

NARRATIVE REVIEW



# Current and evolving standards of care for patients with ARDS

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## Abstract

Care for patients with acute respiratory distress syndrome (ARDS) has changed considerably over the 50 years since its original description. Indeed, standards of care continue to evolve as does how this clinical entity is defined and how patients are grouped and treated in clinical practice. In this narrative review we discuss current standards – treatments that have a solid evidence base and are well established as targets for usual care – and also evolving standards – treatments that have promise and may become widely adopted in the future. We focus on three broad domains of ventilatory management, ventilation adjuncts, and pharmacotherapy. Current standards for ventilatory management include limitation of tidal volume and airway pressure and standard approaches to setting PEEP, while evolving standards might focus on limitation of driving pressure or mechanical power, individual titration of PEEP, and monitoring efforts during spontaneous breathing. Current standards in ventilation adjuncts include prone positioning in moderate-severe ARDS and veno-venous extracorporeal life support after prone positioning in patients with severe hypoxemia or who are difficult to ventilate. Pharmacotherapy current standards include corticosteroids for patients with ARDS due to COVID-19 and employing a conservative fluid strategy for patients not in shock; evolving standards may include steroids for ARDS not related to COVID-19, or specific biological agents being tested in appropriate sub-phenotypes of ARDS. While much progress has been made, certainly significant work remains to be done and we look forward to these future developments.

**Keywords:** Acute respiratory distress syndrome, Mechanical ventilation, Prone position, Extra-corporeal life support, Acute respiratory failure

## Introduction

In the more than 50 years, since the modern advent of acute respiratory distress syndrome (ARDS), clinical management has progressed significantly—both in ventilatory management, the mainstay of supportive care, and in ventilatory adjuncts. Progress has also been made in the realm of pharmacotherapy, though this too remains largely as general supportive care rather than specific disease modifying drugs. In this state-of-the-art review we provide updates on the treatment standards for the clinical care of adults with ARDS across these 3 domains and categorize these as Current standards—those for which there is a strong evidence-base and should be widely

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implemented—and Evolving standards—those for which there is rationale but which might not yet be applied in all settings because of weaker evidence or feasibility (Table 1). It is important to emphasize that ARDS (as indicated in its name) is a syndrome, not a disease, and as such there exists significant heterogeneity in terms of outcomes and response to treatments among patients meeting the same ARDS criteria [1, 2]. As we discuss different treatments, we will attempt to highlight this heterogeneity and point out which therapies are applicable to all and which are more nuanced.

## Defining ARDS

### Current and evolving standards

While acute respiratory distress syndrome (ARDS) has likely existed, since time in immemorial, it emerged as an important clinical entity in the late 1960s with the advent of positive pressure mechanical ventilation and the development of intensive care units. In their seminal case series Ashbaugh and colleagues succinctly described the central tenets of the syndrome that still hold true more than 50 years later [3]. These include acute onset of

## Take-home message

The clinical management of adults with acute respiratory distress syndrome (ARDS) continues to progress and evolve. In this review we provide updates across the domains of ventilatory management, ventilatory adjuncts and pharmacotherapy, categorizing these as Current Standards – those for which there is a strong evidence-base and which should be widely implemented – and Evolving Standards – those for which there is rationale but which might not yet be applied in all settings because of weaker evidence or feasibility.

hypoxemia refractory to supplemental oxygen treatment, decreased lung compliance, diffuse pulmonary infiltrates seen on chest radiograph, and characteristic pathological findings of diffuse alveolar damage including hyaline membranes, hemorrhage, edema, and atelectasis.

Following this initial description in 1967, ARDS was not given formal defining criteria until the development of the Murray Lung Injury Score in 1988 [4], and then later the first American-European Consensus Definition of ARDS [5]. Most recently the syndromic definition of ARDS was updated in 2012 with the publication

**Table 1 Current and evolving standards of care in ARDS**

Current standards	Evolving standards
<b>Ventilatory support</b>	<b>Ventilatory support</b>
Tidal volume limitation—target 6 ml/kg PBW	Driving pressure limitation < 15 cmH <sub>2</sub> O
Plateau pressure limitation < 30 cmH <sub>2</sub> O	Minimize delivered mechanical power
PEEP titrated to oxygenation using a PEEP/FiO <sub>2</sub> table or set to keep Pplat < 30	Individual titration of PEEP using one of several methods <ul style="list-style-type: none"> <li>• Best compliance</li> <li>• Measured recruitability (R:I)</li> <li>• Transpulmonary pressure</li> <li>• EIT</li> </ul>
	Spontaneous breathing when appropriate—monitored to avoid dyssynchrony or large efforts
	Use of Helmet NIV or HFNO in mild-moderate ARDS to avoid intubation
<b>Ventilation adjuncts</b>	<b>Ventilation adjuncts</b>
Prone positioning (16 h/day) in early moderate to severe ARDS (P/F < 150)	Neuromuscular blockade when indicated <ul style="list-style-type: none"> <li>• Severe hypoxemia</li> <li>• Severe dyssynchrony</li> <li>• Markedly increased respiratory drive</li> <li>• Difficult to safely ventilate</li> </ul>
vvECMO after prone positioning if: <ul style="list-style-type: none"> <li>• P/F &lt; 80</li> <li>• Difficult to safely ventilate</li> </ul>	
<b>Pharmacotherapy</b>	<b>Pharmacotherapy</b>
Early steroids for ARDS with COVID-19	Early steroids for other causes
Conservative fluid strategy for patients not in shock	Conservative fluid strategy for patients in septic shock
	Testing specific biological agents in sub-phenotypes of ARDS more likely to respond to specific Rx

of the Berlin definition [6, 7]. In this classification, ARDS was characterized by the acute onset (within 1 week) of bilateral chest radiograph opacities not fully explained by cardiac failure, and was divided into mild, moderate, and severe subgroups according to degree of hypoxemia measured with at least 5 cm of water positive pressure using upper limits of PaO<sub>2</sub>/FiO<sub>2</sub> of 300, 200, and 100 mm Hg, respectively. In the derivation and validation of this definition using prior ARDS cohorts, approximately 25% of patients were characterized as mild, 50% moderate and 25% severe, with a stepwise increments of mortality from 27% in mild ARDS to 45% in the severe group [6]. This distribution of ARDS severity and respective mortality rates were subsequently replicated in the prospective LUNG-SAFE observational study [8]. The Berlin definition remains the current standard for ARDS diagnosis in 2020, but we anticipate ongoing evolution of the ARDS definition in the future [7].

## Ventilatory management

### Pressure and volume limitation

#### Current standards

Lung protective ventilation entered mainstream clinical practice with the publication of the first ARDS Network study in 2000; this landmark study demonstrated that limiting plateau pressure and reducing tidal volume ( $V_T$ ) to 6 mL/kg predicted body weight (PBW), compared with  $V_T$  of 12 mL/kg, improved survival, shortened duration of mechanical ventilation, attenuated systemic inflammation and reduced the incidence and amount of extra-pulmonary organ failure [9]. Of course these findings were built on more than two decades of laboratory work from Webb and Tierney to Saumon and Dreyfuss, followed by early observational studies in patients by Hickling and colleagues [10–12]. An expert panel convened in the early 1990s called for randomized clinical trials of lung-protective ventilation [13], and this led to several smaller studies [14–17], that ultimately informed this practice-changing trial [9]. Twenty years later the volume and pressure limitation strategies tested in the first ARDS Network trial remain central to the standard of care in lung protective ventilation—targeting tidal volume of 6 mL/kg predicted body weight (PBW), with adjustments between 4–8 mL/kg PBW to keep plateau pressure below 30 cmH<sub>2</sub>O allowing permissive hypercapnia while minimizing dyssynchrony due to high respiratory drive [18].

#### Evolving standards

Increasing recognition of the heterogeneity of ARDS led to the call for a more individualized approach to pressure and volume limitation in ventilatory management. In 2015, Amato and colleagues published a secondary

individual patient data meta-analysis of several RCTs showing that driving pressure ( $\Delta P$  = plateau pressure – PEEP) was the critical mediator between tidal volume limitation and improved survival in ARDS [19]. While this paper continues to generate discussion, proponents claim that a focus on  $\Delta P$  is superior to simple tidal volume limitation, because it is a measure of tidal volume corrected for respiratory system compliance [20]. Building on this, Gattinoni et al. introduced the concept of mechanical power as a unifying theory of ventilator-induced lung injury [21]. The simplified version of this calculation allows one to estimate mechanical power with only  $V_T$ , respiratory rate, peak pressure and  $\Delta P$  [21], and day 1 mechanical power calculated in this manner has been associated with mortality [22]. Furthermore, a recent analysis of a large registry of over 13,000 patients with hypoxemic respiratory failure showed that exposure to higher intensity of mechanical ventilation (higher driving pressure or mechanical power), even for relatively brief periods, was independently associated with increased mortality over the entire duration of ventilation; with stronger association in those with worse baseline hypoxemia [23]. Nevertheless, randomized trials demonstrating the superiority of a ventilatory strategy focused on limiting driving pressure or mechanical power are still needed, and a recent small trial ( $n=31$ ) suggest a  $\Delta P$ -limited strategy may be feasible [24].

### PEEP and lung recruitment

#### Current standards

Positive end expiratory pressure (PEEP) has been used in ARDS to improve oxygenation and recruit atelectatic lung tissue, since the first description of the syndrome, but debate about exactly what level to use in which patient has been raging ever since [3]. Suter and Fairley showed that the ‘best’ PEEP that maximized oxygen delivery also maximized respiratory system compliance and was inversely proportional to the baseline functional residual capacity, i.e., the size of the baby lung [25].

There are many methods for selecting PEEP. Two common approaches are to target respiratory mechanics (e.g., use the highest PEEP that maintains the plateau pressure below 30 cmH<sub>2</sub>O as used in the ExPress trial, [26]), or to target oxygen saturation (e.g., the use of a PEEP-FiO<sub>2</sub> table, which assigns higher levels of PEEP at higher required FiO<sub>2</sub>). A PEEP-FiO<sub>2</sub> table was used in the original ARDS Network trial of low tidal volume [9], and was subsequently compared to a modified table assigning higher PEEP at moderate FiO<sub>2</sub> tables in the ALVEOLI and LOVS trials [27, 28]. Individually, none of these trials (ExPress, ALVEOLI, LOVS) comparing higher (day 1 mean 15.3 cmH<sub>2</sub>O) versus lower (day 1 mean 9.0 cmH<sub>2</sub>O) PEEP strategies showed a difference

in mortality. However, when combined in an individual patient data meta-analysis, significant heterogeneity of treatment effect emerged, with higher PEEP lowering mortality in patients with baseline  $\text{PaO}_2/\text{FiO}_2$  below 200, and a trend for increased mortality in patients with  $\text{PaO}_2/\text{FiO}_2$  between 200–300 [29]. Similar differential mortality effects have been demonstrated in these trial populations when grouped according to inflammatory profile [30], and according to oxygenation response to PEEP increase [31]. Despite the ongoing debate of higher versus lower PEEP, in clinical practice, PEEP levels are often moderate—around 8–10 cm of water, even in severe ARDS [8]. From a physiological and clinical standpoint, in severe ARDS, where lung compliance is low, it makes intuitive sense to cycle tidal volume (and  $\Delta P$ ) from a higher opening pressure or higher PEEP. However, the extent to which higher PEEP will be tolerated, is largely dependent on the severity of lung injury, its impact on pulmonary circulation and the patient's cardiovascular reserve. These need to be frequently evaluated at the bedside when adjusting PEEP. In part, these complex and dynamic influencing factors have made protocolized PEEP strategies challenging to study.

Recruitment maneuvers—sustained inflations, intermittent sighs, or stepwise increases in airway pressure—are sometimes recommended in combination with higher PEEP—but their role and benefit to harm ratio need to be determined in further studies. The routine use of aggressive staircase recruitment in ARDS patients is not recommended after a large randomized trial found an increased mortality in the group treated with a recruitment maneuver combined with decremental PEEP titration based on best compliance [32]. Similarly, recruitment with high frequency oscillatory ventilation (HFOV) is not routinely recommended for most ARDS patients, since two trials showed no survival advantage and a potential signal for harm [33, 34].

### ***Evolving standards***

The individual titration of PEEP, with the target of using higher levels of PEEP in patients who are more recruitable, has been a long-sought goal. Indeed, analyses from a recent trial suggest outcomes may be worse when ventilatory strategy is misaligned with lung morphology [35]. In the past it was suggested that setting PEEP 2 cm of water above the lower inflection point of the volume-pressure curve would keep the lung open, [36]; however, we now recognize that with that technique recruitment often occurs throughout inspiration [37, 38]. Numerous emerging methods are available to help guide PEEP titration by bedside clinicians. One simple approach is to start with PEEP prescribed by a PEEP/ $\text{FiO}_2$  table and then titrate PEEP up or down to achieve the lowest possible driving

pressure [39]. Another bedside method for assessing the impact of PEEP is the recruitment:inflation (R:I) ratio, which informs how many new lung units are recruited versus existing lung units stretched for a given change in PEEP [40]. This can be easily calculated with online tools (rtmaven.com), with values  $>0.5$  indicating higher amounts of recruited lung.

Another technique for setting PEEP is to measure esophageal pressure (as surrogate for pleural pressure) to estimate end-expiratory transpulmonary pressure ( $P_{Lexp}$ ); the PEEP can then be set to maintain  $P_{Lexp}$  around 0. This approach was compared with the original ARDS Network lower PEEP- $\text{FiO}_2$  table in a single-center study, leading to large increases in PEEP with concomitant improvements in oxygenation and even a hint at a mortality benefit [41]. A subsequent multi-center study then compared this approach with a higher PEEP- $\text{FiO}_2$  table; this led to similar levels of PEEP between the two groups, and perhaps unsurprisingly, no differences in clinical outcomes were detected [42].

Electrical impedance tomography (EIT) is a non-invasive, radiation free, imaging method for assessing lung morphology, and guiding ventilatory strategy. EIT can be used to titrate PEEP and balance the competing interests of recruiting atelectatic lung units while limiting overdistention in those already aerated, by assessing aeration loss and overdistention [43, 44]. Although physiologically promising, its availability is currently limited and its use is largely confined to research. Before it is widely adopted for clinical use, large randomized clinical studies would be needed to demonstrate clinical advantages and generalizability.

### **Spontaneous breathing in ARDS patients**

#### ***Evolving standards***

Spontaneous breathing during mechanical ventilation has long been recognized to improve oxygenation, and to minimize diaphragm atrophy; therefore, it may confer advantage in ventilated patients [45]. Partially assisted breathing is commonly employed even in moderate-severe ARDS patients and is associated with improved outcomes in observational data [46]. However, there are concerns of treatment indication bias in these data, and spontaneous breathing with or without assistance may lead to further lung injury; this has been termed patient self-inflicted lung injury (P-SILI), though we note that this does not imply any intent on behalf of the patient [47]. In the early phase of ARDS, augmented spontaneous breathing may induce patient-ventilator dyssynchrony and high tidal volumes which could promote lung injury.[48] Airway pressure release ventilation (APRV) is a time-cycled mode in which airway pressure alternates between high and low pressure settings, but also allows

spontaneous breathing [49]. Although a single center RCT recently showed improved physiological and clinical outcomes [50], a pediatric ARDS trial was stopped early because of increased mortality in the APRV arm [51], and a recent meta-analysis 14 studies showed improvements in oxygenation with APRV but no difference in ICU stay and mortality between groups [52].

Non-invasive ventilation (NIV) and high-flow nasal oxygen (HFNO) are increasingly being considered for use in the early phase of ARDS, particularly following the publication of the FLORALI study [53]. This three-arm trial suggested that HFNO was better than facemask NIV in preventing intubation and even reducing mortality in more severe hypoxemia. While NIV may be useful in selected patients, NIV delivered by facemask does not seem protective for patients with early ARDS, especially those with moderate or severe ARDS [54]. However, a small single-center RCT showed reduced need for intubation and a trend toward improved mortality with helmet NIV compared to NIV delivered by face mask [55]. The clinical benefits of HFNO in de novo situations of respiratory failure have been systematically reviewed, showing that it reduced the need for intubation and invasive ventilation [56]. More recently, a network meta-analysis demonstrated that both HFNO and helmet NIV each lowered mortality compared with standard oxygen therapy in patients with acute hypoxemic respiratory failure [57], but the relative benefit of HFNO versus helmet NIV remains to be determined.

## ARDS due to COVID-19

### *Evolving standards*

In 2020 the coronavirus disease 2019 (COVID-19) pandemic has swept across the world and has resulted in thousands of patients with severe respiratory failure and ARDS, often overwhelming regional healthcare systems. Early in the pandemic as intensivists were grappling with a new disease, several reports were published (and extensively promulgated on both social and mainstream media) suggesting that ARDS due to COVID-19 was different than non-COVID ARDS and that different ventilatory strategies should be used [58, 59]. As more information has emerged in the last several months; however, it appears that ARDS due to COVID-19 often looks like and behaves similarly to ARDS from other causes [60–62]. On the other hand, COVID-19 ARDS is still an area of uncertainty. While further knowledge about COVID-19 treatment will undoubtedly emerge, at this stage it seems reasonable to us to apply the same ventilatory approach to patients with COVID-19 ARDS [63], taking into account, of course, the specific physiology/biology of the individual patient.

## Ventilation adjuncts

### **Prone positioning**

#### *Current standards*

Prone positioning is one of the most effective strategies in patients with moderately-severe ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150$  mmHg) and is the cornerstone of adjunctive therapies in these patients as it improves survival [64]. Prone positioning frequently leads to an improvement of gas exchange but the improved survival does not depend on improved oxygenation [65, 66]. This improved survival is likely mediated through a decrease in ventilator-induced lung injury due to a more uniform distribution of volume and distending forces across the lung. Several clinical trials have convincingly demonstrated that prone positioning applied early and for at least 16 h/day in ARDS patients with  $\text{P}/\text{F} < 150$  mmHg reduces mortality [64, 67]. Current guidelines recommend long daily sessions of prone positioning in moderate to severe ARDS [68]. Of note, the LUNGSAFE study reported that only 16.3% of eligible patients were treated with proning [8]. Logistical difficulties, fear of complications, and under-recognition of the hypoxemia criteria all contribute to the relatively low implementation of prone positioning [69]. However, indications for its use are straightforward: to achieve improved survival, patients with moderate to severe ARDS need prone-positioning early and for a prolonged (e.g., 16 h) duration, with the concurrent use of lung-protective ventilation and experienced staff to minimize the procedural risks. In short, prone positioning should be applied as a first-line therapy in moderately-severe and severe ARDS and generally be continued daily until  $\text{PaO}_2/\text{FiO}_2$  is stable above 150 mmHg in the supine position [64].

#### *Evolving standards*

In patients with ARDS due to COVID-19, use of prone positioning for a prolonged period of time (36 h) was safe and associated with a more pronounced impact on oxygenation compared to 16 h of prone positioning [70]. Earlier in the disease course, awake spontaneous breathing COVID-19-patients has been described and promoted, with most patients responding with an increase in arterial oxygenation while prone position [71]. However, the efficacy of prone-positioning in spontaneously ventilated patients remains experimental and limited to case series.

### **Neuromuscular blockade**

#### *Current standards*

As discussed above, high respiratory drive and subsequent strong spontaneous respiratory effort in ventilated patients with ARDS may result in severe patient-ventilator dyssynchrony and increased lung injury. Therefore, it has been proposed that early neuromuscular blockade

might prevent these effects and improve outcomes. In 2010, Papazian and colleagues published a multicenter RCT showing that 48 h of cisatracurium infusion improved adjusted survival and increased time off the ventilator compared with deep sedation without paralysis in patients with moderate-severe ARDS [72]. Despite these encouraging results, neuromuscular blockade was commonly (38% of severe ARDS) but not universally adopted in clinical practice [8]. Some reluctance to use paralysis may arise because of concerns about long-term effects on muscle strength [73], or about the need for concomitant deep sedation [74].

Furthermore, the recent ROSE trial draws into question the utility of neuromuscular blockade in all patients with moderate-severe ARDS. In this study, patients with moderate-to-severe ARDS were randomly assigned to infusion of cisatracurium and concomitant deep sedation, or to usual-care with lighter sedation targets [75]. The trial was stopped early for futility and did not show a difference in mortality between groups. For now, although the evidence is inconclusive, we suggest that neuromuscular blocking agents should not be used routinely in all patients with moderately severe ARDS, but should be reserved for those patients, where there is specific indication, e.g., those in whom lung protective ventilation is not possible because of severe patient-ventilator asynchrony or markedly increased respiratory drive, those with persistent high driving pressure, or who are difficult to oxygenate or ventilate [76].

### **Inhaled nitric oxide (iNO)**

#### **Current standards**

Inhaled nitric oxide (iNO) mediates a selective vasodilation of the pulmonary circulation of ventilated regions, reduces right-to-left shunting and, transiently, improves oxygenation in some patients with ARDS [77]. To date, there are no studies that have demonstrated beneficial effects of iNO on clinical outcomes in ARDS patients, even for patients with very severe hypoxemia [78]. As such, and given the high costs of iNO in many jurisdictions, we do not recommend the routine use of iNO in patients with ARDS.

### **Extracorporeal lung support**

#### **Current standards**

Veno-venous extracorporeal membrane oxygenation (vvECMO) has been proposed for patients with severe ARDS based on two potential mechanisms: (1) providing adequate oxygenation to prevent or reverse tissue hypoxia, and (2) allowing for a reduction in the intensity of mechanical ventilation substantially reducing VILI. In the first of the two modern-era ECMO RCTs, the CESAR trial compared transfer to an ECMO center and possible

ECMO versus ongoing usual care at the referring center in patients with severe ARDS [79]. The primary outcome of death or severe disability at 6 months was significantly lower in the ECMO center group. However, the study has several methodological limitations and its interpretation is complicated by the large number of control patients who did not receive lung-protective ventilation, and the significant number of patients in the ECMO group who did not actually receive ECMO. During the 2009 influenza pandemic, several observational studies suggested beneficial effects of vvECMO in influenza A(H1N1)-related ARDS [80, 81], though similarly low mortality rates were also reported in series, where ECMO was not widely applied [82, 83].

Recently, the EOLIA RCT studied early vvECMO in adults with severe ARDS and significant hypoxemia ( $P/F < 80$ ) or who were difficult to safely ventilate compared with ongoing conventional treatment with ECMO rescue if required [84]. Strengths of this trial include high adherence to conventional lung protective ventilation and prone positioning in excess of 90% in the control group, and ultra-protective ventilation facilitated by vvECMO uniformly used in the intervention group. Mortality was lower in the vvECMO group (35% versus 46%) despite a high rate of rescue crossover, though the effect did not reach nominal statistical significance ( $p = 0.09$ ). The key secondary endpoint of death or crossover to ECMO was highly significant, most other secondary endpoints favored the ECMO group, and adverse events were evenly distributed, leading editorialists to suggest that 'ECMO probably has some benefit in this context, despite the trial not being traditionally positive' [85]. In keeping with this thought are results of a meta-analysis combining the CESAR and EOLIA trials, which shows a statistically significant reduction in mortality [86]. Furthermore, a post hoc Bayesian analysis of EOLIA suggested that vvECMO was very likely to reduce mortality in patients with severe ARDS across a broad set of underlying prior assumptions [87]. All of these data suggest that vvECMO should be considered in patients still meeting EOLIA inclusion criteria, after less invasive therapies including prone positioning have been implemented or considered [88]. In other words, currently available data suggest that outcomes in ECMO are best when used in severe ARDS patients who are younger, with reversible etiology, few co-morbidities and when employed in experienced centers [89].

#### **Evolving standards**

The role of vvECMO in the supportive care of patients with COVID-19 ARDS was initially questioned, but a recent analysis from the ELSO registry showed mortality of around 40% in these patients, similar to patients

receiving vvECMO for other causes of ARDS and suggesting similar indications could be used [89].

The role of ECLS to facilitate ultra-lung protective ventilation is an evolving area, with a recent individual-patient data analysis from CESAR and EOLIA showing that vv-ECMO was most beneficial in patients with only 1 or 2 organ failures and was not as helpful in those with the most severe hypoxemia [90]. This concept has been explored with lower flow extra-corporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) in pilot studies [91], a single small RCT [92], and is the subject of ongoing RCTs. Because of the uncertainty around efficacy and potential risks, we believe that this indication of ECLS should be reserved for patients in the context of clinical trials at the current time.

## Pharmacotherapy

### Steroids

#### *Evolving standards*

Due to their anti-inflammatory and immune-modulating properties, glucocorticoids have been considered and studied as a therapy for ARDS for decades. Many such trials have been small single center studies with potential for bias. One exception to this was the ARDS Network late ARDS steroid trial, which showed no differences overall, but a suggestion of harm if steroids were started more than 2 weeks after ARDS onset [93]. Meta-analyses of all these trials have suggested that steroids may decrease mortality, some with statistical significance [94], some without [95]. However, these meta-analyses predated a recently published multicenter RCT in 277 patients by Villar et al. that found that early administration of dexamethasone (20 mg/day from days 1–5, and 10 mg/day from days 6–10) reduced duration of mechanical ventilation and mortality. A subsequent sequential meta-analysis published this year does show a significant reduction in mortality with the use of corticosteroids, but the low number of total patients randomized raised concerns about false positive results in the sequential analysis [96]. Thus, the role for corticosteroids in early ARDS remains controversial.

A number of recent studies have evaluated the role of corticosteroids in respiratory failure due to COVID-19. The RECOVERY trial demonstrated that low-dose dexamethasone for 10-day reduced mortality in hospitalized patients with COVID-19 who required oxygen or respiratory support [97]. A recent prospective meta-analysis of clinical trials of critically ill patients with COVID-19 included more than 1700 patients from 12 countries and demonstrated that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality [98]. Thus, in contrast to ARDS from other causes, we have a moderate degree of certainty that corticosteroids may improve

outcomes in patients with COVID-19, although some basics of this disease are not yet understood. The extent to which these results might apply to non-COVID ARDS are uncertain, but we hope that these positive results from the pandemic will spur renewed interest in steroid RCTs in other patients.

### Fluid management

#### *Current standards*

The clinical axiom that ARDS patients who are not in shock should be treated with a conservative fluid treatment strategy is supported by the FACCT trial, which showed improved lung function and more ventilator-free days with this strategy [99]. These findings have been extended with similar outcomes using a simplified version of the conservative strategy, considering only CVP and urine output, enacted once the blood pressure is stabilized off vasopressors [100]. It has been recommended that patients with ARDS who no longer have shock should have their overall fluid balance reduced by 500–1000 mL per day by use of diuretics, and reducing intravenous fluids until they are euvolemic.

#### *Evolving standards*

A secondary analysis of the FACCT trial found significant heterogeneity of treatment effect in terms of mortality based on baseline central venous pressure levels; those with CVP of 8 or less had significantly lower mortality when managed with the *conservative* fluid strategy [101]. This result, which might initially seem paradoxical, suggests it may be avoidance of excess fluid administration that is of most value, rather than diuresis. This same dataset was examined for the effect of hypo- and hyper-inflammatory phenotypes, and again the fluid restrictive strategy was beneficial in the hyper-inflammatory group, while the opposite was true in the hypo-inflammatory group [102]. These findings are in keeping with a recent clinical trial in septic children in Africa, and with an ovine sepsis study suggesting harm and inflammation with fluid administration [103, 104]. A large RCT is ongoing in patients with septic shock, many of whom will likely have ARDS, comparing a strategy of restrictive fluid and early vasopressors with liberal fluids, which will likely inform future practice in this area (NCT03434028).

### Other specific pharmacotherapies

#### *Evolving standards*

Multiple pharmacological therapies to improve clinical outcomes of ARDS have been evaluated, but none of them have proved effective. Surfactant,  $\beta$ 2-adrenergic agonists, prostaglandin E1, activated protein C, several antioxidants, omega-3 supplementation, ketoconazole, recombinant human factor VIIa, statins, interferon beta,

vitamin C, and many others have been tested in clinical and pre-clinical trials without showing beneficial outcomes [95, 105]. Given the lack of specificity of the Berlin definition of ARDS, it is perhaps unsurprising that pharmacotherapies targeting specific biological pathways have failed to show benefit in outcomes. Subsumed within the Berlin definition of ARDS are multiple etiologies and dysfunctional biological pathways. While the definition probably captures a consistent physiological end-manifestation of critical illness, it does not capture biological uniformity. Therefore, for biological therapies, and perhaps even some supportive therapies, more considered approaches that seek to enrich the study population to test interventions are needed. Interestingly, PROSEVA, ACURASYS, and DEXA-ARDS trials, where positive findings were observed with interventions, tested efficacy in an enriched population based on severity of ARDS [64, 72, 106]. Elsewhere, investigators have sought phenotypes in secondary analyses of RCT based on biological markers, with hypo- and hyper-inflammatory phenotypes being consistently identified [107]. As with interventions of PEEP or fluids, retrospective analyses of ARDS clinical trials have suggested there may be subsets of patients for whom pharmacotherapies such as statins may be of benefit [30], but the findings have not always been consistent [108]. Further research is needed to identify subgroups of patients that benefit from specific pharmacological treatments.

## Conclusion

In this review we have chronicled current and evolving standards of care from the definition itself and across the domains of ventilatory management, ventilatory adjuncts and pharmacotherapy for adults with ARDS. While it is clear that much progress has been made, there remains much work to be done. Now, 10 years after the Berlin definition was conceived, an update to our standard definition of ARDS is needed. This may then impact future research with targeted investigations in patients most likely to benefit. Areas ripe for investigation are many and across all domains, including for example ultra-protective ventilation facilitated by ECLS, stromal cell therapies, and prospective replication of effects by hyper/hypo inflammatory sub-phenotype. We look to these future developments with much anticipation.

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## Compliance with ethical standards

### Conflicts of interest

NF declares personal fees from Getinge and Xenios, outside the present work. ASN declares personal fees from Dräger, outside the present work. AS declares personal fees from Apeiron, Baxter, and Xenios, outside the present work. CS's laboratory is financially supported by the Wellcome Trust, the Medical Research Council, GlaxoSmithKline plc, AstraZeneca, and the NIHR Cambridge Biomedical Research Centre.

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