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NARRATIVE REVIEW

Emerging pharmacological therapies for ARDS: COVID-19 and beyond

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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. The purpose of the review is to critically appraise 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 anticoagulant 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 been 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.

Keywords: Pharmacologic therapy, Acute respiratory failure, Acute respiratory distress syndrome, Coronavirus, Mesenchymal stromal cells

Introduction

Acute respiratory distress syndrome (ARDS) 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. The prior disappointing experience with potentially promising therapies that have

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subsequently failed in large-scale clinical trials must also be borne in mind [3].

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 anticoagulant 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.

Take home message

Several ARDS therapies show promise in clinical studies, 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. Attention is now focused on identifying biologically homogenous subtypes within ARDS, to enable us to identify more specific 'precision medicines' for this severe syndrome.

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 or to prevent ARDS development (Figs. 1, 2).

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 multicenter study examined the efficacy of high-dose dexamethasone regimen in patients with established moderate to severe ARDS (i.e., *P/F* ratio < 200 mmHg at 24 h following ARDS diagnosis). Although terminated early for low recruitment, it was found that the mean number of ventilator free days was 4.8 days higher and the number of patient deaths was lower (21% versus 36%) following early treatment with dexamethasone [4]. The authors highlight the dosing regimen and time of administration as key to the use of steroid therapy in ARDS. Additional studies, focused on this specific moderate to severe ARDS population (diagnosed within 24 h), will be required to confirm and extend these interesting findings.

Ulinastatin

Ulinastatin is a urinary glycoprotein and protease inhibitor with potent antioxidant and anti-inflammatory effects [5]. 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 [5]. Ulinastatin therapy also significantly lowered inflammatory cytokines and increased antioxidant activities [5]. 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

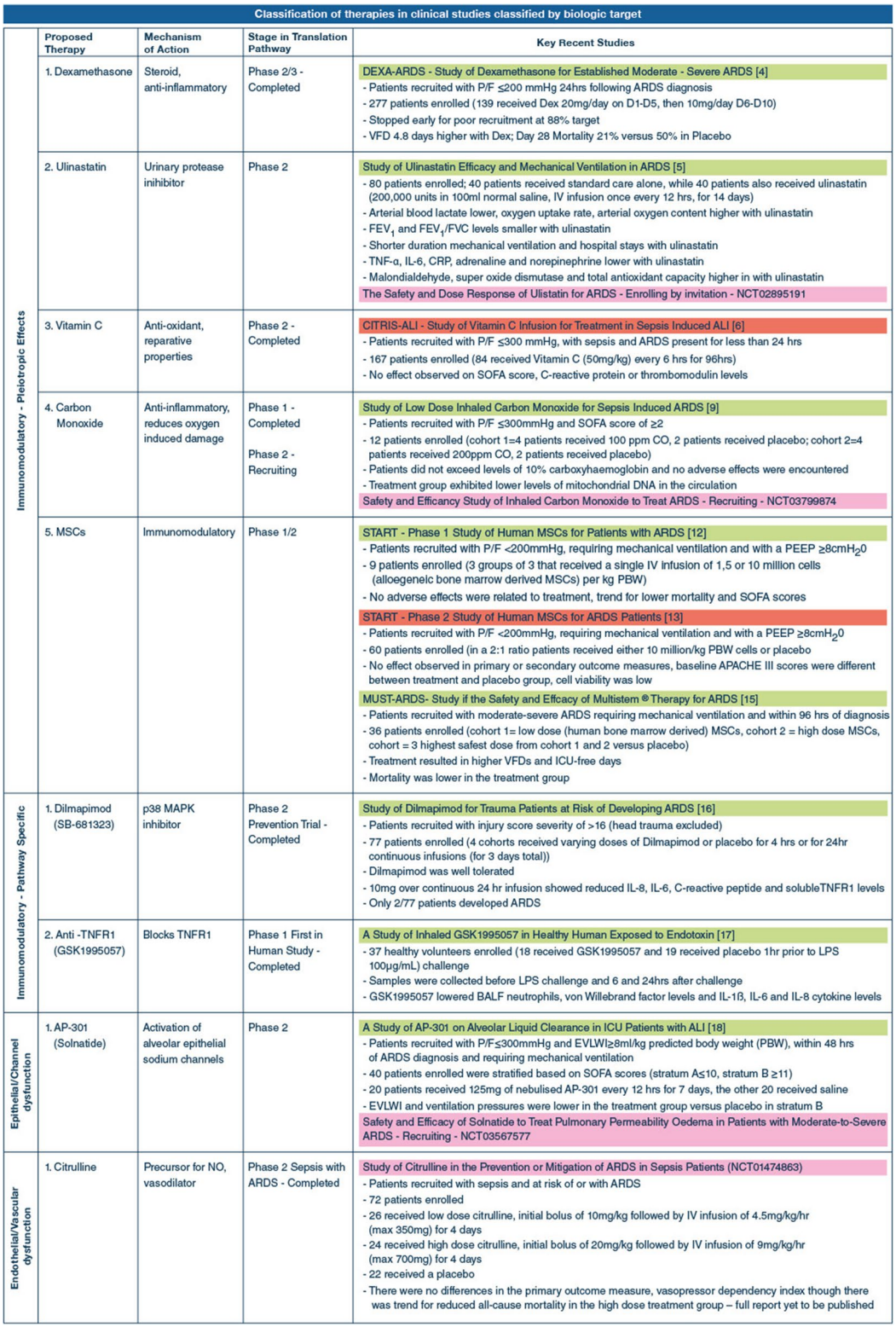
Vitamin C is recognized for its antioxidant and reparative properties. In a phase 2 study of patients with sepsis-induced ARDS, vitamin C did not reduce SOFA scores, which was the primary outcome, nor did it have an effect on biomarkers, even at high doses [6]. Of the secondary outcomes, vitamin C did 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 [6]. A phase 2 trial is currently recruiting SARS-CoV-2 patients for treatment with vitamin C (NCT04254533).

Carbon monoxide

Carbon monoxide (CO) is a gas produced endogenously by heme oxygenase, 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 CO [8]. In an exploratory phase 1 study, eight patients with ARDS were treated with inhaled low-dose CO (100–200 parts per million), which was well tolerated with trends toward a difference in lung injury severity score and a trend toward improved SOFA scores in the treatment group [9]. A phase 2 efficacy study of CO in ARDS is currently recruiting.

Mesenchymal stromal cell (MSC) therapies

MSCs have immunomodulatory and pro-reparative effects and show efficacy in preclinical 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



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	Steroid, anti-inflammatory	Phase 2/3 - Completed	DEXA-ARDS - Study of Dexamethasone for Established Moderate - Severe ARDS [4] - Patients recruited with P/F ≤200 mmHg 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 inihibitor	Phase 2	Study of Ulinastatin Efficacy and Mechanical Ventilation in ARDS [5] - 80 patients enrolled; 40 patients received standard care alone, while 40 patients also received ulinastatin (200,000 units in 100ml 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 Ulistatin 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 [6] - Patients recruited with P/F ≤300 mmHg, with sepsis and ARDS present for less than 24 hrs - 167 patients enrolled (84 received Vitamin C (50mg/kg) every 6 hrs for 96hrs) - No effect observed on SOFA score, C-reactive protein or thrombomodulin levels
	4. 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 Efficancy Study of Inhaled Carbon Monoxide to Treat ARDS - Recruiting - NCT03799874
	5. MSCs	Immunomodulatory	Phase 1/2	START - Phase 1 Study of Human MSCs for Patients with ARDS [12] - Patients recruited with P/F <200mmHg, requiring mechanical ventilation and with a PEEP ≥8cmH_20 - 9 patients enrolled (3 groups of 3 that received a single IV infusion of 1,5 or 10 million cells (alloegenelc 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_20 - 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 if the Safety and Effcacy 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 24hr 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 solubleTNFR1 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 Human Exposed to Endotoxin [17] - 37 healthy volunteers enrolled (18 received GSK1995057 and 19 received placebo 1hr prior to LPS 100μg/mL) challenge - Samples were collected before LPS challenge and 6 and 24hrs after challenge - GSK1995057 lowered BALF neutrophils, von Willebrand factor levels and IL-1ß, IL-6 and IL-8 cytokine levels
Epithelial/Channel dysfunction	1. AP-301 (Solnatide)	Activation of alveolar epithelial sodium channels	Phase 2	A Study of AP-301 on Alveolar Liquid Clearance in ICU Patients with ALI [18] - Patients recruited with P/F≤300mmHg and EVLWI≥8ml/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. 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 – full report yet to be published

Fig. 1 Classification of therapies in clinical studies by biologic target

	Proposed Therapy	Mechanism of Action	Stage in Translation Pathway	Key Recent Studies
Endothelial/Vascular dysfunction	2. ACE2 (GSK2586881)	Recombinant protein, down regulates angiotensin II	Phase 2 – Completed	**A Study of GSK2586881 in Patients with ALI [22]** - 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 [24]** - 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 - 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 IU 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 IU) or placebo) - There was no differences in the primary outcome measure, P/F but the treatment group showed better alveolar perfusion and CO2 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 PaCO2, reduced length of ICU stay and lowered ICU mortality

Fig. 1 continued

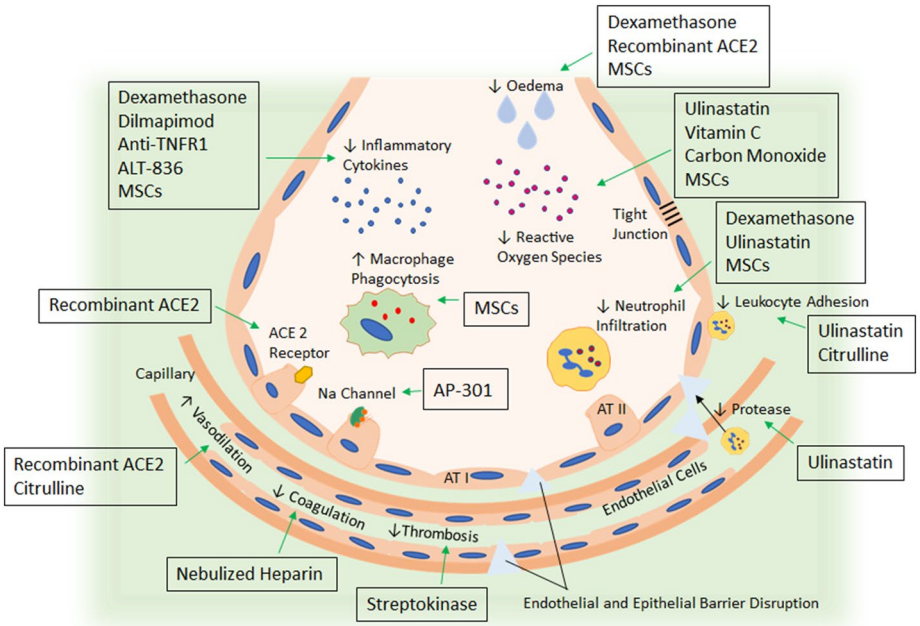


Fig. 2 Pharmacological therapies and their targets, in clinical testing for ARDS therapy

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 to prevent ARDS

Dilmapimod

The p38 mitogen-activated protein kinase (MAPK) pathway is activated during cellular stress and drives downstream production of inflammatory cytokines [16]. Dilmapimod is a specific p38MAPK inhibitor and potent anti-inflammatory. In a small dose response study in trauma patients at risk for ARDS development, a 24-h dilmapimod infusion was well tolerated and reduced the concentrations of the pro-inflammatory cytokines IL-6, IL-8 and soluble tumor 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 antagonizes 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 edema. 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 channels. Nebulized AP-301 every 12 h 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 (< 48 h of diagnosis) stratified based on SOFA score (SOFA score ≥ 11) [18]. Another, larger phase 2 study of AP-301 for the treatment of pulmonary edema in patients with moderate–severe ARDS is currently recruiting (NCT03567577), while another is recruiting COVID-19 ARDS patients (EudraCT Number: 2020-001244-26).

Citrulline

This nonessential 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 [19]. Citrulline deficiency may cause NOS to produce harmful nitrites, while a drop in NO can induce vasodilation, leukocyte adhesion, and alter other important aspects of endothelial function [19]. A recently completed, small phase 2 study of lower-dose ($n=26$) versus higher-dose ($n=24$) 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 edema, 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 [20] and reduces post-injury lung fibrosis [21]. 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 [22].

Anticoagulants and thrombolytic therapies

Dysfunction of coagulation in ARDS plays a key role in ARDS pathogenesis. Consequently, anticoagulants 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 [23]. Studies have observed that increased TF in the serum of ARDS patients correlates with higher mortality [23]. 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 [24]. 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

Both heparin and antithrombin have been shown to dampen inflammation and ALI in preclinical models without negatively impacting systemic coagulation [25]. Nebulized heparin 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 1, Fig. 3).

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, are 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 edema 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 antioxidant and anti-inflammatory effects in vivo and has been shown to ameliorate lung injury and mortality in single- and dual-hit ARDS preclinical 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 edema 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 etiologic 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]. Interestingly, a recent study by Ziegler et al. showed that IFN-γ upregulates ACE2 expression in lung epithelial cells and hence could aid SARS-CoV-2 viral entry [40]. Anti-IFN-γ therapy may have potential as a therapy for COVID-19.

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 [41]. Pirfenidone, a NLRP3 inflammasome inhibitor, was shown to suppress oxidative stress and apoptosis in vitro [42]. 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 [42]. In a recently published abstract, tetracycline, another NLRP3 inflammasome inhibitor, was shown to reduce mortality, vascular leakage, and neutrophil infiltration in a murine LPS ALI model [43]. Caspase activation

Table 1 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 edema, 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 edema 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 neutralization	1. Anti-IFN-γ reduced lung inflammation and mortality in a H1N1 lung injury mouse model [39]
4. Pirfenidone	NLRP3 inflammasome inhibitors	1. Pirfenidone inhibited lung injury and inflammation, caspase activation, and fibrosis in a murine LPS model [42] 2. A phase 3 study of pirfenidone for SARS-CoV-2 is underway. NCT04282902
5. Tetracycline	NLRP3 inflammasome inhibitors	1. Tetracycline reduced inflammation, apoptosis, and mortality in an endotoxin-induced ALI model [43]
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 [48] 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 [50, 51]
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 [53, 54]
Endothelial/vascular dysfunction		
1. Haptoglobin	Scavengers of plasma-free hemoglobin	1. Haptoglobin dampened oxidative stress and lung injury in a pneumonia model and was protective against injury in a blood lung injury model [55, 56]
Anticoagulants		
1. Antithrombin	Endogenous anticoagulant	1. Nebulized antithrombin attenuated lung injury induced by intra-tracheal acid and endotoxin [25]
Pro-resolution effects		
1. 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 [58]

and pro-inflammatory cytokine release were also diminished [43]. 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 [44, 45], 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 [45, 46]. TRPV4 −/− mice are protected against VILI [47] and chemically

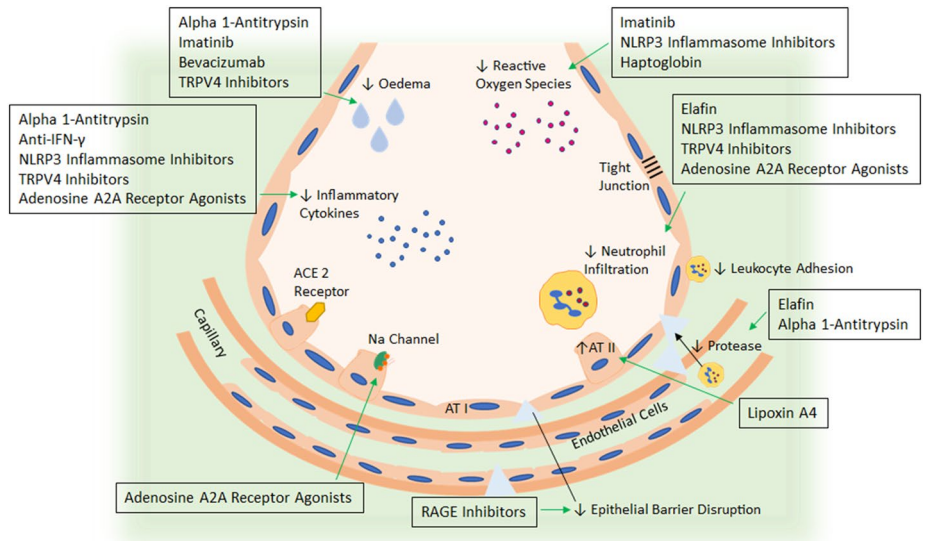


Fig. 3 Pharmacological therapies and their targets, in preclinical testing for ARDS therapy

induced ALI [44], while TRPV4 channel inhibitors GSK2220691 and GSK2337429A also reduced ALI [44]. The TRPV4 inhibitors, GSK634775 and GSK1016790, attenuated acid instillation or chlorine gas-induced lung injury, decreasing lung edema, improving oxygenation, and attenuating immune cell infiltration and pro-inflammatory cytokine release [48]. 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 [49].

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 [50]. The adenosine A2A receptor agonist GW328267C enhanced alveolar fluid clearance in models of acid instillation, LPS, and live E.coli-induced lung injury [50]. Another adenosine A2A receptor agonist, CGS-21680, improved lung compliance and reduced neutrophil infiltration and pro-inflammatory cytokine release in a rat VILI model [51].

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 marker of epithelial lung injury, are increased in ARDS patients, and can predict ARDS development in 'at risk' patients [52]. RAGE appears to drive lung injury also, as evidenced by the finding that blockade of RAGE (using peptides, monoclonal antibodies, or soluble RAGE decoy receptors) reduced acid-induced lung injury in mice [53] and piglets [54].

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 increased survival in a preclinical model of *S. aureus* pneumonia [55]. Transgenic mice overexpressing haptoglobin were also protected from hemoglobin-included lung injury [56].

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, promoted ATII proliferation and limited apoptosis in vitro [57]. In a murine LPS-induced ALI model, lipoxin A4 enhanced alveolar epithelial type II cell proliferation, decreased apoptosis by limiting caspase 3 activation and limited epithelial–mesenchymal transition as evidenced by immunofluorescent staining [58].

Lipoxin A4 warrants further investigation in other preclinical 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 repurpose existing drugs to treat COVID-19-induced ARDS (Table 2). There are two distinct strategies being pursued, namely strategies that are targeted at the virus itself (reducing replication, ACE-2 receptor binding, etc.) and strategies that modulate the host immune response to the virus infection (targeted or nonspecific immune-modulating drugs). Much of the data available in studies to date come from clinical case series, retrospective analyses, or uncontrolled clinical trials, and so definitive proof of efficacy for interventions is lacking. Nevertheless, given the urgent need for information on which to base treatment decisions, we have included such studies where better designed studies are lacking.

A positive effect of this global focus on severe COVID-19 disease should be 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 [59], is an analogue of adenosine that disrupts viral RNA polymerase and viral replication [60]. Remdesivir inhibits MERS-CoV and SARS-CoV in vitro and in vivo [60]. A recent study showed that remdesivir was particularly effective against SARS-CoV-2 infection in vitro [61]. 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 [62]. 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 USA. A recently completed phase 3 study of 237 COVID-19 patients in China showed no significant improvement in clinical outcomes although there was a trend for enhanced recovery time with remdesivir treatment [63]. Most recently, a randomized, blinded, placebo controlled trial in over 1000 patients demonstrated that Remdesivir shortened the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection [64]. The results of several other phase 2/3 remdesivir clinical trials are awaited (Table 2).

Favipiravir

Favipiravir is a broad-spectrum antiviral RNA polymerase inhibitor, already approved for use in influenza A and B [65]. A recent, open-label, control study, showed that favipiravir exhibited significant improvements in chest CT scans and viral clearance in COVID-19 patients [66]. 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 combination 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%) [67]. 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 [67]. Of relevance, another recently completed phase 2 study showed that early combined treatment of lopinavir/ritonavir with IFN-β1β and ribavirin reduced viral shedding and shortened hospital stays compared to lopinavir/ritonavir alone in mild–moderate COVID-19 patients [68].

Umifenovir

Umifenovir (also known as arbidol), an antiviral approved for influenza that can affect viral interaction and binding via ACE2, was recently shown to enhance viral clearance in comparison with lopinavir/ritonavir treatment, in a retrospective study of 50 COVID-19 patients [69]. An unreviewed 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, found no differences between these two treatments [70]. 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 its 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 [71]. These drugs also suppress pro-inflammatory cytokine release [72]. Chloroquine has specifically been shown to inhibit influenza A H5N1 virus-induced lung injury in preclinical models [73] and SARS-CoV-2 infection in vitro [61]. A small clinical study recently showed that hydroxychloroquine in combination with azithromycin reduced viral load in 20 patients with

Table 2 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 [60, 61] Remdesivir potentially beneficial in report of 61 patients with SARS-CoV-2 [62] Trend for enhanced recovery in a phase 3 study of 237 patients with COVID-19 [63] Remdesivir shortened the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection [64]	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 Patients. NCT04321616 6. DISCOVERY—Trial of Treatments for COVID-19 in Hospitalized Adults. NCT04315948 7. 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 [66] No benefit over arbidol in open-label trial [70]	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 [67] Triple therapy with lopinavir/ritonavir, IFN-β1β, and ribavirin reduced viral shedding and hospital stays in a phase 2 study [68]	1. ELACOI—The Efficacy of Lopinavir + Ritonavir and Arbidol Against Novel Coronavirus Infection. NCT04252885 2. The Efficacy and Safety of Lopinavir–Ritonavir in Hospitalized Patients with Novel Coronavirus Pneumonia. ChiCTR2000029308 3. Treatment of Moderate to Severe Coronavirus Disease in Hospitalized Patients. NCT04321993 4. REMAP-CAP—Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia. NCT02735707 5. DISCOVERY—Trial of Treatments for COVID-19 in Hospitalized Adults. NCT04315948 6. The SOLIDARITY Trial. ISRCTN83971151
4. Umifenovir (arbidol)	Inhibits viral interaction and binding with host cells via ACE2	Retrospective analysis showed that arbidol treatment ($n = 16$) in comparison with lopinavir/ritonavir treatment ($n = 36$) reduced viral load in SARS-CoV-2 patients [69] No benefit over favipiravir in open-label trial [70]	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 [61] Hydroxychloroquine plus azithromycin reduced viral load in 20 COVID-19 patients [74] Concerns regarding cardiotoxicity and QT prolongation in COVID-19 [75, 76] A large observational study in 14,888 COVID-19 patients treated with either hydroxychloroquine or chloroquine reported that these drugs increased the risk of mortality and increased the risk of de novo ventricular arrhythmia [77]	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 4. HYDRA—Study of Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection. NCT04315896 5. THDMS-COVID-19—Various Combinations 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 Patients. NCT04321616 9. DISCOVERY—Trial of Treatments for COVID-19 in Hospitalized Adults. NCT04315948 10. The SOLIDARITY Trial. ISRCTN83971151

Table 2 (continued)

Proposed therapy	Mechanism of action	Published findings to date	Randomized controlled clinical trials in progress (selected from clinicaltrials.gov)
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 [78]	1. CamoCO-19—The Impact of Camostat Mesilate on SARS-CoV-2 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 [79]. Identified using a drug discovery search engine platform Baricitinib well tolerated and potentially beneficial over standard care in small clinical study [80]	1. Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients. NCT04321993 2. BARI-COVID—Pilot Study of Baricitinib in Symptomatic Patients Infected by SARS-CoV-2. NCT04320277
9. Inactivated convalescent plasma	IV immunoglobulins	Enhanced viral clearance and clinical outcome in 5 patients in a case study of SARS-CoV-2 [82] Well tolerated in expanded access trial (un-reviewed preprint) [83]	1. Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19. NCT04292340 2. Anti-COVID-19 Convalescent Plasma Therapy. NCT04338360
Immunomodulatory—pleiotropic effects			
1. Methylprednisolone	Steroid, anti-inflammatory	Retrospective studies of 46 and 201 patients with SARS-CoV-2 ARDS show that early and careful administration may have beneficial role [88, 89]. Steroid use may hinder viral clearance in MERS coronavirus infection [87]	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. MP-C19—Efficacy of Methylprednisolone for Patients With COVID-19 Severe ARDS. NCT04323592 4. REMAP-CAP—Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707
2. Thalidomide	Immunomodulator, anti-IL-6, pro-apoptotic	Therapeutic in preclinical model of viral ARDS [91]	1. Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate COVID-19. NCT04273529 2. 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 [92, 94] Triple therapy with IFN-β1β, lopinavir/ritonavir, and ribavirin reduced viral shedding and hospital stays in a phase 2 study [68]	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. DISCOVERY—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 preclinical 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 [95]	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 Inhale of MSC-Derived Exosomes for Treating Severe Novel Coronavirus Pneumonia. NCT04276987 7. MACOVIA—Study of MultiStem Administration for COVID-19-Induced ARDS

Table 2 (continued)

Proposed therapy	Mechanism of action	Published findings to date	Randomized controlled clinical trials in progress (selected from clinicaltrials.gov)
Immunomodulatory—pathway specific			
1. Tocilizumab 2. 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 [99]	1. Favipiravir Combined With Tocilizumab in the Treatment of Coronavirus 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 [103]	1. ESCAPE—Personalized 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 SARS-CoV-2 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 [104]	1. CHARTER study—Nebulized Heparin for patients with COVID-19 ARDS. ACTRN:1260000517976

SARS-CoV-2 infection [74]. Conversely, concerns have been raised regarding potential adverse effects (e.g., cardiotoxicity) with chloroquine and hydroxychloroquine, particularly at high doses and when used in combination with azithromycin, in COVID-19 patients [75, 76]. A major observational study in 14,888 COVID-19 patients treated with either hydroxychloroquine or chloroquine, alone or in combination with a macrolide, found that these patients had an increased risk of mortality and an increased risk of de novo ventricular arrhythmia [77]. A number of other and larger clinical investigations of chloroquine and hydroxychloroquine, alone or in combination with other antivirals, are underway (Table 2).

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 [78]. A protease inhibitor of TMPRSS2 blocked viral entry in vitro and may be a promising therapeutic option [78]. 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 [79] 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 [80]. Other larger 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 [78]. Convalescent plasma has also been shown to reduce viral load and mortality in critically ill H1N1 patients [81] 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 [82]. An un-reviewed preprint of the results from a large expanded access trial of 5000 COVID-19 patients treated with convalescent plasma (NCT04338360) showed that treatment was well tolerated [83]. Other trials assessing the safety and efficacy of anti-SARS-CoV-2-inactivated convalescent plasma in COVID-19 patients are underway.

Angiotensin II

SARS-CoV-2 binds to the ACE receptor on lung epithelial cells, which is a key step in virus infection of these cells. This also leads to a decrease in ACE2 and an increase in detrimental angiotensin II. Losartan, which is an angiotensin II receptor antagonist, is currently under investigation in SARS-CoV-2 patients (NCT04328012).

Immunomodulatory—pleiotropic effects

Methylprednisolone

The role of steroids indications for COVID-19 patients is unclear, with effects reported that might be harmful or beneficial depending on the specific clinical context [84–86]. Some evidence suggests that steroid use may hinder viral clearance in MERS coronavirus infection [87]. However, 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 [85, 86]. 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 [88]. Another larger retrospective study of 201 COVID-19 patients showed that methylprednisolone treatment in those with ARDS reduced the risk of death [89]. Currently, there are a number of phase 2/3 clinical trials investigating the efficacy and safety of methylprednisolone in patients with COVID-19 ARDS. Hopefully, these studies should provide clarity on the role of steroids in these patients. The recent press release suggesting a mortality benefit for Dexamethasone in COVID-19 patients in the RECOVERY trial is of particular interest in this regard.

Thalidomide

Thalidomide, an immunomodulatory drug that acts to enhance apoptosis, inhibits IL-6 and promotes T cell responses and has been shown to lead beneficial effects in preclinical bacterial- and viral-induced ARDS [90, 91]. Clinical phase 2 investigations of thalidomide for therapy against SARS-CoV-2 infection are underway.

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 toward MERS and SARS [92] and, as such, interferons have been investigated, as an adjunct to antivirals, in these viral infections [93]. A recent study published as an un-reviewed preprint has observed that SARS-CoV-2 infection is potentially sensitive to type I interferons [94]. As mentioned previously, a recent phase 2 study of triple therapy with lopinavir/ritonavir, ribavirin, and IFN-β1β enhanced the recovery of patients with SARS-CoV-2 infection compared to lopinavir/ritonavir alone [68]. There are a number of other phase 2/3 clinical trials investigating the efficacy of both type I or type III interferons (including REMAP-CAP, DisCoVeRy, and SOLIDARITY), either as sole agents or as co-therapies in patients with SARS-CoV-2 (Table 2).

Mesenchymal stromal cell (MSC) therapies

The immunomodulatory effects of MSCs have 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 with the placebo [95]. A number of other trials are investigating the effects of MSCs and MSC-derived exosomes in patients with SARS-CoV-2 infection (Table 2).

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 hemophagocytic lymphohistiocytosis (HLH) [96]. This has led to interest in specific anti-cytokine therapies.

Tocilizumab and sarilumab

Tocilizumab and sarilumab 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 [97, 98]. One recent non-controlled retrospective study of 21 patients with COVID-19, published as an un-reviewed preprint, suggested that tocilizumab treatment may have decreased white cell counts and improved CT lung opacity and lung oxygenation [99]. 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 [100–102]. However, in a post hoc analysis anakinra improved survival in the subgroup of sepsis patients with features of HLH (ferritin elevation in excess of 2000 ng/ml, coagulopathy, and liver enzyme elevations) [103]. 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. Anticoagulant 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 [104]. 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 [105].

Finding ARDS therapies—future directions

Improved preclinical models

Understanding and, where relevant, addressing limitations to current preclinical models 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 clinically relevant experimenal 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 of 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 modeling longer durations of ARDS, while challenging, may be a useful step prior to embarking on clinical studies. Multicenter 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 [106] may enhance the likelihood of finding effective therapies. One key issue relates to the heterogeneity of ARDS and the nonspecific 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. The use of adaptive clinical trial designs, which permits modifications of the trial and/or statistical procedures after its initiation, e.g., to favor recruitment to intervention arms where favorable outcome data appears to be emerging, may also enhance the potential to identify effective interventions. The REMAP-CAP trial is an example of such a trial in a relevant clinical population.

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 [107].

ARDS phenotyping based on the focal versus diffuse distribution of lung infiltrates is also potentially feasible [108], as are transcriptomics-based approaches [109]. 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 is 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, anticoagulant 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.

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Author contributions
SH drafted the manuscript; BM and JL wrote the first and subsequent drafts of the manuscript. All authors critically revised the manuscript for important intellectual content.

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