

JAMA Clinical Guidelines Synopsis

Caring for Patients With Acute Respiratory Distress Syndrome

Summary of the 2023 ESICM Practice Guidelines

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The acute respiratory distress syndrome (ARDS) is a constellation of conditions sharing the central feature of noncardiogenic pulmonary edema, typically mediated by diffuse alveolocapillary permeability and inflammation, that results in impaired gas exchange severe enough to pose an immediate threat to life.¹ ARDS was first described more than 50 years ago and arises from conditions such as trauma, massive blood transfusion, septic shock, or pneumonia.¹ The development of ARDS is ominous. While advances in intensive care over the past decades have resulted in improved outcomes, hospital mortality rate due to ARDS is still 40%.² Arguably, the most striking example of ARDS is the severe respiratory failure that develops secondary to SARS-CoV-2 infection, responsible for a massive death toll worldwide, not to mention the colossal burden on hospital and intensive care services.

Typically, patients with ARDS require complex multidisciplinary care in an intensive care unit (ICU). Not only is the support for severe acute respiratory failure challenging to provide, but these patients often have multiorgan dysfunction: balancing how best to support one organ without compromising the function of another adds additional complexity. Clinical trials in patients with ARDS demonstrate that even modest adjustments to organ support, such as the size of tidal volumes set on the ventilator, have large effects on survival.³ There is therefore considerable interest in how best to optimize care for patients with ARDS, and more than 1100 randomized trials of interventions are registered on ClinicalTrials.gov.⁴ Consequently, maintaining and disseminating contemporary summaries of this evidence to ensure care is up to date, of high quality, and reproducible across every ICU and hospital where patients with ARDS are cared for is an important health care priority. To this end, several professional societies support efforts to generate evidence-based ARDS guidelines. One of the most comprehensive was the 2017 American Thoracic Society and European Society of Intensive Care Medicine (ESICM) ARDS Clinical Practice Guidelines.⁵

The ESICM has released updated ARDS guidelines,⁶ and we summarize the guidelines' methods, findings, and implications, together with reflections on next steps.

The ESICM ARDS Clinical Practice Guideline Methodology

The executive leadership of ESICM invited 3 cochairs to select an expert panel and focus on 3 broad areas: ARDS definition, ARDS phenotyping, and respiratory support for the care of patients with ARDS. The cochairs, together with a methodologist, divided respiratory support into 7 domains. The expert panel framed patient-or-population intervention comparison outcome questions within each of the 7 domains and assessed the evidence using GRADE methodology. They also provided an expert narrative review on definition and phenotyping. The panel parsed deliberations to subgroups, but all panelists voted to approve (with at least

GUIDELINE TITLE ESICM Guidelines on Acute Respiratory Distress Syndrome: Definition, Phenotyping and Respiratory Support Strategies

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DEVELOPER European Society of Intensive Care Medicine (ESICM)

TARGET POPULATION Adult patients with or at risk for acute respiratory distress syndrome (ARDS)

MAJOR RECOMMENDATIONS

- For nonintubated patients with acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema or chronic lung disease
 - Use high-flow nasal oxygen (HFNO) vs conventional oxygen therapy to reduce risk of intubation (strong recommendation; moderate level of evidence)
- For intubated patients with ARDS
 - Use low tidal volume ventilation (ie, 4-8 mL/kg predicted body weight) vs larger tidal volumes to reduce mortality (strong recommendation; high level of evidence)
 - Do not use prolonged high-pressure recruitment maneuvers (strong recommendation; moderate level of evidence) or brief high-pressure recruitment maneuvers (weak recommendation; high level of evidence)
- For intubated patients with moderate to severe ARDS
 - Use prone position to reduce mortality (strong recommendation; high level of evidence)
 - Do not routinely use continuous infusions of neuromuscular blockade to reduce mortality (strong recommendation; moderate level of evidence)
 - Refer patients who meet criteria for ECMO (extracorporeal membrane oxygenation) to ECMO centers (strong recommendation; moderate evidence)

80% agreement) all statements made in the document. Consistent with GRADE, the panel organized statements as strong (recommendation) or weak (suggestion), and characterized the supporting evidence as strong, moderate, or weak.

Key Takeaways Regarding These Clinical Practice Guidelines

The most notable feature of the update is the number of changes since 2017, reflecting the large amount of evidence generated in the last 6 years (see Table 3 in the main guidelines document).⁶

Definition

The implementation of any treatment guideline requires practical and robust criteria for timely patient identification. Hence, the panel reviewed the current ARDS definition, but viewed revising the current definition as beyond its purview. By requiring the patient to be ventilated and receiving at least 5 cm H₂O positive end-expiratory pressure (PEEP),⁷ the current definition continues to exclude patients cared for in settings with limited access to mechanical ventilation.⁸ It also complicates the identification and labeling of patients with ARDS for whom strategies like high-flow nasal oxygen (HFNO) might be deployed prior to intubation. The panel labeled these patients as having acute hypoxemic respiratory failure (AHRF) not otherwise explained by preexisting lung disease or heart failure.

How Best to Care for Patients With AHRF Prior to Intubation

The 2017 guideline⁵ made no recommendations regarding support strategies for patients at risk for ARDS not yet receiving invasive mechanical ventilation (IMV). In recent years, however, multiple studies assessed whether noninvasive approaches could safely reduce the need for intubation and IMV. Because IMV can exacerbate lung injury (so-called ventilator-induced lung injury) and is associated with additional iatrogenic and nosocomial complications, the avoidance of IMV may improve patient outcome. Traditionally, patients not meeting criteria for intubation are provided low-flow (<15 L/min) supplemental oxygen. HFNO is a newer technique that is simple to deploy, well tolerated by patients, and provides such high flow (up to 60 L/min) that it creates positive pressure support. Reviewing many trials, the panel concluded that HFNO is superior to routine supplemental oxygen and should be tried prior to intubation. The panel thought there was insufficient evidence to recommend other preintubation strategies, such as noninvasive ventilation via a sealed mask or helmet.

How Best to Provide Respiratory Support to the Intubated Patient With ARDS

Consistent with the 2017 guideline, the panel recommended use of low tidal volume ventilation (setting tidal volumes at 4-8 mL/kg predicted body weight). The pooled estimate across 7 randomized trials did not demonstrate an improvement in mortality, but the panel nonetheless strongly recommended this approach, based on pathophysiological rationale. The panel also made new statements regarding PEEP. Typically, patients start PEEP at 5 cm H₂O, and then PEEP is titrated, together with the percentage of inspired oxygen, to avoid hypoxemia. Although there is a strong physiological rationale for alternative PEEP strategies (eg, using higher PEEP to potentially facilitate alveolar recruitment, or titrating PEEP to individualized measures of lung mechanics and PEEP responsiveness), the panel concluded that there was strong evidence of no benefit with these alternative PEEP titrations and therefore made no recommendations as to their use. Another potential strategy to protect against unwanted alveolar collapse is use of intermittent lung recruitment maneuvers; the panel noted that such strategies remain of unproven benefit and, indeed, could be harmful. Their use is not recommended.

Additional Strategies for Intubated Patients With ARDS and Persistent Moderate to Severe Hypoxemia

The panel continued to recommend use of proning (placing the patient in a prone position for several hours per day to facilitate ven-

tilation-perfusion matching) as the first-line strategy when faced with continued hypoxemia. The pooled estimate of randomized trials of proning did not demonstrate clinical benefit, but the panel based its recommendation for proning on the improved mortality shown in the PROSEVA trial, considered the most robust and relevant trial (28-day mortality: 16% for proning vs 32.8% for supine positioning; absolute mortality benefit for proning: -16.7% [95% CI, -24.4% to -9.0%]).⁹

The panel newly recommended against the routine use of continuous neuromuscular blockade, which was previously argued to reduce patient-ventilator asynchrony, noting inconsistent results across the 2 major trials.^{10,11} Unlike the 2017 statement, the panel made no statement regarding high-frequency oscillation ventilation because this strategy is less commonly used following evidence of no benefit and probable harm. The panel also recommended extracorporeal membrane oxygenation (ECMO), a change from the prior guideline, based largely on the recent EOLIA trial.¹² EOLIA reported lower mortality in patients randomized to ECMO, but the finding was not statistically significant at the 95% confidence level (60-day mortality, 35.4% ECMO vs 45.6% control; absolute mortality benefit for ECMO, -10.1% [95% CI, -22.2% to 2.0%]). However, post hoc bayesian analyses and the panel's pooled estimate both suggested that ECMO reduced mortality.¹³ The panel found no evidence to support extracorporeal CO₂ removal.

COVID-19-Specific Statements

The panel generally considered that most strong recommendations for ARDS not related to COVID likely apply to COVID, though their recommendations were weaker because there was typically less direct evidence. One COVID-specific suggestion was to consider awake proning in eligible patients who are not yet intubated.

Implications and Next Steps**Defining the Patients for Whom the Guideline Applies**

A new definition of ARDS is critically needed, both to guide care of patients in settings with limited access to mechanical ventilation and to aid in the identification of patients for whom strategies like HFNO might be deployed prior to intubation. ARDS is presumably a subset of AHRF, but the clinical relevance and need to define ARDS and AHRF as separate conditions remains a source of ongoing confusion. Development of a new definition will likely require a more structured effort with greater stakeholder representation, akin to that conducted in psychiatry, rheumatology, and other areas of medicine with complex overlapping syndromes.¹⁴

Subdividing Patients Based on Treatment Response

The panel recognized the rising interest in subdividing ARDS into groups of patients who might have discrete subtypes that reflect differential treatment responses. At this point, ARDS subtypes are described retrospectively as possible treatable traits. But it is unclear if any such subtypes represent a true subcategorization of ARDS or rather clusters of disease mechanisms that underpin acute illnesses more broadly, regardless of whether ARDS is present.¹⁵ Future trials may generate robust evidence supporting the administration of subtype-specific treatment. Presumably, once subsets of patients with critical illness are shown to respond differently to therapies, features that characterize these subsets will be incorporated in critical illness syndrome definitions, just as has happened in many

other areas of medicine. In other words, defining and subtyping syndromes are interrelated activities.

Considering COVID-19 a Special Case

The most notable subtype in the current guideline is the division of ARDS as due to COVID or not. While the reasons are understandable (eg, many trials exclusively enrolled patients with COVID), they also highlight some challenges. First, non-COVID ARDS is heterogeneous. Why therefore should COVID be a special case? It is possible that COVID has some relatively unique pulmonary pathology, but a similar argument may be made for other conditions that predispose to ARDS. Second, the severe respiratory failure of COVID may also be heterogeneous. For example, some patients with COVID will have severe secondary bacterial pneumonia, others will have pulmonary manifestations of SARS-CoV-2 thrombotic coagulopathy. Third, SARS-CoV-2 has mutated since 2019, with potential variant-based differences in pulmonary manifestations. These issues are not unique to COVID, but rather further highlight the challenges of predicting treatment effects from trials testing interventions in broad syndromes without a clear understanding of the evolving mechanisms by which interventions work or do not work in individual patients.

Optimizing the Process for Guideline Development

The ESICM practice guideline is a comprehensive and thoughtful document, representing a considerable investment of time and effort. However, in an ideal world, one could imagine some process improvements. First, the large number of changes since 2017 suggests more frequent updates may be useful. Second, the panel only had access to the published literature. However, the generation of evidence statements across multiple clinical trials can be enhanced by access to individual patient data from the individual trials. The World Health Organization used such a process during COVID.^{16,17} Access to individual patient data is particularly valuable when heterogeneity of treatment effect is considered likely, which appears to be the case for ARDS. Third, the panel followed several steps to provide rigor and consistency, such as use of GRADE methodology. However, other aspects, such as the processes for selecting the panel, generating narrative reviews, deciding which questions would be addressed, and summarizing evidence, are less clearly specified, leaving open the possibility that a different panel may have reached different conclusions. For example, for low tidal volume ventilation,

alternative PEEP titration strategies, and prone positioning, the 95% CIs for the pooled estimates were all wide and crossed 1.0, suggesting important differences in mortality (beneficial or harmful) were not ruled out. Yet, the panel strongly recommended some interventions and not others and inconsistently stated the pooled estimates represented strong evidence of no effect. Improvements to the guideline-making processes such as these would require significant funding and infrastructure, beyond the scope of most professional societies, and would likely require multinational government support.

From Guideline Development to Adoption in Practice

The generation of evidence-based treatment guidelines is a necessary but insufficient step to ensuring high adoption of evidence-based practice across all clinical settings. For example, despite longstanding recommendations to use low tidal volume ventilation, it is adopted in less than two-thirds of patients.¹ The optimal adoption of new evidence is a perennial and generic challenge across medicine, but there are particular challenges in the ICU, where care is provided by a large multidisciplinary team. ICU team members engage in profession-specific continuing education, which may be inconsistent across professions; team members rotate or turn over frequently, which challenges institutional memory; and care must be provided 24 hours per day, requiring frequent handovers from shift to shift. Given the rapidly changing evidence regarding the care of these critically ill patients, it is essential to determine optimal methods for knowledge transfer in this setting.

Conclusions

The COVID-19 pandemic showed to the world the devastating consequences of ARDS, a syndrome that remains common and deadly even outside of pandemics. Many studies aimed to find the optimal care for this syndrome, and the latest guidelines are testament to how quickly the evidence base is changing. The new ARDS guidelines also highlight the need to generate more precise effect estimates for many aspects of respiratory support, as well as a need to better define and subtype patients who broadly meet syndrome definitions. Ultimately, the challenge is to ensure that every patient benefits from care provided by a team fully conversant with the latest evidence. To that end, these guidelines are extremely valuable, and we applaud ESICM for supporting this effort.

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