Inching Toward Progress:

The Multidisciplinary Management of the Acute Respiratory Distress Syndrome

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Interests: Protocolized critical care medicine delivery, improving systems and processes in the intensive care unit, interstitial lung disease, music and medicine history

Purpose and Overview: The acute respiratory distress syndrome is one of the most common entities encountered in the ICU and is a significant cause of morbidity and mortality. In the last 2 decades, few single interventions have made a significant impact on ARDS outcomes. Yet, reports are emerging that the incidence and mortality of ARDS may be decreasing. The effective and ineffective treatment of ARDS will be discussed, and it may the combination of small interventions that have the biggest outcome on the future of ARDS management.

Objectives:

1. Understand the limitations in the 1994 definition of ARDS and appreciate the advantages of the new definition of ARDS recently published
2. Review the limited number of therapeutic interventions that have positively affected outcomes in ARDS, as well as appreciate some of the failed or inconclusive pharmaceutical options for ARDS
3. Consider the multidisciplinary interventions that together as part of a bundle may be the future of a comprehensive ARDS management program in advanced ICUs

Description and Definitions

In the earliest parts of the 19th century, scientists began to describe a type of pulmonary edema on necropsy specimens in patients without heart failure.[1] It took over one hundred years before a more accurate description of these patients appeared, and in that time, clinicians made no distinction between pulmonary edema from cardiac versus noncardiac causes.[2] What was distinctive, however, was that this syndrome of bilateral radiographic infiltrates of rapid onset was almost universally fatal in a few days.

The concept of positive pressure ventilation appeared during the Renaissance when Swiss physician Paracelsus wrote of using 'Fire Bellows' connected to a tube inserted into patient's mouth as a device for assisted ventilation (although some credit his contemporary Andreas Vesalius with the first report).[3] Positive pressure bellows ventilation was eventually banned in the middle of the 19th century out of concerns for its safety and effectiveness, and it was not for another one hundred years before the concept was revisited.[4]

In the mid-1950s, technological advances in positive pressure mechanical ventilation and in methods of securing airway access allowed for more survival of these patients, providing an opportunity for study.[5] Arguably, the modern era of critical care medicine began in 1967 with the first description of what we now know as the acute respiratory distress syndrome (ARDS). Writing in *The Lancet* in a classic article in the critical care literature, David Ashbaugh and colleagues described 12 patients at the University of Colorado Medical Center with a constellation of physiology and radiographs similar to the respiratory distress syndrome seen in infants.[6] They observed the common physical and physiological characteristics of this otherwise disparate group of patient who presented with variable predisposing insults such as near-drowning, sepsis, viral syndromes, and trauma. Four years later, Petty and Ashbaugh published another review in which the term **"adult" respiratory distress syndrome** was used (in order to contrast the otherwise similar version, the infant respiratory distress syndrome).[7]

In 1992, the American-European Consensus Conference was convened in order to establish what, until last month, has been the standard definition of the acute respiratory distress syndrome. First, the term "adult" was dropped. Then, in order to fully realize accurate clinical and epidemiological research four criteria were determined:[8] 1. Acute onset, 2. Bilateral radiographic infiltrates, 3. No evidence of elevated left atrial pressure in order to distinguish the noncardiogenic pulmonary

edema of ARDS from that of cardiogenic cause, and 4. A ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) of ≤ 200. As pulmonary artery catheters were still commonplace in the management of ARDS at that time, criterion 3 could be met if the pulmonary artery occlusion pressure was ≤ 18.

In the last two decades, limitations in this definition have become apparent. First, the term "acute" warrants further clarification from the AECC definition, especially when considering a patient for time-sensitive therapy or for enrollment in an ARDS clinical trial. Clinical consensus is generally that the syndrome occurs with 72 hrs of identification of a known ARDS risk factor (Table 1).[9] But, an elusive secondary cause may delay the recognition of ARDS sometimes up to a week. And, implicit in this shortcoming in the AECC definition is that a predisposing risk factor should be identified. The necessity of risk identification, however, was not included in the 1994 statement. This lends itself to misdiagnosis of ARDS in some cases when a predisposition is not readily found.

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Nonpulmonary sepsis
Gastric Aspiration	Acute pancreatitis
Chest trauma/lung contusion	Nonchest trauma
Inhalation injury	Massive transfusions
Near-drowning	Surface burns

Table 1 Common risk factors for ARDS

The AECC also did not account for the unique pathophysiological changes that occur in ARDS. These changes distinguish ARDS from some of the other clinical causes of refractory hypoxemia and bilateral radiographic infiltrates (severe viral pneumonia, for example). Whether accounting for pathophysiology in the definition can distinguish ARDS as opposed to the degree of hypoxemia, or perhaps more importantly could accurately predict a patient's outcome, was not known then.

Finally, the ability to distinguish the infiltrative pattern of ARDS on chest radiography from hypervolemia has long been a known limitation of the AECC definition. We recognize now, though, that volume overload can coexist with

ARDS as long as the patient's respiratory failure cannot be fully explained by the hypervolemia (and, as stated previously, a risk factor is identified).[10]

Therefore, a new ARDS Task Force has published an updated definition of ARDS (see Table 2). The prior limitations were mostly addressed. Patients must be identified within one week of risk factor identification, thereby also addressing the risk factor-presence requirement. Hypervolemia and/or congestive heart failure is allowable provided the respiratory failure is not fully explained by it. Heart failure must be objectively excluded, though, if no risk factor is obviously present. Categories have been added – mild, moderate, and severe. The term *acute lung injury*, previously added to encompass similar pathophysiology but less severe hypoxemia, has been excluded. Multiple ancillary variables were considered in order to identify patients with severe ARDS, including measurements of respiratory system compliance, dead space, and even ventilator requirements. None of these performed better in predicting mortality than a $PaO_2/FiO_2 \leq 100$ in the validation cohort analysis, so physiological parameters were not included.

Timing	Within one week of a known clinical insult or new or worsening respiratory symptoms
Chest Imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	$200 < PaO_2/FiO_2 \leq 300$ with PEEP ≥ 5
Moderate	$100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5
Severe	$PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5

Table 2[11] The Berlin Definition of the Acute Respiratory Distress Syndrome (published ahead of print, May 21, 2012)

Pathophysiology

The predisposing injury leading to ARDS results in several pathophysiological changes at every level of the alveolar-capillary compartment (Figure 1).[12] The

barrier formed by the type I pneumocytes is disrupted in the initial, or *exudative*, phase of ARDS. A protein-rich edema fluid may flood the alveolus, noted as the typical bilateral infiltrates on chest x-ray. Inflammation is perpetuated by a host of cytokines, including TNF-α, IL-1, IL-8. Injury to the type II pneumocytes inhibits surfactant function and prohibits the effective removal of the edema fluid.[13] The physiological consequences are refractory hypoxemia and a decrease in respiratory system compliance.

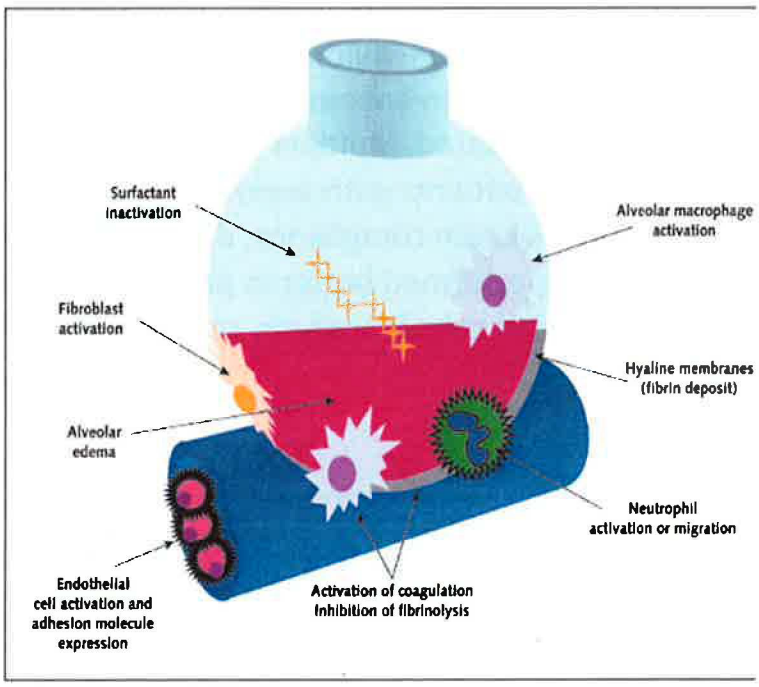


Figure 1[14] The normal and injured alveolus during the acute phase of ARDS.

On the endothelial side, there is a decrease in the anticoagulant proteins C and S and an increase in the expression of the procoagulant tissue factor. Fibrinoysis may be inhibited as plasminogen activator factor 1 increases.[13] Small-vessel thrombosis can then result in increased dead space ventilation.

Patients may recover from the acute phase completely with little clinical consequences. Some, however, progress to a more prolonged *fibroproliferative* phase in which neovascularization and epithelial cell regeneration occurs more slowly. Eventually, a more chronic *fibrosis* phase results, leading to more long-term morbidity in survivors (ventilator dependence, physical debility, etc.). Why

some survivors resolve the acute phase without progressing to the more chronic phases is not known.

As these processes are *heterogeneous*, regional over-distention from mechanical ventilation can occur with significant consequences. The combination of decreased respiratory system compliance, increased dead space ventilation, and refractory hypoxemia all lead to increased work of breathing by the patient. Acute respiratory failure is often the result requiring endotracheal intubation and mechanical ventilatory support.

Pharmacotherapy & ARDS

The search for a drug – any drug – that may be an effective treatment for ARDS has not been successful despite decades of research. Trial design, mechanism of drug delivery, and timing of administration are some of the barriers that have prohibited clinical trials from reaching clinical important outcomes. Many of the high-impact clinical trials have been conducted by the NIH/NHLBI ARDS Network, a consortium of academic centers throughout the United States. A summary of just a few of these pharmacotherapies follow:

Corticosteroids

Systemic corticosteroids in ARDS have long been a target for clinical trials, but to date no clinical trial has definitively shown a benefit.[15,16] They remain attractive to investigators as the inflammatory cascade in the evolution of ARDS would seem to lend itself amenable to anti-inflammatory therapies.[2] Today, the use of corticosteroids for "salvage" therapy, intended to target the fibroproliferative phase, has been the focus.[17] But, determining exactly when the patient has transitioned to the fibroproliferative phase is challenging, though the general timeframe is 7 days from onset of ARDS.[12] One very small study showed a physiologic benefit of high-dose methylprednisolone started after day 7 of ARDS, but the crossover to the treatment group was 50%. And, patients were not analyzed within the group they were randomized.[18]

The ARDS Network also made an effort in a multicenter trial of patients with ARDS for at least 7 days, intending to target the fibroproliferative phase. 180 patients were randomized to systemic corticosteroids versus placebo, with a primary endpoint of 60-day mortality. For patients enrolled after day 7, there was

no survival benefit. More ominously, patients in the steroid treatment group that enrolled after day 14 had a significant increase in mortality.[19] As such, the optimal role and timing of steroids in ARDS remains unknown.

Inhaled pulmonary vasodilators

Inhaled therapies are attractive for their primary delivery directly to the lung. In ARDS, the selective pulmonary vasodilator properties of nitric oxide and prostacyclins are particularly attractive, in that they are delivered only to alveolar-capillary units that are effectively aerated and perfused (V/Q matched).[20] The bulk of the literature is for inhaled nitric oxide. While numerous multicenter studies of nitric oxide in ARDS have demonstrated an improvement in oxygenation with inhaled nitric oxide therapy, none have improved important clinical outcomes such as mortality or ventilator-free days.[21,22] The oxygenation benefit is lost after approximately 48 hours, and the theory is that over time, there is collateral systemic absorption of nitric oxide, resulting in worsening of intrapulmonary shunt.[20]

In one of the largest randomized-controlled studies of inhaled nitric oxide, investigators attempted to obviate these collateral effects by the use of low-dose therapy. 385 patients were enrolled with ARDS < 72 hrs after onset. No survival benefit was found with a constant dose of 5 ppm iNO.[23]

A 2010 Cochrane Review of inhaled prostacyclins, such as epoprostenol, did not find enough randomized-controlled studies to complete their review.[24]

β-agonists

β_2-adrenergic agonists modulate the expression of the epithelial apical sodium channel as well as the expression of the Na^+,K^+-ATPase pump on the alveolar epithelial layer.[25-27] Thus, β_2-adrenergic agonist therapy has been theorized to accelerate alveolar fluid reasborption in order to improve clinical outcomes in ARDS.[28,29]

Because of this physiology, two recent studies were conducted assessing the efficacy of β_2-adrenergic agonists in patients with acute lung injury and ARDS. The first multicenter trial randomized 282 patients to either aerosolized albuterol or saline placebo. The primary outcome variable, ventilator-free days, was not significantly different between the two groups. This trial was stopped early for

futility by its data safety monitoring board, especially as the statistics were trending toward more days ***on*** the ventilator for the albuterol group.[30]

The second trial researched the use of the IV β_2-adrenergic agonist salbutamol. Patients with ARDS and on mechanical ventilation < 72 hours were randomized to a continuous infusion of salbutamol versus placebo over seven days. The primary outcome was 28-day mortality. Like the aerosolized study, this trial was also stopped early after a planned interim analysis showed no efficacy for IV salbutamol. Even more, a significant increase in the risk of death was found in the treatment group (RR 1.55, 95% CI 1.07–2.24).[31] These results call into question the routine use of β_2-adrenergic agonists for patients with ARDS unless there is another clear indication (for example, severe bronchospasm).

Surfactant

Exogenous surfactant therapy is a standard life-saving intervention for the prevention and treatment of the neonatal respiratory distress syndrome (NRDS).[32] As the pathophysiology of ARDS resembles both experimental surfactant depletion and NRDS, there is logical pathway leading to clinical trials of surfactant therapy.

In ARDS, there are absolute reductions in surfactant concentrations, and the surfactant present in the ARDS lung is dysfunctional [33,34] As Figure 2 depicts, the whole life cycle of surfactant may be affected: synthesis, release, incorporation into epithelial membrane, and recycling. But, despite the logical connection between surfactant and the ARDS pathophysiology leading to successful treatment, no trial to date of exogenous surfactant therapy has demonstrated any clinically meaningful benefit.

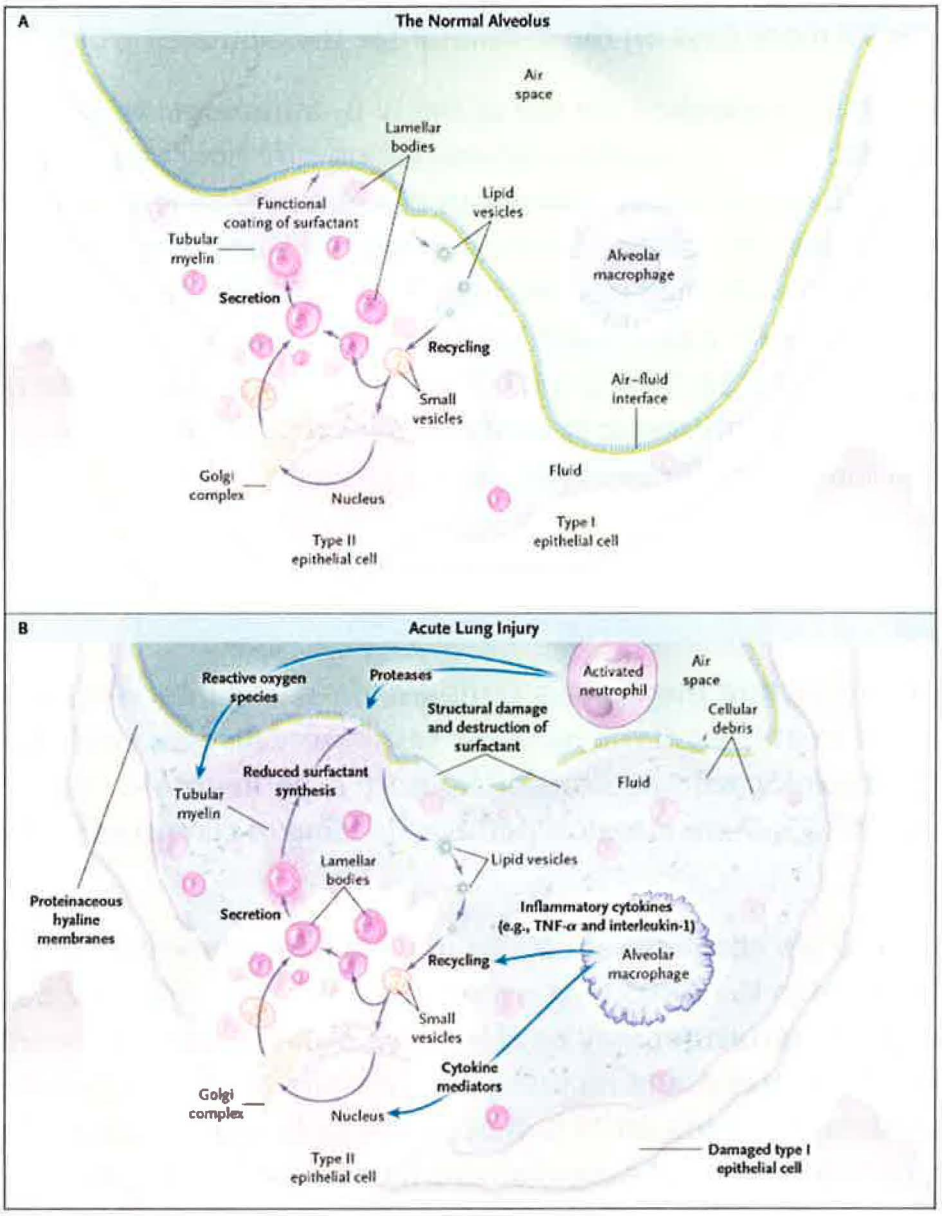


Figure 2[33] Surfactant production and recycling in the normal alveolus (A) and in the alveolus of acute lung injury (B)

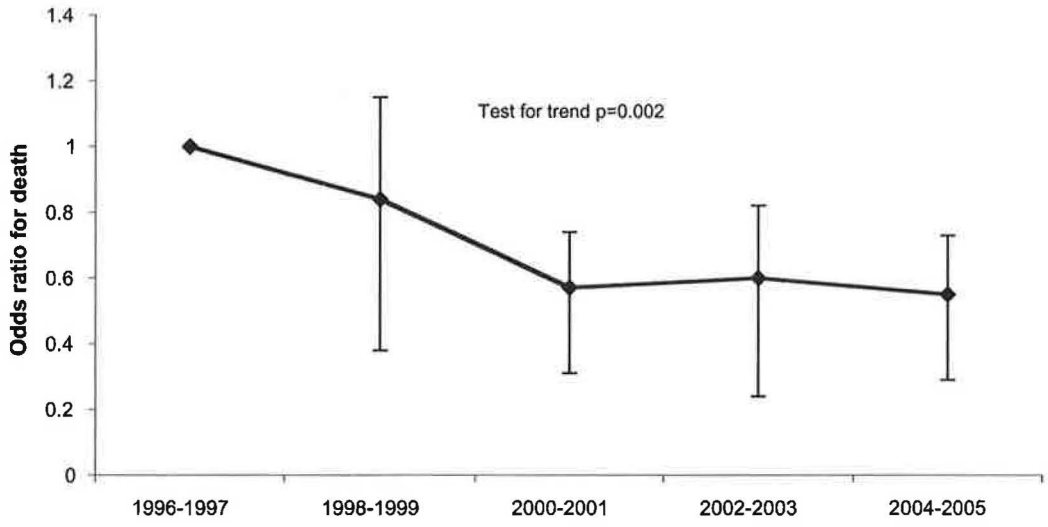
In just one example, two parallel but nearly identical multicenter/multinational trials randomized 448 patients with ARDS to intratracheal recombinant surfactant protein C-based surfactant. The primary outcome variable was the number of ventilator-free days during the 28 days following treatment. Although there was a significant improvement in oxygenation in the treatment group, there was no difference in ventilator-free days.[35]

Other studies using different preparations of surfactant,[36] different methods of delivery,[37] and at high doses[38] all failed to meet any clinically important endpoints.

Incidence & Mortality of ARDS Decreasing?

Despite the lack of a pharmaceutical option for the treatment of ARDS, there has been progress. In the early-to-mid 1990s, the mortality of the syndrome was been reported to be as high as 58%.[39,40] These figures, however, were conducted around the same time as the initiation of the ARDS Network and prior to the publication of the ARMA trial (to be discussed) that demonstrated the first intervention that could reduce mortality in ARDS.

For example, a population-based cohort study in the Seattle area – conducted between 1999 and 2000 – found an in-hospital mortality of 38.5%.[41] The overall mortality since then may have improved. Analyzing ARDS Network studies between 1996 and 2006, crude mortality declined from 35% in 1996 to a low of 25% in 2005 (Figure 3).[42]



Points represent adjusted 60-day mortality for the enrollment period, and error bars the 95% confidence intervals.

Figure 3[42] Adjusted 60-day mortality among Acute Respiratory Distress Syndrome (ARDS) Network patients, 1996–2005.

As the mortality of ARDS may have improved, perhaps the incidence has decreased as well. In a population-based cohort study in Olmsted County, Minnesota, conducted between 2001 and 2008, the age- and sex-specified incidence of ARDS decreased from 81 to 38.3 cases per 100,000 person-years ($p < 0.001$).[43] Interestingly, almost the entire decrease in incidence was in hospital-acquired ARDS. Could ARDS be a preventable, "nosocomial" complication? To what do we attribute such progress?

Nonpharmacotherapy & ARDS

Lung protective ventilation

Today, there is but one therapeutic intervention that has demonstrated an improvement in the survival of ARDS – low tidal volume, or "lung protective" ventilation. The traditional approach to mechanical ventilation was to use tidal volumes approaching 10 to 15 mL per kilogram of ideal body weight (normal subjects at rest have tidal volumes of 7 to 8 mL per kilogram of ideal body weight).[44] These tidal volumes were deemed necessary to achieve a normal pH on arterial blood gas analysis. Unfortunately, ventilating the lungs damaged by ARDS with large tidal volumes can lead to a *ventilator-induced lung injury* (VILI). As the pathophysiological changes seen in ARDS are heterogeneous, the ventilator pressures required to recruit atelectatic segments in one area may come at the expense of overdistention ("stretch" injury, or "barotrauma") in otherwise normal areas of the lungs (Figure 4).

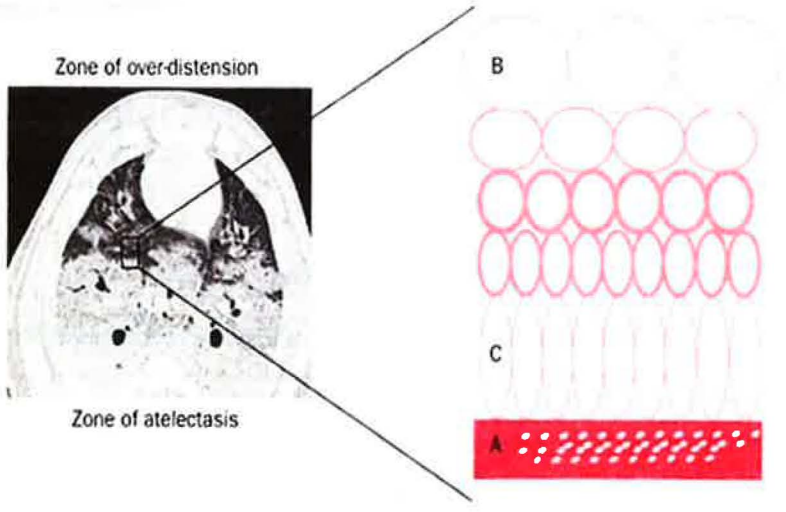


Figure 4[45] A mechanism of ventilator-induced lung injury, "barotrauma"

Further, as VILI may further compromise the ARDS-induced injury to the pulmonary epithelium and endothelium, release of inflammatory mediators can perpetuate the damage and cause injury to other organs (a phenomenon known as biotrauma).[46,47]

Thus, the question that needed answer was, Which is more harmful - lower tidal volumes which may result in a respiratory acidosis and borderline oxygenation, or traditional tidal volumes which may lead to excessive stretch and ventilator-induced lung injury?

In 2000, the ARDS Network published the results of a multicenter clinical trial (ARMA) in which patients with ARDS were randomized to a tidal volume strategy of 6 mL per kilogram of predicted body weight versus 12 mL per kilogram of predicted body weight.[48] At the time of publication, there was criticism for the group's selection of such a large tidal volume difference.[49,50] The control group tidal volume was selected as it fit into the range of standard practice at the time, and it was felt to be clinically and ethically legitimate in that there was an absence of a rigorously validated standard of care for ventilation of patients with ARDS.[51,52]

The trial was stopped early by its monitoring board at the fourth interim analysis after 861 patients were randomized. There was a significant improvement in mortality in the 6 mL per kilogram group (31% versus 39.8%, $p = 0.007$). The group also had decreased levels of inflammatory markers such as IL-6 (suggesting that ventilator-induced stretch injury was diminished), a decrease of nonpulmonary organ failure (suggesting a decrease in biotrauma), and less time on the ventilator.[2,48]

Positive End-expiratory Pressure

The search continues for the optimal amount of positive end-expiratory pressure (PEEP) to administer a patient on a ventilator with ARDS. Maintaining PEEP throughout the respiratory cycle could improve oxygenation in ARDS was known before the ARMA trial came along.[53,54] In addition to preventing the collapse of surfactant deficient alveoli to improve oxygenation and overall alveolar recruitment, PEEP can prevent "atelectotrauma," another form of ventilator-induced lung injury caused by the repetitive opening and closing of alveoli.[2,55,56]

The ARMA trial used a fixed PEEP/FiO_2 ladder, in which the PEEP was set for a given FiO_2, and the ventilator was adjusted up and down by steps depending on the oxygenation needs. In a followup study (ALVEOLI), the ARDS Network randomized patients to a high versus low PEEP strategy. Ventilator management was otherwise with a low tidal volume strategy, 6 mL per kilogram predicted body weight. While the higher PEEP group had improved oxygenation and better respiratory system compliance, there was no benefit in survival, in time on the ventilator, or in nonpulmonary organ failure.[57] But, both groups had 28-day mortality rates of around 25%, providing some validation of the low-tidal volume strategy in the first study.

Subsequent trials to assess the best PEEP strategy for patients have been variably successful but not enough to establish them as the standard of care like low tidal volume ventilation.[58,59] A 2010 meta-analysis suggested that sicker patients with the worst oxygenation would benefit the most from a higher PEEP strategy.[60] In reality, assessing how much of the ARDS lung is recruitable with PEEP is done at the bedside more in a trial-and-error fashion until more objective testing of recruitability is easily available.[61]

Fluid Management

In the pathophysiology of ARDS, lung water fills the alveolus and overwhelms the normal clearance mechanisms that include the active extrusion of sodium into the interstitial space by means of the Na^+,K^+–ATPase located on the basolateral membrane of type II cells. Further, the permeability of the microvascular membrane increases, resulting in a marked increase in the amount of fluid and protein leaving the vascular space. Noncardiogenic pulmonary edema, such as that in ARDS, has a high protein content because the more permeable microvascular membrane has a reduced capacity to restrict the outward movement of larger molecules like plasma proteins.[25,62]

The accumulation of this extravascular lung water (EVLW) has clinical consequences in its effects on respiratory mechanics and oxygenation. Indeed, in clinical trials wherein EVLW is measured and reduced, important clinical outcomes like length of stay and ventilator days are improved.[63] These measurements are difficult to perform consistently at the bedside and hence have not come into everyday use. Other strategies, such as the use of colloid combined with diuretics in patients with hypoproteinemia,[64] are still in need of additional larger clinical trials.

Cumulative fluid balance alone can be independently associated with hospital survival in ARDS. Reviewing the earliest ARDS Network cohort of patients, researchers found that a negative fluid balance on hospital day 4 was associated with a significantly lower mortality when adjusted for confounding variables.[65] But, unstable hemodynamics may prevent targeting a negative fluid balance and is probably harmful given that early resuscitation in such patients is beneficial.[2,66] As with the measurement of EVLW, the most accurate and reliable method for assessing the adequacy of volume resuscitation is controversial and not firmly established in these patients.[67]

The ARDS Network designed a 2x2 factorial trial wherein patients with acute lung injury were randomized to either a conservative or liberal fluid management strategy and further randomized to the management of their volume targets by either central venous catheter (central venous pressure) or by pulmonary artery catheter (pulmonary artery occlusion pressure). The primary endpoint was death at 60 days. Using a complex and inclusive treatment algorithm, no difference in the primary endpoint was found between the two groups. However, there was significant improvement in the number of ventilator-free days with a conservative fluid strategy (–136±491 ml at day 7) compared to the liberal-strategy group (6992±502 ml at day 7). Nonpulmonary organ failures (in particular, renal failure) were not increased.[68] It is important to note that patients were not in the diuresis section of the algorithm until their mean arterial pressure was > 60 or they were off vasopressors, thus recommending a fluid-conservative strategy only when shock is resolved.

On the other side of the trial, there was no difference in either the primary outcome or any of the secondary outcomes between patients managed with a central venous catheter or a pulmonary artery catheter. There were more catheter-related complications in the pulmonary artery catheter groups (predominately arrhythmias).[69]

Emerging Multidisciplinary Therapies

Extracorporeal Membrane Oxygenation

Extracorporeal Membrane Oxygenation (ECMO) for adults has seen renewed interest for the management of ARDS in the last 5 years. Prior to 2009, only two randomized-controlled trials of extracorporeal life support (ECLS) for ARDS

existed, and neither of these showed a survival benefit.[70,71] The 2009 novel influenza A(H1N1) pandemic, however, led to a worldwide increase in the number of ICU admissions for acute respiratory failure. And, venovenous ECMO was reported to be of benefit in this subpopulation of patients in various articles.

For example, a major observational study appeared when investigators in Australia and New Zealand reported their experiences with pandemic H1N1.[72] The observed cohort was young (median age 36) and exceptionally ill – the median PaO_2/FiO_2 ratio was 56. Remarkably, 71% of the patients (48/68) who were managed with vvECMO survived to ICU discharge, and all 48 were still alive at the time of the article publication (16 were still in the hospital).

Interestingly, that same issue of *JAMA* (November 4, 2009) had two other country-specific reports of their novel 2009 influenza A(H1N1) experience (Mexico and Canada). Both of these reports had similarly young and very sick patient populations. But, the Canadian study is especially notable for a 14.3% 28-d mortality (similar to the Australia/New Zealand survival report) and only a 4.2% vvECMO utilization.[73]

A similar report of very sick patient with ARDS secondary to novel 2009 influenza A(H1N1) from the United States, however, did not require any "rescue" therapies (such as vvECMO) to achieve a survival of 83% to hospital discharge.[74] These contrary reports raise concerns that vvECMO may not be the ultimate answer for patients in need of ARDS rescue. Care must be taken in generalizing these reports to the population at-large. No doubt selection bias arises in observational reports, so whether vvECMO truly improves survival in patients that would die without it can only be answered in a randomized-controlled trial.

Thus, in the last 15 years only one clinical trial comparing vvECMO to conventional mechanical ventilation for severe ARDS has been published. In the CESAR trial,[75] 180 patients in the UK were randomized to conventional mechanical ventilation or to ECMO *consideration*. Patients randomized to the ECMO arm were transferred to a single center where a comprehensive ARDS management program existed and that included ECMO. Of the 90 patients transferred to the ECMO site (Glenfield Hospital, Leicester, UK), 68 actually underwent the intervention. The others were managed with conventional mechanical ventilation supplemented by alternative rescue therapies (steroids, prone ventilation). The primary outcome of death or disability at 6 months was met in 37% of the ECMO-consideration group versus 53% in the conventional therapies group. The control

group of this study has been the focus of much criticism, as there was no standardized protocol for "conventional therapy." Indeed, the trial may demonstrate that patients with severe ARDS could have better outcomes if treated at a highly-experienced center with a clear treatment algorithm that may include ECMO.

Where ECMO fits into the list of "rescue therapies" is unknown and based on center experience. But, as CESAR suggests, it may have a role as part of a comprehensive ARDS program. ECMO requires very close coordination between the intensive care unit team, cardiothoracic surgery, and the ECMO perfusionist who ultimately manages the treatment at the bedside. The surgeon's role is in placement of the large-bore vascular access catheters and can be done at the bedside. At St. Paul University Hospital, when venovenous ECMO is used (as opposed to venoarterial ECMO in which the patient also receives cardiac support), a single-site approach with a dual-lumen cannula is employed (Figure 5):

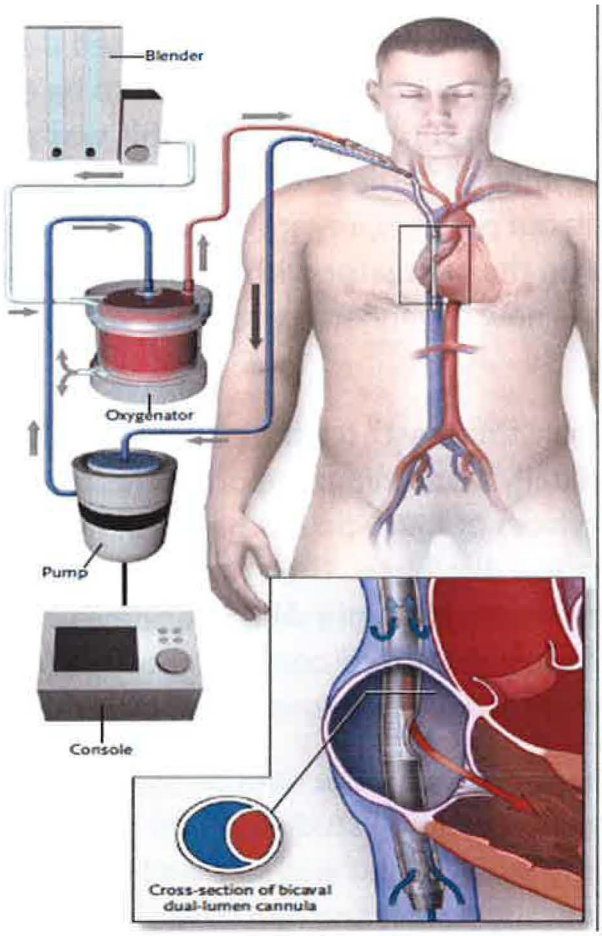


Figure 5[76] Single-site approach to venovenous ECMO cannulation

Cardiovascular/thoracic surgery follows along with the ICU team after ECMO is initiated to ensure the cannula remains in place properly and for monitoring of complications. The most common complication not directly related to the ECMO circuit is bleeding either from the cannulation site or internally (pulmonary, GI, intracranial). Anticoagulation is required to maintain the patency of the ECMO circuit; hence the risk of bleeding is not insignificant. The benefit of using ECMO is to allow true lung-protective ventilator settings without compromising oxygenation or ventilation. The risk of complications increases the longer the patient is on the ECMO circuit, so selecting patients with an apparent reversible cause of respiratory failure is important (patients in the CESAR study were on ECMO on average of 9 days).[75]

Physical Therapy

The notion of physical therapy for patients with ARDS requiring mechanical ventilation may seem like a dangerous recommendation. Delicately balancing oxygen delivery and demand could be compromised if a patient was awakened too early and mobilization initiated. Focus tends to be on the organ systems that more imminently threaten survival.[77] Indeed, this was a prevailing attitude in most intensive care units until the late 1990s. Daily sedative interruption for most mechanically ventilated patients, regardless of the level of ventilator support, results in less time on the ventilator without increased morbidity or "unplanned" extubations.[78] This is now a standard part of the management of mechanically ventilated patients.

As this paradigm of "total rest" for the patient has shifted to sedation minimalization and daily awakening, opportunities for active patient mobilization have emerged. Survivors of ARDS do not have pulmonary impairment one and two years after hospital discharge. Their main complications are weakness and decreased functional levels from pre-ARDS baselines.[79,80] In a cohort of ARDS survivors, only half were employed one year after their hospitalization, and the reasons reported were fatigue, weakness, and generally poor functional status.[79]

Until recently, there was very little data on the effect of physical activity in critical illness. Two observational studies at LDS Hospital in Salt Lake City established that early mobilization was safe and feasible once the patient was awake, hemodynamically stable, and had oxygen requirements of 50% or less. Since the patients were in another ICU for an average of 10 days prior to transfer

to the intervention ICU, it remained unclear if earlier therapy was beneficial or if patients were improving with time and merely ready for ambulation.[81,82]

The prospective first study compared early ICU mobilization to usual care. Enrollment occurred with the first 48 hours on mechanical ventilation. A multidisciplinary management team of an ICU nurse, a nursing assistant, and a physical therapist administered a treatment protocol that consisted of four escalating levels of activity depending on the patient's level of consciousness and their achievement of mobility goals. Patients in the treatment group were out of bed earlier, and they had a significant reduction in ICU and hospital length of stay.[83]

A more recent trial of early physical therapy in the ICU sought to demonstrate a faster return to independent functional status at hospital discharge –defined as the ability to perform six activities of daily living and the ability to walk independently. Patients randomized to the treatment group received early exercise and mobilization during their daily sedative interruption. The control group had therapy at the discretion of the managing physicians. More patients returned to functional independence than in the usual care group (59% versus 35%, p = 0.02), and there was a significant decrease in delirium and an increase in days off mechanical ventilation.[84] These same investigators have reported on the feasibility of performing early physical therapy on an ARDS cohort with substantial ventilator requirements (see Figure 6).[85]

Activity	UE/LE Exercise	Bed Mobility	Sit	Stand	Chair	Eat[a]	Groom	Ambulate
F_{IO_2}, %	50 (40–60) Maximum 100	50 (40–60) Maximum 100	50 (40–60) Maximum 60	50 (40–60) Maximum 75	50 (40–60) Maximum 75	50 (40–60) Maximum 100	50 (40–60) Maximum 100	50 (40–60) Maximum 60
PEEP, cm H_2O	5 (5–8) Maximum 12	5 (5–8) Maximum 10	5 (5–7) Maximum 10	5 (5–7) Maximum 12	5 (5–7) Maximum 12	5 (5–8) Maximum 12	5 (5–8) Maximum 12	5 (5–5.5) Maximum 10

Figure 6[85] Median level of ventilator support for mechanically ventilated patient cohort receiving early physical and occupational therapy in the ICU

The investigators are careful to point out, however, the importance of the multidisciplinary requirements for this intervention. "Such conditions require careful, coordinated planning with multiple care providers (physicians, nurses, therapy staff) before initiating mobilization."[85] The effects of early mobility on the aforementioned functional deficits of ARDS survivors are unknown.

Nutrition

The literature is rather sparse on the timing of nutritional supplementation in medical ICU patients. The American Society of Parenteral and Enteral Nutrition (ASPEN) Guidelines of 2009 recommend starting nutrition early (within the first 48 hours) in critically ill patients (not necessarily just for patients with ARDS), but this recommendation was based on papers predominately on surgical patients.[86] And, enteral supplementation should be the preferred route over parenteral unless not tolerated. In fact, *delaying* TPN one week versus starting early in patients insufficiently nourished via the enteral route may lead to faster ICU and hospital discharges, as reported in a multicenter trial in 2011.[87]

Full-strength enteral nutrition was the recommended goal in the 2009 ASPEN guidelines, if tolerated.[86] However, disparate reports exist, all smaller studies, variably targeting 100% of caloric needs early[88] versus permissively underfeeding for better outcomes.[89,90] Specific to patients with acute lung injury and ARDS, the ARDS Network conducted a multicenter trial to see if initial lower-volume trophic enteral nutrition feeding would increase ventilator-free days and decrease gastrointestinal intolerances compared with initial full enteral feeding to caloric goals.

In the EDEN study, patients were randomized to receive either trophic or full enteral feeding for the first six days of the development of ALI/ARDS requiring mechanical ventilation. Trophic feeding rate was 10 mL/hr for the first 272 patients enrolled, but this was later changed to 20 ml/hr when a parallel study arm was closed, in order to approximate the same calories. A total of 1000 patients were enrolled with a primary study outcome of ventilator-free days to study day 28. Although the trophic feeding was much better tolerated in terms of gastrointestinal complications (lower gastric residual volumes and less vomiting), there was not an increase in ventilator-free days. Survival and hospital discharge was also similar (Figure 7)[91] Despite the seemingly negative results of the trial, the authors mentioned that the trophic arm was very popular with their ICU nurses. At Vanderbilt, this has become their standard as it frees the nurse up for other patient-care activities rather than concentrating on reaching a target goal rate in the first week.[92]

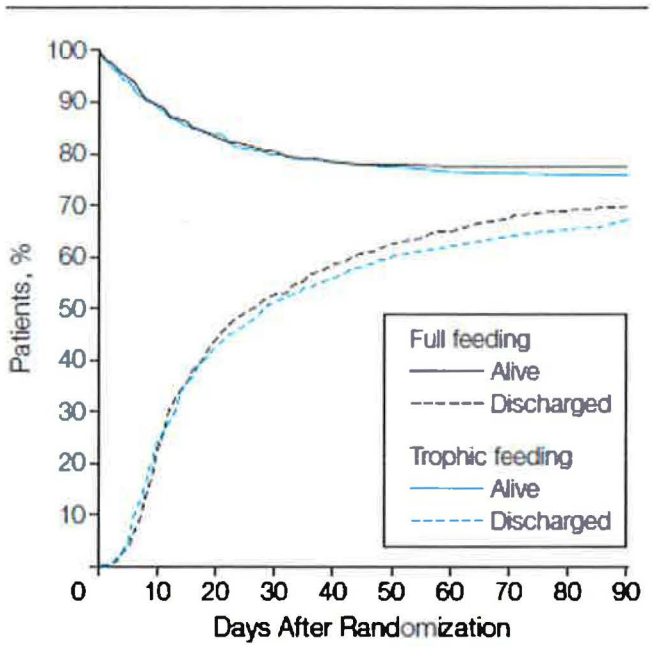


Figure 7[91] Survival and Hospital Discharge, Full versus Trophic Feeding in Patients with Acute Lung Injury

Can ARDS Be Prevented?

Despite these effective and/or emerging treatment options for ARDS, the true challenge lies in prevention. While we may know the predisposing factors that CAN lead to ARDS, the vast majority of patients presenting with a predisposing factor do not develop ARDS. A multicenter, multidisciplinary trial conducted to formulate a prediction model for acute lung injury found that only 7.2% of patients admitted to the hospital with a predisposing condition will go on to develop ALI/ARDS.[93]

That study, conducted by the US Critical Injury and Illness Trials Group (USCIITG) and included UT-Southwestern, published the first predictive scoring model that may allow us to identify these patients early. In a multicenter cohort study, investigators identified predisposing conditions and risk modifiers that could predict the development of ALI/ARDS from routinely available clinical data at admission. Points are given for various predisposing conditions and/or traumas, and for modifiable risks such as FiO_2 requirements or chronic health conditions like diabetes or obesity.

The Lung Injury Prediction Score (LIPS, Figure 8) model discriminated patients who developed ALI from those who did not. After ROC analysis to determine to optimal score cutoff, positive and negative likelihood ratios (95% CI) for development of ALI were 3.1 (2.9–3.4) and 0.4 (0.3–0.5), respectively, with a sensitivity of 0.69 (0.64–0.74) and specificity of 0.78 (0.77–0.79). While not superlative predictive power, such a model may allow identification of patients who can benefit from interventions to prevent disease progression and also aid the timely and efficient enrollment of patients into future ALI prevention trials.[93]

	LIPS Points	Examples
Predisposing Conditions		
Shock	2	
Aspiration	2	
Sepsis	1	(1) Patient with history of alcohol abuse
Pneumonia	1.5	with septic shock from pneumonia
High-risk surgery*		requiring $F_{IO_2} > 0.35$ in the
Orthopedic spine	1	emergency room: Sepsis + shock +
Acute abdomen	2	pneumonia + alcohol abuse +
Cardiac	2.5	$F_{IO_2} > 0.35$
Aortic vascular	3.5	1 + 2 + 1.5 + 1 + 2 = 7.5
High-risk trauma		(2) Motor vehicle accident with
Traumatic brain injury	2	traumatic brain injury, lung contusion,
Smoke inhalation	2	and shock requiring $F_{IO_2} > 0.35$
Near drowning	2	Traumatic brain injury + lung
Lung contusion	1.5	contusion + shock+ $F_{IO_2} > 0.35$
Multiple fractures	1.5	2 + 1.5 + 2 + 2 = 7.5
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI > 30)	1	(3) Patient with history of diabetes
Hypoalbuminemia	1	mellitus and urosepsis with shock
Chemotherapy	1	Sepsis + shock + diabetes
$F_{IO_2} > 0.35$ (> 4 L/min)	2	1 + 2 − 1 = 2
Tachypnea (RR > 30)	1.5	
$Sp_{O_2} < 95\%$	1	
Acidosis (pH < 7.35)	1.5	
Diabetes mellitus†	−1	

Figure 8[93] Lung Injury Prediction Score (LIPS) Calculation Worksheet, with examples

Other preventive methods may be in the selection of lung-protective settings at the time of presentation, BEFORE the development of ARDS, in at-risk patients. In fact, the incidence of ARDS development was so significant in a prospective study of protective versus conventional tidal volume settings in patients without ARDS at randomization, the trial was stopped early for safety concerns.[94]

As mentioned earlier, a population-based cohort study in Olmsted County conducted between 2001 and 2008, found the age- and sex-specified incidence of

ARDS decreased from 81 to 38.3 cases per 100,000 person-years ($P < 0.001$).[43] Almost the entire reduction in incidence was in patients that developed ARDS *after* admission. The authors speculate that this finding is coincident with several changes in the delivery of healthcare in their institution. This includes low-tidal volume ventilation for all patients with an ARDS risk factor, restrictive transfusion protocols, development of a dedicated sepsis team, and computerized alerts in their charting system for early antibiotic administration reminders.[43]

This kind of "bundled" calls to mind some of the other protocolized bundles that exist in the ICU, such as the central line bundle with its five key elements shown together to reduce the incidence of catheter-related blood stream infections.[95] The components of a possible "ARDS Bundle" would be just one element of a comprehensive ARDS management program that included rescue therapies when appropriate (such as ECMO, as in the CESAR trial) and a multidisciplinary plan for all patient during their ICU stay in order to not only effect survival but lead to improved longitudinal outcomes after ICU and hospital discharge. Perhaps it is not one major intervention but several small pieces combined together that will lead to the next leap forward in ARDS morbidity and mortality.

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