 patients received 200ppm CO, 2 patients received placebo) - Patients did not exceed levels of 10% carboxyhaemoglobin and no adverse effects were encountered - Treatment group exhibited lower levels of mitochondrial DNA in the circulation Safety and Efficacy Study of Inhaled Carbon Monoxide to Treat ARDS – Recruiting – NCT03799874

6. MSCs	Immunomodulatory	Phase 1/2	START – Phase 1 Study of Human MSCs for Patients with ARDS [12] - Patients recruited with P/F < 200 mmhg, requiring mechanical ventilation and with a PEEP ≥ 8cmH_2O - 9 patients enrolled (3 groups of 3 that received a single IV infusion of 1, 5 or 10 million cells (allogeneic bone marrow derived MSCs) per kg PBW) - No adverse effects were related to treatment, trend for lower mortality and SOFA scores START – Phase 2 Study of Human MSCs for ARDS Patients [13] - Patients recruited with P/F < 200mmhg, requiring mechanical ventilation and with a PEEP ≥ 8cmH_2O - 60 patients enrolled (in a 2:1 ratio patients received either 10 million/kg PBW cells or placebo - No effect observed in primary or secondary outcome measures, baseline APACHE III scores were different between treatment and placebo group, cell viability was low MUST-ARDS – Study of the Safety and Efficacy of MultiStem® Therapy for ARDS [15] - Patients recruited with moderate-severe ARDS requiring mechanical ventilation and within 96 hrs of diagnosis - 36 patients enrolled (cohort 1 = low dose (human bone marrow derived) MSCs, cohort 2 = high dose MSCs, cohort 3 = highest safest dose from cohort 1 and 2 versus placebo) - Treatment resulted in higher VFDs and ICU-free days - Mortality was lower in the treatment group
Immunomodulatory – Pathway Specific			
1. Dilmapimod (SB-681323)	p38 MAPK inhibitor	Phase 2 Prevention Trial – Completed	Study of Dilmapimod for Trauma Patients at Risk of Developing ARDS [16] - Patients recruited with injury score severity of > 16 (head trauma excluded) - 77 patients enrolled (4 cohorts received varying doses of Dilmapimod or placebo for 4 hrs or for 24 hr continuous infusions (for 3 days total)) - Dilmapimod was well tolerated - 10mg over continuous 24 hr infusion showed reduced IL-8, IL-6, C-reactive peptide and soluble TNFR1 levels - Only 2/77 patients developed ARDS
2. Anti-TNFR1 (GSK1995057)	Blocks TNFR1	Phase 1 First in Human Study – Completed	A Study of inhaled GSK1995057 in Healthy Humans Exposed to Endotoxin [17] - 37 healthy volunteers enrolled (18 received GSK1995057 and 19 received placebo 1 hour prior to LPS (100 µg/mL) challenge - Samples were collected before LPS challenge and 6 and 24 hrs after challenge - GSK1995057 lowered BALF neutrophils, von Willebrand factor levels and IL-1β, IL-6 and IL-8 cytokine levels
Epithelial/Channel dysfunction			
1. AP-301 (Solnatide)	Activation of alveolar epithelial sodium channels	Phase 2	Study of AP-301 on Alveolar Liquid Clearance in ICU Patients with ALI [18] - Patients recruited with P/F ≤ 300mmhg and EVLWI ≥8 ml/kg predicted body weight (PBW), within 48 hrs of ARDS diagnosis and requiring mechanical ventilation - 40 patients enrolled were stratified based on SOFA scores (stratum A ≤ 10, stratum B ≥ 11) - 20 patients received 125mg of nebulised AP-301 every 12 hrs for 7 days, the other 20 received saline - EVLWI and ventilation pressures were lower in the treatment group versus placebo in stratum B Safety and Efficacy of Solnatide to Treat Pulmonary Permeability Oedema in Patients With Moderate-to-Severe ARDS – Recruiting – NCT03567577

Endothelial /Vascular Dysfunction			
1. Levosimendan	Calcium sensitizer, vasodilator	Pilot study – Completed Phase 3 – Recruiting	Pilot Study of Levosimendan Effects on Right Ventricular Afterload in Patients with ARDS [19] - Patients recruited with septic shock & ARDS, requiring ventilation and within 3 days of diagnosis - 35 patients enrolled (18 received a 24 hr infusion of 0.2mg.kg levosimendan, 17 placebo - The treatment group showed decreases in mean pulmonary arterial pressure, pulmonary vascular resistance index and pulmonary artery occlusion pressure - The treatment group also showed increases in the right ventricular ejection fraction, stroke index and cardiac index Study of Levosimendan on the Prognosis of ARDS Patients – Recruiting – NCT04020003
2. Citrulline	Precursor for NO, vasodilator	Phase 2 Sepsis with ARDS – Completed	Study of Citrulline in the Prevention or Mitigation of ARDS in Sepsis Patients (NCT01474863) - Patients recruited with sepsis and at risk of or with ARDS - 72 patients enrolled - 26 received low dose citrulline, initial bolus of 10mg/kg followed by IV infusion of 4.5mg/kg/hr (max 350mg) for 4 days - 24 received high dose citrulline, initial bolus of 20mg/kg followed by IV infusion of 9mg/kg/hr (max 700mg) for 4 days - 22 received a placebo - There were no differences in the primary outcome measure, vasopressor dependency index though there was trend for reduced all-cause mortality in the high dose treatment group
3. ACE2 (GSK2586881)	Recombinant protein, down regulates angiotensin II	Phase 2 – Completed	A Study of GSK2586881 in Patients with ALI [23] - Patients recruited with ARDS and infection/pneumonia/sepsis within 48 hrs of diagnosis - 5 patients were enrolled in part A, a phase 1b dose escalation study (4 IV doses, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg at baseline, 2, 4 and 18 hours) - 39 patients were enrolled in part B, a phase 2a study (19 received twice daily doses of 0.4mg/kg GSK2586881 over three days, 20 received a placebo) - In phase 1b there were no hemodynamic changes or adverse effects associated with treatment - In phase 2a there were no differences between treatment and placebo in P/F or SOFA scores
Anti-coagulant Effects			
1. ALT-836	Anti-TF, blocks coagulation cascade and subsequent proinflammatory cytokine release	Phase 1 – Completed Phase 2 – Completed	Dose Escalation and Safety Study of Anti-TF in ARDS Patients [25] - Patients recruited with P/F ≤ 300mmhg with suspected or proven infection and requiring mechanical ventilation within 48 hrs of ARDS diagnosis - 18 patients enrolled (3 cohorts of 6 patients with 5:1 ratio of drug (single dose of 0.01, 0.08 or 0.1 mg/kg) to placebo - Dose dependent haematuria was recorded in 9 patients but was self-resolving in 8 of those - Anti-TF overall was safe in these ARDS patients Safety and Efficacy of Anti-TF in Septic Patients with ARDS (NCT00879606) - Patients recruited with P/F ≤ 300mmhg, suspected or proven infection and requiring mechanical ventilation - 150 patients enrolled (patients in part one received single dose of anti-TF (0.06mg/kg) or placebo, patients in part two received 4 doses (0.06mg/kg) or placebo) - Primary outcome measures were safety 28 days after treatment and VFDs at day 28 – Results not posted

2. Heparin	Anti-coagulant	Phase 2/3 – Completed	A Study of Inhaled Heparin in Critically Ill Patients [26] - Patients recruited with respiratory failure requiring mechanical ventilation for more than 48 hrs - 50 patients enrolled (25 patients received inhaled heparin (25,000 U while ventilated (cut off at 14 days) and 25 patients received placebo) - No effect on primary outcome measure, P/F but VFDs at day 28 in those that survived was higher in the treatment group (22±4 vs 18± 7), and treatment overall was safe in patients Prevention Study of Nebulised Heparin in Cardiac Surgery Patients at Risk of Lung Injury [27] - Patients recruited undergoing elective cardiac surgery with cardiopulmonary bypass - 40 patients enrolled (20 patients received prophylactic single nebulised 10ml dose of heparin (50,000 U) or placebo - There was no differences in the primary outcome measure, P/F but the treatment group showed better alveolar perfusion and CO_2 elimination post-surgery
3. Streptokinase	Thrombolytic	Phase 2 – Completed	Study of Nebulised Streptokinase Versus Nebulised Heparin in Patients with Severe ARDS [28] - Patients recruited with P/F < 100mmhg and nonresponsive to recruitment manoeuvre, prone position and neuromuscular block - 60 patients enrolled (20 received nebulized heparin (10,000 IU 4 hourly), 20 received nebulized streptokinase (250,000 IU 4 hourly) and 20 received the standard-of-care - P/F higher in streptokinase group from day 1 to day 8 - Streptokinase decreased plateau pressures, improved compliance, reduced $PaCO_2$, reduced length of ICU stay and lowered ICU mortality

Table 2: Classification of Therapies in Preclinical Studies Classified by Biologic Target

Proposed Therapy	Mechanism of Action	Key Studies and Finding(s)
Immunomodulatory – Pleiotropic Effects		
1. Elafin	Protease inhibitor, antimicrobial	1. A protease resistant Elafin variant demonstrated enhanced anti-inflammatory activity in a murine LPS ALI model. [30]
2. Alpha-1-Antitrypsin	Protease inhibitor, anti-inflammatory, anti-apoptotic	1. Alpha-1-antitrpysin improved lung oxygenation and reduced lung permeability and inflammatory cytokines following injurious mechanical ventilation and LPS challenge in rodents. [33] 2. Alpha-1-antitrpysin did not exert beneficial effects in a similar murine injury model. [34]
Immunomodulatory – Pathway Specific		
1. Imatinib	Protein-tyrosine kinase inhibitor	1. Imatinib lowered pulmonary oedema, oxidative stress, apoptosis and mortality in a LPS ALI mouse model. [36] 2. Imatinib decreased pulmonary infiltrates and TNF-α release in a dual hit, VILI and LPS mouse model. [35] 3. A first in human study of Imatinib in the human inhaled endotoxin model of lung Injury was completed in 2017. Results remain pending. NCT03328117
2. Bevacizumab	Anti-VEGF	1. Bevacizumab reduced VEGF-induced pulmonary oedema in the mouse lung. [37] 2. A phase 2 study of Bevacizumab in ARDS was withdrawn and is currently seeking funding. NCT01314066 3. Another phase 2 study of Bevacizumab for SARS-CoV-2 is currently recruiting. NCT04275414
3. Anti-IFN-γ	IFN-γ neutralisation	1. Anti-IFN-γ reduced lung inflammation and mortality in a H1N1 lung injury mouse model. [39]
4. Pirfenidone 5. Tetracycline	NLRP3 inflammasome inhibitors	1. Pirfenidone inhibited lung injury and inflammation, caspase activation and fibrosis in a murine LPS model. [41] 2. A phase 3 study of Pirfenidone for SARS-CoV-2 is underway. NCT04282902 3. Tetracycline reduced inflammation, apoptosis and mortality in an endotoxin-induced ALI model. [42]
Epithelial/Channel dysfunction		
1. GSK634775 2. GSK1016790	TRPV4 inhibitors	1. TRPV4 channel inhibitors improve lung function and potentiate anti-inflammatory responses following acid instillation or chlorine gas exposure in murine models. [47] 2. A first in human study of GSK2798745 following LPS challenge in healthy volunteers was terminated early due to a lack of positive outcomes (NCT03511105).
3. GW328267C 4. CGS-21680	Adenosine A2A receptor agonists	1. Adenosine A2A receptor agonists are reparative and anti-inflammatory in the lung following infection, acid or mechanical injury. [49, 50]
5. RAGE Inhibitors	RAGE neutralization	1. RAGE inhibition (peptides, monoclonal antibodies or soluble RAGE decoy receptors) restored lung function in acid instillation lung injury models in mice and in piglets. [52, 53]
Endothelial/Vascular Dysfunction		
6. Haptoglobin	Scavengers of plasma free haemoglobin	1. Haptoglobin dampened oxidative stress and lung injury in a pneumonia model and was protective against injury in a blood lung injury model. [54, 55]
Pro-Resolution Effects		
7. Lipoxin A4	Endogenous pro-resolving lipid mediator	1. Lipoxin A4 protects against alveolar type II apoptosis, enhances their proliferation and inhibits epithelial-mesenchymal transition following LPS challenge in mice. [57]

Table 3: Emerging Therapies for SARS-CoV-2

Proposed Therapy	Mechanism of Action	Published Findings to Date	Randomized Controlled Clinical Trials in Progress (Selected from clinicaltrials.gov)
Antiviral Therapies/Strategies			
1. Remdesivir (GS-5734™)	Nucleoside based RNA polymerase inhibitor	Therapeutic in preclinical models of MERS-CoV and SARS-CoV and inhibits SARS-CoV-2 infection *in vitro*. [59, 60] Remdesivir potentially beneficial in report of in 61 patients with SARS-CoV-2 [61].	1. Expanded Access Remdesivir (RDV; GS-5734™). NCT04302766 2. ACTT – Adaptive COVID-19 Treatment Trial. NCT04280705 3. Study of the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease. NCT04292899 4. A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment. NCT04292730 5. The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients. NCT04321616 6. The SOLIDARITY Trial. ISRCTN83971151
2. Favipiravir	Broad-spectrum RNA polymerase inhibitor	Blocks viral replication and recently shown to improve chest opacities and reduce viral load in SARS-CoV-2 patients. [63] No benefit over Arbidol in open label trial. [67]	1. THDMS-COVID-19 – Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquin for Treatment of COVID-19. NCT04303299 2. Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019. NCT04310228 3. Clinical Study To Evaluate The Performance And Safety Of Favipiravir in COVID-19. NCT04336904
3. Lopinavir/ritonavir	HIV protease inhibitors	Unsuccessful in a recent trial of 199 patients, infection was at advanced stage and very severe however. [64]	1. ELACOI – The Efficacy of Lopinavir + Ritonavir and Arbidol against Novel Coronavirus Infection. NCT04252885 2. Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment. NCT04276688 3. The Efficacy and Safety of Lopinavir-Ritonavir in Hospitalized Patients with Novel Coronavirus Pneumonia. ChiCTR2000029308 4. Treatment of Moderate to Severe Coronavirus Disease in Hospitalized Patients. NCT04321993 5. REMAP-CAP – Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707 6. The SOLIDARITY Trial. ISRCTN83971151
4. Arbidol (Umifenovir)	Inhibits viral interaction and binding with host cells via ACE2	Retrospective analysis showed that Arbidol treatment (n=16) in comparison to Lopinavir/ritonavir treatment (n=36) reduced viral load in SARS-CoV-2 patients. [65] No benefit over Favipiravir in open label trial. [67]	1. UAIIC – Study of Umifenovir in COVID-19. NCT04350684 2. Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia caused by Novel Coronavirus. NCT04260594 3. ELACOI – Efficacy of Lopinavir + Ritonavir & Arbidol against Novel Coronavirus Infection. NCT04252885
5. Chloroquine 6. Hydroxychloroquine	Antimalarial drugs	Inhibits viral entry and SARS-CoV-2 infection *in vitro*. [60] Hydroxychloroquine plus azithromycin reduced viral load in 20 COVID-19 patients. [71]	1. COPCOV – Chloroquine Prevention of Coronavirus Disease in the Healthcare Setting. NCT04303507 2. Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease. NCT04307693 3. HC-nCoV – Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV. NCT04261517

		Concerns regarding cardiotoxicity and QT prolongation in COVID-19. [72]	4. HYDRA – Study of Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection. NCT04315896 5. THDMS-COVID-19 – Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquin for Treatment of COVID-19. NCT04303299 6. REMAP-CAP – Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707 7. CLOCC – Combination Therapy With Camostat Mesilate + Hydroxychloroquine for COVID-19. NCT04338906 8. The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients. NCT04321616 9. The SOLIDARITY Trial. ISRCTN83971151
7. TMPRSS2 inhibitor (camostat mesilate)	Protease Inhibitor	*In vitro* study showing SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by protease inhibitor. [73]	1. CamoCO-19 – The Impact of Camostat Mesilate on COVID-19 Infection. NCT02735707 2. CLOCC – Combination Therapy With Camostat Mesilate + Hydroxychloroquine for COVID-19. NCT04338906
8. Baricitinib	JAK inhibitor	Anti-inflammatory and inhibitor of ACE2 mediated viral entry, may be promising for viral ARDS. [74] Identified using a drug discovery search engine platform. Baricitinib well tolerated and potentially beneficial over standard care in small clinical study. [75]	1. Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients. NCT04321993 2. BARI-COVID – Pilot Study Baricitinib in Symptomatic Patients Infected by COVID-19. NCT04320277
9. Inactivated Convalescent Plasma	IV immunoglobulins	Enhanced viral clearance and clinical outcome in 5 patients in a case study of SARS-CoV-2. [77] Convalescent plasma well tolerated, improved oxygenation and reduced vial load in 7 of 10 patients [78].	1. Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19. NCT04292340
Immunomodulatory – Pleiotropic Effects			
1. Methylprednisolone	Glucocorticoid, anti-inflammatory	Retrospective studies of 46 and 201 patients with SARS-CoV-2 ARDS shows that early and careful administration may have beneficial role.[79, 80] Corticosteroid use may hinder viral clearance in MERS coronavirus infection [81].	1. Steroids-SARI – Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure. NCT04244591 2. Efficacy and Safety of Corticosteroids in COVID-19. NCT04273321 3. REMAP-CAP – Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707
2. Thalidomide	Immunomodulator, anti-IL-6, pro-apoptotic	Therapeutic in pre-clinical models of ARDS and a case study of one patient with SARS-CoV-2. [83, 84]	1. The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19. NCT04273581

3. Type I and Type III Interferons	Antiviral, anti-inflammatory and anti-fibrotic	Interferons affect SARS and MERS differentially but SARS-CoV-2 is particularly sensitive to interferon treatment. [85, 87]	1. Study of IFN-α1β in the Treatment of Patients with Novel Coronavirus. NCT04293887 2. Study of Pegylated Interferon Lambda Treatment for COVID-19. NCT04343976 3. A Study of Interferon-β1α in COVID-19. NCT04350671 4. DIC – A Study of Interferon-β1α, Compared to Interferon-β1β and the Base Therapeutic Regiment in COVID-19. NCT04343768 5. Double Therapy With IFN-β1β and Hydroxychloroquine. NCT04350281 6. Trial of Treatments for COVID-19 in Hospitalized Adults. NCT04315948 7. REMAP-CAP – Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707
4. MSCs	Immunomodulatory and pro-resolution effects	Promising in pre-clinical and phase 1/2 ARDS studies. [10, 11, 15] ACE2-/- MSCs were well tolerated, improved pulmonary function and immune response in a case series of 7 COVID-19 patients. [88]	1. REALIST – Study of MSC Repair in COVID-19 induced ARDS. NCT03042143 2. Study of UC-MSC Treatment for the 2019-Novel Coronavirus Pneumonia. NCT04269525 3. Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19. NCT04252118 4. Study of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia. NCT04339660 5. Study of Mesenchymal Stem Cells for Severe Corona Virus Disease 2019. NCT04288102 6. Pilot Study of Inhaled of MSC Derived Exosomes for Treating Severe Novel Coronavirus Pneumonia. NCT04276987 7. MACOVIA – Study of MultiStem Administration for COVID-19 Induced ARDS
Immunomodulatory – Pathway Specific			
1. Acterma (Tocilizumab) 2. Kevzara (Sarilumab)	Human monoclonal antibody, IL6R antagonist	Improved chest CT, lung oxygenation and reduced immune cell counts in a retrospective study of 21 patients with SARS-CoV-2. [92]	1. Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019. NCT04310228 2. Efficacy and Safety of Tocilizumab in the treatment of New Coronavirus Pneumonia. ChiCTR2000029765 3. TOCIVID-19 – Tocilizumab in COVID-19 Pneumonia. NCT04317092 4. TACOS – Tocilizumab vs CRRT in Management of Cytokine Release Syndrome in COVID-19. NCT04306705 5. Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. NCT04315298 6. TOCIVID – Anti-IL-6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure. NCT04322773 7. Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients. NCT04321993
3. Anakinra	Human monoclonal antibody, IL1-R antagonist	Post-hoc analysis confirmed improved survival in a subgroup of sepsis patients. [96]	1. ESCAPE – Personalised Immunotherapy for SARS-CoV-2 Associated with Organ Dysfunction. NCT04339712 2. Study of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients with COVID-19. NCT04324021 3. CORIMUNO-ANA – Efficacy of Anakinra In Patients With Covid-19 Infection. NCT04341584 4. COV-AID – Treatment of COVID-19 Patients With Anti-interleukin Drugs. NCT04330638 5. REMAP-CAP – Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707

Other Potential Therapies			
1. Heparin	Anticoagulant	Low molecular weight heparin associated with better prognosis in severe COVID-19 patients with markedly elevated D-dimers [97].	1. CHARTER study – Nebulized Heparin for patients with COVID-19 ARDS. ACTRN:1260000517976

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE, (1967) Acute respiratory distress in adults. Lancet 2: 319-323
2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, (2016) Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 315: 788-800
3. Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, Aguilar G, Alba F, Gonzalez-Higueras E, Conesa LA, Martin-Rodriguez C, Diaz-Dominguez FJ, Serna-Grande P, Rivas R, Ferreres J, Belda J, Capilla L, Tallet A, Anon JM, Fernandez RL, Gonzalez-Martin JM, (2020) Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 8: 267-276
4. Ji M, Chen T, Wang B, Chen M, Ding Q, Chen L, Fang Y, Yu X, Chen Y, Wang X, He Y, Jiang Y, (2018) Effects of ulinastatin combined with mechanical ventilation on oxygen metabolism, inflammation and stress response and antioxidant capacity of ARDS. Exp Ther Med 15: 4665-4670
5. Fowler AA, 3rd, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, Fisher B, Thacker LR, 2nd, Natarajan R, Brophy DF, Sculthorpe R, Nanchal R, Syed A, Sturgill J, Martin GS, Sevransky J, Kashiouris M, Hamman S, Egan KF, Hastings A, Spencer W, Tench S, Mehkri O, Bindas J, Duggal A, Graf J, Zellner S, Yanny L, McPolin C, Hollrith T, Kramer D, Ojielo C, Damm T, Cassity E, Wieliczko A, Halquist M, (2019) Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. JAMA 322: 1261-1270
6. Ginde AA, Brower RG, Caterino JM, Finck L, Banner-Goodspeed VM, Grissom CK, Hayden D, Hough CL, Hyzy RC, Khan A, Levitt JE, Park PK, Ringwood N, Rivers EP, Self WH, Shapiro NI, Thompson BT, Yealy DM, Talmor D, (2019) Early High-Dose Vitamin D3 for Critically Ill, Vitamin D-Deficient Patients. N Engl J Med 381: 2529-2540
7. Ryter SW, Otterbein LE, Morse D, Choi AM, (2002) Heme oxygenase/carbon monoxide signaling pathways: regulation and functional significance. Mol Cell Biochem 234-235: 249-263
8. Jahn N, Lamberts RR, Busch CJ, Voelker MT, Busch T, Koel-Simmelink MJ, Teunissen CE, Oswald DD, Loer SA, Kaisers UX, Weimann J, (2015) Inhaled carbon monoxide protects time-dependently from loss of hypoxic pulmonary vasoconstriction in endotoxemic mice. Respir Res 16: 119
9. Fredenburgh LE, Perrella MA, Barragan-Bradford D, Hess DR, Peters E, Welty-Wolf KE, Kraft BD, Harris RS, Maurer R, Nakahira K, Oromendia C, Davies JD, Higuera A, Schiffer KT, Englert JA, Dieffenbach PB, Berlin DA, Lagambina S, Bouthot M, Sullivan AI, Nuccio PF, Kone MT, Malik MJ, Porras MAP, Finkelsztein E, Winkler T, Hurwitz S, Serhan CN, Piantadosi CA, Baron RM, Thompson BT, Choi AM, (2018) A phase I trial of low-dose inhaled carbon monoxide in sepsis-induced ARDS. JCI Insight 3
10. Devaney J, Horie S, Masterson C, Elliman S, Barry F, O'Brien T, Curley GF, O'Toole D, Laffey JG, (2015) Human mesenchymal stromal cells decrease the severity of acute lung injury induced by E. coli in the rat. Thorax 70: 625-635
11. Horie S, Gaynard S, Murphy M, Barry F, Scully M, O'Toole D, Laffey JG, (2020) Cytokine pre-activation of cryopreserved xenogeneic-free human mesenchymal stromal cells enhances resolution and repair following ventilator-induced lung injury potentially via a KGF-dependent mechanism. Intensive Care Med Exp 8: 8
12. Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee JW, Rogers AJ, Levitt J, Wiener-Kronish J, Bajwa EK, Leavitt A, McKenna D, Thompson BT,

Matthay MA, (2014) Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med 3: 24-32

13. Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, Rogers AJ, Gotts JE, Wiener-Kronish JP, Bajwa EK, Donahoe MP, McVerry BJ, Ortiz LA, Exline M, Christman JW, Abbott J, Delucchi KL, Caballero L, McMillan M, McKenna DH, Liu KD, (2018) Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med 7: 154-162
14. Yip HK, Fang WF, Li YC, Lee FY, Lee CH, Pei SN, Ma MC, Chen KH, Sung PH, Lee MS, (2020) Human Umbilical Cord-Derived Mesenchymal Stem Cells for Acute Respiratory Distress Syndrome. Crit Care Med 48: e391-e399
15. Jacono F, Bannard-Smith J, Brealey D, Meyer N, Thickett D, Young D, Bentley A, McVerry B, Wunderink RG, Doerschug KC, Summers C, Rojas M, Jenkins ED, Ting A (2019) Primary Analysis of a Phase 1/2 Study to Assess MultiStemÂ® Cell Therapy, a Regenerative Advanced Therapy Medicinal Product (ATMP), in Acute Respiratory Distress Syndrome (MUST-ARDS)B14 LATE BREAKING CLINICAL TRIALS, pp. A7353-A7353
16. Christie JD, Vaslef S, Chang PK, May AK, Gunn SR, Yang S, Hardes K, Kahl L, Powley WM, Lipson DA, Bayliffe AI, Lazaar AL, (2015) A Randomized Dose-Escalation Study of the Safety and Anti-Inflammatory Activity of the p38 Mitogen-Activated Protein Kinase Inhibitor Dilmapimod in Severe Trauma Subjects at Risk for Acute Respiratory Distress Syndrome. Crit Care Med 43: 1859-1869
17. Proudfoot A, Bayliffe A, O'Kane CM, Wright T, Serone A, Bareille PJ, Brown V, Hamid UI, Chen Y, Wilson R, Cordy J, Morley P, de Wildt R, Elborn S, Hind M, Chilvers ER, Griffiths M, Summers C, McAuley DF, (2018) Novel anti-tumour necrosis factor receptor-1 (TNFR1) domain antibody prevents pulmonary inflammation in experimental acute lung injury. Thorax 73: 723-730
18. Krenn K, Lucas R, Croize A, Boehme S, Klein KU, Hermann R, Markstaller K, Ullrich R, (2017) Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. Crit Care 21: 194
19. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Carbone I, Tritapepe L, Pietropaoli P, Westphal M, (2006) Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 34: 2287-2293
20. Ware LB, Magarik JA, Wickersham N, Cunningham G, Rice TW, Christman BW, Wheeler AP, Bernard GR, Summar ML, (2013) Low plasma citrulline levels are associated with acute respiratory distress syndrome in patients with severe sepsis. Crit Care 17: R10
21. Klein N, Gembardt F, Supe S, Kaestle SM, Nickles H, Erfinanda L, Lei X, Yin J, Wang L, Mertens M, Szaszi K, Walther T, Kuebler WM, (2013) Angiotensin-(1-7) Protects From Experimental Acute Lung Injury. Critical Care Medicine 41: e334-e343
22. Zambelli V, Bellani G, Borsa R, Pozzi F, Grassi A, Scanziani M, Castiglioni V, Masson S, Decio A, Laffey JG, Latini R, Pesenti A, (2015) Angiotensin-(1-7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental Acute Respiratory Distress Syndrome. Intensive Care Med Exp 3: 44
23. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL, (2017) A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 21: 234
24. Bastarache JA, Fremont RD, Kropski JA, Bossert FR, Ware LB, (2009) Procoagulant alveolar microparticles in the lungs of patients with acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 297: L1035-1041

25. Morris PE, Steingrub JS, Huang BY, Tang S, Liu PM, Rhode PR, Wong HC, (2012) A phase I study evaluating the pharmacokinetics, safety and tolerability of an antibody-based tissue factor antagonist in subjects with acute lung injury or acute respiratory distress syndrome. BMC Pulm Med 12: 5
26. Dixon B, Schultz MJ, Smith R, Fink JB, Santamaria JD, Campbell DJ, (2010) Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: a randomized controlled trial. Crit Care 14: R180
27. Dixon B, Smith R, Santamaria JD, Orford NR, Wakefield BJ, Ives K, McKenzie R, Zhang B, Yap CH, (2015) A trial of nebulised heparin to limit lung injury following cardiac surgery. Anaesth Intensive Care 44: 28-33
28. Abdelaal Ahmed Mahmoud A, Mahmoud HE, Mahran MA, Khaled M, (2019) Streptokinase Versus Unfractionated Heparin Nebulization in Patients With Severe Acute Respiratory Distress Syndrome (ARDS): A Randomized Controlled Trial With Observational Controls. J Cardiothorac Vasc Anesth 34: 436-443
29. Kerrin A, Weldon S, Chung AH, Craig T, Simpson AJ, O'Kane CM, McAuley DF, Taggart CC, (2013) Proteolytic cleavage of elafin by 20S proteasome may contribute to inflammation in acute lung injury. Thorax 68: 315-321
30. Small DM, Zani ML, Quinn DJ, Dallet-Choisy S, Glasgow AM, O'Kane C, McAuley DF, McNally P, Weldon S, Moreau T, Taggart CC, (2015) A functional variant of elafin with improved anti-inflammatory activity for pulmonary inflammation. Mol Ther 23: 24-31
31. Wang T, Zhu Z, Liu Z, Yi L, Yang Z, Bian W, Chen W, Wang S, Li G, Li A, Martin GS, Zhu X, (2017) Plasma Neutrophil Elastase and Elafin as Prognostic Biomarker for Acute Respiratory Distress Syndrome: A Multicenter Survival and Longitudinal Prospective Observation Study. Shock 48: 168-174
32. Greene C, Taggart C, Lowe G, Gallagher P, McElvaney N, Oâ€™Neill S, (2003) Local Impairment of Antiâ€“Neutrophil Elastase Capacity in Community-Acquired Pneumonia. The Journal of Infectious Diseases 188: 769-776
33. Wang X, Gong J, Zhu J, Jin Z, Gao W, (2019) Alpha 1-antitrypsin for treating ventilator-associated lung injury in acute respiratory distress syndrome rats. Exp Lung Res 45: 209-219
34. Juschten J, Ingelse SA, Maas MAW, Girbes ARJ, Juffermans NP, Schultz MJ, Tuinman PR, (2019) Antithrombin plus alpha-1 protease inhibitor does not affect coagulation and inflammation in two murine models of acute lung injury. Intensive Care Med Exp 7: 36
35. Rizzo AN, Sammani S, Esquinca AE, Jacobson JR, Garcia JG, Letsiou E, Dudek SM, (2015) Imatinib attenuates inflammation and vascular leak in a clinically relevant two-hit model of acute lung injury. Am J Physiol Lung Cell Mol Physiol 309: L1294-1304
36. Stephens RS, Johnston L, Servinsky L, Kim BS, Damarla M, (2015) The tyrosine kinase inhibitor imatinib prevents lung injury and death after intravenous LPS in mice. Physiol Rep 3
37. Watanabe M, Boyer JL, Crystal RG, (2009) Genetic delivery of bevacizumab to suppress vascular endothelial growth factor-induced high-permeability pulmonary edema. Hum Gene Ther 20: 598-610
38. Ranieri VM, Pettila V, Karvonen MK, Jalkanen J, Nightingale P, Brealey D, Mancebo J, Ferrer R, Mercat A, Patroniti N, Quintel M, Vincent JL, Okkonen M, Meziani F, Bellani G, MacCallum N, Creteur J, Kluge S, Artigas-Raventos A, Maksimow M, Piippo I, Elima K, Jalkanen S, Jalkanen M, Bellingan G, Group IS, (2020) Effect of Intravenous Interferon beta-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA
39. Liu B, Bao L, Wang L, Li F, Wen M, Li H, Deng W, Zhang X, Cao B, (2019) Anti-IFN-gamma therapy alleviates acute lung injury induced by severe influenza A (H1N1) pdm09 infection in mice. J Microbiol Immunol Infect

40. Grailer JJ, Canning BA, Kalbitz M, Haggadone MD, Dhond RM, Andjelkovic AV, Zetoune FS, Ward PA, (2015) Critical role for the NLRP3 inflammasome during acute lung injury. J Immunol 192: 5974-5983
41. Li Y, Li H, Liu S, Pan P, Su X, Tan H, Wu D, Zhang L, Song C, Dai M, Li Q, Mao Z, Long Y, Hu Y, Hu C, (2018) Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Molecular Immunology 99: 134-144
42. Bode C, Peukert K, Schewe J-C, Putensen C, Latz E, Steinhagen F, (2019) Tetracycline alleviates acute lung injury by inhibition of NLRP3 inflammasome. European Respiratory Journal 54: PA2175
43. Morty RE, Kuebler WM, (2014) TRPV4: an exciting new target to promote alveolocapillary barrier function. Am J Physiol Lung Cell Mol Physiol 307: L817-821
44. Michalick L, Kuebler WM, (2020) TRPV4 - A Missing Link Between Mechanosensation and Immunity. Frontiers in Immunology 11
45. Scheraga RG, Southern BD, Grove LM, Olman MA, (2017) The Role of Transient Receptor Potential Vanilloid 4 in Pulmonary Inflammatory Diseases. Front Immunol 8: 503
46. Hamanaka K, Jian M-Y, Townsley MI, King JA, Liedtke W, Weber DS, Eyal FG, Clapp MM, Parker JC, (2010) TRPV4 channels augment macrophage activation and ventilator-induced lung injury. American Journal of Physiology-Lung Cellular and Molecular Physiology 299: L353-L362
47. Balakrishna S, Song W, Achanta S, Doran SF, Liu B, Kaelberer MM, Yu Z, Sui A, Cheung M, Leishman E, Eidam HS, Ye G, Willette RN, Thorneloe KS, Bradshaw HB, Matalon S, Jordt SE, (2014) TRPV4 inhibition counteracts edema and inflammation and improves pulmonary function and oxygen saturation in chemically induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 307: L158-172
48. Scheraga RG, Abraham S, Grove LM, Southern BD, Crish JF, Perelas A, McDonald C, Asosingh K, Hasday JD, Olman MA, (2020) TRPV4 Protects the Lung from Bacterial Pneumonia via MAPK Molecular Pathway Switching. J Immunol 204: 1310-1321
49. Hans GF, Stephanie RK, David AL, Michael AM, Mark AS, (2012) The adenosine 2A receptor agonist GW328267C improves lung function after acute lung injury in rats. American Journal of Physiology-Lung Cellular and Molecular Physiology 303: L259-L271
50. Chen CM, Penuelas O, Quinn K, Cheng KC, Li CF, Zhang H, Slutsky AS, (2009) Protective effects of adenosine A2A receptor agonist in ventilator-induced lung injury in rats. Crit Care Med 37: 2235-2241
51. Jabaudon M, Berthelin P, Pranal T, Roszyk L, Godet T, Faure JS, Chabanne R, Eisenmann N, Lautrette A, Belville C, Blondonnet R, Cayot S, Gillart T, Pascal J, Skrzypczak Y, Souweine B, Blanchon L, Sapin V, Pereira B, Constantin JM, (2018) Receptor for advanced glycation end-products and ARDS prediction: a multicentre observational study. Sci Rep 8: 2603
52. Blondonnet R, Audard J, Belville C, Clairefond G, Lutz J, Bouvier D, Roszyk L, Gross C, Lavergne M, Fournet M, Blanchon L, Vachias C, Damon-Soubeyrand C, Sapin V, Constantin JM, Jabaudon M, (2017) RAGE inhibition reduces acute lung injury in mice. Sci Rep 7: 7208
53. Audard J, Godet T, Blondonnet R, Joffredo JB, Paquette B, Belville C, Lavergne M, Gross C, Pasteur J, Bouvier D, Blanchon L, Sapin V, Pereira B, Constantin JM, Jabaudon M, (2019) Inhibition of the Receptor for Advanced Glycation End-Products in Acute Respiratory Distress Syndrome: A Randomised Laboratory Trial in Piglets. Sci Rep 9: 9227
54. Remy KE, Cortes-Puch I, Solomon SB, Sun J, Pockros BM, Feng J, Lertora JJ, Hantgan RR, Liu X, Perlegas A, Warren HS, Gladwin MT, Kim-Shapiro DB, Klein HG, Natanson C, (2018) Haptoglobin improves shock, lung injury, and survival in canine pneumonia. JCI Insight 3
55. Yang F, Haile DJ, Berger FG, Herbert DC, Van Beveren E, Ghio AJ, (2003) Haptoglobin reduces lung injury associated with exposure to blood. Am J Physiol Lung Cell Mol Physiol 284: L402-409

56. Zheng S, D'Souza VK, Bartis D, Dancer RC, Parekh D, Naidu B, Gao-Smith F, Wang Q, Jin S, Lian Q, Thickett DR, (2016) Lipoxin A4 promotes lung epithelial repair whilst inhibiting fibroblast proliferation. ERJ Open Res 2
57. Yang JX, Li M, Chen XO, Lian QQ, Wang Q, Gao F, Jin SW, Zheng SX, (2019) Lipoxin A4 ameliorates lipopolysaccharide-induced lung injury through stimulating epithelial proliferation, reducing epithelial cell apoptosis and inhibits epithelial-mesenchymal transition. Respir Res 20: 192
58. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, Larson N, Strickley R, Wells J, Stuthman KS, Van Tongeren SA, Garza NL, Donnelly G, Shurtleff AC, Retterer CJ, Gharaibeh D, Zamani R, Kenny T, Eaton BP, Grimes E, Welch LS, Gomba L, Wilhelmsen CL, Nichols DK, Nuss JE, Nagle ER, Kugelman JR, Palacios G, Doerffler E, Neville S, Carra E, Clarke MO, Zhang L, Lew W, Ross B, Wang Q, Chun K, Wolfe L, Babusis D, Park Y, Stray KM, Trancheva I, Feng JY, Barauskas O, Xu Y, Wong P, Braun MR, Flint M, McMullan LK, Chen SS, Fearns R, Swaminathan S, Mayers DL, Spiropoulou CF, Lee WA, Nichol ST, Cihlar T, Bavari S, (2016) Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 531: 381-385
59. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS, (2017) Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 9
60. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G, (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30: 269-271
61. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanigan T, (2020) Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med
62. Furuta Y, Komeno T, Nakamura T, (2017) Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 93: 449-463
63. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, (2020) Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering
64. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C, (2020) A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med
65. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, Jianchun, Xue Y, (2020) Arbidol Monotherapy is Superior to Lopinavir/ritonavir in Treating COVID-19. J Infect
66. Wang Z, Chen X, Lu Y, Chen F, Zhang W, (2020) Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Bioscience trends
67. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Ju L, Zhang J, Wang X, (2020) Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv: 2020.2003.2017.20037432

68. Zhou D, Dai SM, Tong Q, (2020) COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother
69. van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL, (1997) Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. J Rheumatol 24: 55-60
70. Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, Jin N, Jiang C, (2013) Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res 23: 300-302
71. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honore S, Colson P, Chabriere E, La Scola B, Rolain JM, Brouqui P, Raoult D, (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents: 105949
72. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, Gold HS, (2020) Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol
73. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S, (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell
74. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J, (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 395: e30-e31
75. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D, (2020) Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect
76. Hung IFN, To KKW, Lee CK, Lee KL, Yan WW, Chan K, Chan WM, Ngai CW, Law KI, Chow FL, Liu R, Lai KY, Lau CCY, Liu SH, Chan KH, Lin CK, Yuen KY, (2013) Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 144: 464-473
77. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L, (2020) Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA
78. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X, (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A
79. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, Dong N, Tong Q, (2020) Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv: 2020.2003.2006.20032342
80. Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y, (2020) Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine
81. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, Jose J, Pinto R, Al-Omari A, Kharaba A, Almotairi A, Al Khatib K, Alraddadi B, Shalhoub S, Abdulmomen A, Qushmaq I, Mady A, Solaiman O, Al-Aithan AM, Al-Raddadi R, Ragab A, Balkhy HH, Al Harthy A, Deeb AM, Al Mutairi H, Al-Dawood A, Merson L, Hayden FG, Fowler RA, Saudi Critical Care

Trial G, (2018) Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med 197: 757-767
82. Kumar V, Harjai K, Chhibber S, (2010) Thalidomide treatment modulates macrophage pro-inflammatory function and cytokine levels in Klebsiella pneumoniae B5055 induced pneumonia in BALB/c mice. Int Immunopharmacol 10: 777-783
83. Zhu H, Shi X, Ju D, Huang H, Wei W, Dong X, (2014) Anti-inflammatory effect of thalidomide on H1N1 influenza virus-induced pulmonary injury in mice. Inflammation 37: 2091-2098
84. Chen C, Qi F, Shi K, Li Y, Li J, Chen Y, Pan J, Zhou T, Lin X, Zhang J, (2020) Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 Pneumonia. Preprints
85. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N, (2020) Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 178: 104791
86. Momattin H, Mohammed K, Zumla A, Memish ZA, Al-Tawfiq JA, (2013) Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy. Int J Infect Dis 17: e792-798
87. Lokugamage KG, Hage A, Schindewolf C, Rajsbaum R, Menachery VD, (2020) SARS-CoV-2 is sensitive to type I interferon pretreatment. bioRxiv: 2020.2003.2007.982264
88. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, Fan J, Wang W, Deng L, Shi H, Li H, Hu Z, Zhang F, Gao J, Liu H, Li X, Zhao Y, Yin K, He X, Gao Z, Wang Y, Yang B, Jin R, Stambler I, Lim LW, Su H, Moskalev A, Cano A, Chakrabarti S, Min KJ, Ellison-Hughes G, Caruso C, Jin K, Zhao RC, (2020) Transplantation of ACE2(-) Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging Dis 11: 216-228
89. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B, (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506
90. Masui-Ito A, Okamoto R, Ikejiri K, Fujimoto M, Tanimura M, Nakamori S, Murata T, Ishikawa E, Yamada N, Imai H, Ito M, (2017) Tocilizumab for uncontrollable systemic inflammatory response syndrome complicating adult-onset Still disease: Case report and review of literature. Medicine (Baltimore) 96: e7596
91. Morrondo CD, Zarza LP, Gil JG, Pinto Tasende JA, Diez PD, Lopez JM, (2016) Benefit of Tocilizumab Therapy for Adult-Onset Still Disease Complicated With Acute Respiratory Distress Syndrome. J Clin Rheumatol 22: 291-293
92. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, (2020) Effective treatment of severe COVID-19 patients with Tocilizumab. ChinaXiV 202003: v1
93. Fisher CJ, Jr., Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ, Iberti TJ, Rackow EC, Shapiro MJ, Greenman RL, et al., (1994) Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 271: 1836-1843
94. Knaus WA, Harrell FE, Jr., LaBrecque JF, Wagner DP, Pribble JP, Draper EA, Fisher CJ, Jr., Soll L, (1996) Use of predicted risk of mortality to evaluate the efficacy of anticytokine therapy in sepsis. The rhIL-1ra Phase III Sepsis Syndrome Study Group. Crit Care Med 24: 46-56
95. Opal SM, Fisher CJ, Jr., Dhainaut JF, Vincent JL, Brase R, Lowry SF, Sadoff JC, Slotman GJ, Levy H, Balk RA, Shelly MP, Pribble JP, LaBrecque JF, Lookabaugh J, Donovan H, Dubin H, Baughman R, Norman J, DeMaria E, Matzel K, Abraham E, Seneff M, (1997) Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit Care Med 25: 1115-1124
96. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM, (2016) 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 44: 275-281

97. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18: 1094-1099
98. Dixon B, Smith R, Artigas A, Laffey J, McNicholas B, Schmidt E, Nunes Q, Skidmore MA, Andrade de Lome M, Moran J, Van Haren F, Doig G, Gupta S, Ghosh A, Said S, Santamaria J, (2020) Can Nebulised Heparin Reduce Time to Extubation in SARS CoV 2 The CHARTER Study Protocol. medRxiv: 2020.2004.2028.20082552
99. Shankar-Hari M, Rubenfeld GD, (2019) Population enrichment for critical care trials: phenotypes and differential outcomes. Curr Opin Crit Care 25: 489-497
100. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, McDowell C, Laffey JG, O'Kane CM, McAuley DF, (2018) Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Respir Med 6: 691-698
101. Constantin JM, Jabaudon M, Lefrant JY, Jaber S, Quenot JP, Langeron O, Ferrandiere M, Grelon F, Seguin P, Ichai C, Veber B, Souweine B, Uberti T, Lasocki S, Legay F, Leone M, Eisenmann N, Dahyot-Fizelier C, Dupont H, Asehnoune K, Sossou A, Chanques G, Muller L, Bazin JE, Monsel A, Borao L, Garcier JM, Rouby JJ, Pereira B, Futier E, (2019) Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 7: 870-880
102. Bos LD, Schouten LR, van Vught LA, Wiewel MA, Ong DSY, Cremer O, Artigas A, Martin-Loeches I, Hoogendijk AJ, van der Poll T, Horn J, Juffermans N, Calfee CS, Schultz MJ, (2017) Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. Thorax 72: 876-883