Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Expert Review

2021 Acute Respiratory Distress Syndrome Update, With Coronavirus Disease 2019 Focus

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Acute respiratory distress syndrome (ARDS) is a heterogeneous lung disease responsible for significant morbidity and mortality among critically ill patients, including those infected with severe acute respiratory syndrome coronavirus 2, the virus responsible for coronavirus disease 2019. Despite recent advances in pathophysiology, diagnostics, and therapeutics, ARDS is dangerously underdiagnosed, and supportive lung protective ventilation and prone positioning remain the mainstay interventions. Rescue therapies, including neuromuscular blockade and venovenous extracorporeal membrane oxygenation, remain a key component of clinical practice, although benefits are unclear. Even though coronavirus disease 2019 ARDS has some distinguishing features from traditional ARDS, including delayed onset, hyperinflammatory response, and pulmonary microthrombi, it clinically is similar to traditional ARDS and should be treated with established supportive therapies.

Key Words: acute respiratory distress syndrome; ventilator-induced lung injury; mechanical ventilation; coronavirus disease 2019; COVID-19; prone position; neuromuscular blocking agents; extracorporeal membrane oxygenation; nitric oxide; positive end-expiratory pressure

ADVANCES in acute respiratory distress syndrome (ARDS) diagnosis and therapy have developed steadily over the last 50 years. However, mortality has remained static at 30%-to-40% the last ten years, and the disease is underdiagnosed, with disparate effects on race, poverty, and sex.[1] Although lung-protective ventilation (LPV) and prone positioning clearly have been shown to reduce mortality, questions remain about the benefit of rescue therapies such as paralysis, inhaled pulmonary-vascular vasodilators, extracorporeal membrane oxygenation (ECMO), and other pharmacologic therapies. Despite the expansion of ARDS management, it remains widely underrecognized, with resulting underutilization of LPV. Morbidity burden remains extremely high in survivors of ARDS who may experience post-traumatic stress disorder, post-intensive care syndrome, long-term physical disability, and neuromuscular weakness.

Although severe coronavirus disease 2019 (COVID-19) often meets diagnostic criteria of traditional ARDS, additional features have been reported, such as delayed onset, binary pulmonary compliant states, and hypercoagulable profile, which have obscured the utility of traditional ARDS therapies. The efficacy of steroids in COVID-19 and need for systemic anticoagulation have been established, but other targeted COVID-19 therapies have not been found to be effective in reducing mortality. Despite its novelty, COVID-19 ARDS has clear crossover with traditional ARDS therapy, and lung-protective ventilation and prone positioning should be widely used.

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ARDS Epidemiology and Diagnosis

Since the seminal work of the ARDS Network trial, there have been minimal improvements in mortality rates and incidence of ARDS.[2] Mortality rates remain between 34.9% and 40%, depending on severity.[3] In addition, recognition of ARDS ranges from 51.3%-to-78.5%, resulting in failure to implement LPV strategies.[4] ARDS mortality rates disproportionately affect black and Hispanic patients compared with white patients and males compared with females, with an outsized burden on low-income patients and patients in developing countries.[1,5] Living in a higher population density and black ethnicity have been shown to have higher risk for hospitalization in COVID-19, although no statistical racial trend has been found for mortality.[6,7] Morbidity in ARDS survivors remains a concern, with a high incidence of critical illness polyneuropathies, cognitive impairment, post-intensive care syndrome, post-traumatic stress disorder, and employment loss.[8,9]

The heterogeneity of causes and presentations of ARDS have resulted in a dangerous underdiagnosis. Traditional risk factors such as pneumonia, aspiration, pulmonary contusion, inhalation injury, sepsis, pancreatitis, blood product transfusion, and smoking history remain important risk factors.[10,11] Diagnosis of ARDS remains largely clinically-based on the Berlin criteria, which require a patient to have bilateral opacification on chest x-ray or computed tomography within seven days of a clinical insult that otherwise cannot be explained by pulmonary edema from heart failure.[12] The Berlin criteria stratify disease severity based on the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FIO_2) as follows: mild (200 mmHg < $PaO_2/FIO_2 \leq 300$ mmHg), moderate (100 mmHg < $PaO_2/FIO_2 \leq 200$ mmHg), and severe ($PaO_2/FIO_2 \leq 100$ mmHg), assuming a positive end-expiratory pressure (PEEP) of 5 cmH_2O. The criteria for the PaO_2/FIO_2 ratio were modified in COVID-19 ARDS to improve detection of mild-moderate disease between 150 mmHg and 200 mmHg, and moderate-severe disease <150 mmHg. Another notable difference with COVID-19 ARDS is the delayed onset of eight-to-12 days from symptom onset, which falls outside the one-week onset of the Berlin ARDS criteria.[12,13] In resource-strained settings, the Kigali modification of the Berlin criteria offers a streamlined algorithm, which uses oxygen saturation/FIO_2 instead of PaO_2/FIO_2 and eliminates the PEEP requirement.[14]

ARDS Pathophysiology

Diffuse alveolar damage occurs in ARDS as a result of neutrophil-related epithelial necrosis, with subsequent interstitial flooding followed by endothelial injury. This results in ventilation-to-perfusion mismatch and right-to-left intrapulmonary shunting, leading to worsened deadspace ventilation and reduced lung compliance. After the initial exudative insult, a fibroproliferative phase of ARDS causes scarring responsible for worsening lung compliance and long-term pulmonary recovery.[2]

The angiotensin-converting enzyme 2 (ACE2) receptor has been implicated as the entry receptor of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2).[15] Mechanisms of pulmonary perfusion dysregulation in COVID-19 include abolition of hypoxic pulmonary vasoconstriction, excessive pulmonary vasoconstriction, and thrombosis.[16] The clinical course on presentation with COVID-19 typically follows one of the following three patterns: hyperacute respiratory failure requiring immediate intubation, indolent course with only moderate work of breathing, or a biphasic course with initially indolent course followed by acute deterioration typically after five-to-seven days.[16]

A host of biomarkers are released in the initial pathophysiologic cascade, providing new opportunities for early diagnosis, which is especially important because ARDS can develop in the absence of traditional risk factors.[17] A recent study suggested that some patients may have increased biomarkers associated with direct lung injury, whereas other patients may have biomarkers associated with hyperinflammatory lung injury.[18] Additional investigations have revealed the possibility of the following two subphenotypes: a hyperinflammatory response characterized by interleukin 6 and 8 and tumor necrosis factor-1, and a hypoinflammatory response associated with fewer biomarkers and an attenuated shock state.[19,20] Stratified fluid management strategies and differing ventilatory managements based on subphenotypes have been suggested.[21,22] Despite there being more than 40 genes associated with the development of ARDS, subphenotypic diagnostics have had little bearing on current clinical practice of ARDS, and no gene-specific loci for ARDS have been identified.[23,24] Early anecdotal reports described high- and low-compliance phenotypes with COVID-19 ARDS.[25] However, this phenotype distinction likely also has minimal clinical significance in the management of COVID-19 ARDS.[26] Patients with COVID-19 ARDS demonstrate significant heterogeneity in respiratory mechanics, similar to patients with ARDS from other causes, and average lung recruitability is similar in patients with and without COVID-19.[27] When hypoxemia and lung mechanics are managed properly, mortality from COVID-19 ARDS is similar to mortality from other causes of ARDS.[28] Spontaneous pneumothorax, pneumomediastinum, and subcutaneous emphysema have been reported as complications of COVID-19 pneumonia and should be ruled out in patients with rapid clinical deterioration in the setting of COVID-19 ARDS.[29]

The RECOVERY trial demonstrated impressive mortality reduction with the use of steroids in COVID-19 ARDS, whereas older studies failed to demonstrate benefit from steroids in traditional ARDS. It is likely that attenuating a dysregulated inflammatory response in all-comers of ARDS may be a target in need of revisitation.[30,31]

Validated ARDS Therapies: LPV, Prone Positioning, and Restrictive Fluid Management

LPV

Despite emerging techniques in diagnostics and therapies, supportive care and LPV strategies aimed at mitigating

iatrogenic damage from mechanical ventilation remain the pillar of ARDS therapy. During mechanical ventilation, lung injury can occur on either end of the pulmonary hysteresis curve where overdistention can cause volutrauma and barotrauma, whereas negative transpulmonary pressures during exhalation can cause atelectrauma from repetitive small airway collapse and reexpansion. A recent systematic review and meta-analysis confirmed the tenets of LPV (ie, tidal volume limited to 4-8 mL/kg [predicted body weight based on height], plateau pressures <30 cmH_2O, and higher PEEP).[32] A significant recent addition revealed that lower driving pressures (defined as plateau pressure minus PEEP) are associated with decreased mortality.[33] Higher PEEP titration generally is considered to be a reasonable strategy to aid in oxygenation.[34] The ART trial, a recent multicenter, randomized controlled trial, showed worsened 28-day mortality with such a strategy, although the results should be interpreted with caution because the trial used recruitment maneuvers as high as 45 cmH_2O.[35] High-frequency oscillation is not recommended in ARDS.[34] Given the similar respiratory mechanics between patients with ARDS from COVID-19 versus other causes, and absence of evidence to the contrary, patients with COVID-19 should be ventilated with traditional lung-protective strategies and individualized levels of PEEP.[32]

Esophageal manometry has gained popularity as a tool for individually tailoring plateau and driving pressures. This technology estimates the transpulmonary pressure (the pressure gradient across alveoli) by accounting for intrapleural pressures, in contrast to traditional direct airway pressure measurements.[36] Measuring the end-inspiratory and end-expiratory pressures in both the airway and the esophagus generates a transpulmonary pressure profile that is useful in obesity, when chest wall compliance can become so poor that the effective PEEP can remain negative even with high PEEP settings. In the 2019 EPVent-2 randomized controlled trial, there was no difference in mortality between ventilation management using esophageal manometry and traditional PEEP/FIO_2 titration. However, the control PEEP was never lower than 20 cmH_2O, and a prone position strategy was not used in the trial, two factors that limit generalizability.[37] Esophageal manometry remains heavily institutionally-dependent with unclear benefit.

Prone Positioning in ARDS and COVID-19

Prone positioning is a well-established therapy in ARDS, with a 90-day mortality benefit first elucidated in the landmark PROSEVA trial.[38] Prone positioning optimizes lung recruitment and lung perfusion while augmenting the functional size of the lung, which can prevent regional barotrauma. Prone positioning also enhances secretion clearance and may decrease rates of ventilator-associated pneumonia.[39] Prone positioning also may alleviate the right ventricular strain that occurs secondary to increased pulmonary vascular resistance during hypoxemia and hypercarbia. Right ventricular strain has been shown to demonstrably improve on echocardiography during prone positioning, with a reduced right ventricular end-diastolic area to left ventricular end-diastolic area (RVEDA/LVEDA) ratio and septal dyskinesia.[40] Prone positioning, in conjunction with LPV, is a well-validated therapy in ARDS, and a clear mortality benefit has been demonstrated when used in a protocolized fashion in ten-to-12-hour sessions.[41] Prone positioning in awake, non-intubated patients with COVID-19 pneumonia has been shown to improve oxygenation, but the effect on survival remains unclear.[42] Successful proning has been described in both awake and intubated pregnant patients with COVID-19.[43] Current guidelines from the National Institutes of Health recommend that mechanically ventilated patients with moderate-to-severe COVID-19 ARDS undergo prone ventilation for 12- to-16 hours per day.[44]

Fluid Management

Fluid overload has deleterious effects in ARDS, as shown by the landmark FACTT trial, in which conservative fluid management resulted in fewer days of mechanical ventilation and intensive care unit (ICU) stay.[45] Positive-pressure ventilation and increased pulmonary vascular constriction can independently increase fluid retention and interstitial edema regardless of fluid administration.[46] Based on recent randomized controlled trials and meta-analyses, a fluid-restrictive strategy remains the preferred management, with benefits including enhanced oxygenation, fewer days on mechanical ventilation, and fewer days in the ICU.[46,47] A recent large, retrospective study also suggested mortality benefit with a fluid restrictive strategy.[48] Although there is no consensus on specific fluid restriction goals, limiting maintenance intravenous fluids and active diuresis are common clinical practices.

ARDS Rescue Therapies: Paralysis, Inhaled Pulmonary Vasodilators, and Venovenous ECMO

Even with the previously discussed standard ARDS therapies, refractory hypoxemia in ARDS is a common clinical feature requiring rescue therapies to maintain adequate oxygenation. Neuromuscular blockade commonly has been used to promote ventilator synchrony, particularly after the landmark ACURASYS trial demonstrated a 90-day mortality benefit from 48 hours of continuous cisatracurium infusion in a multicenter, randomized controlled trial.[49] However, the mortality benefit has come into question with the subsequent ROSE trial in 2019, which demonstrated no mortality benefit.[50] Even though the ROSE trial had a large, randomized cohort, it was unblinded and a significant number of patients who received paralysis were excluded from the trial, which may have favored the control group. In addition, the ROSE trial was stopped for futility, which rendered the trial underpowered. Despite conflicting data, paralysis remains common practice in severe ARDS as both rescue and routine therapy.

Pulmonary vasodilators, such as inhaled nitrous oxide, never have demonstrated mortality benefit and have been believed to contribute to renal injury. However, they remain in clinical use

for refractory hypoxemia.[51] Evidence remains limited. Recent Cochrane reviews suggest that even though inhaled nitrous oxide and inhaled prostaglandins may confer transiently improved oxygenation, they likely are harmful and worsen renal function.[52,53]

Venovenous (VV)-ECMO clearly can improve oxygenation in severe ARDS, but there remains a paucity of clinical trials, including the recent randomized controlled EOLIA trial, which showed no mortality benefit but was limited by significant treatment crossover.[54,55] Proposed benefits of VV-ECMO include the ability to "rest" the lungs to mitigate iatrogenesis or even facilitate extubation followed by physical therapy. Exclusion criteria vary by institution but typically include prolonged mechanical ventilation, older age, obesity, active cancer, neurologic injury, and unwitnessed cardiac arrest. Even though VV-ECMO cannulation is highly dependent on institution and resource availability, it commonly is used as rescue therapy, and referral should be considered early in the disease course. Because of the resource-intensive nature of ECMO and the large pool of potential candidates, patients with COVID-19 should exhaust traditional therapies before initiation of ECMO. Stringency of selection criteria should be adjusted as healthcare systems escalate in surge capacity.[56] The mortality rate of patients with COVID-19 ARDS requiring any form of ECMO has been estimated at 39%.[57] Optimal mechanical ventilation strategies on VV-ECMO in the setting of COVID-19 ARDS remain unclear.[58]

Traditional ARDS Pharmacologic Therapies

Aside from glucocorticoids in COVID-19 ARDS, no other pharmacologic therapy has been shown to decrease mortality in ARDS. Glucocorticoids have been studied extensively in non–COVID-19 ARDS and traditionally have been believed to worsen mortality.[59] Recent randomized trials and meta-analyses have suggested mixed results with some signal of faster clinical improvement with glucocorticoids.[60,61]

Other potential pharmacologic therapies in traditional ARDS, including dual budesonide and formoterol therapy, which has been shown to reduce hospital length of stay, improve oxygenation and perhaps even attenuate severity.[62] Sivelestat sodium, a neutrophil elastase inhibitor, may improve oxygenation but with no mortality or duration benefit.[63] A recent randomized controlled trial showed no improvement with adult surfactant, and this therapy currently is not recommended.[64] Statins also have been investigated as ARDS treatment based on animal studies but have not been found to be beneficial in humans.[65] A summary of recent and pertinent clinical trial outcomes for traditional ARDS can be found in Table 1.[33,35,37,38,45,49,50,54,55,59,60,62,64]

COVID-19 ARDS Pharmacologic Therapies

Patients hospitalized with COVID-19 ARDS requiring supplemental oxygen or invasive mechanical ventilation had

Table 1
Key ARDS Trials

Topic and Trial	Author	Year	Outcome
Restrictive *v* liberal fluid management (FACTT trial)	Wiedemann et al.[45]	2006	Conservative fluid strategy and shortened days of mechanical ventilation and intensive care (−2.5 d [$p < 0.001$] and −2.2 d [$p < 0.001$]), respectively).
Steroids	Steinberg et al.[59]	2006	No statistical 60-d mortality difference with steroid use ($p = 1.0$).
Steroids	Meduri et al.[60]	2016	Improved 28-d mortality with steroid use (20% *v* 33%; $p = 0.006$), decrease in days of mechanical ventilation (−5.7 d $p < 0.001$), and ICU-free days (−4.4 d; $p < 0.001$).
ECMO (CESAR trial)	Peek et al.[54]	2009	Relative risk reduction of death associated with ECMO-capable facility (RR 0.69, $p = 0.03$, NNT 7).
ECMO (EOLIA trial)	Combes et al.[55]	2018	No statistical difference in 60-d mortality with VV-ECMO *v* standard care ($p = 0.09$). Significant crossover likely diluted positive benefit of ECMO.
Prone position (PROSEVA trial)	Guérin et al.[38]	2013	Proning improved mortality in severe ARDS by 16.8% ($p < 0.001$).
Neuromuscular blockade (ACURASYS trial)	Papazian et al.[49]	2010	Neuromuscular blockade reduces mortality with AHR 0.68 ($p = 0.04$).
Neuromuscular blockade (ROSE trial)	Moss et al.[50]	2019	No difference in 90-d mortality with neuromuscular blockade; trial stopped for futility.
Driving pressure	Amato et al.[33]	2015	High driving pressures associated with higher mortality (RR 1.4; $p < 0.001$).
Recruitment maneuvers (ART trial)	Cavalcanti et al.[35]	2017	Large recruitment maneuvers (45 cmH_2O) associated with worse 28-d mortality (HR 1.2; $p = 0.041$).
Esophageal manometry (EPVENT-2 trial)	Beitler et al.[37]	2019	Routine esophageal manometry offers little benefit over empirical PEEP titration.
Budesonide/formoterol	Festic et al.[62]	2017	Combination budesonide and formoterol resulted in better oxygenation ($p = 0.01$).
Surfactant	Willson et al.[64]	2015	Calfactant administration was not associated with improved survival, lengths of stay, or oxygenation.

Abbreviations: AHR, adjusted hazard ratio; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; NNT, number needed to treat; PEEP, positive end-expiratory pressure; RR, relative risk; VV, venovenous.

lower 28-day mortality with the use of dexamethasone 6 mg daily for ten days. There was no mortality benefit for those receiving no respiratory support.[30] In patients with moderate or severe COVID-19 ARDS receiving standard of care, addition of a ten-day course of intravenous dexamethasone (20 mg daily for five days followed by 10 mg daily for five days) increased the number of ventilator-free days during the first 28 days.[31] Studies have failed to demonstrate a benefit with hydrocortisone or methylprednisolone.[66,67] A recent systematic review and meta-analysis demonstrated that corticosteroid treatment for COVID-19 infection was associated with significant reductions in mortality and need for invasive mechanical ventilation, but may be associated with delayed viral clearance and increased secondary infections.[68]

Remdesivir has been shown to shorten time to recovery in adult patients hospitalized with COVID-19 with evidence of lower respiratory tract infection.[69] At the time of this writing, the National Institutes of Health guidelines did not recommend remdesivir for patients who require mechanical ventilation because of insufficient evidence of benefit in this population.[44] Many other therapies currently are being studied, including convalescent plasma, monoclonal antibodies against the surface spike glycoprotein of the SARS-CoV-2 virus, mesenchymal stem cell infusion, ruxolitinib, interferon-α2b, and tocilizumab.[70-76] Hydroxychloroquine has not been associated with a significant clinical benefit.[77,78]

COVID-19 infection results in an inflammatory and prothrombotic state.[79] A systematic review and meta-analysis demonstrated a venous thromboembolism incidence of 14.1% among all patients hospitalized with COVID-19 and 22.7% in patients with COVID-19 who required ICU admission.[80] This was much higher than the incidence of 2.8%-to-5.6% reported in non−COVID-19 hospitalized patients.[81-83] Subgroup analysis of a retrospective study showed that among mechanically ventilated patients, mortality was 29.1% with therapeutic anticoagulation compared with 62.7%. However, the study did not report patient characteristics, indications for anticoagulation, or descriptions of other therapies and did not discuss survival bias.[84] A meta-analysis by the American Society of Hematology compared therapeutic with prophylactic anticoagulation and found that therapeutic anticoagulation decreased pulmonary embolism (odds ratio 0.09) but significantly increased major bleeding (odds ratio 3.84), with a statistically insignificant decrease in mortality.[85] Large multicenter trials comparing therapeutic with prophylactic anticoagulation are in progress. At present, the National Institutes of Health recommends that all hospitalized COVID-19 patients without evidence of venous thromboembolism should be placed on prophylactic anticoagulation, while acknowledging that there is controversy regarding initiating intermediate-dose anticoagulation among critically ill patients.[44]

Although SARS-CoV-2 viral entry into cells is mediated by the ACE2 receptor, and chronic use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers theoretically upregulates ACE2 receptor expression, patients who are on chronic angiotensin-converting enzyme inhibitors or angiotensin- receptor blockers do not have a clinically significantly increased risk of COVID-19 diagnosis or hospitalization.[86] A summary of important COVID-19 ARDS trials can be found in Table 2.[30,31,66,67,69,71,74,76-78]

Table 2
Key COVID-19 ARDS Trials

Topic and Trial	Author	Year	Outcome
Dexamethasone (RECOVERY trial)	Horby et al.[30]	2020	Dexamethasone (6 mg daily for up to 10 d) was associated with lower 28-d mortality among those receiving supplemental oxygen or invasive mechanical ventilation but not those receiving no respiratory support.
High-dose dexamethasone (CoDEX trial)	Tomazini et al.[31]	2020	Dexamethasone (20 mg daily for 5 d then 10 mg daily for 5 d) resulted in a statistically significant increase in number of ventilator-free days over the first 28 d for patients with moderate-to-severe COVID-19 ARDS.
Hydrocortisone (CAPE COVID trial)	Dequin et al.[66]	2020	Low dose hydrocortisone resulted in no significant difference in the rate of treatment failure at d 21 (defined as death or persistent mechanical ventilation or high-flow oxygen)
Methylprednisolone (METCOVID trial)	Jeronimo et al.[67]	2020	Methylprednisolone 0.5 mg/kg twice daily for 5 d did not reduce 28-d mortality.
Remdesivir (ACTT-1 trial)	Beigel et al.[69]	2020	Remdesivir (200 mg loading dose then 100 mg daily for 9 d) was superior to placebo at shortening time to recovery in patients with COVID-19 lower respiratory tract infection.
Tocilizumab (EMPACTA trial)	Salama et al.[76]	2021	Among patients not on mechanical ventilation, tocilizumab reduced the likelihood of progression to mechanical ventilation or death but did not improve survival.
Ruxolitinib	Cao et al.[74]	2020	No statistically significant difference was observed, but ruxolitinib recipients trended toward faster clinical improvement, greater chest CT improvement, and faster recovery from lymphopenia.
Convalescent plasma (PLACID trial)	Agarwal et al.[71]	2020	Convalescent plasma did not reduce progression to severe COVID-19 or all-cause 28-d mortality in patients with moderate COVID-19.
Hydroxychloroquine (ORCHID trial)	Self et al.[77]	2020	Hydroxychloroquine did not significantly improve clinical status at 14 d among adults hospitalized with COVID-19 respiratory illness.
Hydroxychloroquine (RECOVERY trial)	Horby et al.[78]	2020	Hydroxychloroquine did not reduce 28-d mortality in patients hospitalized with COVID-19.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CT, computed tomography.

Conclusion

ARDS is a heterogeneous disease characterized by diffuse alveolar damage with likely variable phenotypic penetration. ARDS remains underdiagnosed and associated with high mortality despite recent advances in diagnostics and therapeutics. LPV and prone positioning remain the mainstay of supportive care. The benefit of rescue therapies remains unclear. Even though a dysregulated inflammatory response and endothelial thrombosis may be key features differentiating COVID-19 from traditional ARDS, ultimately they are the same clinical disease process. COVID-19 ARDS should be treated with the existing validated therapies of LPV and prone positioning.

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Conflict of Interest

The authors have no conflict of interest or financial involvement with this manuscript.

References

1 Cochi SE, Kempker JA, Annangi S, et al. Mortality trends of acute respiratory distress syndrome in the United States from 1999 to 2013. Ann Am Thorac Soc 2016;13:1742–51.
2 Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers 2019;5:18.
3 Villar J, Blanco J, Kacmarek RM. Current incidence and outcome of the acute respiratory distress syndrome. Curr Opin Crit Care 2016;22:1–6.
4 Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788–800.
5 Laffey JG, Madotto F, Bellani G, et al. Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: Insights from the LUNG SAFE prospective cohort study. Lancet Respir Med 2017;5:627–38.
6 Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med 2020;180:1–12.
7 Gu T, Mack JA, Salvatore M, et al. Characteristics associated with racial/ethnic disparities in COVID-19 outcomes in an academic health care system. JAMA Netw Open 2020;3:e2025197.
8 Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med 2016;42:725–38.
9 Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: Different from general critical illness? Curr Opin Crit Care 2018;24:35–40.
10 Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562–72.
11 Calfee CS, Matthay MA, Kangelaris KN, et al. Cigarette smoke exposure and the acute respiratory distress syndrome. Crit Care Med 2015;43:1790–7.
12 Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526–33.
13 Li X, Ma X. Acute respiratory failure in COVID-19: Is it "typical" ARDS? Crit Care 2020;24:198.
14 Riviello ED, Kiviri W, Twagirumugabe T, et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. Am J Respir Crit Care Med 2016;193:52–9.
15 Zamorano Cuervo N, Grandvaux N. ACE2: Evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. Elife 2020;9.
16 Camporota L, Vasques F, Sanderson B, et al. Identification of pathophysiological patterns for triage and respiratory support in COVID-19. Lancet Respir Med 2020;8:752–4.
17 Gibelin A, Parrot A, Maitre B, et al. Acute respiratory distress syndrome mimickers lacking common risk factors of the Berlin definition. Intensive Care Med 2016;42:164–72.
18 Calfee CS, Janz DR, Bernard GR, et al. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. Chest 2015;147:1539–48.
19 Papazian L, Calfee CS, Chiumello D, et al. Diagnostic workup for ARDS patients. Intensive Care Med 2016;42:674–85.
20 Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from 2 randomised controlled trials. Lancet Respir Med 2014;2:611–20.
21 Mrozek S, Jabaudon M, Jaber S, et al. Elevated plasma levels of sRAGE are associated with nonfocal CT-based lung imaging in patients with ARDS: A prospective multicenter study. Chest 2016;150:998–1007.
22 Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med 2017;195:331–8.
23 Reilly JP, Christie JD, Meyer NJ. Fifty years of research in ARDS. Genomic contributions and opportunities. Am J Respir Crit Care Med 2017;196:1113–21.
24 Christie JD, Wurfel MM, Feng R, et al. Genome wide association identifies PPFIA1 as a candidate gene for acute lung injury risk following major trauma. PLoS One 2012;7:e28268.
25 Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323:2329–30.
26 Panwar R, Madotto F, Laffey JG, et al. Compliance phenotypes in early acute respiratory distress syndrome before the COVID-19 pandemic. Am J Respir Crit Care Med 2020;202:1244–52.
27 Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care 2020;24:529.
28 Camporota L, Sanderson B, Dixon A, et al. Outcomes in mechanically ventilated patients with hypoxaemic respiratory failure caused by COVID-19. Br J Anaesth 2020;125:e480–3.
29 Elhakim TS, Abdul HS, Pelaez Romero C, et al. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19 pneumonia: A rare case and literature review. BMJ Case Rep 2020;13(12).
30 Horby P, Lim WS, Emberson JR, (RECOVERY Collaborative Group). Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med 2021;384:693–704.
31 Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA 2020;324:1307–16.
32 Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.
33 Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747–55.
34 Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Respir Res 2019;6:e000420.
35 Cavalcanti AB, Suzumura É A, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA 2017;318:1335–45.
36 Pham T, Telias I, Beitler JR. Esophageal manometry. Respir Care 2020;65:772–92.

37 Beitler JR, Sarge T, Banner-Goodspeed VM, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA 2019;321:846–57.
38 Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.
39 Scholten EL, Beitler JR, Prisk GK, et al. Treatment of ARDS with prone positioning. Chest 2017;151:215–24.
40 Zochios V, Parhar K, Vieillard-Baron A. Protecting the right ventricle in ARDS: The role of prone ventilation. J Cardiothorac Vasc Anesth 2018;32:2248–51.
41 Kallet RH. A comprehensive review of prone position in ARDS. Respir Care 2015;60:1660–87.
42 Thompson AE, Ranard BL, Wei Y, et al. Prone positioning in awake, nonintubated patients with COVID-19 hypoxemic respiratory failure. JAMA Intern Med 2020;180:1537–9.
43 Tolcher MC, McKinney JR, Eppes CS, et al. Prone positioning for pregnant women with hypoxemia due to coronavirus disease 2019 (COVID-19). Obstet Gynecol 2020;136:259–61.
44 National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov. Accessed January 28, 2021.
45 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of 2 fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–75.
46 Vignon P, Evrard B, Asfar P, et al. Fluid administration and monitoring in ARDS: Which management? Intensive Care Med 2020;46:2252–64.
47 Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: A systematic review and meta-analysis. Intensive Care Med 2017;43:155–70.
48 Semler MW, Wheeler AP, Thompson BT, et al. Impact of initial central venous pressure on outcomes of conservative versus liberal fluid management in acute respiratory distress syndrome. Crit Care Med 2016;44:782–9.
49 Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107–16.
50 Moss M, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997–2008.
51 Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. N Engl J Med 2005;353:2683–95.
52 Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016;6:CD002787.
53 Fuller BM, Mohr NM, Skrupky L, et al. The use of inhaled prostaglandins in patients with ARDS: A systematic review and meta-analysis. Chest 2015;147:1510–22.
54 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. Lancet 2009;374:1351–63.
55 Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75.
56 Shekar K, Badulak J, Peek G, et al. Extracorporeal Life Support Organization coronavirus disease 2019 interim guidelines: A consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. Asaio J 2020;66:707–21.
57 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020;396:1071–8.
58 Schmidt M, Pham T, Arcadipane A, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome. An international multicenter prospective cohort. Am J Respir Crit Care Med 2019;200:1002–12.
59 Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671–84.
60 Meduri GU, Bridges L, Shih MC, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: Analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016;42:829–40.
61 Lewis SR, Pritchard MW, Thomas CM, et al. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst Rev 2019;7:CD004477.
62 Festic E, Carr GE, Cartin-Ceba R, et al. Randomized clinical trial of a combination of an inhaled corticosteroid and beta agonist in patients at risk of developing the acute respiratory distress syndrome. Crit Care Med 2017;45:798–805.
63 Pu S, Wang D, Liu D, et al. Effect of sivelestat sodium in patients with acute lung injury or acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. BMC Pulm Med 2017;17:148.
64 Willson DF, Truwit JD, Conaway MR, et al. The adult calfactant in acute respiratory distress syndrome trial. Chest 2015;148:356–64.
65 Chen M, Lu J, Chen Q, et al. [Statin in the treatment of ALI/ARDS: A systematic review and meta-analysis based on international databases]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2017;29:51–6.
66 Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: A randomized clinical trial. JAMA 2020;324:1298–306.
67 Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020 Aug 12;[E-pub ahead of print].
68 van Paassen J, Vos JS, Hoekstra EM, et al. Corticosteroid use in COVID-19 patients: A systematic review and meta-analysis on clinical outcomes. Crit Care 2020;24:696.
69 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813–26.
70 Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: A living systematic review. Cochrane Database Syst Rev 2020;7:CD013600.
71 Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: Open label phase II multicentre randomised controlled trial (PLACID trial). BMJ 2020;371:m3939.
72 Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 2020;324:131–2.
73 Shetty AK. Mesenchymal stem cell Infusion shows promise for combating coronavirus (COVID-19)- induced pneumonia. Aging Dis 2020;11:462–4.
74 Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 2020;146;137−46.e133.
75 Zhou Q, Chen V, Shannon CP, et al. Interferon-α2b treatment for COVID-19. Front Immunol 2020;11:1061.
76 Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021;384:20–30.
77 Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: A randomized clinical trial. JAMA 2020;324:2165–76.
78 Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;383:2030–40.
79 Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58:1116–20.
80 Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4:1178–91.

81 Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341:793–800.

82 Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874–9.

83 Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: Randomised placebo controlled trial. BMJ 2006;332:325–9.

84 Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:122–4.

85 Cuker A, Tseng EK, Nieuwlaat R, et al. ASH 2020 guidelines on the use of anticoagulation in patients with COVID-19: Draft recommendations. Available at: http://www.hematology.org/COVIDguidelines. Accessed January 28, 2021.

86 Morales DR, Conover MM, You SC, et al. Renin-angiotensin system blockers and susceptibility to COVID-19: An international, open science, cohort analysis. Lancet Digit Health 2021;3:e98–e114.