

Precision Medicine and Heterogeneity of Treatment Effect in Therapies for ARDS



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ARDS is a clinically heterogeneous syndrome, rather than a distinct disease. This heterogeneity at least partially explains the difficulty in studying treatments for these patients and contributes to the numerous trials of therapies for the syndrome that have not shown benefit. Recent studies have identified different subphenotypes within the heterogeneous patient population. These different subphenotypes likely have variable clinical responses to specific therapies, a concept known as heterogeneity of treatment effect. Recognizing different subphenotypes and heterogeneity of treatment effect has important implications for the clinical management of patients with ARDS. This review presents studies that have identified different subphenotypes and discusses how they can modify the effects of therapies evaluated in trials that are commonly considered to have shown no overall benefit in patients with ARDS.

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KEY WORDS: acute respiratory failure; ARDS; heterogeneity of treatment effect

ARDS is a severe, life-threatening inflammatory condition of the lung that can be caused by a wide variety of pulmonary and nonpulmonary insults, including both infectious and noninfectious causes.¹ The Berlin Definition for ARDS requires the acute onset of hypoxemia, defined as a ratio of PaO_2 to $\text{FiO}_2 \leq 300$ mm Hg with bilateral airspace disease on chest imaging not primarily due to hydrostatic edema.² The multiple potential causes and the broad definition for ARDS lend to the clinical heterogeneity of this syndrome and contribute to the difficulty in effectively studying treatments for these patients.^{3,4}

Table 1⁵⁻³¹ presents a summary of

randomized controlled trials of therapies for ARDS; although there are a few notable exceptions, the ARDS literature is rife with randomized trials that have not shown a mortality benefit.³² One factor that may contribute to these many indeterminate results is heterogeneity of treatment effect (HTE).

In randomized controlled trials, results are reported as the average of individual treatment effects for all the patients in the study population.^{33,34} However, some of the patients included in the study may have treatment effects that are different from this average effect.^{33,35} These characteristics can influence the baseline risk of developing the

ABBREVIATIONS: HFOV = high-frequency oscillatory ventilation; HTE = heterogeneity of treatment effect; LPV = lung-protective ventilation; NMBA = neuromuscular blocking agent; PEEP = positive end-expiratory pressure; VFD = ventilator-free days

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TABLE 1] Summary of Randomized Controlled Trials of Therapies for ARDS and Corresponding Heterogeneity of Treatment Effects

Therapy	Noteworthy Trial Findings	Heterogeneity of Treatment Effect
Lung-protective ventilation	ARMA: Lower mortality with LPV ⁵	None identified ^{6,7}
Open lung ventilation	ALVEOLI: No difference in hospital mortality ⁸ ExPress: No difference in 28-d mortality ⁹ LOVS: No difference in 28-d hospital mortality ¹⁰ ART: Higher 28-d mortality with open lung ventilation ¹¹	Open lung ventilation associated with lower mortality in: Pao ₂ /Fio ₂ ratio ≤ 200 mm Hg ¹² PEEP responders with improved Pao ₂ /Fio ₂ ratio ^{13,14} PEEP responders with lower driving pressure ¹⁵ Hyperinflammatory phenotype ¹⁶ Open lung ventilation associated with higher mortality in patients with pneumonia requiring vasopressors ¹⁷
HFOV	OSCILLATE: Higher hospital mortality with HFOV ¹⁸ OSCAR: No difference in 30-d mortality ¹⁹	HFOV associated with lower mortality in patients with a Pao ₂ /Fio ₂ ratio < 100 mm Hg (or < 64 mm Hg) ²⁰
Prone positioning	PROSEVA: Lower 28-d mortality with prone positioning ²¹	Mortality benefit limited to a Pao ₂ /Fio ₂ ratio < 150 mm Hg ²¹
NMBA	ACURASYS: Lower adjusted 90-d mortality with NMBA ²² ROSE: No difference in 90-d mortality ²³	NMBA associated with lower mortality in: Pao ₂ /Fio ₂ ratio < 150 mm Hg ²²
Fluid therapy	FACTT: No difference in mortality; more VFDs with conservative fluid strategy ²⁴	Liberal fluid strategy associated with higher mortality in hyperinflammatory phenotype ²⁵ Liberal fluid strategy associated with lower mortality in less inflammatory phenotype
Statins	HARP-2: No difference in 28-d mortality with simvastatin ²⁶ SAILS: No difference in 60-d or hospital mortality with rosuvastatin ²⁷	Simvastatin associated with lower mortality in: Hyperinflammatory phenotype ²⁸ Lower APACHE II score ²⁹ Statins associated with lower mortality in sepsis-related ARDS with a Pao ₂ /Fio ₂ ratio < 100 mm Hg ³⁰ Simvastatin associated with higher mortality in higher APACHE II score ²⁹ None identified for rosuvastatin ³¹

ACURASYS = ARDS et Curarisation; ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; APACHE II = Acute Physiology and Chronic Health Evaluation II; ARMA = Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and Acute Respiratory Distress Syndrome; ExPress = Expiratory Pressure Study; FACTT = Fluids and Catheters Treatment Trial; HARP-2 = Hydroxymethylglutaryl-CoA Reductase Inhibition in Acute Lung Injury to Reduce Pulmonary Inflammation 2; HFOV = high-frequency oscillatory ventilation; LOVS = Lung Open Ventilation Study; NMBA = neuromuscular blocking agent; OSCAR = Oscillation in ARDS; PEEP = positive end-expiratory pressure; PROSEVA = Effect of Prone Positioning on Mortality in Patients with Severe Acute Respiratory Distress Syndrome; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade; SAILS = Statins for Acutely Injured Lungs from Sepsis; VFD = ventilator-free days.

clinical outcome, as well as the likelihood of gaining benefit, or experiencing harm, from the treatment.³⁶ HTE refers to a nonrandom difference in the direction or magnitude of the clinical effect of a treatment between patients that is driven by the interaction between these distinct characteristics, or subphenotypes, and the intervention being studied.^{35,37}

The potential for HTE is an important consideration in clinical trial design and evaluation. Trials that include a more heterogeneous study population are more generalizable to clinical practice and thus have more external validity; however, they will likely have more heterogeneous treatment effects among the participants.³⁸ By contrast, trials with a more homogeneous study population are less likely to have heterogeneous treatment effects but will have lower

external validity.³⁷ Heterogeneity in trials can be limited by enrichment of the study populations, and this can be either prognostic or predictive. Enrichment refers to the selection of patients who are more likely to respond to treatment compared with an unselected group of patients and is based on characteristics that are known prior to randomization.³⁹⁻⁴¹ Prognostic enrichment is used to select patients who are more likely to develop the clinical outcome of interest, whereas predictive enrichment is used to select patients who are more likely to respond to the treatment.^{40,41}

HTE has important implications for the management of ARDS, in which therapies evaluated in clinically heterogeneous patient populations have largely been unsuccessful.^{4,32} These so-called “negative” trials may have been the result of truly ineffective therapies.

Alternatively, therapies may have helped some patients but harmed others, resulting in no net clinical effect in the trial. As such, there is an increasing interest in identifying different subphenotypes among patients with ARDS.⁴² Potential subphenotypes that have been identified as possible effect-modifiers include variables that are physiological (eg, $\text{PaO}_2/\text{FiO}_2$ ratio, respiratory system compliance), clinical (eg, underlying cause, direct vs indirect), and biological (eg, biomarkers, hyperinflammatory vs hypoinflammatory).⁴³

There are several methods to identify HTE from trial data. The most common approach is to use the analyses of subgroups that are reported in the trial itself.^{44,45} Observational studies using secondary analyses of trial data can also be used. Individual patient data meta-analyses can identify important subgroup effects that could not otherwise be detected due to inadequate power.⁴⁶ Latent class analysis identifies subgroups without prespecified assumptions and has been increasingly used to estimate differential treatment effects.⁴⁷

The purpose of the current review was to summarize the key trials of therapies for ARDS, many of which are frequently but incorrectly referred to as negative. It is more correct to state that they did not show benefit, and in most cases they are indeterminate, as few were conducted as noninferiority trials. We present evidence for HTE according to disease severity, cause of ARDS, and inflammatory subphenotypes across different therapies and trials, and review the circumstances under which these treatments may be clinically useful.

Before discussing HTE, however, we want to highlight the notable exception to this trend, which is the limitation of intensity of mechanical ventilation by reducing tidal volume and plateau pressure. The original ARDS Network trial found a 9% absolute risk reduction in mortality.⁵ In secondary analyses, neither oxygenation severity⁶ nor cause of ARDS⁷ was found to interact with this treatment effect. Indeed, it seems likely that limitation of intensity of ventilation is important not just in patients with ARDS but more broadly across the spectrum of acute hypoxemic respiratory failure.⁴⁸

ARDS Severity

Open Lung Ventilation

Open lung ventilation refers to a strategy of higher levels of positive end-expiratory pressure (PEEP) with or without recruitment maneuvers. This approach can

increase end-expiratory lung volume, improve gas exchange, may reduce both lung stress and strain, and can minimize atelectrauma.^{49,50}

Only two studies have shown mortality benefit associated with open lung ventilation.^{51,52} However, these findings were confounded by the concurrent use of higher tidal volumes in control patients. Several small trials that incorporated lung-protective ventilation (LPV) in both treatment and control groups failed to show mortality benefit from open lung ventilation.⁵³⁻⁵⁶ Three larger trials of open lung ventilation that provided concurrent LPV to all patients were similarly unable to show a difference in mortality: the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury (ALVEOLI) trial, the Expiratory Pressure (ExPress) Study, and the Lung Open Ventilation Study (LOVS).⁸⁻¹⁰ Although these trials did not show any mortality benefit from open lung ventilation, they did not reveal any signal for harm.

However, a patient-level analysis of the ALVEOLI, ExPress, and LOVS trials found that open lung ventilation was associated with lower mortality when delivered to patients with $\text{PaO}_2/\text{FiO}_2$ ratios \leq 200 mm Hg (34.1% vs 39.1%; relative risk, 0.90; 95% CI, 0.81-1.00).¹² Conversely, in the population with what we would now call mild ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio, 201-300 mm Hg), there was a signal toward harm with higher PEEP, illustrating HTE with open lung ventilation according to ARDS severity.

More recently, the Alveolar Recruitment in ARDS trial (ART) found that higher PEEP paired with an aggressive lung recruitment maneuver led to increased 28-day mortality compared with a lower PEEP strategy.¹¹ This trial, which was performed exclusively in patients with moderate to severe ARDS, did not identify any significant differences in treatment effects in either subgroup or in exploratory analyses.

Prone Positioning

In early trials of prone positioning, a shorter duration (\leq 8 h) did not decrease mortality in patients with $\text{PaO}_2/\text{FiO}_2$ ratios $<$ 300 mm Hg or $<$ 150 mm Hg.^{57,58} However, application of longer durations of prone positioning led to a nonsignificant trend toward mortality in patients with a $\text{PaO}_2/\text{FiO}_2$ ratio $<$ 100 mm Hg and 132 ± 74 mm Hg.^{59,60}

Based on these findings, the Effect of Prone Positioning on Mortality in Patients with Severe Acute Respiratory Distress Syndrome (PROSEVA) trial included

prognostic enrichment to select patients with a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mm Hg.²¹ In this trial, the application of prone positioning for at least 16 h per day (mean, 17.0 \pm 3 h) led to lower 28-day mortality (16.0% vs 32.8%; hazard ratio [HR], 0.39; 95% CI, 0.25-0.63) and decreased 90-day mortality (23.6% vs 41.0%; HR, 0.44; 95% CI, 0.29-0.67).

Spontaneous Breathing

Diaphragmatic contraction during spontaneous breathing can help to recruit well-perfused dependent segments of the lung that remain poorly ventilated during controlled positive pressure ventilation.⁶¹ However, spontaneous breathing also poses certain risks. It can be associated with increased tidal volumes due to increased patient effort and dyssynchrony.^{62,63} During spontaneous ventilation, the true transpulmonary pressure is the sum of the pressure generated by the ventilator and the respiratory muscles, potentially increasing the true driving pressure, but this increase is not apparent unless special maneuvers are performed on the ventilator.⁶⁴ In addition, in heterogeneous ARDS lungs, changes in pleural pressure during spontaneous breaths are not uniformly transmitted through the airways, potentially leading to pendelluft, where air flows from one lung region to another, such that even a low tidal volume can cause regional overdistension.^{63,65}

Observational studies suggested an association between spontaneous modes of ventilation and increased ventilator-free days (VFD) and shorter ICU lengths of stay compared with controlled ventilation but did not suggest a mortality benefit.^{66,67} The HTE for spontaneous breathing also seems to be driven by the severity of ARDS. Pendelluft occurs more commonly during spontaneous breathing in patients with severe ARDS, and the resulting regional overdistension and lung injury can limit potential benefits of spontaneous breathing.^{64,65}

Neuromuscular Blocking Agents

Spontaneous breathing in ARDS can be associated with increased transpulmonary pressures, regional overdistension due to pendelluft, and large tidal volumes due to increased patient effort and ventilator dyssynchrony.⁶²⁻⁶⁵

The ARDS et Curarisation (ACURASYS) trial was a double-blind, placebo-controlled study that compared 48 h of neuromuscular blocking agents (NMBA) initiated within 48 h of ARDS onset vs deep sedation without NMBA in patients with a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mm Hg.²² Although there was no difference in

overall 90-day mortality between the two groups (40.7% vs 48.8%; $P = .08$), an analysis adjusted for $\text{PaO}_2/\text{FiO}_2$ ratio, plateau pressure, and severity of illness found reduced 90-day mortality in the NMBA group (adjusted HR for death, 0.68; 95% CI, 0.48-0.98). These results, and observations of pendelluft in severe ARDS, suggest there might be HTE for NMBA based on the $\text{PaO}_2/\text{FiO}_2$ ratio; this is further supported by a subgroup analysis that showed no difference in probability of survival in patients with a baseline $\text{PaO}_2/\text{FiO}_2$ ratio ≥ 120 mm Hg.^{22,65}

In the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial, patients with ARDS and a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mm Hg were treated with 48 h of NMBA or with usual care, including light sedation.²³ Unlike the ACURASYS trial, there was no difference in 90-day mortality between the two groups (42.5% vs 42.8; between-group difference, -0.3 percentage point; 95% CI, -6.4 to 5.9).

There are important distinctions between the ACURASYS and ROSE trials that might explain these divergent outcomes. First, the PEEP strategies used in each study were different. As noted earlier, a meta-analysis of three trials of open lung ventilation suggested that higher PEEP is associated with lower mortality in patients with moderate to severe ARDS.¹² The ROSE trial included ventilation with higher levels of PEEP, and this may have also decreased the risk of mortality in the patients in this trial and thus diluted any mortality benefit from NMBA, whereas the ACURASYS trial used lower PEEP. Second, the use of concomitant prone positioning was more common in ACURASYS (28% in the NMBA group, 29% in the control group) than in ROSE (15.8% of patients; between-group difference, 1.9%; 95% CI, -2.6 to 6.4). Third, patients in the control group of the ACURASYS trial were deeply sedated to facilitate blinding, and this use of deep sedation without NMBA could have contributed to worse clinical outcomes in the control group. By contrast, light sedation was used in the control arm of the open-label ROSE trial. Finally, the time between identification of ARDS and enrollment in the ACURASYS trial (median, 16 h; interquartile range, 6-29 h) was considerably longer than that in the ROSE trial (median, 7.6 h; interquartile range, 3.7-15.6 h). The earlier enrollment in the ROSE trial may have preferentially captured more patients with transient ARDS.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) applies a relatively high mean airway pressure that can recruit

collapsed lung and prevent atelectrauma, and it delivers very small tidal volumes, which can prevent volutrauma.⁶⁸ In the Oscillation for ARDS Treated Early (OSCILLATE) trial comparing HFOV vs LPV with high PEEP in patients with a PaO₂/F_{IO}₂ ratio ≤ 200 mm Hg, there was increased in-hospital mortality in the HFOV group (47% vs 35%; relative risk, 1.33; 95% CI, 1.12-1.79).¹⁸ The Oscillation in ARDS (OSCAR) trial also compared HFOV vs conventional LPV in patients with ARDS and a PaO₂/F_{IO}₂ ratio ≤ 200 mm Hg but found no difference in 30-day mortality between the two groups (41.7% vs 41.1%; *P* = .85).¹⁹ The conflicting outcomes between the trials might be due to the differences in the use of LPV in the control arms, relative imbalance between the benefits of recruitment and the harm of increased sedation, the hemodynamic effects of increased sedation, and/or higher airway pressures.^{18,69}

In a patient-level meta-analysis of four trials of HFOV, HTE was identified for the relationship between HFOV and severity of ARDS, based on a PaO₂/F_{IO}₂ ratio at the time of randomization.²⁰ The threshold at which the effect of HFOV shifts from harm to benefit is not entirely clear, but the line of best fit occurs at a PaO₂/F_{IO}₂ ratio of approximately 100 mm Hg (95% CI, 64-117).

Hydroxymethylglutaryl-CoA Reductase Inhibitors (Statins)

The Statins for Acutely Injured Lungs from Sepsis (SAILS) trial, which compared rosuvastatin vs placebo in patients with sepsis-associated ARDS, was stopped early for futility and found no difference in 60-day or in-hospital mortality (28.5% vs 24.9%; *P* = .21).²⁷ Similarly, the Hydroxymethylglutaryl-CoA Reductase Inhibition in Acute Lung Injury to Reduce Pulmonary Inflammation 2 (HARP-2) trial found no difference between simvastatin and placebo on the primary outcome of VFD (12.6 ± 9.9 vs 11.5 ± 10.4; *P* = .21) or secondary outcome of 28-day mortality (22.0% vs 26.8%; *P* = .23).²⁶ Mansur et al³⁰ observed HTE for the effect of statins on mortality in sepsis-associated ARDS; mortality was lower in the cohort of patients with a PaO₂/F_{IO}₂ ratio < 100 mm Hg treated with statins (the most common agent was simvastatin) compared with those who were not (11.5% vs 37.5%; *P* = .0193).

Cause of ARDS

Open Lung Ventilation

In a latent class analysis of the ART trial, Zampieri et al¹⁷ identified three distinct clusters among the patients. The association between open lung ventilation

and mortality was greatest in the cluster of patients with ARDS from pneumonia who required vasopressors, and probability of harm was > 98%. In patients with miscellaneous causes of ARDS, including pneumonia but who did not require vasopressors, the probability of harm was 45%; and in patients with ARDS not due to pneumonia who required vasopressors, the probability of harm was 68%. The authors reasoned that in patients with pneumonia who have heterogeneous areas of dense consolidation, application of open lung ventilation may not be able to recruit collapsed units and could instead lead to hyperinflation and injury in other areas.⁷⁰ They also suggested that the adverse hemodynamic effects and the higher fluid balance associated with recruitment maneuvers and PEEP titration might have contributed to the signal or harm, especially in patients requiring vasopressors.¹¹ Open lung ventilation should increase recruitment and decrease driving pressure.⁷¹ However, if the lung cannot be recruited, the increased airway pressures would increase driving pressure, which is associated with higher mortality.⁷² The lack of meaningful improvement in lung compliance and the resulting absence of reduction in driving pressure in the ART trial might thus have been driven by inclusion of patients with non-recruitable lung.¹¹

Inflammatory Subphenotype

Open Lung Ventilation

Using clinical and biomarker data from the original ARDS Network trial of lower tidal volumes and the ALVEOLI trial, Calfee et al¹⁶ performed a latent class analysis and identified two distinct subphenotypes that modify the effect of open lung ventilation on mortality. The hyperinflammatory subphenotype had more shock, more nonpulmonary sepsis, and higher levels of inflammatory biomarkers (IL-6 and IL-8), differentiating it from the less inflammatory subphenotype. The authors found that among hyperinflammatory patients, open lung ventilation with higher PEEP levels was associated with lower mortality and more VFD, compared with the low PEEP strategy, whereas the opposite was true in the hypoinflammatory patients.

Fluid Therapy

The Fluids and Catheters Treatment Trial (FACTT) was a two-by-two trial of patients with ARDS and a PaO₂/F_{IO}₂ ratio < 300 mm Hg that compared a conservative fluid strategy vs a liberal fluid strategy and pulmonary artery catheters vs central venous catheters.²⁴ There was

no significant difference in mortality between the conservative and liberal strategies (25.5% vs 28.4%; 95% CI for difference, -2.6 to 8.4; $P = .30$) and no mortality difference between catheter type ($P = .24$). However, the conservative fluid strategy was associated with more VFDs (14.6 ± 0.5 vs 12.1 ± 0.5 ; $P < .001$). Using latent class analysis, patients with a hyperinflammatory subphenotype were characterized by higher levels of inflammatory markers (IL-6, IL-8, and soluble tumor necrosis factor receptor-1), lower serum bicarbonate (HCO_3^-) levels, and more hypotension.²⁵ The conservative fluid strategy was associated with lower 90-day mortality in this hyperinflammatory group (40%) compared with the liberal fluid strategy (50%). The direction of treatment effect was opposite in the less inflammatory subphenotype, in which the liberal fluid strategy lowered 90-day mortality compared with the conservative fluid strategy (26% vs 18%; P value for interaction = .0039).

Hydroxymethylglutaryl-CoA Reductase Inhibitors (Statins)

A latent class analysis of the HARP-2 trial identified two subphenotypes; the hyperinflammatory subphenotype had higher levels of IL-6 and soluble tumor necrosis factor receptor-1 and more vasopressor use than the hypoinflammatory subphenotype.²⁸ In patients with the hyperinflammatory subphenotype, simvastatin was associated with lower 28-day mortality compared with placebo (32% vs 45%; $P < .0001$). However, a similar analysis of the SAILS trial found no HTE for mortality according to the inflammatory subphenotype.³¹ The authors suggested that the absence of HTE in the analysis of the SAILS trials might have been due to the use of rosuvastatin, which has less antiinflammatory activity than simvastatin.⁷³ Patients in the SAILS trial had higher $\text{PaO}_2/\text{FiO}_2$ ratios than those in the HARP-2 trial; as outlined earlier, the severity of ARDS can modify the interaction between statins and mortality in ARDS.³⁰

Other Clinical Subphenotypes

PEEP Responders

Patients who respond to open lung ventilation with increased oxygenation might represent another clinical subphenotype. In a secondary analysis of the LOVS and ExPress trials, patients with > 25 mm Hg improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio after application of higher PEEP had lower mortality (OR, 0.80; 95% CI, 0.72-0.89).¹³ A similar relationship was noted in an analysis of six trials of open lung ventilation wherein improved oxygenation

in response to higher PEEP levels was associated with lower hospital and ICU mortality.¹⁴ The relationship between open lung ventilation and mortality in patients who are PEEP responsive also seems to be modified by severity of ARDS, and the relationship was greatest in those with a baseline $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 150 mm Hg.¹³ A subsequent study found that changes in driving pressure with adjustment of PEEP were more strongly associated with mortality (adjusted HR, 1.42 per cm H_2O increase; 95% CI, 1.14-1.78) than changes in $\text{PaO}_2/\text{FiO}_2$ (adjusted HR, 0.95 per 25 mm Hg increase; 95% CI, 0.90-1.00) when the variables were modeled together in the ExPress trial. When the model was applied to the AVEOLI trial cohort, changes in driving pressure were associated with mortality (adjusted HR, 1.50 per 5 cm H_2O ; 95% CI, 1.21-1.85), but changes in the $\text{PaO}_2/\text{FiO}_2$ ratio were not.¹⁵

Novel COVID-19 ARDS

Early reports of COVID-19-associated ARDS suggested there might be distinct subphenotypes based on recruitability and respiratory system compliance and that these could inform decisions about optimal ventilation strategies.^{74,75} However, several other studies have since reported compliance values among their patients with COVID-19-associated ARDS that were lower than these initial reports and more in keeping with typical ARDS.⁷⁶⁻⁷⁹ Furthermore, there is currently no strong evidence to suggest that any of the proposed approaches based on these early reported potential subphenotypes improve clinical outcomes in these patients. As such, experts have largely advocated using evidence-based ARDS management strategies, including LPV, along with higher PEEP and prone positioning when indicated.⁸⁰

One therapy for patients with COVID-19 that does exhibit HTE is the use of glucocorticoids. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial found that dexamethasone reduced 28-day mortality in hospitalized patients with suspected or confirmed COVID-19 (22.9% vs 25.7%; rate ratio, 0.83; 95% CI, 0.75-0.93; $P < .001$).⁸¹ Among these patients, there was a differential response to this therapy based on disease severity, as shown by the level of required respiratory support. The greatest reduction in mortality was noted in the patients who received invasive mechanical ventilation (29.3% vs 41.4%; rate ratio, 0.64; 95% CI, 0.51-0.81) followed by those who required only oxygen (23.3% vs 26.2%; rate ratio, 0.82; 95% CI, 0.72-0.94). There was no benefit, and a possible trend toward harm, in patients who did not require any oxygen

(17.8% vs 14.0%; rate ratio, 1.19; 95% CI, 0.91-1.55). Although this study included patients with COVID-19-associated ARDS, there is currently no further evidence to suggest additional effect modification of dexamethasone therapy among different subgroups of these patients.

Conclusions

Recognizing different subphenotypes among patients with ARDS and understanding how they can modify the effects of different treatments have important implications for the study of these therapies. Furthermore, understanding the role of HTE and delivering therapies tailored to heterogeneous groups of patients with ARDS represents a major paradigm shift in the clinical management of these patients. The studies reviewed here suggest that many treatments which were previously considered to be ineffective might in fact reduce mortality under certain circumstances when they are applied to the appropriate patients. [Figure 1](#) outlines some of these treatments and the potential conditions under which they may be useful.

There are some important considerations about the studies that we have used to illustrate HTE for ARDS

therapies that warrant additional discussion. As mentioned earlier, subgroup analysis is the most common method to identify subphenotypes in which the treatments could have differential effects. However, insufficient statistical power can lead to false-negative findings, and multiple testing can lead to false-positive findings in these analyses.^{82,83} Observational studies, such as individual patient data meta-analyses and latent class analyses, may have larger sample sizes that can in turn confer more power and more precise effect estimates, but these analyses are at risk for confounding.⁸⁴ As such, it is possible that some of the relationships between subphenotypes and treatment modification identified through secondary analyses may be artifactual. Clinical trials performed exclusively in patients with the subphenotypes of interest would provide more definitive evidence of effect modification, but these may be difficult to perform, owing to challenges in enrolling sufficient patients to achieve adequate power.

There are also some challenges to applying these current findings in clinical practice. A variety of the effect modifiers based on some of the physiological and clinical subphenotypes that we have discussed can easily be identified at the bedside. Other effect modifiers, such

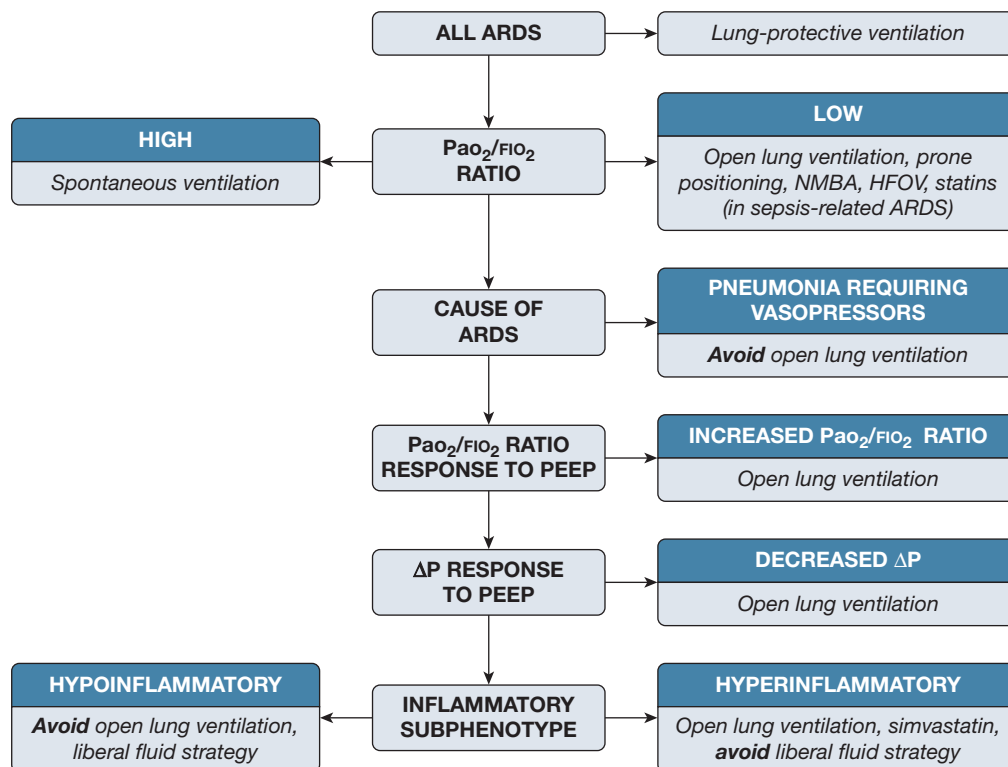


Figure 1 – A potential algorithm outlining different subphenotypes of patients with ARDS and specific therapeutic considerations based on effect modification among these subphenotypes. ΔP = driving pressure; HFOV = high-frequency oscillatory ventilation; HTE = heterogeneity of treatment effect; NMBA = neuromuscular blocking agents; PEEP = positive end-expiratory pressure.

as the inflammatory subphenotypes, are more difficult to apply clinically in the absence of practical and accessible methods to identify these patients. New point-of-care assays that can quantify levels of some biomarkers (eg, IL-6, soluble tumor necrosis factor receptor-1), however, have recently been used to identify inflammatory subphenotypes in patients with COVID-19-associated ARDS.⁸⁵ Furthermore, even if subphenotypes can be identified in real-time, some of the threshold values that were used to classify patients in the secondary analyses may have been arbitrary and thus difficult to extrapolate to clinical use.

The studies we highlighted suggest that there are subphenotypes among patients with ARDS and that these can modify the effects of different treatments. In fact, interventions from so-called “negative trials” may ultimately confer benefit when they are delivered to some of these subphenotypes. This argues for a role of precision medicine in the management of patients with ARDS, in which therapies are delivered based on individual patient characteristics. Although the results of secondary analyses are compelling and hypothesis generating, we would hope to see trials of interventions designed to exploit HTE to better inform future clinical practice. We also look forward to the development of more tools that will allow us to detect these subphenotypes in an effort to provide tailored therapy. Furthermore, it is likely that there are other clinical, biological, or genomic subphenotypes among patients with ARDS. Thus, it remains possible, and even likely, that other therapies that were previously considered ineffective might be found to improve outcomes in selected patients with ARDS. The identification of new subphenotypes can also highlight previously unknown therapeutic targets, which may in turn suggest new treatments for certain patients with ARDS.

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