

Recent advances in understanding acute respiratory distress syndrome

Peter Wohlrab, Felix Kraft, Verena Tretter, Roman Ullrich, Klaus Markstaller, Klaus Ulrich Klein

Angaben zur Veröffentlichung / Publication details:

Wohlrab, Peter, Felix Kraft, Verena Tretter, Roman Ullrich, Klaus Markstaller, and Klaus Ulrich Klein. 2018. "Recent advances in understanding acute respiratory distress syndrome." *F1000Research* 7. <https://doi.org/10.12688/f1000research.11148.1>.



REVIEW

Recent advances in understanding acute respiratory distress syndrome [version 1; peer review: 2 approved]

Peter Wohlrab, Felix Kraft , Verena Tretter, Roman Ullrich, Klaus Markstaller, Klaus Ulrich Klein

Department of Anaesthesia, General Intensive Care and Pain Management, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

V1 First published: 05 Mar 2018, 7(F1000 Faculty Rev):263
<https://doi.org/10.12688/f1000research.11148.1>

Latest published: 05 Mar 2018, 7(F1000 Faculty Rev):263
<https://doi.org/10.12688/f1000research.11148.1>

Abstract

Acute respiratory distress syndrome (ARDS) is characterized by acute diffuse lung injury, which results in increased pulmonary vascular permeability and loss of aerated lung tissue. This causes bilateral opacity consistent with pulmonary edema, hypoxemia, increased venous admixture, and decreased lung compliance such that patients with ARDS need supportive care in the intensive care unit to maintain oxygenation and prevent adverse outcomes. Recently, advances in understanding the underlying pathophysiology of ARDS led to new approaches in managing these patients. In this review, we want to focus on recent scientific evidence in the field of ARDS research and discuss promising new developments in the treatment of this disease.

Keywords

acute respiratory distress syndrome, ventilation, therapeutic targets

Open Peer Review

Approval Status

	1	2
version 1		
05 Mar 2018		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **John Laffey**, University of Toronto, Toronto, Canada
2. **Michael O'Connor**, University of Chicago, Chicago, IL, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Klaus Ulrich Klein (ulrich.klein@meduniwien.ac.at)

Competing interests: None of the authors has to declare any conflict of interest with regard to the present F1000 review. Roman Ullrich received funding from Apeptico GmbH (Vienna, Austria) using funds from grant no. 833159 of the Austrian Research Promotion Agency (FFG) to perform a clinical study investigating AP301 (cited in text PMID: 28750677).

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

Copyright: © 2018 Wohlrab P *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Wohlrab P, Kraft F, Tretter V *et al.* **Recent advances in understanding acute respiratory distress syndrome [version 1; peer review: 2 approved]** F1000Research 2018, 7(F1000 Faculty Rev):263 <https://doi.org/10.12688/f1000research.11148.1>

First published: 05 Mar 2018, 7(F1000 Faculty Rev):263 <https://doi.org/10.12688/f1000research.11148.1>

Introduction

Normal lung function requires dry alveoli situated closely to perfused capillaries to perform sufficient gas exchange. The capillary endothelium controls the balance between fluids by its selective permeable membrane. This allows serum proteins to stay intravascular and to hold back fluids by oncotic forces. Only small amounts of fluid make it into the interstitium, where it gets reabsorbed by the oncotic gradient or the interstitial lymphatic system.

In acute respiratory distress syndrome (ARDS), acute diffuse lung injury leads to the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF α) and interleukin 1 beta (IL-1 β), IL-6, and IL-8, which in turn recruit components of the innate immune system¹⁻⁴. Activated neutrophils produce toxic mediators such as reactive oxygen species (ROS) and proteases damaging the endothelium and alveolar epithelium⁵. Proteins can effuse from the vascular space, which results in the loss of the oncotic gradient between capillaries and the air space, facilitating the advance of fluid into the interstitium and air space⁶. This protein-rich fluid inactivates surfactant, resulting in the collapse of alveoli. This leads to impaired gas exchange, increased dead space, reduced lung compliance, and decreased carbon dioxide (CO₂) elimination⁷.

These acute physiological changes force the patient into a life-threatening situation, making it impossible to maintain the oxygenation and decarboxylation needed. These patients need immediate supportive care in the intensive care unit (ICU). Invasive mechanical ventilation (IMV) is applied in most patients⁸ with ARDS to guarantee sufficient ventilation and tissue oxygenation, especially for the brain, heart, and kidneys. Although IMV can improve the patient's condition, IMV itself can damage the vulnerable lung. This ventilator-induced lung injury (VILI) has been known since the beginning of mechanical ventilation in the 1960s and has three major aspects of injury: (1) volutrauma/barotrauma, (2) atelectrauma, and (3) biotrauma.

Volutrauma describes alveolar membrane damage due to over-distention, especially with high tidal volumes rather than high inspiratory pressure (barotrauma), leading to the rupture of the alveoli along with lung edema, cell death, macroscopic pneumothorax, pneumomediastinum, and subcutaneous emphysema⁹. Atelectrauma, on the other hand, occurs when ventilation with low tidal volumes results in cyclic recruitment and de-recruitment of lung segments. Studies showed that total end-expiratory collapse and reopening of distal airways are accompanied by significant shear stress¹⁰ and regional hypoxia followed by cell damage, surfactant dysfunction, inflammation, and pathological progression of the already-injured lung. These mechanical factors of damage are accompanied by the consecutive release of pro-inflammatory mediators, ROS generation^{11,12}, neutrophil infiltration, immune cell activation¹³, and, finally, owing to the impaired alveolar-capillary barrier, a translocation of bacteria, toxins, inflammatory cytokines, and activated inflammatory cells into the systemic circulation. This can cause end-organ dysfunction and even death by multiple organ system failure¹⁴⁻¹⁷.

This concept is termed biotrauma and may be the primary cause of death in patients with ARDS, as respiratory failure is rarely lethal and most of the time can be sufficiently treated with IMV and extracorporeal decarboxylation and oxygenation. Thus, the management of these patients often represents a tradeoff between maintaining oxygenation and preventing excessive tissue damage.

Recent advances in ventilation

Patients with ARDS rarely die from respiratory failure¹⁸ but rather from the underlying cause during the early period and from pneumonia or sepsis with consecutive multiple organ system failure in the late period¹⁹. Although global mortality is still high (40%), survival has improved over the years²⁰. The reasons for the decreasing mortality remain uncertain. Better supportive care, improved ventilation strategies and protocols such as low tidal volume ventilation (LTVV), and the inclusion of trauma-induced ARDS (patients with trauma-induced ARDS have significantly better outcomes than patients with sepsis-induced ARDS) could contribute to the effect observed²¹.

In 1998, Amato *et al.* published a single-center randomized controlled trial (RCT) (including 53 patients) showing that ventilating ARDS patients with a tidal volume (V_t) of 6 mL/kg predicted body weight (PBW), a positive end-expiratory pressure (PEEP) above the lowest inflection point on a static pressure-volume curve, and an inspiratory pressure of less than 20 cm H₂O above PEEP resulted in a significant reduction of 28-day mortality²². These data were validated in 2000 by the Acute Respiratory Distress Syndrome Network (ARMA) trial, which included 861 patients in a multicenter RCT. In this trial, conventional ventilation (V_t of 12 mL/kg PBW and plateau pressure of less than 50 cm H₂O) was compared with protective ventilation (V_t of 6 mL/kg PBW and plateau pressure of less than 30 cm H₂O)²³. Protective ventilation resulted in significant reductions in the duration of mechanical ventilation and in-hospital mortality. The oxygen partial pressure/fraction of inspired oxygen (paO₂/FiO₂) ratio was lower in the LTVV group compared with conventional ventilation, showing that oxygenation may be a bad surrogate for outcome in ARDS. LTVV improves survival and other clinical outcome parameters by reducing alveolar over-distention^{24,25}. This beneficial effect is corroborated by a recent meta-analysis of four RCTs²⁴ and a subanalysis of the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) trial in patients with moderate to severe ARDS showing that peak inspiratory pressure, besides other factors, is a modifiable risk factor for worse outcome²⁶. Interestingly, a prospective cohort study demonstrated that even by raising the V_t from 6 to 7 mL/kg PBW, ICU mortality increased by as much as 23%²⁷. Despite this breakthrough, a prospective cohort study showed that LTVV is under-utilized in clinical routine²⁸. This was demonstrated by Bellani *et al.* in 2016 in a multicenter observational study (of 3,022 patients with ARDS) showing a mean V_t of 7.5 mL/kg PBW in patients fulfilling ARDS criteria⁸. Also, only PEEP settings were significantly adapted after ARDS recognition, whereas V_t was not⁸.

It has been discussed that the beneficial effect of protective ventilation may be due to auto-PEEP rather than LTVV²⁹. To maintain minute ventilation in LVVT, the respiratory rate needs to be adapted. Increasing the respiratory rate gives the patient less time to complete expiration, creating auto-PEEP by “air trapping”³⁰. A subanalysis showed that the quantity of auto-PEEP in LTVV is negligible³¹. However, there are not enough data to judge the role of auto-PEEP on outcome in protective lung ventilation. The ARMA trial investigated whether sedation should be increased to prevent forced breathing work and patient–ventilator asynchrony by using LTVV³². A *post hoc* analysis showed no significant difference in days of sedation or need of opioids or neuromuscular-blocking agents³³. However, the ACURASYS (ARDS et Curarisation Systematique) trial showed a beneficial effect on 90-day mortality, incidence of barotrauma, and ventilator-free days when neuromuscular relaxation with cisatracurium was applied in the first 48 hours after onset of ARDS^{34,35}. The discussed benefits of neuromuscular blockade in ARDS include avoidance of patient–ventilator asynchrony, which lowers transpulmonary pressure and the resulting stress on the lung. It further leads to reduced muscle work with decreased pulmonary oxygen consumption, allowing further reduction of ventilation targets, thereby mitigating VILI and biotrauma. These studies showed that early neuromuscular blockade was not accompanied by increased ICU-acquired weakness. Cisatracurium has anti-inflammatory properties^{36,37}, though fewer than those of potent anti-inflammatory drugs, which per se did not sufficiently influence outcome in ARDS. Though relatively expensive, cisatracurium seems to be the paralyzing drug of choice in early ARDS, especially because of its favorable pharmacokinetics. Furthermore, cisatracurium is metabolized independently of renal or liver function.

Driving pressure

Although protective ventilation strategies all aim to reduce stress on the lungs and to avoid volutrauma and barotrauma (for example, LTVV, increasing PEEP, or limiting plateau pressure), changes in one parameter may negatively influence others; for example, increasing PEEP will decrease V_t when plateau pressure is limited. Furthermore, V_t titrated to PBW may still lead to regional barotrauma, as functional lung size is drastically reduced in patients with ARDS (‘baby lung’ concept) with heterogeneous distribution of aerated and consolidated lung segments. This is reflected in a lowered compliance of the respiratory system (C_{RS}).

The normalized V_t to actual C_{RS} is termed driving pressure ($\Delta P = V_t/C_{RS}$) and is calculated as the difference between end-inspiratory plateau pressure and PEEP in mechanically ventilated patients. ΔP was significantly associated with increased survival in a pooled retrospective analysis of RCTs focusing on optimal PEEP and V_t settings in ARDS. Interestingly, the beneficial effects of restrictive V_t or increased PEEP were present only when accompanied by a reduced ΔP ³⁸. Whether ΔP is a better

predictor for mortality than plateau pressure³⁹ or V_t during mechanical ventilation in ARDS needs further clarification.

Open lung ventilation

Open lung ventilation combines LTVV with optimal PEEP. This results in a decreased over-distension of the alveoli and a reduction of cyclic atelectrauma. Gattinoni *et al.* showed that, even at PEEP levels as high as 45 mm Hg, the percentage of potentially recruitable lung is extremely variable⁴⁰. Finding the optimal PEEP level for each individual patient may be challenging.

Three major trials compared high versus low PEEP in combination with LTVV with respect to outcome. In the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury (ALVEOLI) trial in 2004, no difference between high and low PEEP was observed⁴¹. The Lung Open Ventilation Study (LOVS) trial in 2008 showed improved oxygenation and less need of rescue strategies in the high PEEP group, but no difference in mortality was found⁴². The Expiratory Pressure (EXPRESS) trial demonstrated more ventilator-free days and more organ failure-free days in the high PEEP group but no difference in mortality⁴³. Currently, there is no universally accepted protocol for open lung ventilation. A meta-analysis of the ALVEOLI, LOVS, and EXPRESS trials in 2010 showed a beneficial effect of high PEEP versus low PEEP only in patients with moderate to severe ARDS⁴⁴.

In a *post hoc* analysis of the LOVS and EXPRESS trials^{42,43}, Goligher *et al.* demonstrated that mortality was reduced in patients who were PEEP-responsive compared with patients who were not⁴⁵. Oxygenation change due to increased PEEP was associated with reduced hospital mortality. The relationship of PaO_2 to FiO_2 is also related to cardiac output, oxygen consumption, extrapulmonary shunt, hypoxic pulmonary vasoconstriction, and fractional inspiratory oxygen. The influence of a number of potentially confounding variables on PaO_2/FiO_2 may explain the difficulty of LOVS and EXPRESS to demonstrate a significant effect of PEEP on mortality. The appropriate selection of patients (responders and non-responders to PEEP) for RCTs testing PEEP in patients with ARDS may bring new insights.

A trending method to find the optimal PEEP is to calculate the transpulmonary pressure (P_{tp} = alveolar pressure – pleural pressure) by using an esophageal balloon catheter to measure esophageal pressure as a surrogate for pleural pressure. As the pressure to open the lung must overcome chest, abdominal, and alveolar pressure, P_{tp} is representing the force affecting lung distention and stretch. Titrating the PEEP to P_{tp} and maintaining end-inspiratory P_{tp} of less than 25 cm H₂O reduce cyclic atelectasis and over-distension⁴⁶. This approach was evaluated by comparing P_{tp} -guided PEEP with ARMA trial protocol-guided PEEP. The goal of the study was to maintain the PaO_2 at 55–120 mm Hg or peripheral capillary oxygen saturation (SpO_2) at 88–98%.

P_{tp} -guided PEEP titration resulted in higher PEEP levels and improved PaO_2/FiO_2 ratios after 72 hours. No differences in ventilator-free days, ICU stay, or 28-day mortality were found⁴⁶.

Cyclic atelectrauma

Rapid changes of oxygen partial pressure caused by cyclic recruitment and derecruitment of atelectasis (CA) during IMV may contribute to lung damage⁴⁷. Within-breath CA results in varying shunt fractions and altered gas exchange, thereby causing rapid respiratory-dependent alveolar PaO_2 changes⁴⁸. These partial pressure of oxygen (PO_2) oscillations likely cause intermittent hypoxia/hyperoxia injury to the lungs and therefore could represent an additional mechanism of lung and remote organ biotrauma⁴⁹. Numerous studies have provided evidence for the existence of rapid PaO_2 changes during respiratory failure^{50–52}. The changes originate in the diseased lungs and are forwarded with the circulation to the arterial system^{48,53,54}. This might promote injury in end organs such as the brain⁵⁵. Further investigations are needed to validate this separate mechanism of biotrauma in ARDS.

Prone position

Prone position can be considered to improve oxygenation in patients with ARDS. It optimizes the blood flow to the dependent lung, reduces atelectasis, facilitates secretion drainage, increases functional residual capacity, and reduces plateau pressure. Gattinoni *et al.* showed that patients with ARDS had improved oxygenation when in the prone position⁵⁶. In this RCT, response to prone position led to a decreased need for PEEP and FiO_2 . Recently, the Prone Severe ARDS Patients (PROSEVA) trial showed a mortality benefit in patients with severe ARDS (16% versus 32.8%)⁵⁷. In 2010, a further meta-analysis of 10 RCTs demonstrated that there was a significant reduction in mortality in patients with severe ARDS⁵⁸. However, some trials did not see a beneficial effect of prone position on mortality, especially in patients with moderate or mild ARDS⁵⁹. PROSEVA excluded patients with mild or moderate ARDS. This might be the reason why PROSEVA could show a survival benefit whereas others could not. Despite some limitations (2,015 patients were not screened, differences in baseline characteristics, and excluding patients if PaO_2/FiO_2 was reduced by 20% while in prone position, and so on), the trial indicates the potential benefits of early long proning of patients with severe ARDS in experienced centers.

Lung imaging

For decades, chest radiographs and computed tomography (CT) have been essential tools in diagnosing and monitoring ARDS. These solid techniques were complemented in recent years with new approaches of functional lung imaging, such as positron emission tomography (PET), lung ultrasound, and electrical impedance tomography (EIT), especially for ventilator adaptation and recruitment during IMV or research purposes^{60,61}.

At the bedside, lung ultrasound can be used to non-invasively assess pleural effusion, alveolar interstitial syndrome, pneumothorax, lung consolidation, and phenotyping of ARDS and may

help to rule out cardiogenic pulmonary edema in the early stages⁶². It is a cost-effective and easy-to-repeat examination and is more accurate than supine chest radiographs. Cianchi *et al.*⁶³ showed in a small sample of patients with ARDS (12) that the use of lung ultrasound reduced the number of chest radiographs and CT scans, thereby lowering radiation exposure as well as disconnection of ventilators and the potential of adverse events when leaving the ICU^{64,65}.

PET is helpful in understanding pathophysiologic processes of different phenotypes of ARDS and has been used in numerous clinical⁶⁶ and experimental⁶⁷ studies of VILI. Inflammatory and metabolic distribution and activity as well as regional perfusion and function of the lung can be examined by the application of radioactively labeled molecules such as 2-[¹⁸F]-fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) or [¹³N]nitrogen (¹³N₂). Still, an implementation of PET as a routinely used diagnostic addition to CT scans is limited by availability, especially for modern PET/CT or PET/magnetic resonance imaging scanners.

EIT is a functional imaging technique with great potential in mechanically ventilated patients⁶⁸. This radiation-free bedside tool measures changes in impedance from differing regional density. It can be used for regional ventilation analysis with dynamic changes in real time.

Subphenotypes in acute respiratory distress syndrome

A new approach to ARDS defines subphenotypes within ARDS and puts less emphasis on PaO_2/FiO_2 ratio and the Berlin definition of ARDS. The heterogeneity of ARDS may contribute to the poor track record of phase 2 and 3 trials of novel therapeutics. It seems that some subgroups of patients benefit more from specific therapeutic approaches than others (for example, early relaxation and low PEEP versus high PEEP). Calfee *et al.* identified subphenotypes within ARDS by applying latent class modeling on two National Heart, Lung, and Blood Institute ARDS RCTs (ARMA and ALVEOLI)⁶⁹. Phenotype 2 is characterized by higher plasma levels of inflammatory biomarkers, a higher prevalence of vasopressor use, lower serum bicarbonate levels, and higher prevalence of sepsis. Patients with phenotype 2 ARDS had increased mortality and fewer ventilator-free and organ failure-free days. Response to treatment in a randomized trial of PEEP strategy differed on the basis of the subphenotype. Applying high PEEP to phenotype 2 patients resulted in a reduction in mortality. The identification of ARDS subphenotypes may be useful to select patients for specific therapies and assign them to future RCTs⁶⁹.

New therapeutic targets

Currently, there are no specific pharmacotherapies evaluated and recommended routinely. Treatment modalities involve supportive care combined with protective ventilation strategies.

Aspirin

Multiple studies investigated strategies to prevent ARDS in high-risk patients after stratification by the Lung Injury Prediction Score (LIPS). In murine models of acid aspiration-induced lung injury, aspirin could increase oxygenation and

decrease neutrophil recruitment and edema. These findings were translated into the LIPS-A trial, a multicenter, double-blinded, placebo-controlled clinical trial. After random assignment, patients with a LIPS of more than 4 received either 325 mg loading dose and 81 mg/day aspirin or placebo for 7 days. The primary endpoint of this trial was the development of ARDS by day 7. The secondary endpoints were ventilator-free days, hospital and ICU length of stay, and 28-day and 1-year survival. There was no significant decrease in the incidence of ARDS at day 7 or in any of the secondary endpoints. This phase 2b trial did not support the continuation to a longer phase 3 trial⁷⁰.

β₂ agonists

Similar to LIPS-A, the LIPS-B trial investigated whether aerosolized β₂-agonists can prevent the development of ARDS. In this multicenter, randomized, double-blinded, placebo-controlled trial, patients with a LIPS of more than 4 received budesonid and formoterol or placebo for 5 days. The primary endpoint was the change in SpO₂-to-FiO₂ ratio⁷¹. LIPS-B could demonstrate the feasibility of inhaled budesonid and formoterol in patients at high risk for ARDS. Patients who received treatment had improved oxygenation, lower rates of ARDS, and shorter hospital length of stay. LIPS-B is the first prevention trial to suggest efficiency of the intervention for preventing ARDS.

Stem cells

A further approach to enhance lung tissue repair is the use of stem cells. Animal models showed that stem cells secrete growth factors and cytokines modulating inflammation, promoting tissue repair, and increasing bacterial clearance⁷². They also may differentiate into mature cells to replace injured tissue. A phase 1 RCT including 12 patients who received allogenic adipose-derived stem cells⁷³ showed an amelioration of epithelial cell injury. The authors claimed that the clinical effect with the doses used was weak and that further optimization is needed. The treatment arm showed a trend toward reduced IL-6 levels at day 5. However, these results were not statistically significant ($p = 0.06$).

AP301

The nano-peptide AP301 is a promising new agent in treating ARDS. The structure of the synthetic peptide is based on the lectin-like domain of human TNFα⁷⁴. AP301 activates the pulmonary epithelial and endothelial sodium channel ENaC that promotes the alveolar liquid clearance⁷⁵. The beneficial effect of AP301 was demonstrated in animal models of pulmonary edema⁷⁶. Recently, a phase 1 single-center randomized clinical trial including 48 male volunteers was assessed⁷⁷. Oral inhaled AP301 was well tolerated by all participants and no adverse effects were reported⁷⁷. Krenn *et al.* performed a double-blind, placebo-controlled trial including 40 patients with ARDS treated with inhaled AP301 or placebo for 7 days⁷⁸. There was no difference in mean baseline-adjusted extravascular lung water index between the groups. An exploratory *post hoc* subgroup analysis indicated reduced extravascular lung water index in patients with Sequential Organ Failure Assessment (SOFA) scores of at least 11 receiving AP301⁷⁸.

SB-681323

SB-681323 is a further agent directly targeting the pathophysiological process underlying ARDS. This selective p38 alpha inhibitor may dampen the inflammatory response by interfering with the mitogen-activated protein kinase (MAPK) pathway. This pathway is subsequently involved in the activation of cytokines. A phase 2a multicenter study is investigating the safety and tolerability of intravenous SB-681323 in patients at risk of developing ARDS and evaluates its efficiency by measuring biomarkers linked to the p38 alpha regulatory mechanisms⁷⁹.

Interferon beta-1a

Interferon beta-1a induces the upregulation of cluster of differentiation 73 (CD 73). This molecule is responsible for the endothelial barrier function and leads to the prevention of vascular leakage, the main pathophysiological event in ARDS. Treatment with interferon beta-1a was associated with an 81% reduction in odds of 28-day mortality⁸⁰. However, these findings need to be validated in larger prospective RCTs. Currently, a phase 3 clinical trial comparing the efficiency of interferon beta-1a compared with placebo control is underway.

MicroRNA

MicroRNAs (miRNAs) are small non-coding RNAs involved in the post-transcriptional regulation of various genes' expression⁸¹. Recently, Cardinal-Fernández *et al.* suggested a few miRNAs as disease biomarkers and therapeutic agents in ARDS⁸². In 2012, Cai *et al.* investigated the effect of miRNA in a lipopolysaccharide (LPS)-induced acute lung injury mouse model⁸³. The miRNA miR-16 was significantly downregulated in LPS-induced lung injury. Cell culture experiments demonstrated that miR-16 binds to the 3'-untranslated region (3'-UTR) of IL-6 and TNFα and significantly downregulates their expression levels⁸⁴. Further investigations revealed that miR-16 was downregulated in mice exposed to hyperoxia⁸⁵. The authors exposed A549 cells to hyperoxia and overexpressed miR-16. This resulted in increased ENaCβ levels and the suppression of transforming growth factor-beta (TGF-β), an inhibitor of ENaC. This study suggests that miR-16 promotes the resolution of pulmonary edema in ARDS by enhancing the expression of ENaC.

In a further study, miR-127 was downregulated in LPS-induced lung injury. An *in vivo* lung injury model showed that overexpression of miR-127 leads to reduced pulmonary vascular permeability, inflammatory cell infiltration, cytokine levels, and activation of complement and STAT3 (signal transducer and activator of transcription 3) signaling⁸⁶.

As mentioned above, granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances the repair mechanisms in injured lung tissue and increases the alveolar macrophage function⁸⁷. In response to hyperoxia, epithelial cells express high miR-133 levels⁸⁸, leading to the suppression of GM-CSF. Manipulations on miR-133 may provide novel interventions to reduce lung injury.

In addition to pulmonary endothelial and epithelial tissue damage, macrophages play an important role in promoting and resolving inflammation⁸⁹. Alternatively, activated macrophages

can participate in the resolution of inflammation in ARDS by GM-CSF⁸⁹. miRNAs may control signaling pathways contributing to macrophage phenotypes. miR-155, miR-127, and miR-429 regulate their targets to promote a pro-inflammatory macrophage phenotype^{90,91}. Let-7e, miR-127, miR-320b, and miR-146a promote an immunosuppressor macrophage phenotype^{86,92–94}. Interestingly, miR-429 promotes the pro-inflammatory macrophage phenotype by the inhibition of the dual specificity protein phosphatase 1 (DUSP-1) protein. Like SB-681323 mentioned earlier, DUSP-1 protein is a key player in p38 MAPK signaling pathways.

Furthermore, circulating miRNAs could represent novel biomarkers for ARDS. Sun *et al.* demonstrated that circulating miR-181b levels were reduced in ARDS patients compared with controls⁹⁵. The authors also showed that the substitution of miR-181b reduced lung injury and mortality in a mouse lung injury model⁹⁵. A further study concluded that miR-125b may be a promising biomarker in patients with ARDS. Increased miR-125b levels resulted in an improvement of lung function in LPS-injured mice⁹⁶. Despite these findings, the prognostic value of circulating miRNAs in ARDS remains unexplored.

C5a

C5a is a complement cleavage product acting as a potent anaphylatoxin promoting the appearance of neutrophil extracellular traps (NETs). NETs consist of nuclear chromatin, containing histones and other nuclear proteins. These extracellular histones may trigger the release of TGF- β via granules of platelets and therefore be involved in tissue remodeling during ARDS. NETs mediate apoptosis in epithelial and endothelial cells and the production of inflammatory mediators during ARDS⁹⁷. Interception of NETs showed promising beneficial effects in different lung injury models. Administering neutralizing antibodies directed against NETs reduced pulmonary vascular permeability and the volume of extravascular lung water⁹⁸. In a murine lung injury model, the degradation of NET structures with DNaseI reduced lung injury and mortality⁹⁸. Eculizumab is a monoclonal anti-C5 antibody approved for the treatment of hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria⁹⁹. Eculizumab may block C5-induced NET release in ARDS, leading to improved outcomes.

Conclusions

Recent advances in understanding the pathophysiology of ARDS have led to improved outcomes. LTVV combined with open lung strategies are the hallmarks of ARDS management and

have contributed to new insights in understanding lung injury. Prone position and neuromuscular relaxation may be beneficial in selected patients. Currently, no pharmacological treatments exist, although promising ongoing trials are being assessed. Studying the regulatory roles of miRNAs may contribute to a better understanding of how to control inflammatory target gene expression in ARDS. Modulation of miRNA expression could represent a novel therapeutic approach to treat the underlying cause of ARDS.

Abbreviations

ΔP , driving pressure; ARDS, acute respiratory distress syndrome; CA, cyclic atelectasis; C_{RS} , respiratory system compliance; CT, computed tomography; DUSP-1, dual specificity protein phosphatase 1; EIT, electrical impedance tomography; ENaC, epithelial sodium channel; FiO_2 , fraction of inspired oxygen; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; LIPS, Lung Injury Prediction Score; LPS, lipopolysaccharide; LTVV, low tidal volume ventilation; MAPK, mitogen-activated protein kinase; miRNA, microRNA; NET, neutrophil extracellular trap; PaO_2 , oxygen partial pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PET, positron emission tomography; P_{tp} , transpulmonary pressure; RCT, randomized controlled trial; ROS, reactive oxygen species; SpO_2 , peripheral capillary oxygen saturation; TGF β , transforming growth factor beta; TNF α , tumor necrosis factor alpha; VILI, ventilator-induced lung injury; V_t , tidal volume; ARMA, Acute Respiratory Distress Syndrome Network trial; ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury trial; LOVS, Lung Open Ventilation Study; EXPRESS, Expiratory Pressure Study; PROSEVA, Prone Severe ARDS Patients trial.

Competing interests

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

Grant information

None of the authors has to declare any conflict of interest with regard to the present F1000 review. Roman Ullrich received funding from Apeptico GmbH (Vienna, Austria) using funds from grant no. 833159 of the Austrian Research Promotion Agency (FFG) to perform a clinical study investigating AP301 (cited in text PMID: 28750677).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Parsons PE, Eisner MD, Thompson BT, *et al.*: Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med.* 2005; **33**(1): 1–6; discussion 230–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Martin TR: Lung cytokines and ARDS: Roger S. Mitchell Lecture. *Chest.* 1999; **116**(1 Suppl): 2S–8S.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Colletti LM, Remick DG, Burch GD, *et al.*: Role of tumor necrosis factor-alpha in

- the pathophysiologic alterations after hepatic ischemia/reperfusion injury in the rat. *J Clin Invest*. 1990; 85(6): 1936–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Miller EJ, Cohen AB, Matthay MA: Increased interleukin-8 concentrations in the pulmonary edema fluid of patients with acute respiratory distress syndrome from sepsis. *Crit Care Med*. 1996; 24(9): 1448–54.
[PubMed Abstract](#)
 5. Aldridge AJ: Role of the neutrophil in septic shock and the adult respiratory distress syndrome. *Eur J Surg*. 2002; 168(4): 204–14.
[PubMed Abstract](#)
 6. Calandrino FS Jr, Anderson DJ, Mintun MA, et al.: Pulmonary vascular permeability during the adult respiratory distress syndrome: a positron emission tomographic study. *Am Rev Respir Dis*. 1988; 138(2): 421–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 7. Kiiski R, Takala J, Kari A, et al.: Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1992; 146(5 Pt 1): 1131–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 8. Bellani G, Laffey JG, Pham T, et al.: Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*. 2016; 315(8): 788–800.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 9. Dreyfuss D, Soler P, Bassett G, et al.: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis*. 1988; 137(5): 1159–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Mead J, Takishima T, Leith D: Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol*. 1970; 28(5): 596–608.
[PubMed Abstract](#) | [Publisher Full Text](#)
 11. Chapman KE, Sinclair SE, Zhuang D, et al.: Cyclic mechanical strain increases reactive oxygen species production in pulmonary epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2005; 289(5): L834–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. Spassov SG, Donus R, Ihle PM, et al.: Hydrogen Sulfide Prevents Formation of Reactive Oxygen Species through PI3K/Akt Signaling and Limits Ventilator-Induced Lung Injury. *Oxid Med Cell Longev*. 2017; 2017: 3715037.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 13. Ranieri VM, Suter PM, Tortorella C, et al.: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999; 282(1): 54–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
 14. Slutsky AS: Ventilator-induced lung injury: from barotrauma to biotrauma. *Respir Care*. 2005; 50(5): 646–59.
[PubMed Abstract](#)
 15. Curley GF, Laffey JG, Zhang H, et al.: Biotrauma and Ventilator-Induced Lung Injury: Clinical Implications. *Chest*. 2016; 150(5): 1109–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 16. Dreyfuss D, Saumon G: From ventilator-induced lung injury to multiple organ dysfunction? *Intensive Care Med*. 1998; 24(2): 102–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Verbrugge SJ, Sorm V, van 't Veen A, et al.: Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental *Klebsiella pneumoniae* inoculation. *Intensive Care Med*. 1998; 24(2): 172–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Bersten AD, Edibam C, Hunt T, et al.: Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med*. 2002; 165(4): 443–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Montgomery AB, Stager MA, Carrico CJ, et al.: Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1985; 132(3): 485–9.
[PubMed Abstract](#)
 20. Zamboni M, Vincent JL: Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest*. 2008; 133(5): 1120–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 21. Erickson SE, Martin GS, Davis JL, et al.: Recent trends in acute lung injury mortality: 1996–2005. *Crit Care Med*. 2009; 37(5): 1574–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 22. 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(6): 347–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Brower RG, Matthay MA, Morris A, et al.: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000; 342(18): 1301–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 24. Putensen C, Theuerkauf N, Zinserling J, et al.: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med*. 2009; 151(8): 566–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Petrucci N, De Feo C: Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2013; (2): CD003844.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 26. Laffey JG, Bellani G, Pham T, et al.: Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med*. 2016; 42(12): 1865–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 27. Needham DM, Yang T, Dinglas VD, et al.: Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome. A prospective cohort study. *Am J Respir Crit Care Med*. 2015; 191(2): 177–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 28. Kalhan R, Mikkelsen M, Dedhiya P, et al.: Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med*. 2006; 34(2): 300–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. de Durante G, del Turco M, Rustichini L, et al.: ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002; 165(9): 1271–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Younes M, Kun J, Webster K, et al.: Response of ventilator-dependent patients to delayed opening of exhalation valve. *Am J Respir Crit Care Med*. 2002; 166(1): 21–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Hough CL, Kallet RH, Ranieri VM, et al.: Intrinsic positive end-expiratory pressure in Acute Respiratory Distress Syndrome (ARDS) Network subjects. *Crit Care Med*. 2005; 33(3): 527–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Kallet RH, Campbell AR, Dicker RA, et al.: Effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med*. 2006; 34(1): 8–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 33. Kahn JM, Andersson L, Karir V, et al.: Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. *Crit Care Med*. 2005; 33(4): 766–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Papazian L, Forel JM, Gacouin A, et al.: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010; 363(12): 1107–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 35. Alhazzani W, Alshahrani M, Jaeschke R, et al.: Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2013; 17(2): R43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 36. Forel JM, Roch A, Marin V, et al.: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med*. 2006; 34(11): 2749–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 37. Fanelli V, Morita Y, Cappello P, et al.: Neuromuscular Blocking Agent Cisatracurium Attenuates Lung Injury by Inhibition of Nicotinic Acetylcholine Receptor- $\alpha 1$. *Anesthesiology*. 2016; 124(1): 132–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 38. Amato MB, Meade MO, Slutsky AS, et al.: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015; 372(8): 747–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 39. Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, et al.: A Quantile Analysis of Plateau and Driving Pressures: Effects on Mortality in Patients With Acute Respiratory Distress Syndrome Receiving Lung-Protective Ventilation. *Crit Care Med*. 2017; 45(5): 843–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 40. Gattinoni L, Caironi P, Cressoni M, et al.: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006; 354(17): 1775–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. 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(4): 327–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. 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(6): 637–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 43. 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(6): 646–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

44. **F** 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(9): 865–73. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
45. Goligher EC, Kavanagh BP, Rubenfeld GD, *et al.*: Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med*. 2014; 190(1): 70–6. [PubMed Abstract](#) | [Publisher Full Text](#)
46. **F** Talmor D, Sarge T, Malhotra A, *et al.*: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008; 359(20): 2095–104. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
47. Baumgardner JE: New images, new insights for VILI. *J Appl Physiol* (1985). 2011; 111(5): 1233–4. [PubMed Abstract](#) | [Publisher Full Text](#)
48. Baumgardner JE, Markstaller K, Pfeiffer B, *et al.*: Effects of respiratory rate, plateau pressure, and positive end-expiratory pressure on P_{aO_2} oscillations after saline lavage. *Am J Respir Crit Care Med*. 2002; 166(12 Pt 1): 1556–62. [PubMed Abstract](#) | [Publisher Full Text](#)
49. Prabhakar NR: Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *J Appl Physiol* (1985). 2001; 90(5): 1986–94. [PubMed Abstract](#) | [Publisher Full Text](#)
50. Williams EM, Viale JP, Hamilton RM, *et al.*: Within-breath arterial PO_2 oscillations in an experimental model of acute respiratory distress syndrome. *Br J Anaesth*. 2000; 85(3): 456–9. [PubMed Abstract](#) | [Publisher Full Text](#)
51. Yokota H, Kreuzer F: Alveolar to arterial transmission of oxygen fluctuations due to respiration in anesthetized dogs. *Pflügers Arch*. 1973; 340(4): 291–306. [PubMed Abstract](#) | [Publisher Full Text](#)
52. Bergman NA: Cyclic variations in blood oxygenation with the respiratory cycle. *Anesthesiology*. 1961; 22: 900–8. [PubMed Abstract](#)
53. Klein KU, Hartmann EK, Boehme S, *et al.*: PaO_2 oscillations caused by cyclic alveolar recruitment can be monitored in pig buccal mucosa microcirculation. *Acta Anaesthesiol Scand*. 2013; 57(3): 320–5. [PubMed Abstract](#) | [Publisher Full Text](#)
54. Klein KU, Boehme S, Hartmann EK, *et al.*: Transmission of arterial oxygen partial pressure oscillations to the cerebral microcirculation in a porcine model of acute lung injury caused by cyclic recruitment and derecruitment. *Br J Anaesth*. 2013; 110(2): 266–73. [PubMed Abstract](#) | [Publisher Full Text](#)
55. Klein KU, Johannes A, Brückner M, *et al.*: Systemic PaO_2 Oscillations Cause Mild Brain Injury in a Pig Model. *Crit Care Med*. 2016; 44(5): e253–63. [PubMed Abstract](#) | [Publisher Full Text](#)
56. Gattinoni L, Tognoni G, Brazzi L, *et al.*: Ventilation in the prone position. The Prone-Supine Study Collaborative Group. *Lancet*. 1997; 350(9080): 815. [PubMed Abstract](#) | [Publisher Full Text](#)
57. **F** Guérin C, Reigner J, Richard JC, *et al.*: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013; 368(23): 2159–68. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. **F** Sud S, Friedrich JO, Taccone P, *et al.*: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med*. 2010; 36(4): 585–99. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
59. Abroug F, Ouannes-Besbes L, Dachraoui F, *et al.*: An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. *Crit Care*. 2011; 15(1): R6. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. **F** Bellani G, Rouby JJ, Constantin JM, *et al.*: Looking closer at acute respiratory distress syndrome: the role of advanced imaging techniques. *Curr Opin Crit Care*. 2017; 23(1): 30–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. **F** Pesenti A, Musch G, Lichtenstein D, *et al.*: Imaging in acute respiratory distress syndrome. *Intensive Care Med*. 2016; 42(5): 686–98. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
62. Copetti R, Soldati G, Copetti P: Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. *Cardiovasc Ultrasound*. 2008; 6: 16. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Cianchi G, Bonizzoli M, Pasquini A, *et al.*: Ventilatory and ECMO treatment of H1N1-induced severe respiratory failure: results of an Italian referral ECMO center. *BMC Pulm Med*. 2011; 11: 2. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
64. Fanara B, Manzoni C, Barbot O, *et al.*: Recommendations for the intra-hospital transport of critically ill patients. *Crit Care*. 2010; 14(3): R87. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. **F** Simon M, Braune S, Laqmani A, *et al.*: Value of Computed Tomography of the Chest in Subjects With ARDS: A Retrospective Observational Study. *Respir Care*. 2016; 61(3): 316–23. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
66. **F** Bellani G, Guerra L, Musch G, *et al.*: Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med*. 2011; 183(9): 1193–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. Borges JB, Costa EL, Bergquist M, *et al.*: Lung inflammation persists after 27 hours of protective Acute Respiratory Distress Syndrome Network Strategy and is concentrated in the nondependent lung. *Crit Care Med*. 2015; 43(5): e123–32. [PubMed Abstract](#) | [Publisher Full Text](#)
68. **F** Frenichs I, Amato MB, van Kaam AH, *et al.*: Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the T_Ranslational EIT developmeNt stuDy group. *Thorax*. 2017; 72(1): 83–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. **F** Calfee CS, Delucchi K, Parsons PE, *et al.*: Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014; 2(8): 611–20. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
70. **F** Kor DJ, Carter RE, Park PK, *et al.*: Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. *JAMA*. 2016; 315(22): 2406–14. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
71. Festic E, Carr G, Hinds RF, *et al.*: Lung Injury Prevention Study With Budesonide And Beta Agonist, Formoterol (lips-B): A Multicenter Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2016; 193: A7851. [Reference Source](#)
72. **F** McIntyre LA, Moher D, Fergusson DA, *et al.*: Efficacy of Mesenchymal Stromal Cell Therapy for Acute Lung Injury in Preclinical Animal Models: A Systematic Review. *PLoS One*. 2016; 11(1): e0147170. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
73. **F** Zheng G, Huang L, Tong H, *et al.*: Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. *Respir Res*. 2014; 15(1): 39. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. Mascher D, Tschewenka W, Mascher H, *et al.*: Sensitive determination of the peptide AP301—a motif of TNF- α —from human plasma using HPLC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2012; 908: 18–22. [PubMed Abstract](#) | [Publisher Full Text](#)
75. Shabbir W, Scherbaum-Hazemi P, Tzotzos S, *et al.*: Mechanism of action of novel lung edema therapeutic AP301 by activation of the epithelial sodium channel. *Mol Pharmacol*. 2013; 84(6): 899–910. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Tzotzos S, Fischer B, Fischer H, *et al.*: AP301, a synthetic peptide mimicking the lectin-like domain of TNF, enhances amiloride-sensitive Na^+ current in primary dog, pig and rat alveolar type II cells. *Pulm Pharmacol Ther*. 2013; 26(3): 356–63. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. Schwameis R, Eder S, Pietschmann H, *et al.*: A FIM study to assess safety and exposure of inhaled single doses of AP301-A specific ENaC channel activator for the treatment of acute lung injury. *J Clin Pharmacol*. 2014; 54(3): 341–50. [PubMed Abstract](#) | [Free Full Text](#)
78. Krenn K, Lucas R, Croizé A, *et al.*: Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. *Crit Care*. 2017; 21(1): 194. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Singh D, Smyth L, Borrill Z, *et al.*: A randomized, placebo-controlled study of the effects of the p38 MAPK inhibitor SB-681323 on blood biomarkers of inflammation in COPD patients. *J Clin Pharmacol*. 2010; 50(1): 94–100. [PubMed Abstract](#)
80. **F** Bellingan G, Maksimow M, Howell DC, *et al.*: The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study. *Lancet Respir Med*. 2014; 2(2): 98–107. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
81. Shimon Y, Friedlander G, Hetzroni G, *et al.*: Regulation of gene expression by small non-coding RNAs: a quantitative view. *Mol Syst Biol*. 2007; 3: 138. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. **F** Cardinal-Fernández P, Ferruelo A, Esteban A, *et al.*: Characteristics of microRNAs and their potential relevance for the diagnosis and therapy of the acute respiratory distress syndrome: from bench to bedside. *Transl Res*. 2016; 169: 102–11. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
83. Cai ZG, Zhang SM, Zhang Y, *et al.*: MicroRNAs are dynamically regulated and play an important role in LPS-induced lung injury. *Can J Physiol Pharmacol*. 2012; 90(1): 37–43. [PubMed Abstract](#) | [Publisher Full Text](#)
84. Song XW, Li Q, Lin L, *et al.*: MicroRNAs are dynamically regulated in hypertrophic hearts, and miR-199a is essential for the maintenance of cell size in cardiomyocytes. *J Cell Physiol*. 2010; 225(2): 437–43. [PubMed Abstract](#)
85. Tamarapu Parthasarathy P, Galam L, Huynh B, *et al.*: MicroRNA 16 modulates epithelial sodium channel in human alveolar epithelial cells. *Biochem Biophys*

- Res Commun.* 2012; **426**(2): 203–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Xie T, Liang J, Liu N, *et al.*: **MicroRNA-127 inhibits lung inflammation by targeting IgG Fcγ receptor 1.** *J Immunol.* 2012; **188**(5): 2437–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 87. Paine R 3rd, Wilcoxon SE, Morris SB, *et al.*: **Transgenic overexpression of granulocyte macrophage-colony stimulating factor in the lung prevents hyperoxic lung injury.** *Am J Pathol.* 2003; **163**(6): 2397–406.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 88. Sturrock A, Mir-Kasimov M, Baker J, *et al.*: **Key role of microRNA in the regulation of granulocyte macrophage colony-stimulating factor expression in murine alveolar epithelial cells during oxidative stress.** *J Biol Chem.* 2014; **289**(7): 4095–105.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 89. Herold S, Mayer K, Lohmeyer J: **Acute lung injury: how macrophages orchestrate resolution of inflammation and tissue repair.** *Front Immunol.* 2011; **2**: 65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 90. **F** Xiao J, Tang J, Chen Q, *et al.*: **miR-429 regulates alveolar macrophage inflammatory cytokine production and is involved in LPS-induced acute lung injury.** *Biochem J.* 2015; **471**(2): 281–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 91. Guo Z, Ren T, Xu L, *et al.*: **The microRNAs expression changes rapidly in mice lung tissue during lipopolysaccharide-induced acute lung injury.** *Chin Med J (Engl).* 2013; **126**(1): 181–3.
[PubMed Abstract](#)
 92. **F** Zhou X, Li X, Ye Y, *et al.*: **MicroRNA-302b augments host defense to bacteria by regulating inflammatory responses via feedback to TLR/IRAK4 circuits.** *Nat Commun.* 2014; **5**: 3619.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 93. Androulidaki A, Iliopoulos D, Arranz A, *et al.*: **The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs.** *Immunity.* 2009; **31**(2): 220–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 94. **F** Ying H, Kang Y, Zhang H, *et al.*: **MiR-127 modulates macrophage polarization and promotes lung inflammation and injury by activating the JNK pathway.** *J Immunol.* 2015; **194**(3): 1239–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 95. **F** Sun X, Icli B, Wara AK, *et al.*: **MicroRNA-181b regulates NF-κB-mediated vascular inflammation.** *J Clin Invest.* 2012; **122**(6): 1973–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 96. Guo Z, Gu Y, Wang C, *et al.*: **Enforced expression of miR-125b attenuates LPS-induced acute lung injury.** *Immunol Lett.* 2014; **162**(1 Pt A): 18–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
 97. Bosmann M, Grailer JJ, Ruemmler R, *et al.*: **Extracellular histones are essential effectors of C5aR- and C5L2-mediated tissue damage and inflammation in acute lung injury.** *FASEB J.* 2013; **27**(12): 5010–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 98. **F** Caudrillier A, Kessenbrock K, Gilliss BM, *et al.*: **Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury.** *J Clin Invest.* 2012; **122**(7): 2661–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 99. Hillmen P, Young NS, Schubert J, *et al.*: **The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria.** *N Engl J Med.* 2006; **355**(12): 1233–43.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:



Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Michael O'Connor**

Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL, USA

Competing Interests: No competing interests were disclosed.

2. **John Laffey**

University of Toronto, Toronto, ON, Canada

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research