**REVIEW**

Recent advances in understanding and treating ARDS [version 1; referees: 2 approved]

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**Abstract**

Acute respiratory distress syndrome represents a complex syndrome with considerable morbidity and mortality, for which there exist no targeted treatment strategies. However, recent advances in clinical care have improved outcomes, and we will review a number of these approaches here, as well as explore the mechanisms underlying the benefit of intervention that might point us in the direction toward future treatment and preventive strategies for this devastating syndrome.

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This article is included in the F1000 Faculty Reviews channel.

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**How to cite this article:** Baron RM and Levy BD. Recent advances in understanding and treating ARDS [version 1; referees: 2 approved] F1000Research 2016, 5(F1000 Faculty Rev):725 (doi: 10.12688/f1000research.7646.1)

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**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Competing interests:** The authors declare that they have no competing interests.

**First published:** 22 Apr 2016, 5(F1000 Faculty Rev):725 (doi: 10.12688/f1000research.7646.1)
Introduction
The acute respiratory distress syndrome (ARDS), first described in 1967, remains difficult to treat and has significant morbidity and mortality. Risk factors for ARDS include factors resulting from direct injury to the lung (e.g., pneumonia and gastric aspiration) or indirect injury (e.g., sepsis and pancreatitis). These conditions result in inflammatory lung injury and hypoxemia that arise from disruption of the alveolar-capillary membrane and influx of protein-rich edema fluid, producing physiologic lung dysfunction. Remarkably, despite intense investigation and numerous large-scale clinical trials, no targeted medical therapies have yet been developed nor proven effective, and there exist no universally agreed-upon biomarkers that might predict severity of illness, or clinical outcomes, or both. These challenges in characterization and treatment likely result from the heterogeneity of ARDS as well as the difficulty of treating a “syndrome” rather than a molecularly confirmed disease; however, a number of management strategies have proven beneficial and have resulted in reductions in mortality.

It is unlikely, as is the case for many serious ailments, that there is a “one size fits all” treatment for ARDS, and thus improved understanding of the disease process and appropriately characterizing severity of illness will be critical for making advances in treatment strategy. Furthermore, the National Institutes of Health (NIH) has recognized the importance of addressing strategies to prevent ARDS development, thus forming the new version of the ARDS Network under the heading of “PETAL” (Prevention and Early Treatment of Acute Lung Injury). Therefore, in this brief review, we set out to discuss some of the recent advances in understanding and treating ARDS, as well as to address the possible biological mechanisms underlying these mechanisms, to attempt to shed light on potential areas for future scientific investigation. We focus our discussion on significant articles that have modified mortality from ARDS, and we summarize a proposed overall approach to ARDS.

Advances in defining acute respiratory distress syndrome and improving mortality prediction: the Berlin Criteria
From 1994 to 2012, ARDS was defined on the basis of the American-European Consensus Conference (AECC) criteria: (a) acute onset of hypoxemia defined by partial pressure of arterial oxygen/fraction of inspired oxygen (P_{O2}/F_{O2}, or P/F) ratio of >200 with (b) new bilateral infiltrates (c) not attributable to heart failure as defined by pulmonary capillary wedge pressure (PCWP) (as measured by a Swan-Ganz catheter) of not more than 18 mmHg (or absence of suspected left atrial hypertension/cardiogenic pulmonary edema if PCWP was not available). These criteria were adopted with the goal of more uniformly defining the syndrome and identifying appropriate patients for ARDS therapies and enrollment in clinical trials. Although these criteria facilitated these goals, it was felt that certain improvements in the definition might improve the clinical phenotyping and risk stratification of ARDS subjects, including a more explicit definition of “acute” onset of hypoxemia, further definition of the dependence of the P/F ratio on ventilator settings (in particular, the positive end-expiratory pressure (PEEP) setting), improved criteria for chest radiograph interpretation of “bilateral infiltrates”, and more explicit guidance with defining the contribution of cardiogenic pulmonary edema to the clinical picture.

In 2012, the European Society of Intensive Care Medicine convened an expert panel to improve the reliability and validity of the ARDS definition, termed the Berlin Criteria. These newer criteria improve upon the old, in part through the following: (a) defining three categories of ARDS severity on the basis of P/F ratio: P/F ratio $\leq$300 and >200 (“mild” ARDS, which was previously categorized as acute lung injury under AECC criteria), P/F ratio of between 100 and 200 (“moderate” ARDS), and P/F ratio of <100 (“severe” ARDS); (b) defining “acute” onset of bilateral infiltrates as within 7 days of exposure to an ARDS risk factor or worsening respiratory symptoms; (c) more definitive chest radiograph criteria were provided (with retention of the description of bilateral infiltrates consistent with pulmonary edema and not fully explained by effusions, lobar/lung collapse, or nodules), and use of chest computed tomography was allowed for fulfilling the radiographic definition as well; (d) use of the PCWP for defining cardiogenic pulmonary edema was removed (given the declining use of Swan-Ganz catheters), and it was acknowledged that cardiogenic and non-cardiogenic pulmonary edema can coexist. However, determination of whether the bilateral infiltrates are attributable to a cardiogenic cause cannot be based solely upon clinical decision making. If a risk factor for ARDS is not identified, then some objective criteria of cardiac function, such as echocardiography, are required to exclude a sole cardiogenic cause for pulmonary edema; and (e) minimum use of PEEP of at least 5 cm H$_2$O on the mechanical ventilator (or delivered by non-invasive ventilation only in the mild ARDS category) in assessing the severity of oxygenation impairment using the P/F ratio.

Implications of the Berlin Criteria
The Berlin Criteria were derived and validated, and additional variables that were considered in the definition (lung compliance, radiographic severity, levels of PEEP, and exhaled minute ventilation) did not improve severity prediction and therefore were not incorporated into the final criteria (although the authors acknowledged that analysis of these factors plays an important role in bedside clinical care). Of note, defining the “severe ARDS” category called attention to the most afflicted group (with a P/F ratio of <100), which has the highest mortality irrespective of ventilator strategy and therefore might benefit from applications of more advanced ARDS rescue strategies (see discussions below). Specifically, mortality rates in the mild, moderate, and severe groups were 27%, 32%, and 45%, respectively, and the Berlin Criteria improved mortality prediction beyond that of AECC; however, as acknowledged by the authors, there are clearly limitations to clinical criteria in defining a syndrome. Ideally, the use of additional biologic predictors might have the capacity to improve prediction of outcome and risk stratification. Although the hunt for predictive biomarkers for ARDS development and outcome is still under way, existing studies suggest the promise of using plasma biomarkers—e.g., interleukin-8 (IL-8), tumor necrosis factor alpha (TNF$\alpha$), surfactant protein-D (SPD), and mitochondrial DNA—to improve prediction of outcomes beyond clinical classification algorithms (e.g., Acute Physiology and Chronic Health Evaluation scoring systems). Recent studies suggest that ARDS might be better predicted by specific biomarkers, such as plasma levels of the soluble form of the receptor for advanced glycation end products (sRAGE) as a marker of lung...
epithelial injury, and plasma levels of tumor necrosis factor receptor-1 (TNFR1), IL-6, IL-8, and plasminogen activator inhibitor-1 (PAI1) as markers of a hyperinflammatory ARDS subphenotype. Although the Berlin Criteria have enhanced our clinical phenotyping systems, ongoing work in clinical/biological phenotyping of critically ill subjects will ideally facilitate additional prevention trials, allowing investigators to target specific risk groups with modifiable risk factors for ARDS development.

Advances in mechanical ventilation support of patients with acute respiratory distress syndrome: low tidal volume ventilation

In a seminal study performed by the ARDS Network in 2000, mechanical ventilatory support of ARDS patients with 12 ml/kg (ideal body weight) tidal volume was compared with low tidal volume ventilation at 6 ml/kg, and there was a significant reduction in mortality with low tidal volume ventilation (38% to 31%) at 90 days. This study prompted the widespread use of low tidal volume ventilation in supporting patients with ARDS and has led to ongoing studies to investigate the mechanisms underlying this profound benefit (see below). In addition, this important trial has prompted additional recent trials investigating whether low tidal volume ventilation might also benefit other populations of patients, such as those undergoing mechanical ventilation for an operative procedure (i.e. whether patients without significant pre-existing lung injury might be similarly injured with potentially injurious mechanical ventilator settings, thereby being placed at risk for the development of ARDS). This question remains a point of clinical debate in setting mechanical ventilation parameters for critically ill patients without the presence of ARDS. Although it is known that normal laboratory mice exposed to high tidal volume ventilation develop lung injury, it is not clear whether this is the case for humans without pre-existing lung injury. Interestingly, a recent article reported that the use of a “prophylactic” protective ventilation strategy improved clinical outcomes (relative to higher tidal volumes usually used during anesthesia in patients without pre-existing lung injury with the goal of preventing atelectasis) in intermediate- and high-risk patients undergoing abdominal surgery.

Potential mechanisms underlying the protective nature of low tidal volume ventilation

The findings of improved mortality with low tidal volume ventilation prompted widespread investigation into the mechanisms underlying this protection, resulting in a vast expansion in our understanding of factors driving mechanotransduction-related lung injury. Physiologic lung improvements as a result of low tidal volume ventilation have been attributed to a number of factors, including most grossly, reduced incidence of barotrauma (application of high pressures to the lung resulting in injury), volutrauma (application of high tidal volumes—i.e. lung stretching—resulting in injury), and perhaps improved hemodynamics (blood pressure and organ perfusion) as a result of less overdistention of the lung and improved venous return to the heart; however, ventilation at low tidal volumes can result in collapse of the lung parenchyma, and trials of high-frequency oscillatory ventilation that allowed for very small tidal volumes did not prove beneficial, supporting the complexity of ARDS pathophysiology and management. Mechanical ventilation without maintenance of open lung units has the potential to exacerbate lung injury as a result of opening and closing of lung units, termed “atelectrauma”, which has led to widespread studies of optimal application of PEEP to maintain open lung units, and a recent meta-analysis suggested that higher levels of applied PEEP might be beneficial in patients with moderate ARDS. Beyond physiologic benefits of low tidal volume ventilation, numerous studies have called attention to the concept of “biotrauma” as a result of injurious mechanical ventilation, in which stretching of lung units might activate cellular signaling cascades resulting in lung inflammation, increased release of pro-inflammatory mediators (e.g., IL-6), and effects on non-pulmonary tissues resulting in multi-system organ failure. Potential physiologic benefits of low tidal volume ventilation have recently been reviewed in detail.

Advances in adjunctive therapy for severe acute respiratory distress syndrome: neuromuscular blockade

Neuromuscular blockers (NMBs) have been used for a long period of time in the intensive care unit, largely to facilitate mechanical ventilation of ARDS subjects when sedation alone was insufficient, usually in the setting of severe gas exchange impairment, or to facilitate other advanced therapies for ARDS, such as prone positioning (see below), or to do both; however, protocolized care for use of NMBs in ARDS has not been uniformly applied, and concerns regarding adverse effects of NMBs (e.g., prolonged neuromuscular weakness) without clear data showing benefit of NMBs limited widespread use until recently. Papazian et al. examined 340 intubated patients in a multi-center trial with severe ARDS (P/F ratio of <150), who were randomly assigned to receive NMB (cisatracurium besylate) versus placebo for 48 hours. All patients received low tidal volume ventilation and were on at least 5 cm H₂O PEEP. The adjusted 90-day in-hospital mortality rate was lower with NMB versus placebo, and no increased neuromuscular weakness was observed in the NMB group. Additionally, an increased number of ventilator-free days was observed in the NMB group. Of note, both groups received deep sedation. This study has raised important questions about the utility of NMB in ARDS, and there is sufficient uncertainty about its widespread use that the NIH PETAL Network is addressing this issue in one of its first network trials. Thus, further data will be available in the future to help guide clinical practice. Residual questions that remain include whether patients solely with severe ARDS might benefit from NMB, what the optimal NMB infusion duration might be, whether similar benefits might be observed with NMB agents other than cisatracurium besylate, and what the independent effects of heavy sedation apart from NMB might be.

Potential mechanisms underlying the benefit of neuromuscular blockade

Although much of the mechanism remains to be learned regarding protective effects underlying NMB (and additional significant information is likely to be gained from the upcoming PETAL Network NMB trial and planned associated ancillary studies), there exist data to support a number of possible pathways of benefit: (a) NMBs counteract patients bucking the ventilator, thereby limiting lung injury arising from ventilator dysynchrony—that is, an increased rate of pneumothoraces (consistent with barotrauma) was observed in the placebo group; (b) NMBs might result in less biotrauma as evidenced by less end-organ failure associated with their use.
well as reduction in lung (IL-1β, IL-6, and IL-8) and serum (IL-1β
and IL-8) cytokines in patients on NMB23; (c) NMBs limit expiratory
muscle function and therefore reduced respiratory system collapse
derecruitment that might result in improved respiratory system
compliance and improved ventilation-perfusion matching21,22. Inter-
estingly, a recent preclinical study suggests that the mechanism
of protection of NMBs might relate to direct anti-inflammatory effects
of blocking the nicotinic acetylcholine receptor-α1, independent of
effects on improving ventilator dysynchrony24.

Advances in adjunctive therapy for severe acute respiratory distress syndrome: prone positioning
Although it was realized in the 1970s that prone positioning
improved oxygenation in ARDS, numerous studies over ensuing
decades demonstrated improvement in oxygenation but failed
to show improved mortality from prone positioning. This lack of
mortality benefit, coupled with concerns regarding possible adverse
events from proning patients (e.g., facial edema, skin breakdown
at areas of pressure necrosis, transient desaturation as well as less
commonly dislodgement of lines, endotracheal tubes, and hemo-
dynamic instability), led to limited/sporadic use across clinical
ARDS centers25. In 2013, Guérin et al. examined prone posi-
tioning (at least 16 hours per day) versus standard positioning in
466 subjects with severe ARDS (within 36 hours of intubation and
after a stabilization period of 12 to 24 hours; P/F ratio of < 150),
FiO2 of at least 0.6, low tidal volume ventilation, and PEEP of at
least 5 cm H2O and found a striking 28-day mortality benefit of
prone positioning (32.8% supine versus 16% prone), and a mortal-
ity benefit persisted until day 9026. Of note, there was no significant
difference in complications between the prone and supine groups
(except for an increased rate of cardiac arrests in the supine group);
however, the authors acknowledge that this study was carried out
in centers with substantial experience and expertise in prone posi-
tioning. This lack of expertise in prone positioning, the potential
complications that might arise from proning, and the potential
difficulty in selecting optimal patients who might benefit from
proning (a highly selected group of patients was included in the
most recent trial) have led to variability in uniform adoption of
prone positioning in ARDS clinical centers.

Potential mechanisms underlying the benefit of prone positioning
Although a number of studies over many years examined poten-
tial benefits of proning, a mortality benefit to the degree described
above was only recently observed. Some of the earlier studies were
small studies and in addition studied patients in later ARDS phases
when prone positioning might be less likely to reverse the disease
process. It is possible that more routine use of low tidal volume
ventilation in this most recent study is a factor, as well as the more
prolonged period of proning that was employed in this study com-
pared with other trials27. Of note, differential use of neuromuscular
blockade (increased NMB was used in the prone position group)
has been cited as an important factor to consider in interpreting
this trial (see Advances in adjunctive therapy for severe acute
respiratory distress syndrome: neuromuscular blockade section
above). Some earlier studies suggested that the most afflicted
patients (i.e., those with the lowest P/F ratios) might benefit from
proning, prompting the selection of the patient population in the
most recent study28. In general, potential benefits of proning
might include (a) improved lung ventilation perfusion matching,
(b) improved right ventricular dysfunction29,30, and (c) recruitment
of lower-lobe atelectatic lung units (perhaps related to reduced
compression of lung units in the prone position) and decreased
intrapulmonary shunting, as well as potentially improved main-
tenance of open lung units, thus limiting ventilator-induced lung
injury (through mitigating repeated opening and closing of lung
units that generates lung injury). It is believed that some patients
also experience improved secretion clearance gravitationally in the
prone position31.

Conclusions
Although ARDS represents a complex syndrome with consider-
able morbidity and mortality, recent advances in clinical care have
improved outcomes, as described in this review. Support of ARDS
patients with low tidal volume ventilation has become the stand-
ard of care, and this approach has revealed important underlying
mechanisms that have led to new areas of investigation in lung
injury. Use of the Berlin Criteria has aided in the identification
of the most afflicted ARDS patients who might benefit from res-
cue therapies, and targeting of neuromuscular blockade and prone
positioning in severe ARDS has recently proven beneficial in terms
of improved ARDS mortality. Ongoing studies will be important
for providing additional information for helping us target these
modalities to the patients most likely to benefit from them as well
as to gain further understanding of the mechanisms underlying
benefit of these modalities. An additional area of clinical care and
investigation not reviewed here in detail is the use of conservative
fluid strategy to decrease ventilator time in patients with ARDS30,31,
although more recent data have called attention to the possibility
that a more restrictive fluid management strategy is associated with
cognitive dysfunction32. Fluid management in critical illness is cur-
rently under review33, and the information that is gleaned may help
guide clinical practice in the future.

Although targeted medical therapies have not yet proven beneficial
in clinical trials, promising targets32,34, including those in an ongoing
NIH-funded trial in mesenchymal stromal cells35,36, are under inves-
tigation; however, it is widely appreciated that the heterogeneity of
the syndrome might require a more targeted/personalized approach
toward ameliorating complex biologic pathways that might be dif-
ferentially activated with different host responses and at different
time points in each illness. Increasingly, it is appreciated that efforts
targeted at prevention of ARDS represent a growing opportunity
for investigation and treatment1, both in optimally identifying
at-risk subjects and in selecting those most likely to benefit from
early interventions. Of note, prevention studies will be a major
focus of the NIH PETAL Network. In conclusion, although ARDS
represents a challenging syndrome to characterize, manage, and
treat, recent advances have improved clinical outcomes, and excit-
ing approaches on the horizon hold promise for allowing us to gain
insights into novel treatment strategies.

Competing interests
The authors declare that they have no competing interests.

Grant information
The author(s) declared that no grants were involved in supporting
this work.
Open Peer Review

Current Referee Status: ✔ ✔

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The referees who approved this article are:

1 Jason Bates, University of Vermont College of Medicine, Burlington, Vermont, USA
   Competing Interests: No competing interests were disclosed.

2 Gregory Downey, Departments of Medicine and Pediatrics, National Jewish Health, Denver, Colorado, USA
   Competing Interests: No competing interests were disclosed.