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Review Article

Ventilatory strategies and supportive care in acute respiratory distress syndrome

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While antiviral therapy is an important component of care in patients with the acute respiratory distress syndrome (ARDS) following influenza infection, it is not sufficient to ensure good outcomes, and additional measures are usually necessary. Patients usually receive high levels of supplemental oxygen to counteract the hypoxemia resulting from severe gas exchange abnormalities. Many patients also receive invasive mechanical ventilation for support for oxygenation, while in resource-poor settings, supplemental oxygen via face mask may be the only available intervention. Patients with ARDS receiving mechanical ventilation should receive lung-protective ventilation, whereby tidal volume is decreased to 6 ml/kg of their predicted weight and distending pressures are maintained $\leq$30 cm H_2O, as well as increased inspired oxygen concentrations and positive end-expiratory pressure (PEEP) to prevent atelectasis and support oxygenation. While these measures are sufficient in most patients, a minority develop refractory hypoxemia and may receive additional therapies, including prone positioning, inhaled vasodilators, extracorporeal membrane oxygenation, recruitment maneuvers followed by high PEEP, and neuromuscular blockade, although recent data suggest that this last option may be warranted earlier in the clinical course before development of refractory hypoxemia. Application of these "rescue strategies" is complicated by the lack of guidance in the literature regarding implementation. While much attention is devoted to these strategies, clinicians must not lose sight of simple interventions that affect patient outcomes including head of bed elevation, prophylaxis against venous thromboembolism and gastrointestinal bleeding, judicious use of fluids in the post-resuscitative phase, and a protocol-based approach to sedation and spontaneous breathing trials.

Keywords Acute respiratory distress syndrome, hypoxemia, influenza, mechanical ventilation, respiratory failure.

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Introduction

Patients who develop respiratory failure and the acute respiratory distress syndrome (ARDS) in the setting of influenza infection are at high risk of morbidity and mortality. While antiviral therapy is an important component of care for these patients, it is not sufficient to ensure a good outcome, and additional measures are necessary. The purpose of this review is to consider the other facets of high-quality supportive care in ARDS that are used together with antimicrobial therapy to improve outcomes in these patients.

After discussing how to recognize patients with ARDS, the review addresses the core strategies in ARDS management including supplemental oxygen administration, lung protective ventilation, and use of positive end-expiratory pressure (PEEP) with an emphasis on the physiologic rationale and evidence supporting their use. The review then considers adjunctive measures that have been proposed and studied in the care of patients with ARDS as well as "rescue strategies" that may be employed in those patients with severe, refractory hypoxemia. While considerable attention is focused on these complicated strategies, simple, often overlooked measures may also be of great importance to the patient, so the review concludes by considering other aspects of supportive care including prophylaxis against intensive care unit (ICU) complications and sedation and fluid management strategies that also affect patient outcomes.

Recognizing the patient with acute respiratory distress syndrome

One of the key elements of managing patients with respiratory failure following influenza infection is to recognize when the patient has developed ARDS. This should lead to initiation of important changes in patient management

(discussed below), although it should be recognized that such interventions are not restricted to patients with ARDS and can be used in other situations to address particular physiologic challenges in a given patient. The criteria for diagnosing ARDS were recently revised and are listed in Table 1. Referred to as the Berlin Criteria,[1] these criteria refine the original American–European Consensus diagnostic criteria[2] with the major changes being elimination of the distinction between acute lung injury (ALI) and ARDS and designation of three mutually exclusive subgroups of ARDS based on the decrement in the ratio of the arterial partial pressure of oxygen (P_aO_2) to the fractional concentration of inspired oxygen (F_IO_2), a marker of the severity of hypoxemia referred to as the P_aO_2/F_IO_2 or P/F ratio.

In resource-limited settings, it may not be possible to perform all testing such as echocardiography or arterial blood gas analysis to ensure patients meet each specified criteria. In such situations, it would be prudent to consider any patient with hypoxemia and bilateral opacities on chest radiography as having ARDS unless there is strong clinical suspicion for cardiogenic pulmonary edema or volume overload. The arterial saturation measured by pulse oximetry (S_pO_2) can be substituted for the P_aO_2 to calculate the S_pO_2/F_IO_2 ratio,[3] which may be more a feasible method of identifying severely ill patients in these resource-limited environments.

Beyond recognizing when patients have developed ARDS, it is important to recognize patients who may be at risk of this problem, such as a patient intubated for respiratory failure following influenza infection. In such cases, the clinician can take steps to prevent ARDS by avoiding overly large tidal volumes and ensuring patients receive a tidal volume of 8 ml/kg of their predicted body weight. This approach makes good clinical sense in light of the known pathophysiology of ARDS and the known relationship between excessive tidal volumes and lung inflation pressures and ventilator-induced lung injury (discussed below). In addition, a recent meta-analysis[4] suggests that ventilation with tidal volumes of 6–8 ml/kg in patients without ARDS is associated with decreased development of lung injury and decreased mortality when compared with ventilation with tidal volumes of 9–12 ml/kg, although the conclusions of this analysis are limited to some extent by the heterogeneity of the included studies, particularly with regard to the clinical setting in which mechanical ventilation was used.

Table 1. Definitions of the acute respiratory distress syndrome

American–European Consensus Definition[2]
Acute onset
Impaired oxygenation: $P_aO_2/F_IO_2 \leq 200$ (ARDS); P_aO_2/F_IO_2 201–300 (acute lung injury)
Bilateral opacities on chest radiograph
Pulmonary artery wedge pressure <18 mm Hg or no clinical evidence of left atrial hypertension
Berlin Criteria[1] Within 1 week of known clinical insult or new or worsening respiratory symptoms
Bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse, or nodules
Respiratory failure not explained by cardiac failure or fluid overload
Need objective assessment such as echocardiography to exclude hydrostatic edema if no risk factor present
Impaired oxygenation:
Mild: $200 < P_aO_2/F_IO_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H_2O
Moderate: $100 < P_aO_2/F_IO_2 \leq 200$ with PEEP ≥ 5 cm H_2O
Severe: $P_aO_2/F_IO_2 \leq 100$ with PEEP ≥ 5 cm H_2O

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure.

Primary physiologic challenges in patients with acute respiratory distress syndrome

There are two primary physiologic challenges that the clinician must address in patients with ARDS. The first and most obvious problem is the severe hypoxemia that develops as a result of impairments in gas exchange stemming from collapse of alveoli due to the loss of alveolar surfactant, referred to as atelectasis, and the filling of alveoli with protein-rich edema fluid. As a result of these problems, patients with ARDS have extensive areas of what is referred to as "shunt" physiology in which mixed venous blood bypasses non-functioning alveoli and, as a result, cannot be loaded with oxygen before returning to the arterial circulation. The severity of the gas exchange problems can be quantified using the arterial blood gas to calculate the alveolar–arterial oxygen difference ($[A\text{-}a]\Delta O_2$, the difference between the alveolar and arterial partial pressures of oxygen) or by measuring the P_aO_2/F_IO_2 ratio described above. The larger the $(A\text{-}a)\Delta O_2$ or the lower the P_aO_2/F_IO_2 ratio, the worse the patient's gas exchange. Table 2 lists data from the control groups from several major studies of patients with ARDS and illustrates the severity of hypoxemia in these patients. P_aO_2/F_IO_2 ratios below 100, as seen in the report by Davies *et al.*[5] represent very severe gas exchange problems.

Another important problem in patients with ARDS is the significant decrease in respiratory system compliance that results from a combination of accumulation of the protein-rich edema fluid in the alveolar and interstitial spaces, and the loss of surfactant and the resultant increase in alveolar surface tension. Because of the decreased compliance, elevated distending pressures are often required to deliver a given tidal volume, which may contribute to ongoing lung injury. The basic management steps discussed below are intended to address both physiologic challenges.

Table 2. Severity of gas exchange abnormalities in representative trials of patients with acute respiratory distress syndrome

Study	P_aO_2 (mm Hg)	P_aO_2 / F_IO_2
ARMA[11]	84 ± 28	135 ± 58
Brower *et al.*[12]	78 ± 22	168 ± 66
Steinberg *et al.*[13]	70 ± 14	126 ± 40
Mercat *et al.*[15]	Not reported	143 ± 57
Davies *et al.*[5]	Not reported	56 (IQR 48–63)
Papazian *et al.*[51]	85 + 28	115 ± 21

Reported data are from the control groups in each study.
IQR, interquartile range.

The basic steps in acute respiratory distress syndrome management, their physiologic rationale, and supporting evidence

At a minimum, patients with ARDS should receive supplemental oxygen. While this is typically delivered by invasive mechanical ventilation in most settings, in more resource-limited environments, supplemental oxygen delivered by nasal cannula or face mask may be all that is feasible. Because of the gas exchange problems noted above, high inspired oxygen concentrations are necessary to support oxygenation and patients may be treated using face masks with reservoir bags, often referred to as non-rebreather masks. Depending on the patient's inspiratory flow rates and minute ventilation, however, even this system may not be able to deliver adequately high inspired oxygen concentrations necessary to treat the hypoxemia. High-flow oxygen delivery systems, which deliver 30–40 l/minutes of gas flow to the mask, overcome this problem and more reliably deliver high inspired oxygen concentrations, but these systems are unlikely to be available in resource-limited settings and may still not be sufficient to treat hypoxemia when patients have severe gas exchange abnormalities.

For patients placed on invasive mechanical ventilation, two interventions are indicated to address the physiologic challenges noted above. First, to limit the high distending pressures resulting from the low compliance, patients with ARDS should be placed on what is referred to as "lung protective ventilation," in which their tidal volume is decreased to 6 ml/kg of their predicted body weight, a value derived from the patient's gender and height. Second, in an effort to counteract the hypoxemia stemming from alveolar filling and atelectasis, patients should receive PEEP in addition to a high inspired oxygen concentration.

At first glance, it might not make intuitive sense to decrease the volume of lung inflation in a patient having problems with hypoxemia, but there is both a strong physiologic rationale and evidence base to support this practice, as well as the use of PEEP. Figure 1 displays an idealized volume–pressure relationship for the respiratory system during inhalation and exhalation and illustrates the physiologic rationale. The slope of this relationship represents the compliance of the respiratory system, and the goal should be to ventilate patients on the steepest portion of the relationship where smaller pressure changes are necessary to achieve the desired tidal volume. Lowering the tidal volume helps avoid the upper, flat portion of this relationship (denoted by the letter A) where large changes in pressure are necessary to achieve small volume changes. The high distending pressures used in this range can overstretch alveoli and cause ventilator-induced lung injury, thereby worsening the underlying ARDS. Application of PEEP helps avoid the lower, flat portion of this relationship (B) by preventing repetitive opening and closing of the alveoli, which is thought to lead to further lung injury by what is often referred to as "atelectrauma." This benefit can be further appreciated in Figure 2. Application of PEEP at the level denoted in Panel B leads to higher lung volume at the start of inhalation and therefore less atelectasis compared with when no PEEP is applied in Panel A, and also leads to initiation of inhalation at a steeper, more compliant portion of the volume–pressure relationship.

Beyond this physiologic rationale, there is strong evidence in the literature supporting these practices. After studies in animal models suggested that inappropriate ventilator strategies, in particular high tidal volumes and high distending pressures, caused problems such as increased pulmonary capillary permeability[6] and pulmonary edema,[7] uncontrolled

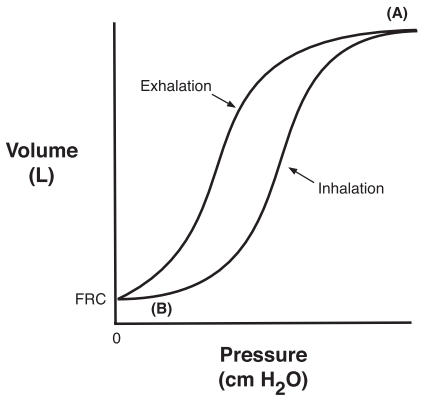

Figure 1. Idealized volume–pressure relationship of the respiratory system demonstrating the rationale behind core ventilatory strategies in patients with acute respiratory distress syndrome. Lowering the tidal volume helps avoid the upper, flat portion of this relationship (A), where large changes in pressure are necessary to achieve small volume changes. Application of positive end-expiratory pressure helps avoid the lower, flat portion of this relationship (B) by preventing repetitive opening and closing of the alveoli. Note: FRC refers to functional residual capacity: the volume of air left in the lungs at the end of normal exhalation.

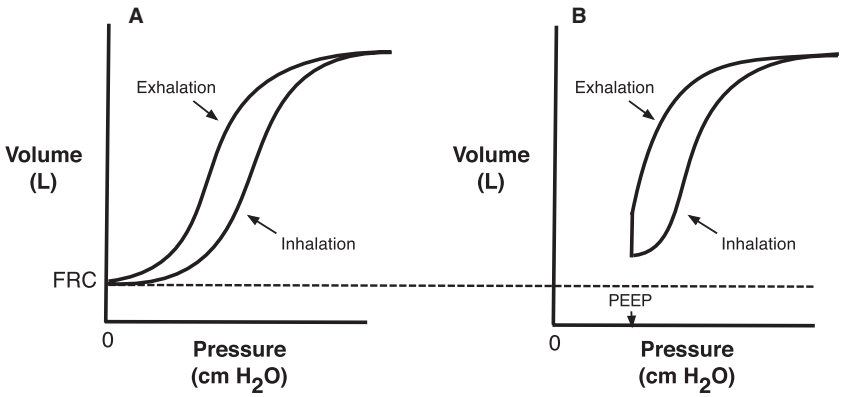

Figure 2. Idealized volume–pressure relationships demonstrating the benefit of positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome. In Panel A, PEEP is not applied, and the pressure in the respiratory system approaches zero at the end of exhalation. Lung volume returns to a low level marked by the dotted line and inhalation begins on the flat, less compliant portion of the volume–pressure relationship. In Panel B, PEEP is applied at a level marked above the *x*-axis. At the end of exhalation, lung volume is higher than in Panel A (dotted line) and inhalation begins at the steeper, more compliant portion of the volume–pressure relationship. Note: FRC refers to functional residual capacity: the volume of air left in the lungs at the end of normal exhalation.

trials demonstrated a benefit from lowering the tidal volume in humans with ARDS.[8] Small randomized studies, however, found conflicting results regarding patient outcomes,[9,10] prompting initiation of the ARMA trial, a multicenter randomized controlled trial comparing ventilation at 6 ml/kg or lower to 12 ml/kg of predicted body weight.[11] This landmark study demonstrated improvements in important patient outcomes, as individuals receiving lower tidal volumes (i.e., lung protective ventilation) had significantly lower mortality (31% versus 40%, $P = 0{\cdot}007$) and more ventilator-free days (12 ± 11 versus 10 ± 11; $P = 0{\cdot}007$) than those receiving higher tidal volumes. Given these results, the lower tidal volume approach was incorporated into subsequent major ARDS trials examining additional interventions, with similar or lower mortality rates being reported in these studies than those seen in the intervention group in the ARMA trial.[12–15] The lung protective ventilation approach outlined in the ARMA trial[11] has since become the standard of care for management of patients with ARDS.

As noted above, it should be recognized that the use of lower tidal volumes, as well as increased PEEP, should not necessarily restricted to only those patients who meet criteria for ARDS, but can also be considered in other situations where it is felt they can address important physiologic problems in a given patient.

Adjusting tidal volume and positive end-expiratory pressure

Rather than being placed on a tidal volume on 6 ml/kg immediately following intubation, which can lead to increased atelectasis and worse hypoxemia, the patient should be stabilized on a normal tidal volume of 8–10 ml/kg before the tidal volume is decreased in incremental fashion over a period of 4 hours to 6 ml/kg. Based on the approach used in the ARMA study,[11] the goal of decreasing tidal volume is to achieve a target distending, or plateau pressure $\leq$30 cm H_2O. If the target plateau pressure is not achieved with the initial tidal volume adjustment, tidal volume is decreased further until this goal is achieved or a minimum tidal volume of 4 ml/kg is reached.

While tidal volume is adjusted to achieve a satisfactory plateau pressure, PEEP can be set in one of several ways. In the control and intervention arm of the ARMA trial, PEEP was adjusted along with F_IO_2 in a protocol-directed manner based on the patient's P_aO_2 and oxygen saturation (S_aO_2). In other studies, PEEP has been set based on a target plateau pressure,[15] based on the analysis of the volume–pressure relationship of the respiratory system[16] or based on the esophageal manometry and assessments of transpulmonary pressure.[17] To date, the literature has not established that any of these methods of selecting PEEP are better than the others. Given the ease of the ARMA protocol and the mortality benefit achieved in that study, PEEP adjustment based on the PEEP–F_IO_2 protocol used in ARMA is likely the most feasible approach until more data are available. A question also remains as to whether protocols targeting higher average PEEP are more effective than protocols targeting lower PEEP. The ALVEOLI trial[12], a randomized controlled trial of patients with ALI and ARDS (based on the former American–European Consensus diagnostic criteria), found no differences in outcomes between these two approaches, but a more recent meta-analysis[18] suggested that higher PEEP was associated with improved hospital survival in patients with moderate–severe ARDS.

Ventilator modes and adjunctive strategies in acute respiratory distress syndrome

Although there are many ventilator modes that can be employed in the management of patients with respiratory failure, volume assist-control remains the preferred mode for achieving the goals of lung protective ventilation in ARDS. Randomized, controlled trials demonstrating superiority of volume assist control over other modes in the management of ARDS are lacking at this time, but it is the mode used in the majority of major clinical trials in patients with ARDS and was the mode used in the ARMA trial,[11] which, as noted above, showed a clear mortality benefit. The pressure and volume targets of lung protective ventilation can be achieved with other modes such as pressure assist control or pressure-regulated volume control, but they have not been adequately studied in ARDS and their use requires adequate understanding of their different operating principles to achieve the goals of lung protective ventilation.

High-frequency oscillatory ventilation is another ventilatory strategy often mentioned in the care of patients with ARDS,[19] in which very low tidal volumes are delivered at a high frequency and higher average mean airway pressure. While there is evidence demonstrating the safety of this approach and improvements in oxygenation,[20] there is no evidence from randomized trials demonstrating mortality benefits over volume assist control, the primary mode used in major ARDS trials.[20–22] In fact, the most recent of these trials[22] suggested that high-frequency oscillatory ventilation was associated with increased in-hospital mortality when used early in the course of ARDS treatment.

Interest has also been raised as to whether non-invasive modalities such as continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NIPPV) offer a viable alternative to invasive mechanical ventilation in ARDS. Although these modalities are of benefit in patients presenting with severe exacerbations of chronic obstructive pulmonary disease[23] or cardiogenic pulmonary edema,[24] there is no evidence to suggest they are of benefit in ARDS. No trials have compared these modalities to invasive mechanical ventilation, and the only evidence at present is studies such as that by Ferrer *et al.*[25] in which NIPPV is compared with supplemental oxygen by face mask alone. In this particular trial, NIPPV was associated with decreased need for intubation compared with oxygen by face mask in the overall study population, but among patients with ARDS, there were no differences in outcomes. Clinical reports from the 2009 pandemic indicate that NIPPV was attempted in patients with respiratory failure due to influenza, but most of the patients subsequently received invasive mechanical ventilation as their clinical status declined.[26] Given the lack of data, there is no established role for non-invasive modalities in the management of hypoxemic respiratory failure due to ARDS. Their use should only be considered in patients with mild disease (P_aO_2/F_IO_2 > 200 and no other organ dysfunction) and immunocompromised patients, provided the center is experienced in their application and careful patient monitoring can be ensured.[27]

While there is a dearth of studies regarding non-invasive ventilatory support, multiple studies have sought to determine whether various adjunctive therapies might be of benefit beyond the basic strategies of lung protective ventilation and PEEP application described above. Intravenous corticosteroids,[13] inhaled beta-agonists,[28] exogenous surfactant,[29] and omega-3 fatty acids[30] have all been studied in multicenter randomized trials, but none of these have been shown to improve patient outcomes, and they are not part of standard management protocols. Recent attention has also focused on the potential role of HMG-CoA reductase inhibitors,[31,32] but these have yet to be proven of benefit in large, prospective multicenter trials and are also not part of standard management. None of these studies have specifically examined outcomes in ARDS due to influenza or other respiratory viruses.

Rescue strategies for refractory hypoxemia

Increased inspired oxygen concentrations and PEEP are sufficient to support oxygenation in the majority of patients with ARDS. A select minority, however, have profound hypoxemia that is refractory to standard treatment and may be treated at the discretion of the clinician with one of several "rescue" strategies including ventilation in the prone position, inhaled vasodilators, neuromuscular blockade, recruitment strategies, and extracorporeal membrane oxygenation (ECMO). These strategies, which have been reviewed in detail elsewhere,[33] are each considered briefly below.

Before discussing these interventions, it is important to recognize that their application is complicated by the fact that there is no clear definition of what constitutes "refractory hypoxemia" in the literature. In its broadest sense, the term refers to hypoxemia that persists despite application of high inspired oxygen concentrations and high levels of PEEP, but there are no agreed upon thresholds for P_aO_2, F_IO_2, or PEEP in order to make this designation. The Berlin Definition described above provides a simple, useful tool for classifying the severity of ARDS, particularly for enrollment in clinical trials, but even that definition may not adequately define the need for implementation of a rescue strategy. A P_aO_2/F_IO_2 ratio of 100, for example, may be relatively well tolerated in a 25-year-old patient with no other comorbidities, whereas in an older individual with multi-organ failure or multiple comorbidities, a similar or even higher P_aO_2/F_IO_2 may be problematic and warrant implementation of a rescue strategy. As a result of the lack of

consensus in this area, as well as a lack of clear guidance in the literature regarding when and in what order to implement the various strategies, their application remains highly physician dependent and institution dependent, an important problem when one considers the expense and potential risk associated with some of them.

Prone mechanical ventilation

Many patients with ARDS develop significant atelectasis in the dependent regions of the lungs, which contributes to shunt physiology and hypoxemia. Ventilation in the prone position has been proposed as a way to reverse this problem and improve ventilation–perfusion matching, which in turn improves gas exchange. Other purported benefits include improvements in secretion clearance, increased end-expiratory volume, and decreased mechanical compression of the lungs by the heart. Multiple studies have shown that the technique improves oxygenation, but there are still no data that it improves mortality.[34–36]. One limitation of these studies was that their patient populations included patients with ARDS with a broad range of P_aO_2/F_IO_2 ratios including many patients who would not be considered to have refractory hypoxemia. Whether the technique would yield improved mortality if used only in those with the most severe hypoxemia remains unclear. Other limitations of these studies include the fact that patients in many of these trials were not ventilated according to standardized protocols and did not receive the intervention until later in their disease course or for long enough duration. Drawing on these concerns with earlier trials, Taccone *et al.*[37] conducted a randomized trial of prone positioning initiated early in the hospital course for up to 20 hours per day. As with the earlier trials, they found improvements in oxygenation, but no mortality benefit. No differences were seen in pre-specified subgroups of patients with moderate ($P_aO_2/F_IO_2 < 200$) and severe hypoxemia ($P_aO_2/F_IO_2 < 100$), although there was a non-significant trend toward improvement in the latter group.

The fact that a mortality benefit has not been demonstrated to date is a particularly important limitation of this strategy, particular when one considers the cost of the intervention when specialized beds are used to put patients in the prone position, as well as logistical issues such as the time and labor intensiveness of the strategy, loss of easy access to catheters and indwelling devices, and increased risk of pressure sores and aspiration. Many of the practical considerations necessary to place and maintain patients in the prone position have been reviewed elsewhere.[38]

Recruitment maneuvers

Recruitment maneuvers involve intentional, short-term use of high transpulmonary pressures in an effort to reverse atelectasis and increase end-expiratory lung volume. This theoretically improves gas exchange and prevents ventilator-induced lung injury by avoiding the repetitive opening and closing of collapsed, or atelectatic, alveolar units. A variety of strategies have been proposed including sustained inflation at increased pressure (e.g., 30–45 cm H_2O) for periods of 20–30 seconds,[39,40] transient high levels of pressure control ventilation,[41] intermittent sighs at high distending pressures,[42] and incremental increases in PEEP over a period of several minutes.[43]

The various techniques have not been shown to improve mortality, but may lead to decreased use of other rescue strategies.[44] These strategies do, on average, improve oxygenation, but the observed improvements in oxygenation are not sustained unless increased PEEP is applied after the maneuvers are completed. Data from a systematic review[45] demonstrate that transient hypotension and desaturation are the most common complications, occurring in 12% and 8% of cases, respectively, while more serious adverse events, such as barotrauma and arrhythmia, occur in only 1% of patients treated with these maneuvers. No studies have compared the different types of recruitment maneuvers with each other, and as a result, we lack information about their relative effects on oxygenation or the sustainability of any observed improvements.

Inhaled vasodilators

Regional matching of ventilation and perfusion, one of the primary factors affecting gas exchange, is significantly altered in patients with ARDS due to atelectasis as well as extensive alveolar filling with edema fluid. When administered by the inhaled route, pulmonary vasodilators such as nitric oxide and prostacyclin cause localized vasodilation in well-ventilated lung units, leading to increased perfusion of these units and, as a result, improvements in the ventilation–perfusion matching and arterial oxygenation.[46] The available data demonstrate that administration of inhaled nitric oxide improves oxygenation, although this improvement is transient, not associated with decreased patient mortality or time spent on mechanical ventilation, and may even increase the risk of renal dysfunction[47,48] Fewer studies have examined inhaled prostacyclin, but the general trend in the data is the same: improvements in oxygenation, but no documented improvements in mortality.[49,50] Given the lack of mortality benefit, the potential for renal toxicity, and the extremely high acquisition costs of inhaled nitric oxide, it should not be used on a routine basis and should be reserved for patients refractory to other interventions. Inhaled prostacyclin is less expensive, but does require time on the part of the pharmacist and, where available, the respiratory therapist to set up a system to nebulize the medication. As a result, implementation takes longer than for inhaled nitric oxide, which is delivered via a specialized delivery system that is easily placed in line with the ventilator circuit. Neither therapy is likely to be available in resource-limited settings.

Neuromuscular blockade

Neuromuscular blockade has two potential benefits in refractory hypoxemia: improvements in patient–ventilator synchrony and elimination of muscle activity and the associated oxygen consumption, which can be problematic in the face of limited oxygen supply. Anecdotal accounts suggested that this intervention was employed frequently in the management of severely hypoxemic patients but, until recently, there was little evidence supporting this practice. This changed when Papazian *et al.*[51] reported the results of a multicenter trial investigating whether continuous infusion of cis-atracurium was associated with improved outcomes. Patients with ARDS receiving lung protective ventilation and with P_aO_2/F_IO_2 ratios < 150 were randomized to receive either placebo or a 48-hour infusion of cis-atracurium in addition to other rescue therapies, including prone ventilation and inhaled vasodilators, which could be initiated at the discretion of the treating physician. The hazard ratio for death was lower in the cis-atracurium group (0·68, 95% CI 0·48–0·98, $P = 0·04$) compared with the placebo group, and importantly, there was no difference in the incidence of ICU-acquired paresis between the two groups, a major concern surrounding the use of neuromuscular blocking agents. Questions do remain about the intervention due to the lack of a well-established mechanism accounting for the observed outcomes and about whether a similar benefit would be observed with other, less expensive agents such as vecuronium. Nevertheless, with the established mortality benefit in this trial, neuromuscular blockade may move out of the category of "rescue" strategies and be considered as an accepted early intervention for severe ARDS, particularly in patients with significant patient–ventilator dysynchrony.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation gained considerable attention following the 2009 H1N1 influenza pandemic after several studies documented low mortality rates in patients[5,52,53] with severe hypoxemic respiratory failure treated with this modality. None of these studies were prospective controlled trials, however, a fact that limits the conclusions that can be drawn from their results. The only study to examine the utility of this modality in a randomized, controlled manner was the CESAR trial,[54] in which patients with severe hypoxemic respiratory failure were randomized to continue receiving standard ventilatory support and other rescue modalities at their original hospital or be transferred to a single center to be evaluated for treatment with ECMO. Mortality in the group transferred to the ECMO center was improved relative to the control arm but, importantly, only 75% of those referred to this center were actually started on ECMO. Management practices also varied significantly across the centers providing conventional management, as the study administrators were unable to implement a standardized protocol for conventional management across all participating centers. Given these issues, rather than establishing that ECMO improves mortality, what this trial really established was that transferring patients with ARDS to a center with high levels of experience treating severe respiratory failure is associated with better patient outcomes. The CESAR trial was conducted before the 2009 pandemic and as a result did not include patients with pandemic H1N1 influenza. Pham *et al.*[55] however, have recently reported the results of a cohort study of ECMO use in such patients. Using propensity score analysis to match a prospectively collected cohort of patients with pandemic H1N1 influenza treated with ECMO with similar patients who did not receive ECMO, they found no mortality benefit associated with this intervention. Viewed together with the issues noted above regarding the CESAR trial, this study suggests that while experience with ECMO is increasing over time, further evidence is needed before it should be widely adopted in patients with severe ARDS.

Simple but often overlooked interventions that impact patient outcomes

Amid concern about severe hypoxemia and discussions about implementation of rescue strategies, it is easy to lose sight of simpler measures that may also affect patient outcomes.

Prophylaxis against complications of care in the intensive care unit

Many patients who die from ARDS die not from hypoxemia but, instead, as a result of complications that develop during the course of their ICU stay, including catheter-related blood stream infections, catheter-associated urinary tract infections, venous thromboembolism, ventilator-associated pneumonia, and gastrointestinal bleeding. For these reasons, it is important to institute appropriate prophylactic measures to decrease the risk of these problems. All central venous catheters (CVCs) should be placed with full barrier precautions, and daily assessment made of whether CVCs and urinary catheters can be safely removed. Patients should be placed on prophylaxis against deep venous thrombosis based on published guidelines,[56] while patients receiving mechanical ventilation should undergo daily chlorhexidine oral decontamination[57] and be ventilated with the head of their bed elevated >30 degrees, a measure shown to decrease the risk of ventilator-associated pneumonia.[58] Evidence suggests that use of checklists can increase adherence to these measures.[59]

Sedation practices

While sedatives and analgesics are usually necessary in mechanically ventilated patients for ensuring patient safety and decreasing pain and anxiety, inappropriate use of these

therapies can provoke delirium, oversedation, and other problems that delay liberation from mechanical ventilation and transfer out of the ICU. To reduce the risk of such problems, pain and sedation management in patients with ARDS should rely on target-based sedation protocols[60] and include daily interruption of sedation[61] and, when feasible, paired interruptions of sedation and spontaneous breathing trials,[62] interventions that have been associated in randomized trials with improved outcomes such as reduced sedative exposure, decreased time on mechanical ventilation, and decreased length of ICU and hospital stay.

Fluid management

One factor that often delays separation of the patient from the ventilator as they recover from ARDS is excessive administration of fluids throughout their ICU stay, as the volume-overloaded patient may have impaired gas exchange and decreased compliance that make it difficult for them to pass spontaneous breathing trials. Once the patient is beyond the early, resuscitative phase of their illness, efforts should be made to decrease the amount of volume administered and maintain an even balance between the volume of fluid administered to and eliminated from the patient, referred to as "euvolemia". The benefits of this approach were demonstrated in the Fluid and Catheter Treatment Trial (FACTT)[63] in which patients with ARDS were randomized to a liberal fluid strategy or a more conservative approach that targeted a net even fluid balance over a 7-day period. There were no differences in 60-day mortality between the two groups, but the conservative approach was associated with improved gas exchange and shorter duration of mechanical ventilation without increasing the incidence of acute kidney injury or other non-pulmonary organ failures. While the protocol used in this study is complicated and difficult to implement in more resource-limited settings, it is reasonable to expect that more general approaches targeting euvolemia, rather than strict adherence to the FACTT protocol, may still be of benefit.

The optimal fluid management during the resuscitative phase of ARDS has not been established. Data from trials of sepsis management that do not focus solely on patients with ARDS suggest that crystalloid administration is preferred to starch-based colloid administration, as the latter may be associated with increased incidence of acute kidney injury requiring renal replacement therapy as well as possibly increased mortality.[64,65]

Summary

While patients who develop ARDS following influenza infection are at high risk of morbidity and mortality, adherence to certain evidence-based practices can decrease the likelihood of adverse outcomes. Any patient receiving mechanical ventilation recognized to have ARDS should be started on lung protective ventilation, in which the tidal volume is decreased to ≤6 ml/kg of their ideal body weight to achieve a target plateau pressure of ≤30 cm H_2O. Increased inspired oxygen concentrations and PEEP should be applied to reverse hypoxemia. Volume assist-control remains the primary ventilator mode used to achieve these targets in major trials of patients with ARDS, and there is no evidence to support the use of the non-invasive modalities, CPAP or NIPPV, in the care of these patients. Rescue strategies such as prone ventilation, inhaled vasodilators, recruitment maneuvers, and ECMO may be necessary in cases of refractory hypoxemia, but application of these techniques remains challenging due to a lack of consensus on when and how to implement them. There is now evidence to support the early use of neuromuscular blockade in cases of severe ARDS, and the therapy is now being used more commonly in standard practice rather than solely as a rescue strategy. As important as these interventions may be, the clinician should not lose focus of simpler measures, such as prophylaxis against ICU complications, conservative fluid management strategies, and appropriate sedation strategies that may have an equally large effect on patient outcomes as the more complicated interventions.

Conflicts of interest

The author has no financial or other conflict of interests to report regarding the contents of this manuscript. There are no competing interests. No funding sources were used in the preparation of this manuscript.

References

1 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD *et al.* Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307:2526–2533.

2 Bernard GR, Artigas A, Brigham KL *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149(3 Pt 1):818–824.

3 Rice TW, Wheeler AP, Bernard GR *et al.* Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007; 132:410–417.

4 Neto AS, Cardoso SO, Manetta JA *et al.* Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome. JAMA 2012; 308:1651–1659.

5 Davies A, Jones D, Bailey M *et al.* Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009; 302:1888–1895.

6 Carlton DP, Cummings JJ, Scheerer RG, Poulain FR, Bland RD. Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. J Appl Physiol 1990; 69:577–583.

7 Parker JC, Hernandez LA, Longenecker GL, Peevy K, Johnson W. Lung edema caused by high peak inspiratory pressures in dogs. Role of increased microvascular filtration pressure and permeability. Am Rev Respir Dis 1990; 142:321–328.

8 Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990; 16:372–377.

9 Amato MB, Barbas CS, Medeiros DM *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–354.

10 Brochard L, Roudot-Thoraval F, Roupie E *et al.* Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998; 158:1831–1838.

11 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–1308.

12 Brower RG, Lanken PN, MacIntyre N *et al.* Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–336.

13 Steinberg KP, Hudson LD, Goodman RB *et al.* Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006; 354:1671–1684.

14 Wheeler AP, Bernard GR, Thompson BT *et al.* Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354:2213–2224.

15 Mercat A, Richard JC, Vielle B *et al.* Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299:646–655.

16 Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 2006; 34:1311–1318.

17 Talmor D, Sarge T, Malhotra A *et al.* Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359:2095–2104.

18 Briel M, Meade M, Mercat A *et al.* Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010; 303:865–873.

19 Chan KP, Stewart TE, Mehta S. High-frequency oscillatory ventilation for adult patients with ARDS. Chest 2007; 131:1907–1916.

20 Derdak S, Mehta S, Stewart TE *et al.* High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002; 166:801–808.

21 Bollen CW, van Well GT, Sherry T *et al.* High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. Crit Care 2005; 9:R430–R439.

22 Ferguson ND, Cook DJ, Guyatt GH *et al.* High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013; 368:795–805.

23 Brochard L, Mancebo J, Wysocki M *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995; 333:817–822.

24 Gray A, Goodacre S, Newby DE *et al.* Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008; 359:142–151.

25 Ferrer M, Esquinas A, Leon M *et al.* Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 2003; 168:1438–1444.

26 Rello J, Rodriguez A, Ibanez P *et al.* Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care 2009; 13:R148.

27 Nava S, Schreiber A, Domenighetti G. Noninvasive ventilation for patients with acute lung injury or acute respiratory distress syndrome. Respir Care 2011; 56:1583–1588.

28 Matthay MA, Brower RG, Carson S *et al.* Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. Am J Respir Crit Care Med 2011; 184:561–568.

29 Kesecioglu J, Beale R, Stewart TE *et al.* Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2009; 180:989–994.

30 Rice TW, Wheeler AP, Thompson BT *et al.* Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA 2011; 306:1574–1581.

31 Kor DJ, Iscimen R, Yilmaz M *et al.* Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. Intensive Care Med 2009; 35:1039–1046.

32 Craig TR, Duffy MJ, Shyamsundar M *et al.* A randomized clinical trial of hydroxymethylglutaryl- coenzyme a reductase inhibition for acute lung injury (The HARP Study). Am J Respir Crit Care Med 2011; 183:620–626.

33 Raoof S, Goulet K, Esan A, Hess DR, Sessler CN. Severe hypoxemic respiratory failure: part 2–nonventilatory strategies. Chest 2010; 137:1437–1448.

34 Guerin C, Gaillard S, Lemasson S *et al.* Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004; 292:2379–2387.

35 Gattinoni L, Tognoni G, Pesenti A *et al.* Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001; 345:568–573.

36 Mancebo J, Fernandez R, Blanch L *et al.* A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006; 173:1233–1239.

37 Taccone P, Pesenti A, Latini R *et al.* Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 2009; 302:1977–1984.

38 Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. Am J Respir Crit Care Med 2002; 165:1359–1363.

39 Lapinsky SE, Aubin M, Mehta S, Boiteau P, Slutsky AS. Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. Intensive Care Med 1999; 25:1297–1301.

40 Brower RG, Morris A, MacIntyre N *et al.* Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. Crit Care Med 2003; 31:2592–2597.

41 Gattinoni L, Caironi P, Cressoni M *et al.* Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354:1775–1786.

42 Pelosi P, Cadringher P, Bottino N *et al.* Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 1999; 159:872–880.

43 Bugedo G, Bruhn A, Hernandez G *et al.* Lung computed tomography during a lung recruitment maneuver in patients with acute lung injury. Intensive Care Med 2003; 29:218–225.

44 Meade MO, Cook DJ, Guyatt GH *et al.* Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299:637–645.

45 Fan E, Wilcox ME, Brower RG *et al.* Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med 2008; 178:1156–1163.

46 Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. N Engl J Med 2005; 353:2683–2695.

47 Taylor RW, Zimmerman JL, Dellinger RP *et al.* Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004; 291:1603–1609.

48 Adhikari NK, Burns KE, Friedrich JO *et al.* Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007; 334:779.

49 Walmrath D, Schneider T, Schermuly R *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Respir Crit Care Med 1996; 153:991–996.

50 van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. Chest 2000; 117:819–827.

51 Papazian L, Forel JM, Gacouin A *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–1116.

52 Patroniti N, Zangrillo A, Pappalardo F *et al.* The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med 2011; 37:1447–1457.

53 Noah MA, Peek GJ, Finney SJ *et al.* Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011; 306:1659–1668.

54 Peek GJ, Mugford M, Tiruvoipati R *et al.* Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374:1351–1363.

55 Pham T, Combes A, Roze H *et al.* Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013; 187:276–285.

56 Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: american College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):7S–47S.

57 Koeman M, van der Ven AJ, Hak E *et al.* Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173:1348–1355.

58 Drakulovic MB, Torres A, Bauer TT *et al.* Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999; 354:1851–1858.

59 Winters BD, Gurses AP, Lehmann H *et al.* Clinical review: checklists - translating evidence into practice. Crit Care 2009; 13:210.

60 Brook AD, Ahrens TS, Schaiff R *et al.* Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999; 27:2609–2615.

61 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471–1477.

62 Girard TD, Kress JP, Fuchs BD *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008; 371:126–134.

63 Wiedemann HP, Wheeler AP, Bernard GR *et al.* Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354:2564–2575.

64 Brunkhorst FM, Engel C, Bloos F *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–139.

65 Perner A, Haase N, Guttormsen AB *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–134.