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CONFERENCE REPORTS AND EXPERT PANEL

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

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Abstract

The aim of these guidelines is to update the 2017 clinical practice guideline (CPG) of the European Society of Intensive Care Medicine (ESICM). The scope of this CPG is limited to adult patients and to non-pharmacological respiratory support strategies across different aspects of acute respiratory distress syndrome (ARDS), including ARDS due to coronavirus disease 2019 (COVID-19). These guidelines were formulated by an international panel of clinical experts, one methodologist and patients' representatives on behalf of the ESICM. The review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations. We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence and grade recommendations and the quality of reporting of each study based on the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network guidelines. The CPG addressed

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21 questions and formulates 21 recommendations on the following domains: (1) definition; (2) phenotyping, and respiratory support strategies including (3) high-flow nasal cannula oxygen (HFNO); (4) non-invasive ventilation (NIV); (5) tidal volume setting; (6) positive end-expiratory pressure (PEEP) and recruitment maneuvers (RM); (7) prone positioning; (8) neuromuscular blockade, and (9) extracorporeal life support (ECLS). In addition, the CPG includes expert opinion on clinical practice and identifies the areas of future research.

Keywords: Acute hypoxemic respiratory failure, Acute respiratory distress syndrome, Mechanical ventilation, Extracorporeal membrane oxygenation, Prone position, Non-invasive ventilation, Prognosis, Practice guidelines

Introduction

Acute respiratory distress syndrome (ARDS) is the term applied to a spectrum of conditions with different etiologies which share common clinical-pathological characteristics including: (1) increased permeability of the alveolo-capillary membrane, resulting in inflammatory edema; (2) increased non-aerated lung tissue resulting in higher lung elastance (lower compliance); and (3) increased venous admixture and dead space, which result in hypoxemia and hypercapnia [1]. Over the last 55 years, ARDS definitions have focused primarily on the syndrome's radiological appearance and on the severity of the oxygenation defect (e.g., PaO_2/FiO_2 ratio), which reflect both the original description of the syndrome [2] and its conceptual understanding [1]. The current definition, the definition of Berlin [3], implies that at time of diagnosis the patient receives at least 5 cmH_2O of positive end-expiratory pressure (PEEP). Formally, patients not receiving positive pressure can thus not be considered as suffering from ARDS. Nevertheless, a lot of patients with AHRF, especially when due to bacterial or viral pneumonia or in case of septic shock, have the same disease and are thus also considered in this guideline.

ARDS accounts for ~ 10% of admissions to intensive care unit (ICU) and 23% of ventilated patients, with mortality up to 45% in the severe category [4]. The recognition that patients with ARDS are susceptible to additional lung injury induced by mechanical ventilation (ventilator-induced lung injury, VILI) [5] has led to lung-protective strategies designed to reduce total stress (transpulmonary pressure) and strain (the ratio between tidal volume and functional residual capacity) on the aerated lung tissue [6]. These strategies include lower tidal volume and plateau pressure to protect the 'baby lung' [7]; the use of PEEP and lung recruitment maneuvers (RM) to reduce the amount of non-aerated lung; and ventilation in prone position to increase lung homogeneity, improve ventilation/perfusion ratio and lung/chest wall shape matching, reduce stress and strain, and decrease the risk of VILI [8]. Ventilation in the prone position improves outcomes in patients with moderate-to-severe ARDS [9, 10].

Concomitantly, clinicians and investigators alike have sought to avoid invasive ventilation altogether for patients with early acute hypoxemic respiratory failure (AHRF) using non-invasive respiratory support modalities (e.g., non-invasive ventilation, high-flow nasal oxygen). These therapies seek to improve oxygenation and unload respiratory muscles, thereby reducing inspiratory effort and the risk of patient-self-inflicted lung injury (P-SILI) [11], and allow time for the underlying disease to be treated without the need for sedation and tracheal intubation. For patients with more severe disease, VILI [5] can be theoretically reduced with extracorporeal support techniques which allow partial or total oxygenation and/or carbon dioxide removal and a significant reduction in ventilator mechanical power [12].

The aim of these guidelines is to review and summarize the literature published since the last clinical practice guideline (CPG) of the European Society of Intensive Care Medicine (ESICM) [13] across different aspects of ARDS and AHRF, including ARDS due to coronavirus disease 2019 (COVID-19) in ICU. The scope of this CPG is limited to adult patients and to non-pharmacological respiratory support strategies (except for neuromuscular blockers, which are adjuncts to mechanical ventilation). The document combines a methodologically rigorous evaluation of clinical studies with expert opinion on the respiratory management of patients. This work did not include a cost-effectiveness analysis.

Methods

Topic and panel composition

These guidelines were formulated by an international panel of experts on behalf of the ESICM and address three broad topics within ARDS: (1) definition; (2) phenotyping, and (3) respiratory support strategies. The ESICM Executive Committee selected these three topic areas and nominated three chairpersons (CC, LC, GG) and one methodologist (DP), who arranged the guidelines into nine domains of investigations: (1) definition; (2) phenotyping; (3) high-flow nasal cannula oxygen (HFNO); (4) non-invasive ventilation (NIV); (5) tidal volume setting; (6) PEEP and lung RM; (7) prone positioning; (8) neuromuscular blockade, and (9) extracorporeal life support (ECLS). Each domain was assigned to a group of experts within the panel, and each domain was

coordinated by a 'domain chair'. Panelists were invited to join one or more working groups based on their scientific expertise, geographical representation, and expressed interest. Two additional methodologists and eight patient representatives completed the guideline panel.

Research question selection and literature search

Members of each domain formulated questions according to the Patients or Population- Intervention-Comparison-Outcome (PICO) format. Each PICO question was discussed and agreed with the guideline chairs, methodologists, and the wider panel. For each PICO, a dedicated systematic literature search was performed using the PubMed search engine. For the Definition Domain 1 a systematic review of the literature was not performed and only a discussion was performed by the members on ARDS definition. Phenotypes Domain 2 conducted a systematic review of the literature, summarizing evidence without, however, performing any grading of the evidence. Most studies in this field focused on prognosis in different sub-phenotypes. Few others, investigating the effectiveness of intervention in sub-phenotypes, were meant to generate hypotheses to be verified in future trials more than providing evidence in support of treatments. For both Domains 1 and 2 we preferred a narrative approach over systematic Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments.

Following the literature search, pairs of reviewers from each domain reviewed the titles independently and selected the final list of full-text studies to be included in meta-analysis. The methodologists performed data extraction, synthesis, and risk of bias assessment for individual studies. Details of the meta-analysis procedures are provided in the Supplementary Methods.

Formulation of recommendations and consensus methodology

After reviewing the results of the literature search and meta-analyses, members of each domain formulated statements (recommendations) related to each PICO/narrative question. Recommendations were based on the integration of three main criteria: (1) certainty of evidence (as provided by the methodological assessment); (2) GRADE methodology [8], and (3) expert opinion. Proposed recommendations along with corresponding summaries of evidence were presented and discussed in four online panel-wide meetings which included patient representatives. These meetings were recorded for members who were unable to attend and for accurate reporting of the panel discussion. Following each panel-wide meeting, recommendations were revised based on the feedback received. The finalized recommendations were then sent to each panel member for anonymous online voting. Strong recommendations were phrased as "recommendations," and weak recommendations were phrased as "suggestions." Approval of a recommendation required at least 80% of the panel to be in agreement. Recommendations with less than 80% agreement were reformulated and re-voted until > 80% approval was achieved for all. A detailed description of the methodology is reported in the Supplementary Materials.

Domain 1: ARDS definition

ARDS was first described in 1967 by Ashbaugh and colleagues in 12 patients with new onset hypoxemia refractory to supplemental oxygen, bilateral infiltrates on chest radiograph, and reduced respiratory system compliance. Inflammation, edema, and hyaline membranes were uniformly present in lungs of non-survivors [2]. Subsequently, diagnosis of ARDS evolved from informal pattern recognition to formalized clinical definitions. The Lung Injury Score, proposed in 1988 [14] was supplanted in 1994 by the American-European Consensus Conference (AECC) definition [15], and further updated by an ESICM-sponsored process leading to the 2012 'Berlin Definition' [1, 3]. As part of these 2023 ESICM ARDS Treatment Guidelines, experts from the Definition Domain were charged with highlighting issues that should be addressed in subsequent revisions, based on knowledge accrued in the last decade which may be relevant to the current ARDS definition.

The expert panel discussed expanding the reach of the definition of ARDS and the pros and cons of this expansion. This topic is also important for the application of a definition in resource-poor settings [16]. As an example, the use of HFNO has increased in the past decade, particularly during the COVID-19 pandemic. Proponents suggest that the ARDS definition should be modified to allow patients on HFNO to be eligible for the oxygenation criterion even though they are not being ventilated with PEEP $\geq$ 5 cmH_2O (as required by the Berlin definition). This approach has face validity in many patients with severe hypoxemia, who are treated with high flows and high FiO_2 on HFNO [17]. Some proponents go further to argue that the requirement for PEEP should be removed regardless of oxygen delivery device used, to allow ARDS to be diagnosed in locations without consistent access to HFNO or ventilation. Opponents argue that this approach may dilute severity of illness among patients labeled as ARDS, as it would also capture patients with a better prognosis [18] or affect comparisons among groups. Similarly, the past decade has also seen increased use of the SpO_2/FiO_2 (S/F) ratio rather than the PaO_2/FiO_2 (P/F) ratio as a measure of the degree of hypoxemia [19, 20]. Proponents argue that the S/F

ratio is less invasive and more readily available, noting its use in current randomized controlled trials (RCTs) [21]. The counterargument, however, is that there are inaccuracies in SpO_2 measurements, particularly among patients with darker skin and those in shock and/or with poor distal perfusion. In addition, many patients are treated to keep their SpO_2 in excess of 97%, resulting in an uninformative S/F ratio [22]. Finally, the inclusion of the chest radiograph criterion remains a question given its moderate-to-poor reliability [23, 24] and limited availability in some settings. A recent RCT failed to demonstrate any improvement in chest X-ray interpretation after a standardized ARDS radiograph training exercise [25]. Other approaches to radiography in ARDS that have been debated over the past decade include eliminating the radiographic criterion altogether; allowing unilateral opacities to meet ARDS criteria, as pediatric critical care has done [26]; requiring computed tomography (CT) scanning to meet the full definition (more accurate but less available even in tertiary centers); and allowing lung ultrasound (more available but operating characteristics less well known and requires training in image acquisition) to meet the definition criteria.

The panel also discussed the minimum timeframe for which patients must continue to meet criteria for ARDS. Experts agree that ARDS is not a transient phenomenon, but instead is a syndrome that takes days or weeks to resolve. The prevalence of rapidly improving ARDS (P/F > 300 or extubated within the first 24 h after diagnosis) in six ARDS Network trials was > 10% and increased over time [27]. If the subjects in a trial have a very low risk of the condition that the intervention is hypothesized to prevent (e.g., VILI), the trial will not verify the value of the intervention. These data prompt the question of how long diagnostic criteria must be present before patients can be diagnosed with ARDS. Experts agreed that some minimum period of stabilization and stability prior to diagnosing ARDS is likely appropriate; however, the length of this period remains uncertain. A long stabilization period would increase specificity but prevent early therapeutic interventions. Since oxygenation can be affected by clinical interventions and ventilator settings, experts have considered whether oxygenation failure in ARDS should be judged using standardized ventilator settings, which could identify higher risk patients but may add further feasibility challenges to trial enrollment [28, 29] and may not confer additional clinical advantages.

The expert panel noted the disconnect between the conceptual model of ARDS—a specific type of inflammation and host response to injury [3]—and the lack of measures of inflammation in ARDS definitions. This disconnect is due to insufficient data on operating characteristics or poor feasibility of direct measures of pulmonary inflammation or immune response [1]. While some successes have been documented with the application of sub-phenotypes of ARDS (see Domain 2), much work remains to be done to harmonize a clinically feasible definition with the conceptual pathophysiological model of ARDS. At the same time the panel discussed whether predictive validity for mortality is the best measure of an ARDS definition. Diagnostic accuracy in ARDS is challenging without a universal reference standard. Future work in refining the ARDS definition should carefully consider other facets of validity as well as reliability [30]. At the same time, we need new prospective observational studies to better categorize patients with acute non-cardiogenic hypoxemic respiratory failure, including ARDS, across a broad range of characteristics, including imaging and biomarkers, with the goal of developing more personalized treatments. Until such information becomes available, clinicians may at times wish to use the broader umbrella syndrome of acute hypoxemic respiratory failure when deciding to implement certain therapeutic strategies, particularly those that are not directed against specific ARDS mechanisms.

Domain 2: ARDS phenotyping

This group was charged with identifying key issues relating to phenotyping in ARDS, assessing the current literature to address these questions, and identifying the knowledge gaps to be addressed in future research.

A systematic search was conducted to identify studies satisfying the following criteria: (1) identify a sub-phenotype as per our working definition (see below and as described in the supplement); (2) focus on phenotyping in patients with ARDS; (3) human data; (4) include ≥ 100 patients with ARDS; (5) include sub-phenotypes showing heterogeneity of treatment effect or sub-phenotypes showing differences in patient outcome. Twenty-five papers were included in the final analysis [31–55].

Question 2.1: How do we define an ARDS sub-phenotype?

Based on the currently available literature and consensus within the working group, the following definitions were established:

a. A **phenotype** is a clinically observable set of traits resulting from an interaction of genotype and environmental exposures (i.e., ARDS is a phenotype).
b. A **subgroup** is a subset of patients within a phenotype, which may be defined using any cut-off in a variable. This cut-off can be arbitrary, and frequently patients fall just on either side of it, resulting in patients switching subgroups (e.g., PaO_2/FiO_2 severity classification of ARDS).

c. A **sub-phenotype** is a distinct subgroup (of ARDS patients) that can be reliably discriminated from other subgroups based on a set or pattern of observable or measurable properties. Discrimination is typically based on a data-driven assessment of a multidimensional description of traits. Subphenotypes should also be reproducible in different populations.
d. An **endotype** is a sub-phenotype with distinct functional or pathobiological mechanism, which preferably responds differently to a targeted therapy.

Question 2.2: How do we identify or operationalize an ARDS sub-phenotype?

Accurate classification of the sub-phenotype is critical as exemplified by the results of LIVE trial [38]. The trial randomized patients to either standard lung-protective ventilation or a personalized treatment strategy based on radiological sub-phenotype (focal or diffuse pathology on chest radiograph). Overall, there was no benefit to a personalized treatment strategy; however, misclassification of sub-phenotype resulting in misaligned treatment strategies was common, and the results were "positive" when misclassified patients were excluded. Subphenotype classification in prospective studies likely requires: (1) on-site, real-time testing and rapid results, and (2) operator independence.

Question 2.3: What is the evidence for heterogeneity of treatment effect (predictive enrichment) between sub-phenotypes?

Does sub-phenotyping alter patient response to an anti-inflammatory intervention in ARDS?

In a secondary analysis of the HARP-2 trial [35], patients with the hyper-inflammatory sub-phenotype seemed to benefit from simvastatin, although the interaction term for heterogeneity of treatment effect was not statistically significant. In a secondary analysis of the SAILS trial [36], no heterogeneity of treatment effect was identified for the hypo-inflammatory and hyper-inflammatory sub-phenotypes and treatment with rosuvastatin. In a clustering reanalysis of the SAILS trial, 4 sub-phenotypes were described in which one group ($n=66$) defined by high platelets and low creatinine seemed to benefit from rosuvastatin; however, these sub-phenotypes have not been reproduced in other populations [43].

Does sub-phenotyping alter patient response to PEEP interventions in ARDS?

A secondary analysis of the ALVEOLI trial [31] identified heterogeneity of treatment effect between the hypo-inflammatory and hyper-inflammatory sub-phenotypes and PEEP strategy adopted (higher vs lower PEEP/FiO_2 table). A secondary analysis of the observational LUNG-SAFE study [54] identified a similar pattern, in that patients with the hyper-inflammatory sub-phenotype seemed to benefit from higher PEEP, in contrast to the hypo-inflammatory sub-phenotype. In the LIVE trial described above, a personalized PEEP and prone positioning strategy based on diffuse vs focal radiographic sub-phenotype achieved a reduction in 90-day mortality, when only considering per-protocol treated patients [38]. However, this signal was diluted in the intention to treat analysis due to misclassifications of lung morphology.

Does sub-phenotyping alter patient response to fluid strategies in ARDS?

A secondary analysis of FACTT [33] identified heterogeneity of treatment effect in that patients with the hyper-inflammatory sub-phenotype seemed to benefit from a liberal fluid strategy, in contrast to the hypo-inflammatory sub-phenotype.

Question 2.4: How does sub-phenotyping relate to patient outcome (prognostic enrichment)?

Short term (up to day 90) mortality was found to be different between sub-phenotypes that are based on the following characteristics (see Supplemental Table):

- Systemic inflammatory response gauged by plasma proteins (higher mortality in hyper-inflammatory than in hypo-inflammatory) [31, 34];
- Lung radiographic morphology (higher mortality in non-focal than in focal) [38];
- Recruitability (higher mortality in recruitable than in non-recruitable) [44, 56];
- Clinical features (higher mortality with more organ failure and/or comorbidities and/or acidosis) [47];
- Longitudinal changes in respiratory parameters (higher mortality in upwards trajectory of ventilatory ratio and mechanical power than in steady trajectory) [45]

Question 2.5: What are the research questions related to the use of sub-phenotyping for future trials?

Several research questions remain to be addressed in future studies, particularly regarding: (1) the stability of sub-phenotypes over time, from pre-ARDS through to recovery; (2) whether sub-phenotypes are reproducible across diverse populations; (3) the accuracy and repeatability of a rapid sub-phenotype classification; (4) the pathophysiological pathways that drive the development of sub-phenotypes; (5) the quantification of the attributable mortality of each sub-phenotype; and (6) whether

precision treatment strategy based on sub-phenotypes can improve outcomes after ICU discharge.

Domain 3: High-flow nasal oxygen

Question 3.1: In non-mechanically ventilated patients with acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema or acute exacerbation of chronic obstructive pulmonary disease (COPD), does HFNO compared to conventional oxygen therapy (COT) reduce mortality or intubation?

Background

The effectiveness of COT (i.e., low-flow) delivered via face mask or nasal cannula is limited by low-flow rates (i.e., less than 15 L/min) and lack of humidification of inspired oxygen, which can lead to patient intolerance. HFNO is well tolerated and can deliver heated, humidified oxygen at flow rates up to 60 L/min [57]. At higher flow rates, HFNO can deliver more consistent FiO_2 than COT, decrease anatomical dead space, and provide PEEP up to 3–5 cmH_2O, depending on flow rate and breathing pattern [58]. After the publication of the FLORALI trial in 2015 [59], the use of HFNO in acute hypoxemic respiratory failure increased considerably, which was further augmented during the COVID-19 pandemic.

Summary of the evidence

We evaluated the use of HFNO for patients with AHRF rather than ARDS, given that many patients would not meet the requirement for PEEP of 5 cmH_2O or more using the current Berlin definition. However, most of the patients who progress from HFNO to mechanical ventilation do end up meeting criteria for ARDS. During the COVID-19 pandemic, 93% of patients treated with HFNO who progressed to intubation met criteria for ARDS under the Berlin definition [18]. Given the increasing use of HFNO especially with the COVID-19 pandemic, there is increasing belief that ARDS definition should include those patients with acute hypoxemic respiratory failure on HFNO (see above Domain 1). As such, these PICOs and their recommendation should be applicable to ARDS being managed with HFNO. We excluded trials that included patients with acute cardiogenic pulmonary edema, exacerbation of COPD, acute hypercapnic respiratory failure, or use of HFNO post-extubation. We identified seven RCTs that formed the basis of our recommendations [59–65]. The study by Bouadma and collaborators [65], however, was included only in a sensitivity analysis because of its design and uncertainties in the interpretation of its findings (see Supplementary Materials).

Among 2769 patients included in six trials with a combined 28- or 30-days mortality of 20.5%, there was no statistically significant difference in mortality between HFNO compared to COT (relative risk (RR) 0.95, 95% confidence interval (95% CI) 0.82–1.09). Further, there was no evidence for differences in treatment effect in the subgroups based on immunocompromised or COVID-19 status.

The pooled rate of intubation at 28–30 days among the six analyzed trials was 43%. Meta-analysis identified a significant beneficial effect of HFNO compared to COT in preventing intubation (RR 0.89, 95% CI 0.81–0.97). Individual study estimates of treatment effect for risk of intubation were consistent across most included trials, except for one trial that contributed only 1.6% of weight to the pooled estimate [64]. We did not identify significant differences in intubation rate between HFNO and COT in subgroups of patients based upon immunocompromised state or COVID-19 infection.

Recommendation 3.1

We **recommend** that non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD receive HFNO as compared to conventional oxygen therapy to reduce the risk of intubation
Strong recommendation; moderate level of evidence in favor

We are **unable to make a recommendation** for or against the use of HFNO over conventional oxygen therapy to reduce mortality
No recommendation; high level of evidence of no effect

This recommendation applies also to AHRF from COVID-19
Strong recommendation; low level of evidence in favor for intubation and no recommendation; moderate level of evidence of no effect for mortality, for indirectness.

Expert opinion on clinical application

HFNO was found to be superior to COT in reducing the risk of intubation but not in reducing mortality among patients with AHFR [59–65]. Mechanical ventilation is resource-intensive and is associated with higher need for sedation and immobility, which have been associated with higher rates of complications such as delirium, nosocomial infection, mortality, worse long-term morbidity, including physical and cognitive complications. In addition, input from the patient representatives indicated that most patients would value avoiding intubation if possible. Thus, there may be benefits from preventing intubation, even in the absence of a significant improvement in mortality. HFNO is generally well tolerated by patients and is associated with similar or lower incidence of adverse event rates compared to COT. Therefore, we advocate the use of HFNO compared to COT for patients with AHRF regardless of immunocompromised or COVID-19 status.

Unresolved questions and research gaps

Long-term functional outcome data are missing from randomized controlled trials investigating the use of HFNO in acute respiratory failure. As such, it is unknown whether prevention of intubation can decrease symptoms and long-term functional impairment reported by AHRF survivors. Additionally, it is not clear how long a trial of HFNO should last or whether indices such as respiratory rate - oxygenation (ROX) index or other measures should be utilized to indicate failure of HFNO and need for intubation [66]. Indeed, in some of the trials, patients who failed HFNC had a higher mortality than patients treated with conventional oxygen [59, 67]. It is not clear whether this was due to some delay in intubation or only reflected more severe disease. A future large trial comparing HFNO to COT powered for mortality may be difficult to conduct and interpret due to cross-overs, given the increased adoption of HFNO use after the COVID-19 pandemic. Future clinical trials should examine how HFNO can best be delivered to maximize benefit would guide clinicians on how to use and discontinue HFNO in AHRF. In addition, long-term outcomes (e.g. cognitive, functional, and quality of life) need to be incorporated to determine the long-term impact of HFNO.

Question 3.2: In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD, does HFNO compared to non-invasive ventilation reduce mortality or intubation?

Background

Non-invasive ventilation improves outcomes and has been recommended for patients with acute hypercapnic respiratory failure from acute exacerbations of COPD or patients with cardiogenic pulmonary edema [68]. In most prior guidelines, no specific recommendation has been made for the use of NIV for patients with AHRF from other etiologies due to insufficient evidence. Additionally, concerns have been raised about tolerance of NIV, ability to clear secretions, worsening lung injury from large tidal volumes on inspiratory pressure support (especially given the high inspiratory demand seen in AHRF), and possible harm resulting from delaying intubation.

Early in the COVID-19 pandemic, NIV was frequently used (up to 47% of ICU patients in Wuhan) [69]. Initial clinical practice guidelines from the National Institute of Health and Surviving Sepsis Campaign provided a weak recommendation in favor of HFNO compared to NIV for the treatment of COVID-19 pneumonia, and for use of NIV if HFNO was not available or had failed [70, 71]. This recommendation was based upon data extrapolated from non-COVID-19 related AHRF, and studies in patients with Middle East Respiratory Syndrome (MERS) that showed a high rate of intolerance and failure of NIV, with high mortality among those who failed NIV [59, 72]. In addition, concerns existed regarding the potential for increased aerosol transmission of the virus with NIV [73].

Summary of the evidence

We focused on patients with AHRF and excluded trials that enrolled patients with acute cardiogenic pulmonary edema, exacerbation of COPD, acute hypercapnic respiratory failure, or mechanically ventilated patients who used NIV after extubation or to facilitate extubation. We identified four RCTs that reported mortality [59, 74–76], including two RCTs that enrolled COVID-19 patients. Among other trials, we excluded a three-arm trial where the intervention in the common control arm was COT and there was no direct randomization of patients to HFNO vs NIV [60].

Of the two RCTs enrolling non-COVID-19 patients, one included immunocompromised patients [76], the other non-immunocompromised patients [59]. We did not include one trial in the pooled analysis for intubation as only 7-day intubation outcome was reported [74]. Meta-analysis did not identify a significant difference comparing HFNO to NIV for either mortality (RR 0.75 95% CI 0.51–1.11) or intubation (RR 1.09 95% CI 0.71–1.68).

Meta-analysis did not identify significant differences in mortality in HFNO vs NIV within subgroups of immunocompromised or COVID-19 patients. Regarding intubation, in the trial by Grieco et al. HFNO was associated with a significant increase in the rate of intubation at 28 days compared to NIV in patients with COVID-19 (RR 1.72 95% CI 1.06–2.79) [75]. However, the trial by Nair et al. (not included in the primary meta-analysis because it reported intubation rate only up to day 7) [74] showed a statistically significant effect in the opposite direction (a 19% absolute risk reduction in the HFNO arm).

Recommendation 3.2

We are **unable to make a recommendation** for or against the use of HFNO compared to continuous positive airway pressure (CPAP)/NIV to reduce intubation or mortality in the treatment of unselected patients with acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema or acute exacerbation of COPD.
No recommendation; moderate level of evidence for mortality, low level of evidence for intubation, not in favor nor against.

We **suggest** that CPAP/NIV can be considered instead of HFNO for the treatment of AHRF due to COVID-19 to reduce the risk of intubation (*weak recommendation, high level of evidence*), but **no recommendation** can be made for whether CPAP/NIV can decrease mortality compared to HFNO in COVID-19.
No recommendation; high level of evidence of no effect.

Expert opinion on clinical application

The panel suggest that clinicians managing AHRF patients with CPAP/NIV should have appropriate experience and expertise, and patients should have appropriate monitoring (e.g. clinical signs of respiratory distress, breathing pattern—tidal volume (Vt) and respiratory rate—and inspiratory effort) to avert P-SILI. Additionally, clinicians should consider how well individual patients may tolerate NIV and the risk of adverse events.

Unresolved questions and research gaps

There is an urgent need for RCTs that compare HFNO to NIV/CPAP for patients with AHRF using important endpoints such as mortality, intubation, and total duration of mechanical ventilation. Long-term patient follow-up and cognitive and function outcomes assessments would enable determination of whether observed differences in short-term outcomes (e.g., intubation) are associated with long-term impairment in survivors.

Domain 4: CPAP/NIV

Question 4.1: In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema, obesity hypoventilation or acute exacerbation of COPD, does CPAP/NIV, as compared to conventional oxygen therapy reduce mortality or intubation?

Background

While hypoxemia and ventilatory dysfunction in patients with AHRF can be addressed with different non-invasive modalities, with differential effects on end-expiratory alveolar pressure and/or inspiratory effort [77], a concern regarding the use of CPAP/NIV is the potential delay in intubation, which might lead to worse outcomes, including increased mortality. Moreover, high transpulmonary pressures can be observed during NIV (due to either high level of support, strong inspiratory effort, or both) potentially leading to P-SILI, analogous to the ventilator-induced lung injury described during invasive controlled ventilation [11]. The specific physiological effects need to be considered when selecting non-invasive strategies for AHRF. Of note, patients with AHRF not receiving positive pressure cannot be classified as ARDS patients using the current Berlin definition as they do not receive at least 5 cmH_2O of PEEP. As previously mentioned, the ARDS definition may need include these patients who have the same disease from a pathophysiological point of view.

Summary of the evidence

We included ten randomized controlled trials which enrolled patients with non-COVID-19 and COVID-19 AHRF, immunocompetent and immunocompromised [59, 60, 78–85]. Six of these studies investigated the effect of NIV compared to COT [59, 81–85], while four compared CPAP vs. COT [60, 78–80]. One trial with CPAP performed in COVID-19 patients randomized patients either to CPAP or to HFNO vs. COT [60]. For the main analysis, we combined all ten studies, without any subgroup distinctions. We hypothesized that NIV and CPAP were similarly effective; hence, we included studies adopting either intervention for purposes of the meta-analysis. When the intervention was NIV, the type of ventilator (ICU, dedicated to NIV or home ventilator) and the type of the circuit used (single or double limb circuit) were assumed not to affect outcomes.

We performed a primary meta-analysis focused on five RCTs with low risk of bias and individual moderate to high quality [59, 60, 78, 81, 82]. However, the risk of bias increased when the outcome was intubation, because of lack of blinding. This meta-analysis did not identify a significant effect of CPAP/NIV compared to COT on intubation (RR 0.89, 95% CI 0.77–1.03) or hospital mortality (RR 0.89, 95% CI 0.75–1.05). A secondary analysis was performed including all studies independently from the risk of bias assessment and quality (see Supplementary Materials). This secondary analysis showed a protective effect in terms of intubation rate and mortality. However, according to our predefined statistical planned, when the results of the primary and secondary analysis were inconsistent, the primary analysis prevailed.

Only one study was available in COVID-19 patients [60] which reported a lower intubation rate with CPAP compared to conventional oxygen therapy but no difference in mortality.

Recommendation 4.1

We are **unable to make a recommendation** for or against the use of CPAP/NIV compared to conventional oxygen therapy for the treatment of AHRF (not related to cardiogenic pulmonary edema or acute exacerbation of COPD) to reduce mortality or to prevent intubation.
No recommendation; high level of evidence for mortality, moderate level of evidence for intubation.

We **suggest** the use of CPAP over conventional oxygen therapy to reduce the risk of intubation in patients with acute hypoxemic respiratory failure due to COVID-19.
Weak recommendation; low level of evidence in favor.

In this population, we are **unable to make a recommendation** for or against the use of CPAP over conventional oxygen therapy to reduce mortality.
No recommendation; moderate level of evidence of no effect.

Unresolved questions and research gaps

Analysis of available scientific evidence does not allow conclusions regarding the use of CPAP/NIV over COT to prevent intubation or to reduce mortality in patients with non-COVID-19 AHRF. In the panel's view, it is advisable that future research should better characterize patients at inclusion to identify optimal indications for CPAP/NIV in the management of acute hypoxemic respiratory failure. Given recent physiological evidence [86], the panel suggests focusing on the potential role of high vs. low respiratory drive in determining suitability for NIV and likelihood of success.

Question 4.2: In patients being treated with CPAP/NIV for AHRF, does the use of a helmet interface as compared to face mask reduce intubation or mortality?

Background

NIV in the acute care setting is usually applied via a face mask interface, which can be poorly tolerated resulting in a risk for NIV failure. Helmet is an alternative interface to deliver NIV. Several studies reported that NIV via helmet was well tolerated and reduced skin pressure injuries [87, 88]. Managing patient-ventilator synchrony can, however, be challenging during helmet NIV [89, 90], and specific expertise is needed to optimize ventilatory settings.

Summary of the evidence

Only one small, single-center RCT was identified [91]. Eighty-three patients with hypoxemic respiratory failure requiring NIV were randomized to either face mask or helmet interface. There was a 22.3% mortality reduction (95% CI −41.1 to −1) and a 43.4% reduction of intubation rate (95% CI −59.5 to −22.5) with the helmet. A second publication was a follow-up study of the same dataset, focused on functional outcomes [92]. Although the study had only moderate limitations, the panel had concerns given (a) small sample size and early termination for efficacy might cause an overestimation of the treatment effect, and (b) single-center trial might have issues related to external validity. The panel considered this study as hypothesis-generating rather than conclusive evidence of helmet superiority.

Recommendation 4.2

We are **unable to make a recommendation** for or against the use of helmet interface for CPAP/NIV as compared to face mask to prevent intubation or reduce mortality in patients with acute hypoxemic respiratory failure.
No recommendation; very low level of evidence in favor.

Unresolved questions and research gaps

Additional studies comparing helmet and facemask interface are needed before being able to recommend one of these two interfaces compared to the other.

Question 4.3: In patients with AHRF, does NIV as compared to CPAP reduce mortality or intubation?

Background

NIV can generate high transpulmonary pressure when respiratory drive and effort are high. The application of additional positive pressure assistance during inspiration could lead to higher transpulmonary pressures and total stress applied to the lung, particularly when respiratory drive is high. CPAP may thus benefit patients with acute hypoxemic respiratory failure, possibly lowering the swings in transpulmonary pressure compared to NIV.

Summary of the evidence

We found no randomized study that addressed this PICO question and were thus unable to make a recommendation for or against the use of NIV compared to CPAP for the treatment of ARDS.

Recommendation 4.3

We are **unable to make a recommendation** for or against the use of NIV compared to CPAP for the treatment of AHRF.
No recommendation; no evidence.

Expert opinion on clinical application

Conceptually, the use of CPAP in case of acute hypoxemic respiratory failure is of interest but there are no data available comparing this strategy with NIV.

Unresolved questions and research gaps

Randomized studies are needed to assess whether NIV as compared to CPAP reduces the risk of intubation or decreases mortality.

Domain 5: Low tidal volume ventilation

Question 5.1: In adult patients ARDS and COVID-19-related ARDS, does low tidal volume ventilation alone compared with more traditional approaches to ventilation decrease mortality?

Background

In the early 1960s, researchers and clinicians showed that mechanical ventilation with small Vt caused gradual loss of lung volume with hypoxemia due to right-to-left shunting through regions with poor ventilation. Consequently, use of large tidal volumes of 12–15 mL/kg body

weight was recommended [93]. Recognition of a number of physiological concepts changed this approach and led to the current era of lung-protective ventilation using small Vt: (i) hypercapnia and respiratory acidosis are well tolerated if the patient is well oxygenated, (ii) mechanical ventilation that allows for derecruitment and recruitment of lung units and/or over-distension of lung units associated with high transpulmonary pressures can worsen existing lung injury or may lead to de novo lung injury, and (iii) the effective pulmonary gas volume in patients with ARDS is decreased (baby lung) and thus ventilation with even 'normal Vt' can lead to over-distension and VILI. A corollary of this latter concept is that in patients with severe ARDS, regional lung over-distension can occur even if these patients are ventilated with small tidal volumes [94]. The recognition of VILI lead to the concept of "protective ventilation" as many of the pathophysiological consequences of VILI mimic those of ARDS. This development heralded current use of low Vt ventilation strategies with appropriate levels of PEEP to limit lung distention and atelectrauma.

Use of ventilation strategies with low Vt has been shown in animal and human studies to decrease VILI. In the clinical setting, low Vt ventilation is implemented by delivering tidal volumes in the range of 4–8 mL/kg predicted body weight (PBW)], without aiming for optimal gas exchange, but accepting gas exchange within safety parameters. Traditionally used approaches to invasive mechanical ventilation have not prioritized limiting VILI but have focused on normalizing arterial blood gases.

Summary of the evidence

We identified seven RCTs, that met our inclusion criteria [28, 95–100], and constituted the basis of these recommendations.

ARDS was variably defined in the included trials. Whereas one trial included patients with a Lung Injury Score (LIS) ≥ 2.5 and a risk factor for ARDS [96], another trial included patients with a LIS > 2.5 for < 72 h, bilateral infiltrates, and at least one organ system failure [95]. Other trials included patients based on a PaO_2/FiO_2 ratio ≤ 150 mmHg with infiltrates in at least 3 out of 4 quadrants on chest radiograph and a risk factor for ARDS [100], $PaO_2/FiO_2 \leq 200$ mmHg with bilateral infiltrates [98], $PaO_2/FiO_2 \leq 200$ mmHg on PEEP of 5 cmH_2O with Vt 5 mL/kg for 24 h that persisted for at least 24 h [28], $PaO_2/FiO_2 < 250$ mmHg on PEEP of 5 cmH_2O with a risk factor for ARDS [97], or $PaO_2/FiO_2 < 300$ mmHg with bilateral infiltrates [99].

The target Vt and airway pressure limits in the intervention and control arms of the included trials were variably defined (see Table 1). Importantly, five trials were stopped early [28, 95, 96, 98, 99]. No randomized trials specifically compared these ventilator approaches in patients with COVID-19.

We performed a primary analysis based on studies with moderate to high quality of evidence according to the GRADE method, and a secondary analysis including all the studies.

The primary analysis concerning mortality included three trials [95, 97, 99] and found no evidence of difference in mortality, comparing low Vt strategies to high Vt strategies (RR 0.96 95% CI 0.72–1.28, p value for effect 0.768). The analysis of heterogeneity using the I^2 measure was inconclusive with an estimate of 61% but substantial imprecision (95% CI ranging between 0 and 89%, Cochran's Q test p value $= 0.08$).

The secondary analysis was consistent with the primary analysis with RR 0.82 (95% CI 0.66–1.02) p value for effect 0.069. The analysis of heterogeneity bore inconclusive results because of its imprecision, with $I^2 = 47\%$, 95% CI ranging between 0 and 78%, and the Cochran's Q test p value $= 0.08$).

Not statistically differences were found investigating ventilator-free days and barotrauma in those trials that provided this information (Supplementary Materials).

Although the mortality summary estimate did not achieve statistical significance, in developing our

Table 1 Summary of studies comparing low vs high tidal volume ventilation

	Vt (ml/kg)		Paw Limit (cmH_2O)		Notes
	Interventional Arm	Control Arm	Interventional Arm	Control Arm	
Villar et al. [28]	5–8 PBW	9–11 PBW	PIP 35–40	PIP < 35–40	
Brochard et al. [95]	6–10 ABW	10–15 ABW	Pplat ≤ 25–30	PIP ≤ 60	
Amato et al. [96]	< 6 ABW	12 ABW	PIP < 40 and ΔP < 20	–	RM allowed – Explicit sedation protocol
Stewart et al. [97]	≤ 8 IBW	10–15 IBW	PIP ≤ 30	PIP ≤ 50	
Brower et al. [98]	5–8 PBW	10–12 PBW	Pplat < 30	Pplat < 45–55	
ARDS Net [99]	4–8 PBW	12 PBW	Pplat ≤ 30	Pplat ≤ 50	PP allowed – Explicit weaning protocol
Orme et al. [100]	4–8 PBW	10–15 PBW	Pplat < 40	Pplat < 70	Explicit sedation and weaning protocol

Vt Tidal Volume, *Paw* Airway Pressure, *PBW* Predicted Body Weight, *ABW* Adjusted Body Weight, *PIP* Peak airway pressure, *Pplat* Plateu airway pressure, *ΔP* Driving Pressure, *RM* Recruitment Manouver, *PP* Prone Positioning

recommendation statements, we considered the extremely strong physiologic rationale underpinning the use of low Vt ventilation based on animal and human studies. We downgraded the evidence for one trial that was not published in full [100]. We also downgraded the evidence for two trials that used an explicit protocol to keep PEEP in the intervention arm 2 cmH_2O above the lower inflection point of the pressure–volume curve [28, 96] or at 13 cmH_2O in one trial [28] and permitted the use of RM [96]. Both trials were small, reported few death events, and stopped early for benefit [28, 96]. In developing this recommendation, we also considered that no new trials have published in this area since 2006, tidal volumes were variably calculated using adjusted body weight (ABW), ideal body weight (IBW) and predicted body weight (PBW), and that different gradients were achieved between study arms among the included trials. We also acknowledged that low Vt ventilation strategies may require increased sedation and/or paralysis; these effects, along with those related to permissive hypercapnia, were not explicitly evaluated.

In the absence of evidence directly related to use of the alternative approaches in COVID-19 patients, we downgraded the recommendation due to indirectness of evidence. However, there is no reason to expect that the underlying physiological rationale which supports the use of low tidal volumes should be different for COVID-19 vs. non-COVID-19 ARDS. In developing this recommendation, we considered the balance between patients' values and preferences, desirable and undesirable effects, resource use, acceptability to involved stakeholders, feasibility, and equity.

Recommendation 5.1

We **recommend** the use of low tidal volume ventilation strategies (i.e., 4–8 ml/kg PBW), compared to larger tidal volumes (traditionally used to normalize blood gases), to reduce mortality in patients with ARDS not due to COVID-19.
Strong recommendation based on expert opinion despite lack of statistical significance; high level of evidence.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence for indirectness.

Expert opinion on clinical application

When considering the RCTs, it is important to underscore that Vt was reduced when airway pressure limits (as specified by protocols for the intervention and control arms of each individual trial) were reached. It is also very important to highlight that the Vt used in the control arms can no longer be considered as "conventional", and that no further trials have been conducted in this area for well over a decade. Moreover, it is unlikely that other RCTs will be conducted in the future given a general lack of equipoise in the field regarding this question. At present, the current approach to support patients with ARDS includes limiting Vt to 4–8 mL/kg PBW and maintaining plateau airway pressure (Pplat) < 30 cmH_2O. Although some investigators use the terms IBW and PBW interchangeably, Vt should be measured and adjusted using PBW.

Similarly, it is unlikely that an RCT of low Vt ventilation in COVID-19 related ARDS will be conducted. Although patients with COVID-19 were not included in the RCTs which form the basis of these recommendations, there is biological plausibility for the use of low Vt ventilation in these patients since the underlying respiratory system mechanics are similar [101], and the physiologic mechanisms that underpin the use of low Vt ventilation in non-COVID-19 ARDS are similar. However, the rate of serious and prolonged multidimensional disability, particularly in patients with COVID-19, may be important and may be further exacerbated by the need for prolonged deep sedation with or without paralysis.

Unresolved questions and research gaps

Future studies are needed to evaluate the merits of additional lung-protective strategies (e.g., limited driving pressure or plateau pressure, elastance normalized to PBW, appropriate levels of PEEP) and personalized ventilator targets, particularly the trade-off between tidal volume and respiratory rate to control the overall intensity of mechanical ventilation [102] balanced by the risks of very low tidal volumes (e.g., sedation, dyssynchrony etc.) in patients with lower lung elastance. Long-term multidimensional outcomes for patients and families should be included, and the views of patients and caregivers should be central to determining future research questions and outcomes.

The key research questions to be addressed in future trials include investigation of: (1) the optimal manner to assess whether a given ventilator strategy is likely to worsen VILI, (2) the manner in which we determine optimal Vt (e.g., based on PBW, on driving pressure, or an alternative approach), (3) personalized lung-protective ventilatory strategies based on the physiology of individual patients, and (4) other approaches to remove $PaCO_2$ if the current ventilator strategy is highly likely to worsen VILI.

Domain 6: PEEP and recruitment maneuvers

Question 6.1: In patients with ARDS undergoing invasive mechanical ventilation, does *routine* PEEP titration using a higher PEEP/FiO_2 strategy compared to a lower PEEP/FiO_2 strategy reduce mortality?

Background

In patients with ARDS, surfactant dysfunction, effects of gravity on the edematous lung, and heterogeneous injury

predispose to regional lung derecruitment with alveolar collapse and small airways closure [103]. The resulting mechanical heterogeneity of the lung, with regional differences in alveolar compliance and distension, is thought to be an important driver of ventilation-induced lung injury in ARDS [104, 105]. Positive end-expiratory pressure may offset these forces, promoting lung recruitment and attenuating mechanical heterogeneity. PEEP is also routinely applied to facilitate adequate oxygenation. Yet, excessive PEEP can exacerbate over-distension, potentially predisposing to hyperinflation lung injury and hemodynamic compromise. The following analyses evaluate randomized clinical trials for effects of various PEEP strategies on mortality, ventilator-free days, barotrauma, and hemodynamic compromise.

Summary of the evidence

Three multi-center randomized clinical trials were identified that compared a higher versus lower PEEP/FiO_2 strategy: ALVEOLI [106], LOVS [107], and EXPRESS [108]. ALVEOLI ($n=549$) and LOVS ($n=983$) each evaluated higher versus lower PEEP/FiO_2 titration tables, which specified allowable combinations of PEEP and FiO_2 with instructions to target the lowest allowed combination. The EXPRESS trial ($n=767$) compared PEEP titrated to achieve a plateau pressure of 28–30 cmH_2O (herein identified as the higher-PEEP strategy) versus a minimal distension strategy with PEEP adjusted between 5 and 9 cmH_2O (herein identified as the lower PEEP strategy). Four endpoints were considered in our evidence synthesis: efficacy endpoints (mortality and ventilator-free days), and safety endpoints (barotrauma and hemodynamic instability).

The primary outcome for all three trials was some formulation of mortality, which was not significantly different in any of the three trials nor in the meta-analysis (pooled risk ratio for hospital mortality 0.93; 95% CI 0.83–1.04). Ventilator-free days (VFD) was not pooled since it was only being reported in two trials, one using medians and the other mean values. VFD was not significantly different in ALVEOLI. Though VFD was not reported in LOVS, duration of mechanical ventilation among survivors was not significantly different. In EXPRESS, the higher-PEEP group had significantly more VFD than the lower PEEP group. Incidence of barotrauma did not differ significantly in any of the three trials nor in the meta-analysis (pooled RR 1.17; 95% CI 0.90–1.52). Hemodynamic instability was not meta-analyzed due to reporting differences among trials. In ALVEOLI, hemodynamic instability was not reported directly in the primary publication. In LOVS, hemodynamics was reported as days of vasopressor use and number of vasopressors per day in use, and were comparable between groups. In EXPRESS, significantly more patients in the higher-PEEP group required fluid loading during the first 72 h (75.3 vs. 66.8%; $p=0.01$), but there was no significant difference in patients requiring vasopressor therapy.

Recommendation 6.1

We are **unable to make a recommendation** for or against routine PEEP titration with a higher PEEP/FiO_2 strategy versus a lower PEEP/FiO_2 strategy to reduce mortality in patients with ARDS.
No recommendation; high level of evidence of no effect.

This statement applies also to ARDS from COVID-19.
No recommendation; moderate level of evidence of no effect for indirectness.

Question 6.2: In patients with ARDS undergoing invasive mechanical ventilation, does *routine* PEEP titration based principally on respiratory mechanics compared to PEEP titration based principally on a standardized PEEP/FiO_2 table reduce mortality?

Summary of the evidence

Four randomized clinical trials were identified that compared a mechanics-based PEEP strategy to a standardized PEEP/FiO_2 table: EPVent [109], EPVent-2 [110], Pintado et al. [111], and ART [112]. EPVent ($n=61$) was a single-center trial that compared PEEP titrated with an end-expiratory transpulmonary pressure (PL)/FiO_2 table versus a low PEEP/FiO_2 table. EPVent-2 ($n=200$) was a multi-center trial that compared PEEP titrated with a PL/FiO_2 table versus a high PEEP/FiO_2 table. In EPVent and EPVent-2, transpulmonary pressure was calculated as airway minus pleural pressure, the latter estimated with esophageal manometry. Pintado et al. ($n=70$) was a single-center trial that compared PEEP titrated to achieve highest respiratory compliance (i.e., lowest driving pressure, defined as plateau pressure minus total PEEP) versus a low PEEP/FiO_2 table. ART was a multi-center trial ($n=1010$) that compared PEEP titrated to 2 cmH_2O above that which achieved highest respiratory compliance versus a low PEEP/FiO_2 table. Notably, in ART, patients assigned to the compliance-guided PEEP strategy also underwent a prolonged high-pressure recruitment maneuver of several minutes duration prior to selecting PEEP, which was thought to directly cause cardiac arrest in at least three trial participants.

Mortality was not statistically significant in the EPVent, EPVent-2, or Pintado et al. trials. However, in ART, mortality was significantly higher in the mechanics-based group (RR 1.12; 95% CI 1.00–1.26). The pooled mortality in the meta-analysis was not significant with a mechanics-based PEEP strategy versus a PEEP/FiO_2 table (pooled RR 0.85; 95% CI 0.57–1.29).

Barotrauma did not differ between groups in EPVent, EPVent-2, or Pintado et al. However, in ART, the incidence of barotrauma was significantly greater in the mechanics-based PEEP group (RR 3.56; 95% CI 1.64–7.73). In pooled analysis, there was no significant difference in barotrauma incidence (pooled RR 1.76, 95% CI 0.76–4.06).

The results of ventilator-free days analyses were inconclusive. The ART trial showed a statistically significant one-day reduction of VFDs, a finding that was not confirmed by EPVent-2. Our secondary analysis based on the meta-analysis of those studies using medians also provided a statistically non-significant result (Supplementary Materials).

Hemodynamic instability was not meta-analyzed due to reporting differences among trials. EPVent did not report measures of hemodynamic instability. In EPVent2, shock-free days did not differ significantly between groups. In the trial by Pintado et al., the mechanics-based PEEP group had significantly less hemodynamic instability (hemodynamic failure-free days, defined as cardiovascular sequential organ failure assessment score > 2). By contrast, in ART, the mechanics-based PEEP group had significantly more hemodynamic instability (need to initiate or increase vasopressor or mean arterial pressure < 65 mmHg in the first hour).

Recommendation 6.2

We are **unable to make a recommendation** for or against PEEP titration guided principally by respiratory mechanics, compared to PEEP titration based principally on PEEP/FiO_2 strategy, to reduce mortality in patients with ARDS.
No recommendation; high level of evidence of no effect.

This statement applies also to ARDS from COVID-19.
No recommendation; moderate level of evidence for indirectness.

Expert opinion on clinical application: PEEP titration in ARDS

PEEP titration is a potentially important determinant of patient outcomes in ARDS and one for which the optimal strategy remains to be defined. Trials included in the meta-analysis demonstrated both potential for benefit and harm from studied PEEP titration protocols. While some level of PEEP is thought necessary to prevent progressive derecruitment, what constitutes ideal PEEP to attenuate lung injury and avoid hyperinflation is unknown. In patients with more severe hypoxemia, previous meta-analyses showed potential survival benefit in favor of higher-PEEP levels [113, 114]. However, excessive PEEP unequivocally can cause barotrauma and hemodynamic instability (prompting additional fluid resuscitation or vasopressor escalation, with untoward consequences), though what constitutes "excessive PEEP" is not well defined.

Unresolved questions and research gaps: PEEP titration in ARDS

Between-patient differences in severity and pattern of lung injury, lung and chest wall mechanics, tidal volume, positioning, spontaneous breathing effort, cardiac function, intra-vascular volume, and vascular tone all may contribute to variable effects of PEEP. The individual effect of different levels of PEEP may require studies incorporating a recruitability test pre-randomization to test the effect of PEEP in patients with higher potential for lung recruitment. Also, the hemodynamic cost of higher PEEP including the effects on the total volume of fluids administrated needs further data. Similarly, the use of esophageal pressure-guided PEEP and distending pressure will require further studies to balance dependent lung recruitment while limiting overall lung distension and stress and strain of the non-dependent lung. In the absence of these data how best to individualize PEEP in clinical practice remains unclear. Finally, the interactions between radiological distribution of opacities, recruitability, positioning and PEEP levels need to be elucidated.

Question 6.3: In patients with ARDS undergoing invasive mechanical ventilation, does use of prolonged high-pressure recruitment maneuvers, compared to not using prolonged high-pressure RMs, reduce mortality?

Background

Ventilator recruitment maneuvers, broadly defined, consist of a temporary increase in airway and transpulmonary pressure, to values higher than encountered during tidal ventilation, for the goal of promoting re-aeration of previously gasless regions, i.e., lung recruitment [115]. Because the pressure required to open collapsed lung units generally exceeds closing pressure [116–118], the transient pressure increase with an RM theoretically could be sufficient to achieve a durable increase in end-expiratory lung volume after the RM is completed. The resulting increase in end-expiratory lung volume with an RM may improve gas exchange, homogenize alveolar distension, and decrease lung stress and strain [105, 119], though occurrence and durability of these effects are variable [115, 119]. As a high-pressure maneuver, RMs also may risk complications related to over-distension, including barotrauma, reduced venous return, increase in pulmonary vascular resistance, right ventricular failure—leading to hemodynamic collapse. Several potential strategies for performing RMs have been described and differ by duration, pressure target(s), frequency, and ventilator maneuver.

Pathophysiological considerations

The pre-requisite for RMs to be effective is the prevalence of collapsed but otherwise functional pulmonary units, i.e. units which are "empty" and gasless due to external compressive forces and/or complete gas reabsorption. Recruitment, however, is an umbrella term that includes several realities with different conceptual definitions. Indeed, recruitment has been defined as:

1. Re-aeration of previously gasless pulmonary units (CT scan) [120];
2. Re-aeration of previously gasless and poorly aerated pulmonary units (CT scan) [121];
3. Difference between expected respiratory compliance vs measured after PEEP increased (double pressure–volume, P–V curves) [122];
4. Modifications of different lung ultrasound score (LUS) entities, assessed by a semi-quantitative score [123].

These methods provide largely different recruitment estimates, particularly the imaging-based methods vs. the P-V curve-based method [124]. However, whatever method is used, the common purpose is to achieve open stability of collapsed alveolar units and quantify the resulting anatomical or functional change. PEEP just maintains what has already been opened by a higher opening pressure. The pressures necessary to open the pulmonary units have been reported in few studies in humans with ARDS [116, 117]. The reported opening pressures, as measured by CT scans, have median values between 20 and 30 cmH_2O and range from 10 to 50 cmH_2O, showing a near Gaussian distribution. However, only a small percentage of pulmonary units (about 10%) open pressures greater than 45 cmH_2O—suggesting limited functional gains in applying pressures above 45 cmH_2O; such high pressures have a hemodynamic price, often paid with large amounts of fluids and with additional cardiovascular stress, morbidity and mortality. The median of closing pressures is around 10 cmH_2O, but collapse of pulmonary units is already observed at pressures that may exceed 20-25 cmH_2O [125, 126].

These observations lead to the following considerations:

1. If the plateau pressure is maintained at 30 cmH_2O, a portion of the pulmonary units opened during recruitment maneuvers at pressures higher than the plateau pressure will unavoidably collapse again. This process is associated with deterioration in gas exchange and possible atelectrauma until their collapse is fully established. To keep the lung fully open after recruitment at a pressure of 45 cmH_2O, PEEP values greater than 20–25 cmH_2O are necessary[125, 126].
2. During ultra-protective lung ventilation, a Pplat lower than 30 cmH_2O may encourage progressive lung collapse of the units previously opened by RM performed at pressures greater than 30 cmH_2O.
3. In physiological studies, intermittent 'sighs' have been shown to counteract the lung collapse occurring in lung-protective strategies [127].

All the above considerations and numeric indications refer to the whole respiratory system. A more exact approach would require the partitioning of lung mechanics (i.e., quantify the relative contribution of the chest wall), as the same recruitment airway pressure may have a different effect, depending on the chest wall elastance.

The analysis evaluated randomized clinical trials that assigned patients to undergo an RM versus no RM for their effects on mortality, ventilator-free days, barotrauma, and hemodynamic instability.

Summary of the evidence

A prolonged high-pressure RM was defined as a strategy intended to facilitate lung recruitment in which airway pressure of ≥ 35 cmH_2O was maintained for at least one minute. Five trials were included which evaluated the effects of a prolonged high-pressure RM, versus no such maneuver, on hospital mortality. Hodgson et al. in 2011 ($n=20$) [128] and in 2019 (PHARLAP trial, $n=115$) [129] evaluated a prolonged "staircase" RM in which PEEP was set to 20, 30, and then 40 cmH_2O for 2 min each, followed by a decremental PEEP titration to 15 cmH_2O or until desaturation; the comparison group received no RM and a low PEEP/FiO_2 strategy. Kung et al. ($n=120$) [130] evaluated an RM in which PEEP was set to 35 cmH_2O for two minutes followed by decremental PEEP titration until maximum compliance was identified; the comparison group received no RM and a low PEEP/FiO_2 strategy. Chung et al. ($n=24$) [131] evaluated an RM consisting of raising PEEP from 10 to 40 cmH_2O in increments of 5 cmH_2O, with 40 seconds at each recruitment, followed by a decremental PEEP titration; the comparison group received no RM. The ART trial ($n=1010$) [112] initially evaluated a "staircase" RM in which PEEP was set to 25 cmH_2O for one minute, 35 cmH_2O for one minute, and then 45 cmH_2O for two minutes, followed by a decremental PEEP titration; the comparison group received no RM and a low PEEP/FiO_2 strategy. The ART RM strategy was modified halfway through enrollment to a less aggressive RM due to three cardiac arrests attributed to the intervention. The ART trial was considered the highest quality among included trials. One additional potentially eligible trial [132] was excluded from analyses

as it enrolled only burn patients with ARDS, a unique, population thought not to be generalizable. When considering the impact of the intervention on ICU mortality, five trials were included; the trial by Chung not reporting this outcome was excluded, while the trial by Huh et al. not included in the hospital mortality meta-analysis was included.

The ART was the only trial meeting moderate-high quality standards and entering the primary analysis. In this study, the analysis of mortality at different time points provided non homogeneous findings (Supplementary Materials), but there was a suspicion of increased mortality at 6 months. However, combined in the meta-analysis (our secondary analysis), the intervention showed neither harmful nor beneficial effects on mortality. The analysis of heterogeneity was inconclusive.

The analysis of barotrauma, instead, showed an outlier position of the ART trial, with a clear harmful effect (RR 3.56, 95% CI 1.64–7.73), quite different from the other trials combined in a separate meta-analysis (RR 0.60, 95% CI 0.25–1.41) (see Supplementary Materials). This finding strongly supported our recommendation against the use of recruitment high-pressure recruitment maneuvers.

VFDs were reported by three trials [112, 129, 130]. We based our primary analysis on the ART trial [112] which showed a significant reduction in the mean number of VFD in the intervention arm, given that the other two trials reported medians and interquartile ranges and thus could not be meta-analyzed with the ART trial.

Recommendation 6.3

We **recommend against** use of prolonged high-pressure recruitment maneuvers (defined as airway pressure maintained $\geq$ 35 cmH_2O for at least one minute) to reduce mortality of patients with ARDS.
Strong recommendation; moderate level of evidence against.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; low level of evidence against for indirectness.

Question 6.4: In patients with ARDS undergoing invasive mechanical ventilation, does *routine* use of brief high-pressure recruitment maneuvers, compared to no use of brief high-pressure recruitment maneuvers, reduce mortality?

Summary of the evidence

A brief high-pressure RM was defined as a strategy intended to facilitate lung recruitment in which airway pressure of $\geq$ 35 cmH_2O was maintained for less than one minute. Three trials were included in analyses. Kacmarek et al. ($n=200$) [133] compared a series of two brief RMs (transient increase in PEEP to 35–45 cmH_2O) interspersed with a decremental PEEP trial versus no RM with a low PEEP/FiO_2 table. LOVS ($n=983$) [107] utilized a single brief RM (40 cmH_2O breath hold for 40 seconds; subsequent RMs allowed for ventilator circuit disconnect) with a high PEEP/FiO_2 table compared to no RM with a low PEEP/FiO_2 table. Xi et al. [134] compared a brief RM (40 cmH_2O breath hold for 40 seconds) repeated every 8 hours for up to five days versus no RM. The trial by Xi et al. did not standardize PEEP in either group, and was thus considered separately.

Mortality did not differ significantly between treatment groups in any of the three trials individually, nor in meta-analysis pooling the two trials with standardized PEEP (pooled RR 0.89; 95% CI 0.77–1.04). VFDs did not differ significantly between treatment groups in Kacmarek et al. or Xi et al. VFD was not reported in LOVS.

Barotrauma did not differ significantly between treatment groups in any of the three trials individually, nor in meta-analysis pooling the two trials with standardized PEEP (pooled RR 1.14; 95% CI 0.81–1.62).

Considering hemodynamic instability, in Kacmarek et al. there was no significant difference in incidence of hypotension, arrhythmia, or cardiac arrest. In LOVS, hemodynamics was reported as days of vasopressor use and number of vasopressors per day in use and were comparable between groups. Hemodynamic effects were not well characterized in Xi et al.

Absence of evidence in favor or against the use of recruitment maneuvers, the potential safety issues led to a weak recommendation against their routine use.

Recommendation 6.4

We **suggest against** *routine* use of brief high-pressure recruitment maneuvers (defined as airway pressure maintained $\geq$ 35 cmH_2O for less than one minute) to reduce mortality in patients with ARDS.
Weak recommendation; high level of evidence of no effect.

This suggestion applies also to ARDS from COVID-19.
Weak recommendation; moderate level of evidence of no effect for indirectness.

Expert opinion on clinical application of recruitment maneuvers

Hypotension and desaturation are the most common adverse events described during or immediately after an RM, each occurring in roughly 10% of patients undergoing an RM [119]. Bradycardia, presumably vagally mediated, also may occur [135]. Clinical trial data indicate prolonged high-pressure RMs increase risks, leading not only to hemodynamic instability but increased risk of barotrauma and cardiac arrest [112]. These clinically

important risks outweigh potential benefits and led to the recommendation against their use.

Brief high-pressure RMs also may produce transient, potentially reversible hypotension and bradycardia [115, 135] which can result from acute right heart failure. Existing data do not support routine use of brief RMs, likely because lung mechanical effects from briefly raising airway pressure are transient unless accompanied by other maneuvers to prevent progressive collapse [136]. Nevertheless, brief RMs may have a limited role in attempt to reverse hypoxemia in situations where desaturation is likely caused by derecruitment, for example after ventilator disconnect, suctioning, bronchoscopy or patient repositioning. If performed, brief high-pressure RMs should only be done with a plan to abort the maneuver immediately if cardiovascular instability ensues.

Unresolved questions and research gaps

Brief recruitment maneuvers in the form of "sigh" breaths, performed periodically one or more times every few minutes, may prevent progressive derecruitment that can occur with low airway pressure, low tidal volume ventilation [127, 137]. Whether such periodic maneuvers attenuate ventilation-induced lung injury or pose safety risks, how often they might need to be performed to afford such lung protection (if any), and in whom they might afford benefit based on potential for lung recruitment all warrant further investigation.

Domain 7: Prone positioning

Question 7.1: In intubated patients with ARDS, does prone position compared to supine position reduce mortality?

Background

Prone position was proposed for patients with acute hypoxemic respiratory failure and ARDS in the 1970s. Physiological benefits include improvement of oxygenation, better homogenization of lung stress, and decreased right ventricular strain. Over the years, several trials were conducted comparing prone to supine position, with improved designs on the basis of the critical analysis of previous ones [138–144]. Thus, progressively more hypoxemic patients were selected, the duration of prone ventilation cycles increased, and protective ventilation was combined with pronation. In 2013, the PROSEVA trial demonstrated a clear protective effect of prone ventilation in patients with moderate-to-severe ARDS [9]. In 2017, the ESICM and the American Thoracic Society (ATS) provided recommendations for the use of prone ventilation in ARDS [13] based on both aggregated and individual patient data meta-analysis [10] that included the largest four trials [138, 139, 143, 144]. In the aggregated data meta-analysis, the overall result was non-significant; however, in studies that used duration of proning longer than twelve hours or included patients with $PaO_2/FiO_2 \leq 200$ mmHg, a statistically significant mortality reduction was found. The individual patient meta-analysis [10] identified a survival benefit in patients with $PaO_2/FiO_2 \leq 100$ mmHg. However, this subgroup analysis did not allow any definitive conclusion since the benefits of randomization are not maintained in subgroups (and only one study stratified patients according to the degree of hypoxemia [144]). In general, subgroup analyses in meta-analysis have an exploratory nature, and results should be interpreted cautiously. There were no RCTs identified specifically addressing proning of mechanically ventilated patients in COVID-19.

Summary of the evidence

We based our analysis on the eight trials selected in the previous 2017 guidelines since no further trials on this topic have been conducted since. However, we excluded the 2004 trial that was not restricted to ARDS [139]. Meta-analysis was conducted for the outcome of short-term mortality, defined as either at 28 days or in the ICU, and separately for 90-days mortality.

Relevant clinical heterogeneity was found among the studies in terms of modality of ventilation, dose of daily prone ventilation, patient selection, and timing of application of prone positioning.

Short-term mortality did not differ between prone and supine position (RR 0.79 95% CI [0.61–1.03]). In the subgroup of the first five trials, the short-term mortality did not differ between supine and prone positioning (0.91 [0.77–1.08]). However, the short-term mortality was significantly lower in the prone positioning group of the PROSEVA trial (0.49 [0.35–0.69]), with a statistically significant interaction test (supplement materials).

Longer-term mortality did not differ between prone and supine position (0.81 [0.64–1.02]). In the subgroup of the first five trials the longer-term mortality did not differ (0.93 [0.79–1.09]). 90-days mortality was significantly improved by proning in the PROSEVA trial (0.58 [0.44–0.76]) ($p < 0.01$). In this case as well the interaction test turned out to be statistically significant. The unique findings of the PROSEVA trial were further highlighted by a cumulative meta-analysis that investigated the results of meta-analyses carried over time (Supplementary Materials). Further, the analysis of heterogeneity performed using the double-p plot approach [145], identified the PROSEVA trial as a clear outlier.

Our primary analysis was thus based on the individual evaluation of findings from the PROSEVA trial. The secondary analysis included, instead, all the trials.

Recommendation 7.1

We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as $PaO_2/FiO_2 < 150$ mmHg and PEEP ≥ 5 cmH_2O, despite optimization of ventilation settings) to reduce mortality.
Strong recommendation, high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

Expert opinion on clinical application

The overall risk–benefit balance favors prone position used according to the PROSEVA trial criteria, particularly given that its application is feasible in most ICUs with adequately skilled and staffed caregivers when paying careful attention to the risk of pressure-related skin complications.

Unresolved questions and research gaps

It is unlikely that a trial comparing prone to supine will be conducted in moderate-severe COVID-related ARDS given the lack of equipoise in the field at present. A trial is ongoing in France in adult intubated patients with mild to moderate ARDS (NCT05056090).

Question 7.2: In patients with moderate-severe ARDS, when should prone positioning be started to reduce mortality?

Background

No specific trial was designed to explore the role of predetermined criteria in the decision to start prone position. Therefore, the evidence used for this question is the same as that for previous the question.

Recommendation 7.2

We **recommend** starting prone position in patients with ARDS receiving invasive mechanical ventilation early after intubation, after a period of stabilization during which low tidal volume is applied and PEEP adjusted and at the end of which the PaO_2/FiO_2 remains < 150 mmHg; and proning should be applied for prolonged sessions (16 consecutive hours or more) to reduce mortality.
Strong recommendation; high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

Expert opinion on clinical application

The current recommendation is based on the evidence obtained from one trial (PROSEVA). The stabilization period before proning should take into account the time to optimize the ventilator settings and hemodynamics. Continuing prone position even if there is no significant initial improvement in oxygenation is based on the potential of prone position to protect the lung by homogenization of lung stress and potentially improving trajectory of recovery.

Unresolved questions and research gaps

There is no trial comparing different durations of prone position and no trial testing strategies other than oxygenation to determine when to cease proning sessions. The difference in PaO_2/FiO_2 ratio between prone and subsequent supine position could be used to guide when to cease prone position. Moreover, using respiratory mechanics, e.g., keeping driving pressure within safe ranges, in addition to oxygenation and/or markers of dead-space ventilation, may be taken into account in the decision to stop the sessions. The effect of prolonged sessions of proning in patients showing minimal improvement in gas exchange should be further evaluated.

Question 7.3: In non intubated patients with AHRF, does awake prone positioning (APP) as compared to supine positioning reduce intubation or mortality?

Background

During the recent COVID-19 pandemic, with the spread of non-invasive respiratory support strategies in the wards and ICUs, so-called "awake proning" in non-mechanically ventilated patients was often performed and became the focus of several clinical trials [146]. Indeed, all the high-quality evidence from RCTs derived from studies enrolling only COVID-19 patients.

Summary of the evidence

Three trials comparing APP to a control group in the supine position, all in COVID-19 patients [147–149], were included in the meta-analysis. One of the studies was a meta-trial including six randomized controlled trials conducted in six different countries (Canada, France, Ireland, Mexico, Spain, United States of America) harmonizing the protocols and combining the data [147]. Most patients enrolled in all three trials were treated with HFNO. Specifically, the proportion of patients treated with HFNO at time of inclusion was 100% APP vs 100% control in the meta-trial [147], 86.1% APP vs 74.1% control in the Swedish study [148], and 72.2% APP vs 67.7% control in the third study [149]. The corresponding rates

of non-invasive ventilation were 0% vs 0% [147], 58.3% vs 69.2% [148], and 5.9% vs 10.3% [149].

In the primary analysis, the meta-trial was split into its six individual components and, therefore, performed the meta-analysis over eight trials. Furthermore, the trial performed in Mexico was removed from the meta-trial because it was associated with a significant reduction in intubation rate compared to the five other trials; also, it provided a twofold higher duration of APP than the other trials, and it behaved as an outlier on a plot that highlighted the inconsistency across the studies in the meta-trial. Therefore, the primary analysis was done on two subgroups: one with seven trials and one with Mexico trial only.

The main outcome of the meta-trial was a composite endpoint including mortality and intubation at 28 days. To be reliable, the elements of a composite outcome needs to fulfill three conditions: have similar clinical relevance, occur with the same frequency, and should be affected similarly by the trailed intervention. The composite endpoint selected in the trials included in our review did not meet these criteria and, hence, we investigated separately intubation and mortality, which were at either 28 or 30 days.

APP significantly reduced the risk of intubation in both the primary analysis, focused on five trials with the lower level of bias, and the secondary analysis including all 8 studies (RR 0.84 [0.94–0.87] and 0.84 [0.73–0.96], respectively). In the subgroup of seven trials, the intubation rate did not differ between APP and control groups (0.89 [0.77–1.04]); in contrast, the trial in Mexico reported a significantly lower risk of intubation in APP (0.7 [0.54–0.9]). Although the interaction test was statistically non-significant, a careful the analysis of heterogeneity revealed the trial in Mexico to be an outlier and APP had no overall effect on mortality.

Recommendation 7.3

We **suggest** awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation.
Weak recommendation; low level of evidence in favor.

We are **unable to make a recommendation** for or against APP for non-intubated patients with COVID-19-related AHRF to reduce mortality.
No recommendation; moderate level of evidence of no effect.

We are **unable to make a recommendation** for or against APP for patients with AHRF not due to COVID-19.
No recommendation; no evidence.

Expert opinion on clinical application

APP can be considered in patients with AHRF due to COVID-19. Close monitoring is required to avoid delaying intubation and to regularly assess and manage comfort and tolerance.

Unresolved questions and research gaps

More data are needed on the effect of APP in non-COVID-19 patients with AHRF. Selecting the adequate outcome is an issue, as a composite score has some limitations; mortality is likely the most relevant outcome. Other issues with APP that need clarification include the location (ICU vs non-ICU), the optimal respiratory support (HFNO, CPAP, NIV) and the impact of APP on inspiratory effort, work of breathing and potential lung injury.

Domain 8: Neuromuscular blocking agents

Question 8.1: Does the *routine* use of a continuous infusion of neuromuscular blocking agents (NMBA) in patients with moderate-to-severe ARDS not due to COVID-19 or moderate-to-severe ARDS due to COVID-19 reduce mortality?

Background

The administration of NMBA to mechanically ventilated patients with ARDS reduces the work of breathing and patient–ventilator asynchronyand may affect outcome [150]. However, prolonged use of NMBA is also associated with neuromuscular weakness and requires deep sedation, which itself can result in adverse outcomes [151, 152]. More than a decade ago, the ACURASYS trial reported that the early administration of a 48-h infusion of NMBA in patients with moderate-to-severe ARDS ($PaO_2/FiO_2 < 150$ mmHg with PEEP ≥ 5) resulted in lower mortality than a strategy of deep sedation without routine NMBA use, after an adjusted analysis [153]. Three other smaller trials with similar inclusion criteria and treatment protocols showed benefit with routine NMBA use [154–156]. However, ICU practices have evolved since these trials, with emphasis on lighter sedation and earlier return to spontaneous breathing.

In the recent ROSE trial, which randomized patients with moderate-to-severe ARDS to a 48h continuous infusion of NMBA with concomitant deep sedation (intervention group) or to a usual-care approach without routine neuromuscular blockade and with lighter sedation targets (control group), there was no significant difference in mortality at 90 days [157]. There has been an increased use of NMBA infusions in patients with COVID-19 ARDS who are mechanically ventilated, most commonly to abolish vigorous spontaneous efforts and decrease the generation of high transpulmonary pressures that could aggravate self-inflicted lung

injury or asynchronies [158]. However, randomized trials on NMBA use in patients with COVID-19 are lacking. Given that the ROSE trial excluded a significant number of patients already receiving NMBA, the benefit of early continuous NMBA remains unclear.

Summary of the evidence

Two studies provided different results, for the 90-days outcome with the ACURASYS trial reporting a protective effect [153], and the latest ROSE trial demonstrating a non-significant result [157]. The ACURASYS trial sample size calculation was based on the expectation of a large mortality reduction (15%). The 9% reduction found was not statistically significant ($p = 0.08$). The power for the observed delta was 42%, and 842 patients would have been required assuming a power of 80% given the same difference. The ROSE trial assumed an 8% mortality reduction, and under the assumption of a 90% power, the randomization of about 1400 patients was planned. A meta-analysis of the two studies found an overall non-significant result, with a heterogeneity estimate that was high (I^2 56%), although the imprecision was such that we could not rule out either low or high heterogeneity. The evaluation of overall evidence was moderate against (according to the GRADE after rating down for imprecision), and according to the risk of biases (RoB) 2 assessment tool, there was an overall low risk of bias.

When analyzing the 28-days or ICU mortality, five trials were included [153–157]. Of these, three reported 28-days mortality, and two ICU mortality [153, 157]. Meta-analysis identified no significant mortality reduction in the NMBA group compared to no NMBA, with a 0.80 relative risk (95% CI 0.57, 1.04), p value 0.086.

There were several differences between the two larger studies [153, 157] highlighted. Prone ventilation was less common in the ROSE trial compared to the ACURASYS trial (15.8 vs. 44.8%). The sedation targets for controls were lighter in the ROSE trial, possibly related to a lower number of serious cardiovascular events (14 vs. 4, intervention arm vs. controls) and mortality in the control arm. Higher PEEP strategies were used in the ROSE trial, with an unclear effect on mortality. It is also interesting that the mortality in the intervention arm in the ROSE study was not different from those the control arm in the ROSE and ACURASYS trials. There are two potential explanations for this finding. First, it is possible that patients had the same severity in the two trials, but the intervention overall was not effective in the ROSE trial because the interventions were substantially different, e.g., same pharmacological approach but different ventilatory approach such as PEEP protocols or ventilation in the prone position. Alternatively, it may have been that patients were less severely ill in the ACURASYS trial, but sedation was heavier in the control group (compared to the ROSE trial) causing higher mortality rates.

There were no randomized controlled trials in patients with ARDS due to COVID-19. Only indirect evidence from non-COVID studies was available.

Recommendation 8.1

We **recommend against** the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate-to-severe ARDS not due to COVID-19.
Strong recommendation, moderate level of evidence.

We are **unable to make a recommendation** for or against the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate-to-severe ARDS due to COVID-19.
No recommendation; no evidence.

Expert opinion on clinical application

In the ACURASYS trial, the use of prone ventilation without neuromuscular blockade was associated with deeper sedation targets, which may have contributed to the increased mortality in the control arm [153]. A clear protective effect for pneumothorax was found in the NMBA group compared to controls in the four studies included [153–155, 157]. This finding may support the use of NMBA in those patients at risk of developing a pneumothorax.

Unresolved questions and research gaps

Future research should prioritize other outcomes including successful extubation, re-intubation, paralysis recall, ICU acquired weakness and health-related quality of life and the specific role on NMBA in prone position. Another important area of research is the recognition of poor patient-ventilator interaction in invasively ventilated ARDS patients, as this has potential effects on clinical outcomes and may represent a possible indication for the administration of NMBA. The views of patients and caregivers should be central to determining future research questions and outcomes.

Domain 9: Extracorporeal life support

Question 9.1: In adult patients with severe acute respiratory distress syndrome (ARDS) or COVID-19 does veno-venous extracorporeal membrane oxygenation (VV-ECMO) compared with conventional ventilation improve outcomes?

Background

VV-ECMO is used to support or replace gas exchange. During ECMO, blood is passed through a "membrane lung" which facilitates exchange of oxygen and carbon

dioxide by diffusion. Technological improvements have led to improved gas exchange and reduced complications [159]. ECMO has been used for patients with severe ARDS including more recently patients with COVID-19. High-volume expert centers report better outcomes with ECMO [160]. It is likely that an overall package of care delivered alongside the use of ECMO, including lung-protective ventilation and prone positioning, is required to achieve improved outcomes in patients receiving ECMO.

Summary of the evidence

Two randomized controlled trials informed the basis of these recommendations. The CESAR trial included 180 patients, and the EOLIA trial included 249 patients with ARDS [161]. The EOLIA inclusion criteria were as follows: a $PaO_2/FiO_2 < 50$ mmHg for > 3 hours, or a PaO_2/FiO_2 of < 80 mmHg for > 6 hours, or a pH of < 7.25 with a $PaCO_2$ of ≥ 60 mmHg for > 6 hours, with the respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep a plateau pressure of ≤ 32 cmH_2O [162].

These studies included patients with severe ARDS of any etiology (average PaO_2/FiO_2 values were approximately 75 mmHg), though both were conducted prior to the COVID-19 pandemic. The EOLIA and CESAR trials were considered clinically sufficiently homogenous to be meta-analytically combined. According to the RoB2 tool, there was a high risk of bias with the CESAR trial, as about one-quarter of patient in the intervention arm did not receive ECMO.

Meta-analysis identified a significant decrease in 60-day mortality in patients receiving VV-ECMO compared to conventional mechanical ventilation (RR 0.72; 95% CI 0.57–0.91; moderate confidence). The protective effect was consistent across the 90-days mortality outcomes as well as a composite outcome of mortality and therapeutic failure at 60 days. Observational studies, including a post-hoc Bayesian analysis of the EOLIA study [163], mostly confirmed a protective effect of ECMO [163–171]. However, the very low evidence that they provided did not substantially affect the moderate quality of evidence provided by the meta-analysis of the two randomized trials. The observational studies were not combined in a meta-analysis due to methodological limitations.

There were no randomized controlled trials in patients with COVID-19. The evidence for ECMO in COVID-19 was assessed as weak in favor, being downgraded due to the indirectness of the available RCT evidence. Observational studies in COVID-19 mostly showed a protective effect of ECMO in short-term survival [167, 169–171]. We did not combine the observational studies in a meta-analysis due to methodological limitations.

The use of ECMO is associated with the risk of serious bleeding. In the EOLIA trial, higher rates of bleeding events leading to blood transfusion (46 vs. 28%) and of severe thrombocytopenia (27 vs. 16%) in the intervention arm were reported. However, less ischemic strokes (5% absolute risk reduction; 95% CI, 2–10%) and no differences in hemorrhagic strokes was found [162].

Recommendation 9.1

We **recommend** that patients with severe ARDS not due to COVID-19 as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO center which meets defined organizational standards, adhering to a management strategy similar to that used in the EOLIA trial.
Strong recommendation, moderate level of evidence in favor

This recommendation applies also to patients with severe ARDS due to COVID-19.
Strong recommendation; low level of evidence in favor for indirectness.

Expert opinion on clinical application

A network of ECMO centers with expertise in this technique is likely to be required to effectively provide ECMO. With centralization of patients from non-ECMO centers, an ECMO team with capacity to transfer patients on ECMO (mobile ECMO) is required. Resources and skills to deliver such a service are required.

It is unlikely that an RCT of ECMO in severe ARDS due to COVID-19 will be conducted. In patients with ARDS due to COVID, early mortality up to 90-days was similar to non-COVID ARDS patients when ECMO was initiated in experienced centers. Although patients with COVID will not have been included in the RCTs which form the basis of these recommendations, there is biological plausibility that ARDS due to non-COVID and COVID should have similar outcomes with ECMO. However, the rate of serious and prolonged multidimensional disability, particularly in patients with COVID-19 may be significant, although specific attribution to ECMO rather than severe ARDS is unknown.

Unresolved questions and research gaps

Future research should additionally prioritize long-term multidimensional outcomes for patients and families and ascertain ECMO-specific morbidities. The views of patients and carers should be central to determining future research questions and outcomes.

Table 2 Summary of recommendations

HIGH FLOW NASAL OXYGEN		
Q1	**In non-mechanically ventilated patients with acute hypoxemic respiratory failure (AHRF) not due to cardiogenic pulmonary edema or acute exacerbation of chronic obstructive pulmonary disease (COPD), does high flow nasal oxygen (HFNO) compared to conventional oxygen therapy (COT) reduce mortality or intubation?**	
1	We **recommend** that non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD receive HFNO as compared to COT to reduce the risk of intubation.	MODERATE LEVEL OF EVIDENCE
2	This recommendation applies also to AHRF from coronavirus 2019 (COVID-19)	LOW LEVEL OF EVIDENCE
3	We are **unable to make a recommendation** for or against the use of HFNO over COT to reduce mortality.	HIGH LEVEL OF EVIDENCE
4	This recommendation applies also to AHRF from COVID-19.	MODERATE LEVEL OF EVIDENCE
Q2	**In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD, does HFNO compared to non-invasive ventilation (NIV) reduce mortality or intubation?**	
1	We are **unable to make a recommendation** for or against the use of HFNO compared to continuous positive airway pressure (CPAP)/NIV to reduce intubation or mortality in the treatment of unselected patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD.	MODERATE LEVEL OF EVIDENCE FOR MORTALITY LOW LEVEL OF EVIDENCE FOR INTUBATION
2	We **suggest** that CPAP/NIV can be considered instead of HFNO to reduce the risk of intubation in AHRF due to COVID-19.	HIGH LEVEL OF EVIDENCE
3	**No recommendation** can be made for whether CPAP/NIV can decrease mortality compared to HFNO in COVID-19.	HIGH LEVEL OF EVIDENCE
CONTINUOUS POSITIVE AIRWAY PRESSURE / NON-INVASIVE VENTILATION		
Q1	**In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema, obesity hypoventilation or acute exacerbation of COPD, does CPAP/NIV, as compared to COT reduce mortality or intubation?**	
1	We are **unable to make a recommendation** for or against the use of CPAP/NIV compared to COT for the treatment of AHRF (not related to cardiogenic pulmonary edema or acute exacerbation of COPD) to reduce mortality or to prevent intubation.	HIGH LEVEL OF EVIDENCE FOR MORTALITY MODERATE LEVEL OF EVIDENCE FOR INTUBATION
2	We **suggest** the use of CPAP over COT to reduce the risk of intubation in patients with AHRF due to COVID-19.	LOW LEVEL OF EVIDENCE
3	We are **unable to make a recommendation** for or against the use of CPAP over COT to reduce mortality in AHRF due to COVID-19.	MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE:
NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION
STRONG RECOMMENDATION
WEAK RECOMMENDATION

Table 2 (continued)

Q2	**In patients being treated with CPAP/NIV for AHRF, does the use of a helmet interface as compared to face mask reduce intubation or mortality?**	
1	We are **unable to make a recommendation** for or against the use of helmet interface for CPAP/NIV as compared to face mask to prevent intubation or reduce mortality in patients with AHRF.	? VERY LOW LEVEL OF EVIDENCE
Q3	**In patients with AHRF, does NIV as compared to CPAP reduce mortality or intubation?**	
1	We are **unable to make a recommendation** for or against the use of NIV compared to CPAP for the treatment of AHRF.	? NO EVIDENCE
	LOW TIDAL VOLUME VENTILATION	
Q1	**In adult patients with ARDS and COVID-19-related ARDS, does low tidal volume ventilation alone compared with more traditional approaches to ventilation decrease mortality?**	
1	We **recommend** the use of low tidal volume ventilation strategies (i.e., 4-8 ml/kg PBW), compared to larger tidal volumes (traditionally used to normalize blood gases), to reduce mortality in patients with ARDS not due to COVID-19.	!! HIGH LEVEL OF EVIDENCE
2	This recommendation applies also to ARDS from COVID-19.	!! MODERATE LEVEL OF EVIDENCE
	POSITIVE END-EXPIRATORY PRESSURE AND RECRUITMENT MANEUVERS	
Q1	**In patients with ARDS undergoing invasive mechanical ventilation, does routine positive end-expiratory pressure (PEEP) titration using a higher PEEP/FiO_2 strategy compared to a lower PEEP/FiO_2 strategy reduce mortality?**	
1	We are **unable to make a recommendation** for or against routine PEEP titration with a higher PEEP/FiO_2 strategy versus a lower PEEP/FiO_2 strategy to reduce mortality in patients with ARDS.	? HIGH LEVEL OF EVIDENCE
2	This statement applies also to ARDS from COVID-19.	? MODERATE LEVEL OF EVIDENCE
Q2	**In patients with ARDS undergoing invasive mechanical ventilation, does routine PEEP titration based principally on respiratory mechanics compared to PEEP titration based principally on a standardized PEEP/FiO_2 table reduce mortality?**	
1	We are **unable to make a recommendation** for or against PEEP titration guided principally by respiratory mechanics, compared to PEEP titration based principally on PEEP/FiO_2 strategy, to reduce mortality in patients with ARDS.	? HIGH LEVEL OF EVIDENCE
2	This statement applies also to ARDS from COVID-19.	? MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE:
NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

? NO RECOMMENDATION !! STRONG RECOMMENDATION ! WEAK RECOMMENDATION

Table 2 (continued)

Q3	**In patients with ARDS undergoing invasive mechanical ventilation, does use of prolonged high-pressure recruitment maneuvers (RMs), compared to not using prolonged high-pressure RMs, reduce mortality?**	
1	We **recommend against** use of prolonged high-pressure RMs (defined as airway pressure maintained ≥ 35 cmH_2O for at least one minute) to reduce mortality of patients with ARDS.	MODERATE LEVEL OF EVIDENCE
2	This recommendation applies also to ARDS from COVID-19.	LOW LEVEL OF EVIDENCE
Q4	**In patients with ARDS undergoing invasive mechanical ventilation, does *routine* use of brief high-pressure RMs, compared to no use of brief high-pressure RMs, reduce mortality?**	
1	We **suggest against** *routine* use of brief high-pressure RMs (defined as airway pressure maintained ≥ 35 cmH_2O for less than one minute) to reduce mortality in patients with ARDS.	HIGH LEVEL OF EVIDENCE
2	This suggestion applies also to ARDS from COVID-19.	MODERATE LEVEL OF EVIDENCE
	PRONE POSITIONING	
Q1	**In intubated patients with ARDS, does prone position compared to supine position reduce mortality?**	
1	We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as PaO_2/FiO_2<150 mmHg and PEEP≥5 cmH_2O, despite optimization of ventilation settings) to reduce mortality.	HIGH LEVEL OF EVIDENCE
2	This recommendation applies also to ARDS from COVID-19.	MODERATE LEVEL OF EVIDENCE
Q2	**In patients with moderate-severe ARDS, when should prone positioning be started to reduce mortality?**	
1	We **recommend** starting prone position in patients with ARDS receiving invasive mechanical ventilation early after intubation, after a period of stabilization during which low tidal volume is applied and PEEP adjusted and at the end of which the PaO_2/FiO_2 remains <150 mmHg; and proning should be applied for prolonged sessions (16 consecutive hours or more) to reduce mortality.	HIGH LEVEL OF EVIDENCE
2	This recommendation applies also to ARDS from COVID-19.	MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE:
NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION | STRONG RECOMMENDATION | WEAK RECOMMENDATION

Table 2 (continued)

Q3	**In non intubated patients with AHRF, does awake prone positioning (APP) as compared to supine positioning reduce intubation or mortality?**	
1	We **suggest** awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation.	LOW LEVEL OF EVIDENCE
2	We are **unable to make a recommendation** for or against APP for non-intubated patients with COVID-19-related AHRF to reduce mortality.	MODERATE LEVEL OF EVIDENCE
3	We are **unable to make a recommendation** for patients with AHRF failure not due to COVID-19.	NO EVIDENCE
	NEUROMUSCULAR BLOCKING AGENTS	
Q1	**Does the *routine* use of a continuous infusion of neuromuscular blocking agents (NMBA) in patients with moderate to severe ARDS not due to COVID-19 or moderate to severe ARDS due to COVID-19 reduce mortality?**	
1	We **recommend against** the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS not due to COVID-19.	MODERATE LEVEL OF EVIDENCE
2	We are **unable to make a recommendation** for or against the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS due to COVID-19.	NO EVIDENCE
	EXTRACORPOREAL LIFE SUPPORT	
Q1	**In adult patients with severe ARDS or COVID-19 does veno-venous extracorporeal membrane oxygenation (VV-ECMO) compared with conventional ventilation improve outcomes?**	
1	We **recommend** that patients with severe ARDS not due to COVID-19 as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO centre which meets defined organisational standards, adhering to a management strategy similar to that used in the EOLIA trial.	MODERATE LEVEL OF EVIDENCE
2	This recommendation applies also to severe ARDS from COVID-19.	LOW LEVEL OF EVIDENCE
Q2	**In adult patients with ARDS, does extracorporeal carbon dioxide removal ($ECCO_2R$) compared with conventional ventilation improve outcomes?**	
1	We **recommend against** the use of $ECCO_2R$ for the treatment of ARDS not due to COVID-19 to prevent mortality outside of randomized controlled trials.	HIGH LEVEL OF EVIDENCE
2	This recommendation applies also to severe ARDS from COVID-19.	MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE:
NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION | STRONG RECOMMENDATION | WEAK RECOMMENDATION

Table 3 Comparison between 2017 and 2023 ARDS guidelines

	2017	2023	CHANGE IN RECOMMENDATION	COMMENTS
Definition	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guidelines did not include a Definition domain.
Phenotypes	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guidelines did not include an ARDS Phenotype domain.
High flow nasal oxygen	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guidelines did not include recommendations on high flow nasal oxygen.
Non-invasive ventilation	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guideline did not include recommendations on non-invasive ventilation.
Tidal volume	Available	Available	No change	In agreement with the use of low tidal volume strategies. **2023** guidelines extend this recommendation to patients with COVID-19.
Positive end-expiratory pressure	Available	Available	Change in recommendation	**2017:** suggest that adult patients with moderate or severe ARDS receive higher rather than lower levels of PEEP. **2023:** analysis of data does not allow to make a recommendation for or against higher PEEP strategy.
Recruitment maneuvers	Available	Available	Change in recommendation	**2017:** suggest that adult patients with ARDS receive RMs. **2023:** recommend against RMs due to increased mortality and risks.
Oscillatory ventilation	Available	Not available	Not considered	**2017:** recommend that HFOV not be used routinely in patients with moderate or severe ARDS. **2023:** not examined given the absence of studies since 2017 and the lack of use of HFVO in adults.
Prone position	Available	Available	No change	Agreement with the use of prone position in ARDS. Additions in **2023** are the use of awake proning and the use in COVID-19.
Neuromuscular blockade	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guidelines did not include recommendations on neuromuscular blockade.
Extracorporeal membrane oxygenation	Available	Available	Change in recommendation	**2017:** additional evidence is necessary to make a definitive recommendation. **2023:** recommend ECMO in patients with severe ARDS.
Extracorporeal CO_2 removal	Not available	Available	New recommendation /domain since 2017	No comparison available as the **2017** guidelines did not include recommendations on extracorporeal CO_2 removal. **2023** guidelines recommend against $ECCO_2R$ in ARDS.

AVAILABLE · NOT AVAILABLE · NEW RECOMMENDATION /DOMAIN SINCE 2017 · CHANGE IN RECOMMENDATION · NO CHANGE · NOT CONSIDERED

ARDS: acute respiratory distress syndrome; **COVID-19:** coronavirus disease 2019; **$ECCO_2R$:** Extracorporeal CO_2 Removal; **ECMO:** extracorporeal membrane oxygenation; **HFOV:** High-frequency oscillatory ventilation; **PEEP:** positive end-expiratory pressure; **RM:** recruitment maneuver

Question 9.2: In adult patients with ARDS, does extracorporeal carbon dioxide removal ($ECCO_2R$) compared with conventional ventilation improve outcomes?

Background

$ECCO_2R$ aims to remove carbon dioxide via an extracorporeal circuit. $ECCO_2R$ uses lower extracorporeal blood flow rates (typically between 200 and 1500 mL/min) compared to ECMO because the blood flow rates needed to remove CO_2 are much lower than required to achieve adequate oxygenation. Although $ECCO_2R$ is often defined based on the flow rate through the extracorporeal circuit, it has been suggested that $ECCO_2R$ should be defined based on the clinician's intended use [172]. The primary aim of $ECCO_2R$ in ARDS is to facilitate a reduction in injurious mechanical ventilation.

Summary of the evidence

Two RCTs formed the basis of these recommendations. The Xtravent trial included 79 patients with ARDS with

$PaO_2/FiO_2 < 200$ mmHg who received CO_2 removal using a "pumpless" arterio-venous (approximately 1–2 L/min) approach [173]. The REST trial included 412 hypoxemic patients ($PaO_2/FiO_2 < 150$ mmHg) who received CO_2 removal using a veno-venous low flow (approximately 450 ml/min) approach. The majority of patients had ARDS (approximately 60%) [174]. The Xtravent and REST trials were considered clinically sufficiently homogenous to be meta-analytically combined. There were methodological concerns with the Xtravent trial and some methodological concerns for the REST trial according to the RoB2 assessment. When considering ventilator-free days, methodological concerns were recognized due to lack of blinding.

In meta-analysis of these 2 trials, $ECCO_2R$ did not reduce mortality (RR 1.03; 95% CI, 0.82–1.3; high confidence). Patients receiving $ECCO_2R$ had fewer ventilator-free days to day 28 (mean difference −1.21; 95% CI −3.77 to 1.34; moderate confidence). There were no randomized controlled trials in patients with COVID-19. Evidence was considered applicable to COVID patients although this was not directly investigated and therefore the evidence was downgraded due to the indirectness of the available RCT evidence. The REST trial reported increased serious side-effects attributable to $ECCO_2R$ with nine patients (4.5%) having a cerebral hemorrhage and six patients (3%) having extracranial bleeding compared to none and one (0.5%), respectively, in the control arm [174].

Recommendation 9.2

We **recommend against** the use of $ECCO_2R$ for the treatment of ARDS not due to COVID-19 to prevent mortality outside of randomized controlled trials.
Strong recommendation, high level of evidence of no effect.

This recommendation applies also to patients with severe ARDS due to COVID-19.
Strong recommendation; moderate level of evidence of no effect for indirectness.

Expert opinion on clinical application

The Xtravent trial had blood flows of 1–2 L/min and the REST trial of approximately 450 mL/min. A lower blood flow rate of approximately 500 mL (or approximately 25% CO_2 removal) may be insufficient to achieve a sufficient reduction in injurious ventilation. The resource requirement for $ECCO_2R$ in the REST trial (blood flow < 500 mL) was estimated to be comparable to that of CRRT; however, with higher blood flows the delivery of $ECCO_2R$ requires competencies similar to ECMO centers.

Unresolved questions and research gaps

Although current evidence is against the effectiveness of $ECCO_2R$, uncertainty about the role of $ECCO_2R$ remains. Further research is needed to identify if a specific population of ARDS patients may respond to $ECCO_2R$. In addition, the technique may be device-dependent for both efficacy and safety. Ongoing randomized controlled trials may provide further evidence in this field. When these trials conclude, the ARDS ESICM guidelines group will review and update the current recommendation. Future research should additionally prioritize long-term multidimensional outcomes for patients and families and ascertain $ECCO_2R$ specific morbidity. The views of patients and carers should be central to determining future research questions and outcomes.

Conclusions

In conclusion, these guidelines present 21 evidence-based recommendations (summarized in Table 2) including definition, phenotyping and the respiratory management of ARDS. A summary table comparing the changes in scope and recommendations compared with the 2017 ARDS guidelines are presented in Table 3. Finally, research priorities are identified for future studies.

Supplementary Information

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Data availability
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