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WHAT'S NEW IN INTENSIVE CARE

Adjuvants to mechanical ventilation for acute respiratory distress syndrome

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Introduction

An adjuvant for the acute respiratory distress syndrome (ARDS) is any intervention, in addition to or instead of mechanical ventilation, that is used to facilitate gas exchange or enhance compliance with lung protective ventilation (Table 1). Pharmacologic adjuvants have been the focus of many studies for years and include diuretics, corticosteroids, neuromuscular blocking agents, and inhaled pulmonary vasodilators. Non-pharmacologic agents include prone positioning, high frequency oscillatory ventilation, and extracorporeal life support. These non-pharmacologic options have been the focus of many large trials in recent years. This paper discusses the relative efficacy of these adjuvants and reviews their current use.

Pharmacologic adjuvants

Non-hydrostatic pulmonary edema is one of the hallmarks of ARDS. Additionally, excess fluid administered during the resuscitation phase of septic shock could contribute to the development of abdominal compartment syndrome, further restricting lung expansion. The Fluid and Catheter Treatment Trial (FACTT) assessed a conservative fluid management strategy combined with diuretic administration as a mechanism to improve lung compliance and oxygenation, finding an increased number of ventilator-free days [1]. However, the complex algorithm, lack of mortality benefit, and evidence of increased neurocognitive complications might impact widespread adoption [2]. Evidence of adoption of diuretic administration has not been extensively evaluated following this publication [1]. Variability in use of diuretics for ARDS has been reported across different centers. In a recent survey administered to intensivists in Australia and New Zealand evaluating diuretic use, 74 % of intensivists indicated that they would administer loop diuretics for ARDS; however, approximately 20 % reported that they would not [3]. An observational study evaluating prescribing patterns across 150 ARDS patients demonstrated that loop diuretics were only actually prescribed in 39 % of patients [4]. Despite an increasing focus on the harms associated with a positive fluid balance in patients, there is a lack of evidence on how physicians implement this in practice. Non-invasive hemodynamic monitoring devices leading potentially to more precise evaluations of volume status or a focus on "de-resuscitation" in sepsis have perhaps led to changes in diuretic administration. More insight into current practice, particularly in light of the recent publication of "FACTT lite" which provides a simpler approach to a conservative fluid management strategy, is needed to highlight whether areas for improved compliance with diuresis exist [5].

The early administration of corticosteroids as a mechanism to combat septic shock, as well as the late administration of steroids in the fibroproliferative phase of ARDS, has been evaluated extensively in trials. However, beyond steroid responsive precipitants for ARDS, a role for corticosteroids in routine care of ARDS patients has not been established [6]. Promising preliminary evidence currently exists for its potential role in preventing ARDS in the setting of severe community-acquired pneumonia [7]. Despite these findings, current use of corticosteroid for ARDS patients remains variable but high. One

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Take-home message: Pharmacologic and non-pharmacologic adjuvants to mechanical ventilation have been evaluated extensively in clinical trials; however, reports of their actual use for ARDS are limited. Many non-evidence factors drive adoption and de-adoption in critical care and therefore understanding their real-world use is needed to enhance bedside care.

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Table 1 Reported use of common adjuvants in ARDS

Adjuvant	Reported use in ARDS
Pharmacologic	
Diuretics	39 % of patients with ARDS (single-center retrospective study) [4] Survey of intensivists: 70 % reported use [3]
Corticosteroids	70 % of UK physicians surveyed used corticosteroids in ARDS: Of these, 30 % reported initiating early in ARDS (≤7 days), 53 % reported initiating late in ARDS (>7 days) [9] LUNG SAFE[a]: 17.3 % reported use across all ARDS, 23.3 % severe ARDS [10]
Continuous neuromuscular blocking agents	(Pre-Papazian trial): 15–23 % use in ARDS [9, 13] (Post-Papazian trial): LUNG SAFE: 37.8 % severe ARDS [10]
Inhaled nitric oxide	29–44 % [8, 9, 15] LUNG SAFE: 7.7 % reported use[b] across all ARDS, 13.0 % severe ARDS [10]
Non-pharmacologic	
Prone positioning	(Post-Guerin trial) LUNG SAFE: 7.9 % across all ARDS, 16.3 % severe ARDS [10]
High frequency oscillatory ventilation	(Pre-Ferguson/Young trials): 7–50 % (rescue therapy) [19, 20] (Post-Ferguson/Young trials): LUNG SAFE: 1.5 % severe ARDS [10]
Extracorporeal membrane oxygenation	12-fold increase in rate of use over the past decade (2004–2014) [23] LUNG SAFE: 3.2 % across all ARDS, 6.6 % severe ARDS [10]

ARDS acute respiratory distress syndrome

[a] High corticosteroids dose defined as equivalent to 1 mg/kg methylprednisone

[b] All inhaled vasodilators

study reported use in 41 % of ARDS cases—higher than the use of diuretics or neuromuscular blocking agents [4]. In a 2010 questionnaire in German ICUs regarding ARDS management practices, corticosteroids were used in 52 % of hospitals [8]. In a separate study, 70 % of UK physicians surveyed in 2012 endorsed the use of corticosteroids; however, only 6 % used them routinely [9]. The LUNG SAFE study, a prospective observational study of ARDS across 50 countries, found that actual use of high dose corticosteroids (equivalent to >1 mg/kg methylprednisone) occurred in 17.9 % of patients with ARDS and 23.3 % in the subset with severe ARDS [10].

Neuromuscular blocking agents may minimize ventilator-associated lung injury by preventing large spontaneous tidal volumes, reducing ventilator dyssynchrony, and possibly decreasing the inflammatory response associated with ARDS [11]. In addition, paralysis may stop any subclinical evidence of muscle activity, potentially improving oxygenation through minimization of oxygen consumption. In one trial by Papazian et al., the continuous, early administration of cisatracurium in moderate–severe ARDS (PaO_2/FiO_2 <150) was associated with an improvement in 90-day mortality [12]. The trial found that the beneficial effect of cisatracurium was confined to patients presenting with a PaO_2/FiO_2 <120 suggesting that patients with severe ARDS might receive the greatest benefit from this intervention. Prior to this publication, a large retrospective observational study from 2005 to 2006 evaluated the impact of early administration of paralysis in patients with severe sepsis who were mechanically ventilated and found that 23 % of patients received early paralysis [13]. Following the publication of the study by Papazian et al., only 15 % of UK physicians report using neuromuscular blocking agents "routinely" [9]. Most recently, in the LUNG SAFE study (2014), paralysis was used in 21.7 % of all ARDS patients and in 37.8 % of the severe ARDS subgroup [10].

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator that acts by preferentially diffusing to capillary beds of less inflamed alveoli leading to a reduction in ventilation/perfusion mismatch and pulmonary vascular pressures; it also has anti-inflammatory properties [14]. The use of inhaled nitric oxide as a rescue therapy was characterized across six ARDS Network trials between 1996 and 2006 [15]. Of the patients who received rescue therapy, inhaled nitric oxide was the second most commonly employed agent during that time period (28 % of patients receiving rescue therapies). The most recent meta-analysis of ARDS patients has since demonstrated no mortality benefit associated with NO use regardless of severity [16]. Moreover, the use of NO was associated with an increase in the incidence of renal failure [16]. In surveys, 29–44 % of intensivists from the UK and Germany report administering NO in ARDS [8, 9]. In the LUNG SAFE study, the frequency of use of any type of inhaled vasodilator was found to be much lower: 7.7 % in all ARDS and 13.0 % in the severe ARDS subgroup [10]. However, the impact of the 2014 meta-analysis on frequency of use of NO has not been described.

Non-pharmacologic agents

Theoretically, prone positioning may prevent lung injury by recruiting non-dependent lung, improving respiratory mechanics, and clearing pulmonary secretions. The creation of more homogeneous chest wall compliance, offloading the weight of the heart, and minimizing the weight of the abdominal contents on the diaphragm are mechanisms by which prone positioning may enhance respiratory mechanics and lead to an increase in recruitable lung units. Prior to 2013, studies applied prone positioning to patients with a range of severity of ARDS. While these trials consistently demonstrated an improvement in oxygenation with prone positioning, a reduction in mortality was only seen in post hoc subgroup analyses of the most severe ARDS cohorts. The trial by Guerin et al. in 2013 focused on patients with moderately severe ARDS (PaO_2/FiO_2 <150) demonstrated an absolute mortality risk reduction of 17 % with prolonged intermittent prone positioning [17]. In 2010, 60 % of German centers reported that they proned ARDS patients and 84 % of surveyed UK intensivists in 2012 reported that they would employ prone positioning as a rescue strategy [8, 9]. Since the trial by Guerin et al., patients in the LUNG SAFE study had relatively low rates of proning: 7.9 % of all ARDS (and 16.3 % of severe ARDS patients) [10].

High frequency oscillatory ventilation (HFOV) capitalizes on the concept of open lung ventilation and minimization of cyclic tidal reopening and closing. It is a ventilator modality whereby one attempts to recruit the maximal amount using a high mean airway pressure while achieving CO_2 clearance by ventilating with small tidal volumes delivered at a high frequency. Although early randomized controlled trials (RCTs) of early HFOV in adults suggested the possibility of benefit [18], two recent, high-quality, large-scale trials failed to show any mortality benefit and one trial suggested possible harm [19, 20]. One possible explanation of the lack of benefit was more hemodynamic instability in the HFOV arm, possibly attributable to a decrease in venous return, or impairment of right ventricular afterload with higher mean airway pressure. Occult barotrauma and an increase in sedative requirements are additional plausible mechanisms [19]. Frequency of use as a rescue strategy ranged from 7 to 50 % in earlier literature [9, 15]. Most recently, much lower use has been reported from LUNG SAFE (1.2 % across all ARDS and 1.5 % in the severe ARDS subgroup) [10].

Venovenous extracorporeal membrane oxygenation (ECMO) is a form of partial cardiopulmonary bypass that acts as an oxygenating and ventilatory shunt and can allow a reduction in the intensity of invasive mechanical ventilation or complete lung rest. An RCT (CESAR trial) in 2009 evaluated the impact of transport to an ECMO-capable center in patients with severe ARDS and demonstrated an improvement in disability-free survival. However, some unanswered questions included whether the improved outcome was due to ECMO itself or being managed at an expert center, as not all patients received ECMO. In addition, a lack of compliance with lung protective ventilation in the non-protocolized control arm might have contributed to the difference in outcomes [21]. Given some conflicting recent evidence regarding the benefit of ECMO in very severe ARDS [22], an international multicenter trial is currently underway to evaluate its use in this population (NCT01470703). Extracorporeal CO_2 removal ($ECCO_2R$) can help facilitate a drop in ventilation intensity in patients with significantly impaired compliance in severe ARDS thus allowing "ultra" lung protective tidal volumes [22]. Preliminary research has demonstrated promising results from the combination of "ultra" lung protective ventilation and $ECCO_2R$ and is currently under further evaluation (NCT02282657) [22].

The creation of modern extracorporeal circuitry technology, in combination with the publication of the CESAR trial [17] and the subsequent H1N1 influenza outbreak, has led to an exponential increase in use of ECMO; according to the Extracorporeal Life Support Organization 117 cases of adult respiratory ECMO were reported in 2004, increasing to 1497 cases reported in 2014 [23]. In the LUNG SAFE study, 6.6 % of patients with severe ARDS across the 50 countries received ECMO [10]. Reports of the current use of $ECCO_2R$ specifically for ARDS outside of its application for obstructive lung disease or bridge to lung transplant are not yet known.

The adjuvants reviewed here are only a few of many potential pharmacologic (e.g., aspirin, statins) and non-pharmacologic (e.g., non-invasive ventilation) adjuvants that continue to be assessed. Our review selectively focused on adjuvants studied across multiple large clinical trials over the past few decades.

Factors affecting adoption and de-adoption

Given the heterogeneity of ARDS, decision-making about the use of adjuvant therapy in specific subgroups of patients is complex. For example, in advance of the positive proning trial described above, many clinicians advocated for the use of prone ventilation on the basis of the compelling physiologic rationale and limitations of the existing trials. Since statistically negative trials cannot prove lack of efficacy, arguments can be offered about the use of treatments from these trials in different patient subsets or with different protocols than those studied. In addition, the evolution of the evidence regarding adjuvants spans decades of ARDS research including some

trials conducted before pressure- and volume-limited ventilation became the standard of care, adding to the uncertainty of treatment effects [24].

More importantly, when the evidence base is weak or inconsistent, as it is in much of medicine, factors other than evidence drive adoption and de-adoption. For example, many of the ARDS adjuvants improve oxygenation. Despite the lack of association between oxygenation improvement and mortality, physicians are likely to reach for these adjuvants for the reassurance provided by improving oxygenation. Other factors may also drive adoption and de-adoption including experience with the treatment, cost, availability, perceived risk, and patient comfort [25].

Conclusions

This review highlights adjuvants to standard mechanical ventilation for ARDS patients, the limited evidence base for the use of many of these adjuvants, and the available data regarding how they are deployed in current practice. Given the high costs in terms of equipment and personnel associated with the use of many of these adjuvants, more research surrounding trends in use, the impact of evidence on use, and factors that may influence adoption and de-adoption of these adjuvants is needed.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflicts of interest.

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