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American Association for the Surgery of Trauma/American College of Surgeons Committee on Trauma Clinical Protocol for Management of Acute Respiratory Distress Syndrome and Severe Hypoxemia

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ABBREVIATIONS:

ARDS: Acute respiratory distress syndrome

APRV: Airway pressure release ventilation

BMI: Body mass index

CPAP: Continuous positive airway pressure

HFOV: High Frequency Oscillatory Ventilation

ICU: Intensive care unit

iNO: Inhaled nitric oxide

LRM: Lung Recruitment Maneuver

LTV: Low tidal volume

NMBA: Neuromuscular blocking agents

P/F ratio: PaO_2/FiO_2 ratio

P-SILI: Patient self-induced lung injury

Pplat: Plateau pressure

PEEP: Positive end expiratory pressure

PBW: Predicted body weight

PCV: Pressure control ventilation

RCT: Randomized controlled trial

TBI: Traumatic brain injury

TCAV: Time-controlled adaptive ventilation

TQIP: Trauma Quality Improvement Program

VCV: Volume control ventilation

VT: Tidal volume

VV-ECCO$_2$R: Veno-venous Extracorporeal carbon dioxide removal

VV-ECMO: Veno-venous Extracorporeal Membrane Oxygenation

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute, diffuse lung injury characterized by hypoxemia (**Table 1**). [1 2] It was first described in 1967 in 12 patients as acute hypoxic lung injury with markedly reduced pulmonary compliance related to trauma in 7 patients, and aspiration/viral pneumonia in 5 patients. [3]

Globally, ARDS affects approximately 3 million patients annually, with over 200,000 in the United States. ARDS was present in 10.4% of critically ill patients in a multicenter large international study including nearly 30,000 ICU patients, with a hospital mortality of 46.1% in those with most severe hypoxemia. [4] ARDS accounted for 24% of patients receiving mechanical ventilation in the ICU. Common etiologies of ARDS include pneumonia (bacterial, viral, fungal), aspiration, sepsis, trauma, blood transfusion, burns and inhalation injury, and pancreatitis. A U.S. multicenter study of 2466 moderate/severe ARDS patients reported 28-day mortality rate of 41% (range 16.7% - 73.3%), and confirmed substantial variability in ARDS management, with initial adherence to lung protective ventilation of only 31.4%. [5]

ARDS is still associated with high morbidity and mortality in trauma patients. A systematic review of 43 studies reported an overall median ARDS incidence of 8.4% in trauma. [6] Patients with thoracic injuries, including pulmonary contusions, are particularly at high risk for the development of ARDS, occurring in 10-25% of these patients. [7] Other trauma patients at high risk for ARDS include patients requiring massive transfusion with aggressive fluid and blood product resuscitation, and those with traumatic brain injury. In a meta-analysis of 20 studies (n=2830), approximately one in five patients had ARDS after traumatic brain injury within a

median time of 3 days and was associated with increased mortality and worse neurologic outcome. [8] ARDS can increase the risk of in-hospital death by three-fold in traumatic brain injury patients. [9]

A systematic review and meta-analysis of prognostic factors for development of ARDS following traumatic injury included 39 studies involving over 5.3 million patients and identified the amount of crystalloid resuscitation with the first 24 hours of injury as a modifiable risk factor (adjusted OR 1.19, 95% CI 1.15-1.24 for each additional liter of crystalloid administered within the first 6 hours after injury; high certainty). Non-modifiable prognostic factors with a moderate or high certainty of association with post-traumatic ARDS included increasing age, non-Hispanic white race, blunt mechanism of injury, presence of head injury, pulmonary contusion or rib fracture, and increasing chest injury severity. [10] Early ARDS after trauma due to over-resuscitation has decreased due to improved trauma resuscitation strategies, but ARDS related to TBI and pneumonia/sepsis persists. A recent systematic review (20 studies, n=2830) reported that 19% of patients had ARDS after TBI, with a median time of 3 days. ARDS was associated with higher mortality and worse neurologic outcomes. [11] Other studies have confirmed a second peak of ARDS later in the ICU course related to pneumonia and sepsis. [12]

While the incidence of trauma-induced ARDS has decreased, mortality in trauma patients with ARDS has increased. In the largest study of almost 3 million patients from the National Trauma Data Bank, 1% developed ARDS, but decreased from 1.4% to 0.5% over the 4-year study period. Hospital mortality was 22% in ARDS trauma patients, but increased from 21% to 28% over the study period. ARDS risk factors included direct thoracic injury, increased age, male sex, higher

ISS, lower GCS. [13] In another study of over 800,000 Trauma Quality Improvement Program (TQIP) patients between 2010-2014, the incidence of ARDS decreased over the study years (3% to 1.1%) but ARDS-related mortality increased (18 to 21%, p=0.001). ARDS risk factors included older age, male sex, and African American race. Mortality risk factors included older age, male sex, lower Glasgow Coma Scale and higher ISS. [14]

Because many of the ARDS risk factors are non-modifiable, this protocol focuses on the treatment of ARDS in trauma patients. Providing ARDS patients with optimal, evidence-based care improves outcomes. Protocolized management ensures that ICU teams at the bedside have guidance regarding what constitutes the best evidence-based care. [15]

Protocol Rationale and Goals

The goals of this protocol are to ensure that: 1) ARDS and severe hypoxemia are recognized in the management of the trauma patient and 2) treated with evidence-based strategies to improve outcomes. Importantly, there are no randomized controlled trials specific to the trauma population for ARDS treatment strategies, and post-traumatic ARDS represented only 8-13% of the study cohorts enrolled in existing trials. Thus, these treatment recommendations are mostly extrapolated from the results of randomized controlled trials in medical and non-trauma surgical patients.

While there are many published algorithms and protocols for the management of ARDS and severe hypoxemia, the lack of trauma-specific trials leaves questions as to how to apply them in trauma patients. Given the gaps in the data, there is a need for a consensus clinical ARDS

algorithm and protocol that addresses the specific needs of trauma patients for implementation across all trauma centers with a brief evidence summary to guide management.

Stakeholders from the American Association for the Surgery of Trauma and the American College of Surgeons—Committee on Trauma established a work group to create a clinical protocol. The work group conducted a literature review to identify prospective and retrospective studies related to ARDS and severe hypoxemia in trauma patients. These studies were reviewed by members of the group, and consensus guidelines were generated based on current literature and expert opinion.

The clinical protocol and evidence-based algorithm (**Figure 1**) presented here is based on best available evidence from national and international ARDS guidelines (**Table 2**) and the consensus of experts on this panel. However, treatment decisions regarding ARDS management in trauma patients should be individualized for each patient and do not exclude other treatment strategies as being within the standard of care. Ultimately, the responsibility to implement treatment decisions rest with the treating physician at bedside in the intensive care unit.

EVIDENCE BASE: BRIEF SUMMARY

DIAGNOSIS:

Diagnosis of ARDS (**Table 1**) is delayed or missed in many patients. In the LUNG-SAFE study (largest international ARDS study), ARDS diagnosis was missed in 40% and delayed/missed in two thirds of patients. Early diagnosis of ARDS facilitates early appropriate treatment including protective lung ventilation and other treatment strategies which may improve survival. [16 17]

TREATMENT:

Treatment strategies for ARDS include the three broad categories of mechanical ventilation, pharmacologic treatments, and adjuncts. We provide a brief discussion of the evidence regarding the treatment strategies in each of these categories, with review of appropriate indication and whether the treatment has an impact on mortality or oxygenation (**Table 3**).

MECHANICAL VENTILATION:

Low tidal volume, Low plateau pressure

Protective lung ventilation using low tidal volume (LTV, 4-8 mL/kg predicted body weight) and low plateau pressure (< 30 cm H_2O) is the current standard of care for ARDS management, associated with decreased mortality and prevention of ventilator-induced lung injury. [18] [19] A recent systematic review and meta-analysis of 7 RCTs with 1481 patients concluded "The trend toward lower mortality with LTV ventilation in the primary analysis and the significant relationship between the degree of tidal volume reduction and the mortality effect together suggest, but do not prove, that LTV ventilation improves mortality among critically ill adults with ARDS." Importantly, high PEEP co-intervention with LTV showed a greater mortality benefit (RR 0.58, 95% CI 0.41-0.82) than LTV alone. [20]

In trauma patients with ARDS, LTV ventilation will likely result in hypercapnia, and may have potential adverse effects in patients with traumatic brain injury. In patients with both ARDS and traumatic brain injury, optimal $PaCO_2$ targets with LTV ventilation should be adjusted to maintain adequate cerebral perfusion pressure and cerebral oxygen delivery using a personalized approach based on intracranial pressure and multimodal brain and cerebral monitoring. [21] [22] [23]

Optimal and High versus Low PEEP

Current evidence supports that patients with moderate or severe ARDS ($PaO_2/FiO_2 \leq 200$) should receive higher levels of PEEP, based on a meta-analysis of individual patient data from 3 large RCTs of higher vs. lower PEEP. [24] [25] Patients with moderate/severe ARDS randomized to higher PEEP had significantly lower mortality (adjusted RR, 0.90; 95% CI, 0.81–1.00) and better oxygenation (higher P/F ratio). In contrast, higher PEEP had no significant effect in the patients with mild ARDS (adjusted RR, 1.29; 95% CI, 0.91–1.83; $P = 0.02$ vs. moderate/severe ARDS group). [26] [27] These data support the use of the "HIGH" PEEP Table in moderate/severe ARDS patients in whom it improves oxygenation without reducing pulmonary compliance or worsening hemodynamic status. A recent Bayesian network meta-analysis of 4646 moderate-severe ARDS patients confirmed that the use of higher PEEP was superior to that of lower PEEP for 28-day mortality, and use of a brief recruitment maneuver (<60 seconds) was also associated with a mortality benefit as compared to a lower PEEP strategy. [28]

The use of "optimal PEEP", adjusted to each patient's potential for lung recruitment, has been advocated to achieve maximum lung static compliance, reduce atelectasis, avoid hyperinflation, and improved oxygenation. [29] [30] Studies are now investigating personalized PEEP levels to optimize lung recruitment selected by electrical impedance tomography, transpulmonary pressure with esophageal manometry, and the recently described recruitment-to-inflation ratio. [31] [32] [33]

In trauma patients with traumatic brain injury and ARDS, high PEEP may be detrimental as it can cause increased intracranial pressure by impaired jugular venous outflow, impeding cerebral

venous return to the right atrium, decreased mean arterial pressure, and result in decreased cerebral perfusion pressure. [34] Similarly, high PEEP may be contraindicated in those with hemorrhagic shock requiring ongoing blood product resuscitation or with distributive/neurogenic/septic shock due to vasodilation and hypotension. [35] [36] [37] Therefore, PEEP should be determined individually in trauma patients with ARDS, reviewing the risk/benefit ratio of the potential positive impact of higher PEEP in severe hypoxemia vs. the negative impact of higher PEEP on hemodynamics and intracranial pressure in specific injury patterns. For instance, in trauma patients with severe bilateral pulmonary contusions, higher PEEP may be beneficial, but in those with focal areas of pulmonary contusion PEEP can be detrimental. [38] [39] [40] [41]

Driving Pressure

Driving pressure is calculated as the difference between plateau pressure and PEEP. A secondary analysis of data from 3562 ARDS patients from 9 randomized trials confirmed that reducing driving pressure was strongly associated with increased survival. [42] A recent, large registry analysis of over 13,000 patients receiving mechanical ventilation in 9 ICUs found that increased driving pressure, or mechanical power, was associated with increased mortality and the association was stronger with worse hypoxemia. [43] Increased driving pressure is an indicator of severity of the ARDS, is related to tidal volume in volume control modes, and is associated with more complications and increased mortality. Based on these associations, some authors recommend targeting a driving pressure below 14 cm H_2O. [44] [45] [46] However, at present, there is no randomized trial evidence that a ventilator strategy focused on limiting driving pressure reduces mortality in ARDS. [47] Interestingly, driving pressure was not predictive of ARDS

outcome (mortality or mechanical ventilation duration) in severe trauma patients with chest injuries and ARDS. [48]

Lung Recruitment Maneuver (LRM)

LRMs involve transient increase in airway pressures to open/recruit collapsed lung. [49] LRM strategies include sustained inflation, intermittent sighs, stepwise increase of PEEP or airway pressure and high driving pressure. [50] [51] LRMs are commonly associated with improved oxygenation, reduced intrapulmonary shunt and increased pulmonary compliance, but may also cause hemodynamic compromise and/or barotrauma. [52] The optimal LRM method is not clear.

Current guidelines recommend that patients with moderate or severe ARDS ($PaO_2/FiO_2 \leq 200$) should be considered for LRM to improve oxygenation. A systematic review and meta-analysis of 5 RCTs suggested that LRMs in combination with higher PEEP was associated with reduced mortality. [53] A more recent systematic review including 14 RCTs reported that LRMs were not associated with reduced 28-day mortality (RR = 0.92, 95% confidence interval (95% CI) 0.82-1.04, P = 0.21), but did improve oxygenation (PaO_2/FiO_2 ratio was significantly higher - mean difference = 47.6 mmHg, 95% CI 33.4-61.8, P < 0.001). LRMs were associated with a decreased rate of rescue therapy (RR = 0.69 95% CI 0.56-0.84, P < 0.001), and an increased rate of hemodynamic compromise (RR = 1.19, 95% CI 1.06-1.33, P = 0.002), compared to no-LRM group. [54] Another review of 10 RCTs showed a significant benefit of LRMs for decreased length of hospital stay (mean difference, MD = -1.75; 95% CI, -3.40 to -0.09; p = 0.04; p for heterogeneity = 0.3, I2 = 18%) and improved PaO_2/FiO_2 ratio on the third day (MD = 52.72; 95% CI, 18.77-86.67; p = 0.002). [55]

Given the association of LRM with hemodynamic compromise, caution should be used in trauma patients with ARDS. LRM may be contraindicated in patients with traumatic brain injury and shock states, just as in the discussion regarding high PEEP strategies, a personalized approach to LRM is required in these patients.

Esophageal pressure-guided therapy

Transpulmonary pressure is the pressure distending the lung and is measured via esophageal manometry. In the EPVent-2 Study (n=200), among patients with moderate to severe ARDS, esophageal pressure-guided PEEP, compared with empirical high PEEP-FiO_2, resulted in no significant difference in death and ventilator free days. [56] These findings do not support the use of esophageal pressure-guided PEEP titration in routine ARDS management. Esophageal manometry-guided PEEP titration can be helpful in severe hypoxemia patients as a rescue strategy, particularly in obese patients and those with stiff chest walls. A recent single-institution report in obese ARDS patients confirmed that use of an individualized protocol by a lung rescue team using LRM, esophageal manometry, and hemodynamic monitoring was associated with an almost 50 percent reduction in mortality at 28 days, 3 and 6 months and 1 year. [57] A post-hoc analysis of the EPVent-2 trial reported that that PEEP titrated to end-expiratory transpulmonary pressure closer to 0 cm H_2O was associated with greater survival. [58] To our knowledge, a post-hoc secondary analysis of obese patients in the EPVent-2 trial has not been reported, and a future randomized trial in obese patients is warranted. In a recent expert review, the authors concluded: "Transpulmonary pressure represents a physiologically sound safety limit for mechanical ventilation that should be measured and targeted at least in the most severe ARDS patients. Targeting transpulmonary pressure means 'personalizing' the ventilatory settings." [59]

Airway pressure release ventilation (APRV)

In two recent systematic review/meta-analyses of RCTs, APRV was associated with improved oxygenation, mortality benefit, and increased number of ventilator-free days when compared to conventional ventilation, with no increased risk of barotrauma or worse hemodynamics. [60] [61] These data are limited, however, to inclusion of 5 RCTs with small sample size (n=330), consistent with low quality evidence and moderate heterogeneity. A more recent review of 7 RCTs with 405 patients reported similar findings. [62] A recent adaptation of APRV is time-controlled adaptive ventilation (TCAV) which was developed to minimize dynamic alveolar strain, and gradually "nudge" alveoli open and prevent alveolar collapse using a simple strategy of open-valve CPAP with brief, intermittent releases guided by changes in lung mechanics. This personalized and adaptive approach to mechanical ventilation configures each breath guided by the previous one, but still requires confirmation of efficacy in clinical trials. [63] [64] Studies have confirmed that APRV/TCAV is safe in severe TBI and does not increase intracranial pressure. [65]

High Frequency Oscillatory Ventilation (HFOV)

Two large multicenter RCTs confirmed no benefit of high frequency oscillatory ventilation (HFOV), including The Oscillation in ARDS (OSCAR) trial done in UK [66] or possible harm (higher mortality, RR 1.41; 95% CI 1.21-1.79) in the U.S. Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial. [67] HFOV should not routinely be used in patients with moderate or severe ARDS. The potential use of HFOV as a rescue strategy for severe hypoxemia has been successful in some studies and warrants further investigation.

PHARMACOLOGIC TREATMENT

Conservative Fluid Management

Hypervolemia can cause pulmonary edema with resultant hypoxemia. Randomized trials comparing liberal to conservative fluid management strategies in ARDS have confirmed better outcomes with conservative fluid management, including shortened duration of mechanical ventilation, and decreased ICU and hospital length of stay. [68] [69] [70] The Fluids and Catheters Treatment Trial (FACTT) confirmed that a conservative fluid management strategy for ARDS reduced net fluid balance and improved oxygenation and ventilator-free days. [71] A subsequent study with less strict fluid protocol (FACTT Lite) also confirmed improved outcomes. [72] Additional studies confirm that early diuretic use and conservative fluid management are associated with decreased mortality in ARDS. [73] [74] [75] Diuresis should be considered in ARDS patients without contraindications.

Neuromuscular blockade

As with other rescue strategies for severe hypoxemia, neuromuscular blockade is associated with improved oxygenation, but no improvement in survival based on the most recent systematic review and meta-analysis of 5 RCTs. [76] The French multicenter ACURASYS trial over a decade ago reported significantly lower mortality with a 48-hour infusion of cisatracurium in addition to deep sedation. [77] The multicenter Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial was stopped early for futility after enrollment of 1006 moderate/severe ARDS patients and reported no difference in 90-day mortality (42.5% vs. 42.8%). Based on these results, neuromuscular blockade can be considered in ARDS patients with severe refractory

hypoxemia or ventilator dyssynchrony that cannot be managed with sedation alone (**Figure 2**). Neuromuscular blockade is not required for prone positioning.

Inhaled pulmonary vasodilators (iNO, epoprostenol, etc)

Inhaled nitric oxide (iNO) can be considered as a rescue strategy in cases of severe hypoxemia/ARDS with P/F ratio < 100 when other strategies discussed above have not resulted in improved oxygenation, and before consideration of VV-ECMO. Systematic reviews of all RCTs documented significantly improved oxygenation with iNO treatment, but no mortality benefit. [78] [79] [80] We do not recommend the routine use of iNO in ARDS given no mortality benefit, high expense and potential risk for AKI, but it can be considered as a rescue strategy for patients with severe hypoxemia (**Table 3**). In a report examining ARDS management over a 12-year period of two randomized clinical trials, iNO use increased (24.9 to 65.8%) with no change in prone positioning (16.2 to 18.9%). [81] The increasing use of iNO in severe hypoxemia patients may result in significantly improved oxygenation, which can provide time for treatment of underlying factors contributing to ARDS.

Steroids for ARDS

The DEXA-ARDS multicenter randomized trial (n=277) documented that dexamethasone treatment (20 mg IV daily for 5 days, reduced to 10 mg once daily from day 6 to day 10) was significantly associated with increased ventilator-free days at 28 days (12.3 vs. 7.5 days, $p < 0.0001$) and an absolute 15% (36% vs 21%) reduction in all-cause mortality at 60 days in moderate-to-severe ARDS enrolled 24 hours after onset. [82] However only 21 trauma patients

were included in the DEXA-ARDS study, significantly limiting the generalizability of these conclusions regarding steroids for use in trauma ARDS.

A meta-analysis of 18 RCTs (n=2826) confirmed that the use of corticosteroids reduced mortality in patients with ARDS of any etiology (RR 0.82, 95% CI 0.72-0.95, ARR 8.0%, 95% CI 2.2-12.5%, moderate certainty). Patients who received a longer course of corticosteroids (over 7 days) had higher rates of survival compared to a shorter course. This effect was consistent for all ARDS patients, and all steroid types and dosages studied. [83] But many of these studies did not include trauma-related ARDS patients.

Systemic corticosteroids are recommended for patients with COVID-related ARDS. [84] [85]

ADJUNCTS to MECHANICAL VENTILATION

Prone position

The PROSEVA multicenter trial (27 ICUs) confirmed a significant mortality reduction in ARDS patients enrolled after a 12- to 24-h stabilization period with a PaO_2/FIO_2 ratio < 150 mmHg, with PEEP at least 5 cm H_2O, FIO_2 at least 60%, and tidal volume 6 mL/kg PBW. [86] Patients had on average 4 prone sessions of at least 16 hours duration. Prone position was continued even in the absence of improved oxygenation. This trial validated the results of a previous patient-level meta-analysis from 4 earlier randomized trials which demonstrated significant mortality reduction with prone position in severe ARDS patients. [87] Prone position should be considered in all appropriate patients and maintained daily until the PaO_2/FIO_2 ratio remains >150 mm Hg, with PEEP ≤10 cm H_2O, FIO_2 ≤ 60% for at least 4 hours after the end of the most recent proning

session. Importantly, ICU-specific prone position protocols and appropriate ICU staff training are required for patient safety.

In trauma patients with severe ARDS, specific considerations which require discussion prior to prone position therapy include need for spine stabilization, traumatic brain injury management, pelvic fracture external fixation, and open abdomen. In most cases, these are not absolute contraindications to prone positioning for treatment of severe ARDS given the high ARDS-associated mortality rate.

Veno-venous Extracorporeal carbon dioxide removal (VV-ECCO$_2$R)

LTV is associated with hypercapnia and respiratory acidosis. If the hypercapnia becomes severe, the resulting acute respiratory acidosis may cause adverse effects, including pulmonary hypertension and altered cardiac function. ECCO$_2$R provides CO_2 clearance using a small dual-lumen central venous catheter and a pump at low speed with systemic anticoagulation. Previous studies have demonstrated the feasibility of ECCO$_2$R to facilitate LTV by limiting hypercapnia and the resulting respiratory acidosis. The REST trial [88] evaluated if use of ECCO$_2$R in adults receiving mechanical ventilation for acute hypoxemic respiratory failure (n=405, P/F < 150) to further reduce LTV (≤ 3 ml/kg PBW) compared to conventional LTV (6 ml/kg PBW) would improve 90-day all-cause mortality. The study was stopped due to futility; 90-day mortality 41.5% ECCO$_2$R vs. 39.5% standard care. ECCO$_2$R was associated with increased serious adverse events including intracranial hemorrhage, and higher need for neuromuscular blockade. The prior Xtravent study used the same trial design as the REST trial and showed decreased

ventilator days and no hospital mortality difference, but the mortality rate was low at 16.5%. [89] At present, VV-ECCO$_2$R is not indicated for use in ARDS patients.

Veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO)

VV-ECMO should be considered in severe ARDS patients if the severe hypoxemia rescue strategies described above have failed to improve oxygenation and the patient is a potential ECMO candidate with potentially reversible respiratory failure (**Figure 3**).

Two randomized trials examined the efficacy of VV-ECMO in adults with severe ARDS. The CESAR trial (n=180) reported an ECMO survival benefit in the intention-to-treat analysis (RR 0·69; 95% CI 0·05–0·97, p=0·03), but the study conclusion was limited since 25% of subjects assigned to the ECMO group never received ECMO therapy. [90] The subsequent EOLIA trial randomized 249 patients with severe ARDS to early ECMO (immediate VV-ECMO if P/F < 50 for > 3 hrs; P/F < 80 for > 6 hrs; or arterial blood pH < 7.25 with paCO$_2$ 60 for > 6 hrs) vs. protocolized mechanical ventilation, and 60-day mortality was not statistically different (RR 0.76; 95% CI, 0.55 to 1.04; 35% vs. 46%, p = 0.09). The risk of 90-day treatment failure (death in ECMO cohort, death or crossover to ECMO in control cohort) was significantly higher in the control group. A high percentage of control patients required "rescue" ECMO for refractory hypoxemia (n=35, 28%) with a higher 60-day mortality (57%) and 7 patients required VA-ECMO. [91] A post-hoc Bayesian analysis of EOLIA data reported a high likelihood of survival benefit with ECMO. [92]

In a systematic review and individual patient data meta-analysis of the two ECMO-ARDS RCTs (CESAR and EOLIA) with 429 patients, 90-day mortality was significantly lower with ECMO compared to conventional management (RR 0.75, 95% confidence interval (CI) 0.6–0.94; $P = 0.013$; $I^2 = 0\%$). The RR of 90-day treatment failure (death in ECMO cohort, death or crossover to ECMO in control cohort) was 0.65 (95% CI 0.52–0.8; $I^2 = 0\%$). [93] A systematic review and meta-analysis of 5 studies (2 RCTs and 3 observational studies with matching techniques, n = 773) reported lower 60-day mortality in the VV-ECMO group (RR 0.73, 95% CI 0.58 – 0.92, p = 0.008, I^2 0%), but higher risk (19%) of major hemorrhage. [94]

A TQIP database study (2013-2016) compared trauma patients with ARDS who received ECMO (97) to a propensity-matched cohort of patients who underwent conventional management. ECMO was associated with significant lower overall hospital mortality (23 vs. 50%, p<0.001) but higher rates of complications and prolonged hospital length of stay. [95]

In centers without ECMO capability, planning for early transfer to an ECMO-capable center should be discussed. Common adult ECMO transfer criteria include P/F ratio ≤100 mmHg, no contraindications to ECMO, single-system organ failure, and intubation ≤ 7 days. [96]

FUTURE RESEARCH

As we have reviewed above, most studies regarding the specific efficacy of treatment strategies in adult ARDS patients are in medical and surgical non-trauma patients. Future ARDS studies should aim to include a sub-population of trauma-related ARDS patients to aim to provide better evidence for effective treatments in trauma-related ARDS.

Precision Medicine and ARDS

We recognize that ARDS is a clinically heterogeneous syndrome, and that different patient phenotypes exist which may have quite variable responses to specific ARDS treatment strategies. [97 98 99] In the future, precision medicine may be able to incorporate variability in specific factors and phenotypes to better individualize appropriate therapies for to improve care for trauma patients with ARDS. [100] Even with current limitations, it is important to tailor aspects of ARDS management such as LRM and PEEP to the specific needs of TBI and hemorrhaging patients.

Limitations

While an extensive literature review was conducted and current studies were evaluated and discussed by workgroup members, a formal evaluation of the level of evidence reviewed and the strength of recommendations provided are not included as part of this clinical protocol. We have provided references to formal ARDS guidelines to provide this information (**Table 2)**.

CONCLUSION

ARDS is life-threatening in trauma patients, and clinicians must have knowledge of appropriate evidence-based strategies for optimal management. This clinical trauma protocol outlines effective ARDS treatment strategies with specific reference to their use and potential impact in trauma patients with ARDS. ARDS is a clinically heterogeneous syndrome, and recent studies have reported different phenotypes which have variable clinical responses to specific ARDS treatments. Randomized treatment trials in trauma patients with ARDS are warranted to further determine optimal treatment strategies in this patient cohort.

AUTHORSHIP

All authors participated in the literature review, development of the clinical protocol and algorithm, manuscript writing and critical review of all manuscript revisions.

DISCLOSURE

The authors declare no conflicts of interest

Figure Legends:

Figure 1: **Algorithm of Treatment Strategies for Patients with ARDS**

Figure 2: **Algorithm for use of neuromuscular blocking agents (NMBA) in ARDS**

From: Alhazzani W, Belley-Cote E, Møller MH, et al. Neuromuscular blockade in patients with ARDS: a rapid practice guideline. *Intensive Care Med*. 2020;46(11):1977-1986. doi:10.1007/s00134-020-06227-8

Figure 3: **Algorithm for ECMO in acute respiratory distress syndrome**

From: Abrams D, Ferguson N, Brochard L, et al. NECMO for ARDS: from salvage to standard of care? *Lancet Respir Med*. 2019 Feb;7(2):108-110. doi:10.1016/S2213-2600(18)30506-X

Relative contraindications to VV-ECMO for ARDS include the following:

- Central nervous system hemorrhage
- Significant central nervous system injury
- Irreversible and incapacitating central nervous system or pulmonary pathology
- Systemic bleeding, diffuse alveolar hemorrhage
- Contraindications to anticoagulation (VV-ECMO can be managed with low-dose or without continuous systemic anticoagulation if flow rates are high, but anticoagulation bolus is strongly recommended with ECMO cannulae placement)
- Inability to receive blood product transfusion
- Immunosuppression

- Older age (increasing risk of death with increasing age, but no age threshold is established)
- Mechanical ventilation for more than 7 days with Pplat > 30cm H_2O and FiO_2 > 90%

Obesity with a BMI greater than 40 kg/m^2 (This is a historical relative contraindication due to difficulty in ECMO cannulation and achieving adequate ECMO circuit flow, as well as failure to wean. Increasing data is emerging supporting the use of ECMO in the obese population)

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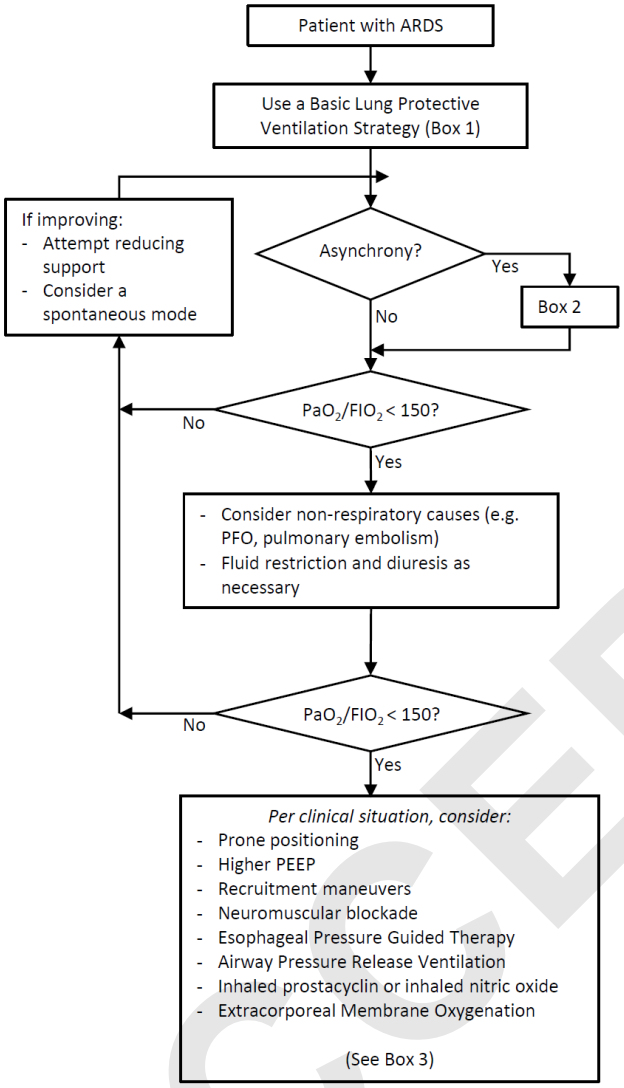
Figure 1



Box 1: Basic Lung Protective Ventilation

- Low tidal volume, low plateau pressure:
  a. Use VCV or PCV, targeting VT 6 mL/kg PBW
  b. Maintain Pplat ≤30 cm H_2O, reduce VT to 5 or 4 mL/kg if necessary
  c. PEEP/FiO_2 per table (see bottom of page)
- Consider maintaining driving pressure ≤12-15 cm H_2O
- If consolidation is asymmetrical, consider placing 'good lung' in dependent position

Box 2: Patient-Ventilator Asynchrony

- Consider minor ventilator adjustments (e.g., flow rate & pattern, inspiratory pause)
- Assess potential to treat with pharmacologic agents (e.g. sedation, neuromuscular blockade)
- For double-triggering, consider increasing VT 1 mL/kg (max 8 mL/kg), provided Pplat <30 cm H_2O
- For flow asynchrony, consider a variable flow pressure breath mode of ventilation (e.g., volume targeted pressure control, pressure support)

Box 3: Adjuncts to Consider

Prone Positioning
- Consider after initial 12-24 hrs of stabilization
- Use 16 hr/day Discontinue when:
  - Instability in prone position
  - Supine x 4 hr, PaO_2/FiO_2 >150 on FiO_2 ≤0.60 & PEEP ≤10

Higher PEEP
- Relative contraindications in TBI, hemorrhagic shock
- Refer to Higher PEEP/Lower FIO_2 table

Recruitment Maneuvers
- Consider for pts with clear de-recruitment, negative Ptp or PaO_2/FIO_2 <150
- Described maneuvers:
  - PCV with P_{high} 40, Pl_{ow} 20-25 for 1-3 min (as tolerated)
  - PCV with delta-P of 15; increase PEEP by 5 cm H_2O to PIP of 40
  - Continuous positive pressure (30-40 cm H_2O), limited to 15-30 s

Neuromuscular Blockade
- Consider use if significant asynchrony present and concern for VILI

Esophageal Pressure (Pes) Guided Therapy
- Consider in BMI > 35 or patients with stiff chest walls
- Requires placement of esophageal pressure catheter

Airway Pressure Release Ventilation (APRV)
- Concern for P-SILI in pt with strong respiratory drive

Inhaled Nitric Oxide (iNO) – 10 ppm
- Consider in PaO_2/FIO_2 <100 and other strategies have not improved oxygenation
  - If positive response (improved oxygenation): reduce FIO2 down to 0.8, then wean iNO, or consider epoprostenol or iloprost
  - If no response, consider stopping

Extracorporeal Membrane Oxygenation (ECMO)
- Consider if (EOLIA criteria):
  - PaO_2/FiO_2 <50 x 3 hrs
  - PaO_2/FiO_2 <80 x 6 hrs
  - pH <7.25 with $PaCO_2$ >60 x6 hrs

FIO_2 /PEEP Tables

Lower PEEP/Higher FIO2 table:

Step:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20	22	24

Higher PEEP/Lower FIO_2 table (from ROSE study):

Step:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FIO_2	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.0
PEEP	5	5	8	10	12	14	16	16	18	20	20	20	20	22	22	22	24

Figure 2

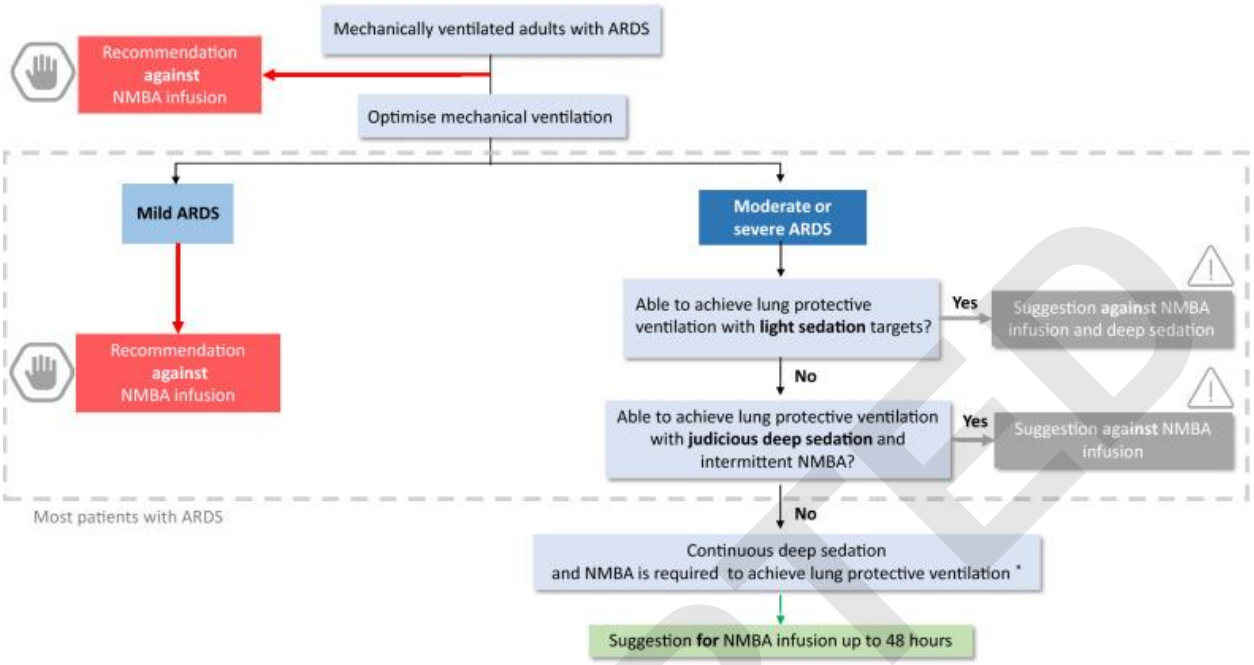


Figure 3

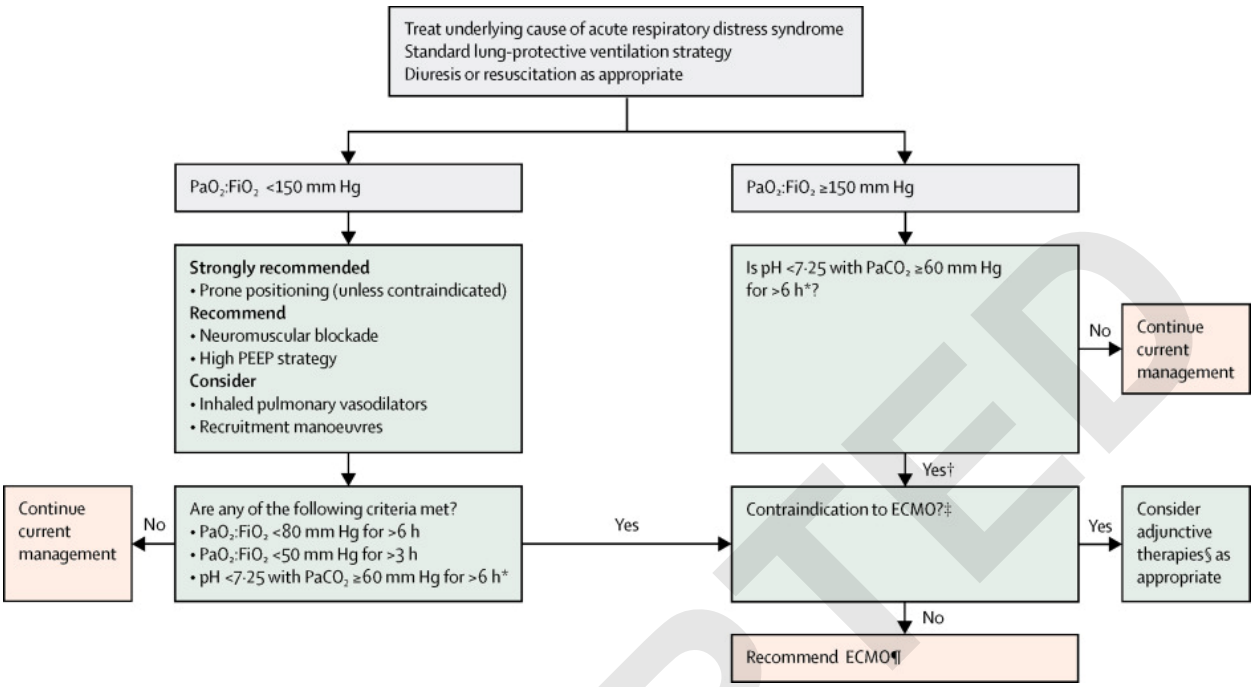


Table 1. Definition of Acute Respiratory Distress Syndrome (ARDS)

The Berlin criteria definition of ARDS includes:
• Onset of hypoxemia within 7 days of a known clinical insult or worsening respiratory symptoms
• Chest imaging with bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
• Pulmonary edema not fully explained by cardiac failure or fluid overload
• Hypoxemia defined as a PaO_2/FiO_2 ratio ≤ 300 mmHg with PEEP or CPAP ≥ 5 cmH_2O
○ ***Mild ARDS***: PaO_2/FiO_2 ratio 201-300 mmHg
○ ***Moderate ARDS***: PaO_2/FiO_2 ratio 101-200 mmHg
○ ***Severe ARDS***: PaO_2/FiO_2 ratio ≤100 mmHg

From: [1] The ARDS Definition Task Force. *Acute respiratory distress syndrome: The Berlin Definition.* JAMA 2012;307:2526-2533.

Table 2: National and International ARDS Guidelines

Organization	Guidelines	Reference
Scandinavian Society of Anaesthesiology and Intensive Care Medicine	Scandinavian clinical practice guideline on mechanical ventilation in adults with the acute respiratory distress syndrome 2015	Claesson J, Freundlich M, Gunnarsson I, Laake JH, Vandvik PO, Varpula T, Aasmundstad TA; Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Scandinavian clinical practice guideline on mechanical ventilation in adults with the acute respiratory distress syndrome. Acta Anaesthesiol Scand. 2015 Mar;59(3):286-97. doi: 10.1111/aas.12449 PMID: 25524779. https://onlinelibrary.wiley.com/doi/epdf/10.1111/aas.12449
American Thoracic Society (ATS) European Society of Intensive Care Medicine (ESICM) Society of Critical Care Medicine (SCCM)	An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in	Fan e, Del Sorbo L, Goligher EC et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med Vol 2017;195(9): 1253–1263 https://pubmed.ncbi.nlm.nih.gov/28459336/

	Adult Patients with Acute Respiratory Distress Syndrome. 2017	
Faculty of Intensive Care Medicine (FICM) Intensive Care Society (ICS)	Formal guidelines: Management of acute respiratory distress syndrome. 2019	Papazian L, Aubron C, Brochard L, et al. Formal guidelines: Management of acute respiratory Distress syndrome Ann Intensive Care 2019;9:69 https://pubmed.ncbi.nlm.nih.gov/31197492/
Japanese Society of Intensive Care Medicine Japanese Respiratory Society Japanese Society of Respiratory Care Medicine	ARDS Clinical Practice Guideline 2021	Tasaka S, Ohshimo S, Takeuchi M *et al.* ARDS Clinical Practice Guideline 2021. J Intensive Care 10**,** 32 (2022). https://doi.org/10.1186/s40560-022-00615-6

Table 3: Current Management Strategies of ARDS and Associated Mortality Benefit

Treatment	Summary	Mortality benefit
Mechanical Ventilation		
Lung protective tidal volume ventilation	Recommend for all ARDS patients Target 4-8 mL/kg predicted body weight (PBW) and low plateau pressure (< 30 cm H_2O)	Yes
High PEEP in moderate/severe ARDS	Recommend for patients with moderate/severe ARDS Possible contraindication in TBI and shock states, individual PEEP titration in these states	Yes
Lung recruitment maneuvers	Consider in patients with moderate/severe ($PaO_2/FiO_2 \leq 200$) ARDS to improve oxygenation	Uncertain
Esophageal pressure-guided therapy	Current data do not support the use of esophageal pressure-guided PEEP titration in routine ARDS management, but may be effective as a rescue therapy in obese patients and those with stiff chest walls	No
Adjuncts		
Prone positioning (16 hrs/day)	Recommend for patients with moderate/severe ARDS Maintained daily until the PaO_2/FIO_2 ratio remains >150 mm Hg, with PEEP ≤10 cm H_2O, $FIO_2 \leq 60\%$ for at least 4 hours after the end of the most recent proning session	Yes
VV-ECMO	Consider for refractory hypoxemia despite maximal therapy with mechanical ventilation, pharmacologic	Yes

	adjuncts, and prone position, in patients without contraindications	
Pharmacologic treatment		
Diuretics for conservative fluid strategy	Consider in ARDS patients without contraindications.	No
Neuromuscular blockade	Consider in ARDS patients with severe refractory hypoxemia and ventilator dysynchrony that cannot be managed with sedation alone	No
Inhaled pulmonary vasodilators	Consider as rescue strategy in severe hypoxemia/ARDS with P/F ratio < 100 when other strategies discussed above have not resulted in improved oxygenation, and before consideration of VV-ECMO	No
Steroids	Recommended for patients with COVID-related ARDS Consider in patient with non-COVID-related ARDS No clear data for trauma-related ARDS	Yes Equivocal No