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Therapeutic Strategies for Severe Acute Lung Injury

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Abstract

Objective—In the management of patients with severe Acute Lung Injury and the Acute Respiratory Distress Syndrome (ALI/ARDS), clinicians are sometimes challenged to maintain acceptable gas exchange while avoiding harmful mechanical ventilation practices. In some of these patients, physicians may consider the use of “rescue therapies” to sustain life. Our goal is to provide a practical, evidence-based review to assist critical care physicians’ care for patients with severe ALI/ARDS.

Data Sources and Study Selection—We searched the Pub Med database for clinical trials examining the use of the following therapies in ALI/ARDS: recruitment maneuvers, high positive end expiratory pressure, prone position, high frequency oscillatory ventilation, glucocorticoids, inhaled nitric oxide, buffer therapy and extracorporeal life support.

Study selection—All clinical trials that included patients with severe ALI/ARDS were included in the review.

Data Synthesis—The primary author reviewed the aforementioned trials in depth and then disputed findings and conclusions with other authors until consensus was achieved.

Conclusions—This article is designed to: a) provide clinicians with a simple, bedside definition for the diagnosis of severe ARDS; b) describe several therapies that can be used in severe ARDS with an emphasis on the potential risks as well as the indications and benefits; and c) to offer practical guidelines for implementation of these therapies.

Keywords

Acute Respiratory Distress Syndrome; pulmonary edema; acute respiratory failure; severe respiratory failure; hypoxemic respiratory failure

INTRODUCTION

In the management of patients with Acute Lung Injury and Acute Respiratory Distress Syndrome (ALI/ARDS), clinicians are sometimes challenged to maintain acceptable gas exchange while avoiding harmful mechanical ventilation practices. In some patients, life threatening hypoxemia is caused by markedly elevated intrapulmonary shunt fraction. In others, dangerously elevated airway pressures are caused by severely reduced respiratory system compliance. Patients may develop life threatening respiratory acidosis caused by a markedly elevated pulmonary dead-space fraction. In these patients, clinicians may consider therapies that have the potential to improve gas exchange even though they may entail some risk and lack strong evidence for improving clinical outcomes; these have been termed “rescue therapies”. However, “rescue” suggests that there are known beneficial effects. Future studies may demonstrate improved outcomes with some of these therapies. Until then, we prefer the term “unproven therapies.” The goals of this commentary are to provide a practical approach to identifying severe ARDS and guide the use of unproven therapies based on physiologic rationale, risks and published evidence. Some of the clinical trials that we cite were underpowered for major outcomes, but they are still of value in guiding the use of therapies in severe ARDS.

DEFINITION

The lack of consensus regarding the definition of severe ARDS has limited our understanding of this subset of high-risk patients and impaired clinicians’ ability to recognize and treat them effectively. Investigators from Canada and Australia defined severe ARDS as the presence of any one of the following criteria while receiving a lung protective ventilation strategy: a) refractory hypoxemia defined as a $\text{PaO}_2 < 60$ mmHg for at least 1 hour while receiving an FiO_2 of 1.0; b) refractory acidosis defined as a $\text{pH} < 7.10$ for at least 1 hour; or c) refractory barotraumas. [1] Because $\text{PaO}_2/\text{FiO}_2$ has not been consistently associated with worse outcomes and varies with positive end-expiratory pressures (PEEP), this criteria alone is not sufficient. [2, 3]

Investigators from the United Kingdom defined severe acute respiratory failure more comprehensively using a lung injury score ≥ 3.0 or uncompensated hypercapnea with a $\text{pH} < 7.20$. [4] The lung injury score takes into account the distribution of chest radiograph abnormalities, the $\text{PaO}_2/\text{FiO}_2$, quasi-static respiratory compliance and the level of PEEP. Another severity score based on lung morphology as determined by computed tomography (CT), found diffuse and hyperattenuated disease to be associated with 75% mortality. [5]

In our opinion, patients with severe ARDS at high risk for death should be identified promptly by first using lung injury score ≥ 3.0 . When these patients start to fail the application of a lung protective ventilation strategy because of severe gas exchange abnormalities, excessively high plateau airway pressures ($> 30\text{-}35$ cm H_2O), or severe respiratory acidosis, then treatment with unproven therapies should be considered (**Table I**). High plateau airway pressures are associated with higher mortality, but this relationship must vary with chest wall compliance, abdominal distension, and time with high plateau pressures. Therefore we suggest a threshold range of 30-35 cm H_2O , to allow individual

clinician judgment. For example, if a patient's chest wall compliance is estimated to be normal and plateau pressures have been elevated for several days, then the threshold of 30 cm H₂O may be more reasonable than 35 cm H₂O

INITIAL EVALUATION

Every patient should be evaluated for an underlying cause of ALI, (especially sepsis, pneumonia, pancreatitis, transfusion associated lung injury) and treated promptly. [6-9]. This includes a meticulous examination looking for occult sources of sepsis (e.g. deep soft tissue infections) and obtaining appropriate diagnostic testing (e.g. sterile samples for microbiologic culture). If an underlying cause is not identified, an alternate diagnosis (e.g. diffuse alveolar hemorrhage) should be considered, as some of these diagnoses can be treated with immunosuppressive agents. This evaluation may require invasive diagnostic testing. [10, 11] In addition, it may be helpful to carry out a transthoracic or transesophageal echocardiography to evaluate right and left ventricular function, cardiac filling pressures, and the presence or absence of right heart failure and a patent foramen ovale.

THERAPEUTIC STRATEGIES

INITIAL INTERVENTIONS

A lung-protective ventilation strategy should be implemented immediately because of the excellent evidence that low tidal volume and low inspiratory pressure ventilation improves survival. [2, 8, 12] PEEP should be set at moderate levels, using the PaO₂/FiO₂ grid used in the ARMA trial, with the goal of obtaining an oxygen saturation of approximately 90%. Tidal volumes as low as 4 ml/kg may be necessary to reach the goal plateau pressure of less than 30 cm H₂O and to avoid ventilator-associated lung injury. Achieving these low tidal volumes and low compliance may require the use of high respiratory rates, as long as intrinsic PEEP is not generated, and permissive hypercapnea. A fluid-conservative hemodynamic management strategy should be instituted if the patient is not in shock (mean systemic arterial pressure >60 mm Hg without vasopressor support). [13] Real time echocardiography may assist in the evaluation and management of acute cor pulmonale. [14]

STRATEGIES TO IMPROVE LIFE THREATENING HYPOXEMIA (Table II)

Recruitment Maneuvers and High PEEP

Rationale: A recruitment maneuver (RM) and high PEEP intend to aerate collapsed and flooded alveoli, which in some patients may improve oxygenation, decrease ventilator-induced lung injury (VILI) from the shear stress of repetitive opening and closing of alveoli, and improve respiratory system compliance. [15] To do so, RM use brief periods in which airway pressures are elevated and sustained at levels that are higher than those that result from tidal ventilation.

Risks: High airway pressures may subject non-collapsed alveoli to over-inflation, decreased alveolar fluid clearance and additional ventilator-associated lung injury, or may cause hemodynamic compromise. [16] High PEEP alone may provide similar benefits without subjecting the lungs to such high inspiratory pressures. [17] Two recent large clinical trials

did not find increased use of vasopressors or neuromuscular blockade associated with a RM and/or high PEEP; however, one of these trials reported that 22% of patients who received a RM experienced hypotension, arrhythmias, desaturation or barotraumas. [1, 21]

The Evidence

RM and High PEEP: Multiple observational studies suggest that a RM may be most effective early on in the course of ARDS and in patients who have more severely impaired gas exchange, reduced compliance, increased dead space ventilation, or diffuse disease. [18, 19]

Three large multi-center clinical trials have compared the efficacy of a lung protective ventilation strategy in combination with a RM and/or high PEEP to lung protective ventilation alone and have found no significant difference in mortality. [1, 20, 21] However, the most recent trials did find significant benefits in multiple secondary outcomes. [1, 21]

In the trial conducted in Canada and Australia (the Lung Open Ventilation Study, or LOV), the high PEEP plus RM study group underwent a 40-second breath hold at 40 cm H₂O and then had PEEP set at 20 cm H₂O with subsequent reductions according to a PEEP/FiO₂ grid. [1] Results showed that the intervention group had fewer episodes of refractory hypoxemia (4.6% vs. 10.2%, p=0.01), and fewer deaths associated with refractory hypoxemia (4.2% vs. 8.9%, p=0.03).

In the trial carried out in France (by the Expiratory Pressure Study Group, termed EXPRESS) the high PEEP-treated group was treated with gradual increases in PEEP until the plateau airway pressures reached 28-30 cm H₂O. [21] The higher PEEP group had more ventilator-free days (medians of 7 vs. 3, p=0.04), more organ failure-free days (6 vs. 2, p=0.04) and a reduced use of rescue therapies for severe hypoxemia (18.7% vs. 34.6%, p<0.001).

Clinical Application: A RM with high PEEP or high PEEP alone should be considered early in the management of severe ARDS with life threatening hypoxemia if plateau airway pressures are below 30 cm H₂O. Do not conduct RMs in patients who are in shock, who have pneumothorax, or in those with focal disease. Prepare the patient with adequate volume resuscitation and sedation to ensure patient-ventilator synchrony. We recommend the use of the RM from the LOV trial because it demonstrated efficacy and safety in the largest number of patients [1]. Optimal PEEP should then be set about 5-10 cm H₂O above the pre-RM PEEP to maintain an open lung. When using high PEEP alone, the ALVEOLI or EXPRESS protocols are reasonable approaches. It is important to assess for improvement in oxygenation and compliance immediately after the intervention and again within 6 to 12 hours. If there is no improvement, do not repeat RM. Also, abort the procedure if the patient develops worsened hypoxemia or hypotension. If dead space ventilation increases after the RM, this suggests alveolar overdistension, so the PEEP should be decreased.

Prone Positioning

Rationale: Prone positioning can promote recruitment of dependent, atelectatic lung regions most affected by ALI/ARDS by relieving external compressive forces, thus improving ventilation-perfusion matching without subjecting lungs to high airway pressures. [22]

Risks: Safety data from randomized trials report infrequent local complications (e.g. facial edema, conjunctival hemorrhage and pressure ulcers) and those due to turning (e.g. dislodging of catheters, endotracheal and thoracostomy tubes).

The evidence: Although prone positioning has failed to demonstrate a survival benefit in hundreds of patients enrolled in four randomized clinical trials; the two trials which proned patients for 20 hours a day did report beneficial trends in mortality. [23-26]

The initial trial, which failed to enroll the number of patients needed to detect the pre-determined effect size, reported a trend for decreased ICU mortality (43% vs. 58%, $p=0.12$) in the prone-treated group and significant improvements in oxygenation and plateau airway pressure when compared to the supine group. [25] The subsequent trial compared protocolized delivery of prone position and lung protective ventilation strategy to protocolized lung protective ventilation strategy alone and reported similar low mortality levels in both groups (31% vs. 32.8%, $p=0.72$). [24] In patients with severe hypoxemia there was a trend towards decrease 28-day mortality (37.8% vs. 46.1%, $p=0.31$) in the prone-treated group.

Clinical Application: Consider proning patients with severe ARDS with life threatening hypoxemia and/or elevated plateau airway pressures (**Tables II, IV**). Develop guidelines to prevent complications. Proning patients for a total of at least 20 hours a day seems to be associated with greater benefit; however, intermittent time in the supine position may be necessary for nursing care and procedures. If there is no improvement in oxygenation by then end of the day, then do not continue with proning and proceed promptly to another therapy.

High Frequency Oscillatory Ventilation

Rationale: High frequency oscillatory ventilation (HFOV) uses high mean airway pressure to achieve lung recruitment and improve oxygenation. [27, 28] Ventilation is achieved with an oscillating piston that creates cycles of pressure above and below the mean airway pressure at a high frequency (180-900/minute) resulting in small tidal volumes (between 1-2.5 ml/kg).

Risks: Potential disadvantages are hemodynamic deterioration, barotrauma or the need for heavy sedation and neuromuscular blockade to reduce ventilator asynchrony. In a large clinical trial, HFOV was not associated with more frequent episodes of intractable hypotension, air leak or mucous plugging. [27]

The evidence: Several small retrospective studies of HFOV in patients with ARDS and severe hypoxemia and/or elevated plateau airway pressures have described significant

improvements in oxygenation and suggested that early initiation may be associated with better outcomes. [29, 30]

Two randomized trials have compared HFOV to conventional mechanical ventilation for safety and efficacy. [27, 31] The initial trial terminated early because of poor patient accrual. The larger trial recruited 148 subjects with early ARDS and found a non-significant trend towards improved 30-day mortality in the HFOV-treated group (37% vs. 52%, $p=0.10$), a temporary improvement in oxygenation, and an increase in PaCO_2 that did not significantly worsen pH. [31] Large, multicenter clinical trials are currently being conducted by Canadian and British investigators comparing clinical outcomes of patients who receive HFOV to those who receive a conventional lung protective ventilation strategy.

Clinical Application: We recommend HFOV early in the course of severe ARDS in patients with severe hypoxemia and/or elevated plateau airway pressures. (Table II, IV). HFOV should not be used in patients with shock, severe airway obstruction, intracranial hemorrhage or refractory barotraumas; it must be used cautiously with severe acidosis because CO_2 excretion may be limited. There are published protocols available for direction. [32]

Inhaled Nitric Oxide

Rationale and risks: Inhaled nitric oxide (NO) induces vasodilatation in aerated portions of the lung, which may cause blood flow to redistribute towards ventilated areas, resulting in improved oxygenation. [33-36] It may also attenuate the activation of polymorphonuclear leukocytes and platelet aggregation. [37] On the other hand, when dissolved in alveolar fluid, NO may react with reactive oxygen species to form reactive nitrogen species, which can be cytotoxic to epithelial cells.

The evidence and risk: Several randomized clinical trials have failed to show a survival benefit for inhaled NO when compared to conventional mechanical ventilation alone. [38-40] About 60% of patients demonstrate improvement in oxygenation, which may last up to four days. Because the dose-response to inhaled NO may be unpredictable, these studies have been criticized. [41] A recently published meta-analysis of 12 randomized controlled trials raised concerns regarding safety. [42] The meta-analysis found a trend towards increased mortality with the use of inhaled NO ($n=1086$; risk ratio 1.10; 95% CI 0.94 to 1.30) and a significantly increased risk for renal dysfunction (risk ratio 1.50; 95% CI 1.11 to 2.02). The authors suggest that the prolonged administration of fixed dosing regimens may have subjected patients to the adverse effects of NO once the oxygenation improvement abated.

Clinical Application: Inhaled NO should be considered in patients with life-threatening hypoxemia that failed previous interventions (Tables II). Initiate inhaled NO at 1 ppm and titrate up every 30 minutes until an improvement in oxygenation is observed, but not to exceed 10 ppm. [35] If there is no immediate response, gradually discontinue its use. If there is a response, the dose should be decreased daily to the lowest dose necessary to maintain the target oxygenation and not used for longer than 4 days.

Glucocorticoids

Rationale and risks: Theoretically, glucocorticoids could halt the progression to severe and persistent ALI/ARDS by inhibiting neutrophil activation, fibroblast proliferation and collagen deposition. [43-45] Large clinical trials of steroids in this population have suggested an increased incidence of serious neuromyopathic events in steroid-treated patients but no increased risk for infection as long as strict infection surveillance is implemented. [46] A subgroup analysis from the largest trial carried out by the ARDS Network investigators in 180 subjects with persistent ARDS found that subjects started on steroids after 14 days of diagnosis had increased mortality. [46]

The evidence: Clinical trials have failed to confirm a survival benefit in patients with early or persistent ALI/ARDS who are treated with corticosteroids. [46-48] Two small randomized trials have examined the physiologic effects of corticosteroids in early hypoxemic respiratory failure due to ARDS (n=91) and severe pneumonia (n=46) and have reported significant improvements in hypoxemia and lung injury scores, observed as early as days 1 and 2 in the treatment group when compared to placebo, and up to one week. [49, 50]

Clinical Application: Consider corticosteroids in patients with life threatening hypoxemia that failed previous therapies. Corticosteroids should not be initiated after day 14, nor in those who require or may require neuromuscular blockade. If corticosteroids are to be used, we recommend the administration of methylprednisilone at low doses (1 mg/kg/day), as was done in the Meduri et al. trial. [49] Assess PaO₂/FiO₂, compliance, and PaCO₂ at baseline and on a daily basis. If no improvement occurs after 3 days, then discontinue treatment. If there is an improvement, then treatment can be extended, though the optimal duration is unknown. Seven days of therapy may be sufficient to improve oxygenation, although some investigators have raised concerns about discontinuing steroids too quickly, with a subsequent flare in inflammation and extubation failures. We suggest that physicians weigh the risks and benefits of prolonged treatment for their individual patients. Underlying infections should be treated appropriately, and strict infection surveillance should be implemented.

STRATEGIES TO IMPROVE LIFE THREATENING RESPIRATORY ACIDOSIS (Table III)

Buffer therapy

Rationale: Although permissive hypercapnea is a well accepted practice, severe respiratory acidosis may deter some physicians from achieving the targets of a low volume, low pressure lung protective ventilation strategy. Realistically, physicians may have varying thresholds for pH levels depending on the presence of shock or multi-organ failure. The urge to increase tidal volumes when plateau airway pressures are above target or when tidal volumes are already at 6 ml/kg should be resisted because this may contribute to additional ventilator associated lung injury.

The evidence and risks: Sodium bicarbonate infusions are commonly used in critical care units to manage life-threatening acidosis, but during the buffering process, CO₂ is released, raising the partial pressure of CO₂. In patients with impaired ventilation, this phenomenon may worsen acidosis. [51] Tris-hydroxymethyl aminomethane (THAM) is a non-bicarbonate

buffer that does not increase CO₂ production and in a small observational study improved pH and PaCO₂ in patients with ALI/ARDS and severe acidosis. [52] THAM infusion is contraindicated in renal insufficiency; its risks include volume overload, hypoglycemia and hyperkalemia.

Clinical Application: For life threatening respiratory acidosis, THAM may be considered if there is no renal dysfunction. The dose is based on the base deficit, and glucose and potassium levels should be monitored. If THAM is contraindicated, bicarbonate infusion may be used cautiously. Renal replacement therapies may be considered to assist with management of acidosis, particularly if other indications for renal replacement exist. If life-threatening acidosis persists, then tidal volumes can be increased by 1-2 ml/kg, and the patient should be considered promptly for ECLS.

STRATEGY FOR REFRACTORY CASES

Extracorporeal Life Support (Tables II, III, IV)

Rationale: Extracorporeal life support (ECLS) for severe ALI/ARDS uses a veno-venous life support circuit that removes blood from the patient and circulates it through a membrane oxygenator in order to relieve the lungs from their main function of gas exchange and allow the lungs to heal. In general, there are two types of ECLS that have been used to manage ARDS: a) extracorporeal membrane oxygenation (ECMO), a high-flow extracorporeal membrane oxygenation circuit; and b) extracorporeal carbon dioxide removal (ECCO2R), a low-flow, mostly extracorporeal CO₂ removal circuit. [53]

Risk: The use of ECLS is associated with significant risks, mostly due to the need for anti-coagulation and large indwelling vascular access. Commonly reported complications include clots in circuit, hemorrhage at cannulation sites, and infection. [54]

The evidence: Two older randomized clinical trials of ECLS in severe ARDS reported dismal outcomes when compared to conventional ventilation. [55, 56] Subsequently published observational studies have reported survival rates ranging between 47-66% in select patients, including use of ECCO2R. [53, 54, 57-59]

The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) investigators recently published the results of their randomized clinical trial of 180 subjects. [60] The ECLS-group was transferred to a tertiary care hospital and treated with a protocol consisting of the prone position, lung protective ventilation strategy and microalbumin infusions; whereas the control group remained at their respective centers and were treated by non-protocolized ventilator strategies. Of those transferred, only 77% received ECMO. Patients were excluded if they had received more than 7 days of high FiO₂ or high pressure ventilation, or had any contraindication to anticoagulation or continued treatment. The intervention group had an improvement in the composite endpoint of survival and absence of severe disability at 6 months. However, the trial did not establish the value of ECMO itself but rather the value of transferring very ill ARDS patients to a regional center in the United Kingdom, which in turn might result in them receiving additional treatment, specifically lung protective ventilation and/or other modalities, including ECMO.

Clinical Application: We suggest ECMO or possibly ECCO2R be considered when patients are refractory to previously mentioned therapies. ECMO or ECCO2R should be carried out as part of a protocol at experienced medical centers. Do not consider its use in patients with contraindications to anticoagulation or those who have been ventilated with high pressures for more than one week.

CONCLUSIONS AND RECOMMENDATIONS

Caring for patients with severe ARDS is a major challenge. The goals of using unproven therapies for severe ARDS are to sustain life, minimize additional lung injury, and avoid placing the patient at excess risk for other non-pulmonary complications. Because physicians practice in a variety of hospital settings and health care systems, the local resources of (1) expertise, (2) technology and (3) finances will guide the use of unproven and newer investigational therapies.

Prompt recognition of patients with severe disease (lung injury score ≥ 3) who then develop life threatening hypoxemia, respiratory acidosis, or consistently elevated plateau airway pressures should trigger the early use of an unproven therapy.

For life threatening hypoxemia, initial management with a RM and/or high PEEP should be undertaken if plateau airway pressures and lack of barotrauma allow. If not, or if these are not effective, then proceed to the prone position or HFOV. If hypoxemia still persists, consider the administration of inhaled NO. If NO fails, glucocorticoids can then be administered. For elevated plateau airway pressures when tidal volumes are 4ml/kg, consider prone positioning or HFOV. For life threatening respiratory acidosis, consider the use of a buffer or continuous veno-venous hemofiltration. It is most important to assess for objective physiologic improvement in the appropriate time period for each intervention. If no benefit is evident, the therapy should be discontinued in order to minimize harm and delay in the initiation of another therapy. If the patient continues to have life threatening hypoxemia, acidosis, or elevated plateau airway pressures, consider ECMO or ECCO2R.

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Table I

Definition of Severe Acute Respiratory Distress Syndrome

I. Lung Injury Score 3 (score is the sum of all components/ # of components)					
Score	0	1	2	3	4
PaO ₂ /FiO ₂	300	225-299	175-224	100-174	<100
CXR alveolar consolidation	none	1 quadrant	2 quadrants	3 quadrants	4quadrants
PEEP	5	6-8	9-11	12-14	15
Compliance	80	60-79	40-59	20-39	19

And**II. Failing a lung protective ventilation strategy due to any one of the following clinical parameters**

- Refractory hypoxemia (O₂ saturation <90% for at least 1 hour on FiO₂ .80)
- Refractory respiratory acidosis (pH 7.10 for at least 1 hour)
- Persistently elevated plateau airway pressures > 30-35 cm H₂O in spite of 4-6 ml/kg predicted body weight tidal volume

Table II**Management Strategy for Life Threatening Hypoxemia**

Step 1. Measure plateau airway pressure. If < 30 cm H₂O, proceed to **Step 2a**. If > 30 , proceed to **Step 2b**.

Step 2a. Implement a recruitment maneuver and/or high positive end-expiratory pressures alone.

Step 2b. Implement the prone position or high-frequency oscillatory ventilation

Step 3. Evaluate effects on oxygenation, static compliance and dead space ventilation. If there is a significant improvement, continue with therapy. If no significant improvement, then proceed to next intervention.

Step 4. Administer inhaled nitric oxide; if no response within several hours, proceed to next intervention

Step 5. Consider administration of glucocorticoids, weighing risks and benefits for individual patients.

Step 6. Consider extracorporeal life support. Candidates should not receive high pressure ventilation for more than 7 days prior to extracorporeal life support.

At each step, it is critical to evaluate effects on oxygenation, static compliance and pulmonary dead space ventilation. If there is a significant improvement, continue with therapy. If no significant improvement, then proceed to next intervention.

Table III**Stepwise Management Strategy for Severe Respiratory Acidosis**

Step 1. Increase respiratory rates to as high as 35/minute, ensuring that intrinsic PEEP is not increased, using conventional humidifiers. If severe respiratory acidosis persists, proceed to Step 2 .
Step 2. Administer buffer therapy. Tris-hydroxymethyl aminomethane may be preferable to bicarbonate, if renal function allows. If severe respiratory acidosis persists, proceed to Step 3 .
Step 3. Evaluate for renal replacement therapy, especially if there are other indications. If severe respiratory acidosis persists, proceed to Step 4 .
Step 4. Consider extracorporeal life support. Candidates should not receive high pressure ventilation for more than 7 days prior to extracorporeal life support

Table IV

Stepwise Management Strategy for Elevated Plateau Airway Pressures (>30-35 cm H₂O) when Tidal Volume set at 6 ml/kg.

Step 1. Decrease tidal volumes to 4 ml/kg. If plateau airway pressure remains > 30-35 cm H ₂ O, proceed to Step 2 .
Step 2. Implement prone position and/or high-frequency oscillatory ventilation alone. If plateau airway pressure remains > 30-35 cm H ₂ O, proceed to Step 3 .
Step 3. Consider extracorporeal life support. Candidates should not receive high pressure ventilation for more than 7 days prior to extracorporeal life support.