What every intensivist should know about acute respiratory distress syndrome and diffuse alveolar damage

O que todo intensivista deve saber a respeito da síndrome do desconforto respiratório agudo e dano alveolar difuso?

ABSTRACT

Acute respiratory distress syndrome is a challenging entity for the intensivist. The pathological hallmark of the acute phase is diffuse alveolar damage, which is present in approximately half of living patients with acute respiratory distress syndrome. It is clear that respiratory support for acute respiratory distress syndrome has gradually been improving over recent decades. However, it is also evident that these procedures are beneficial, as they reduce lung injury and keep the patient alive. This could be interpreted as a time-gaining strategy until the trigger or causal or risk factor improves, the inflammatory storm decreases and the lung heals. However, all except two pharmacological treatments (neuromuscular blockers and steroids) were unable to improve the acute respiratory distress syndrome outcome. The hypothesis that pharmacological negative results may be explained by the histological heterogeneity of acute respiratory distress syndrome has been supported by the recent demonstration that acute respiratory distress syndrome with diffuse alveolar damage constitutes a specific clinical-pathological entity. Given that diffuse alveolar damage is a pathological diagnosis and that open lung biopsy (the most common technique to obtain lung tissue) has several side effects, it is necessary to develop surrogate biomarkers for diffuse alveolar damage. The aim of this narrative review is to address the following three topics related to acute respiratory distress syndrome: (a) the relationship between acute respiratory distress syndrome and diffuse alveolar damage, (b) how diffuse alveolar damage could be surrogated in the clinical setting and (c) how enrichment in diffuse alveolar damage may improve the results of pharmacological clinical trials tried out on patients with acute respiratory distress syndrome.

Keywords: Acute respiratory distress syndrome; Diffuse alveolar damage; Pharmacological treatment; Surrogate biomarkers

INTRODUCTION

Nearly half a century after its first description, acute respiratory distress syndrome (ARDS) continues to be one of the most relevant life-threatening entities in critically ill patients. Despite the great scientific and economic efforts humanity has made to improve ARDS outcome, a recent global survey demonstrated that ARDS has a prevalence of 0.42 cases per intensive care unit (ICU) bed and a mortality rate of 40%. In addition, the clinical management of ARDS has improved dramatically, but this improvement is based on techniques...
(e.g., low tidal volume or low pressure plateau) where the most likely main effect is to avoid lung injury associated with mechanical ventilation. Except for early paralyzation and likely steroids, all pharmacological treatments tried on patients with ARDS were unable to demonstrate a relevant effect.\(^{(3,4)}\)

Diffuse alveolar damage (DAD) is considered the histological hallmark for the acute phase of ARDS.\(^{(5)}\) It has been well known for many years that DAD is present in only half of autopsies from patients with ARDS.\(^{(6,7)}\) However, the recent demonstration that the same proportion occurs in living patients,\(^{(8)}\) as well as the effect that DAD exerts over ARDS outcome, shine a new light on this entity.\(^{(9-11)}\)

The aim of this narrative review is to address three topics about ARDS. First, we address the relationship between ARDS and DAD. Second, we analyze how DAD could be surrogated in the clinical setting. Finally, we address how enrichment in DAD may improve the results of clinical trials tried out on ARDS patients.

**What is the relationship between acute respiratory distress syndrome and diffuse alveolar damage?**

According to the Berlin definition,\(^{(5)}\) ARDS is a clinical construct composed by (i) the presence of at least one risk factor associated to (ii) acute hypoxemia not fully explained by cardiac failure or fluid overload and (iii) bilateral infiltration on radiology. On the other hand, the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias\(^{(12,13)}\) defined two histological, indistinguishable patterns: the acute interstitial pneumonia (AIP) and the DAD. The former term, AIP, is reserved for cases of unknown causes, and the latter term, DAD, is for patients with ARDS. In other words, both terms exhibit the same pathological pattern but differ in the clinical context in which they are diagnosed. The aforementioned consensus defined DAD (or AIP) by the presence of key histological features (diffuse distribution, uniform temporal appearance, alveolar septal thickening due to organizing fibrosis, usually diffuse airspace organization may be patchy or diffuse, hyaline membranes) and pertinent negative findings (lack of granulomas, necrosis, or abscesses, lack of infectious agents, no viral inclusions and negative results with special stains for organisms, lack of prominent eosinophils and neutrophils and negative cultures).

Although it is not unanimously accepted,\(^{(3,4,15)}\) the Berlin definition considered DAD as the hallmark for the acute phase of ARDS.\(^{(5)}\) This discrepancy may be explained by (i) the fact that a high proportion of the knowledge related to the ARDS pathology has been derived from autopsy studies, (ii) the effect of DAD on the ARDS outcome was unknown and (iii) what occurred in patients with mild ARDS was not described.\(^{(3,15,16)}\) In addition, the complexity of diagnosing DAD in patients with ARDS (see below) creates a great challenge for its study.\(^{(14)}\) Despite all of these difficulties, recently, several advances have been reported in understanding the relationship between ARDS and DAD. First, it was demonstrated that approximately half of living patients with ARDS present DAD in the pathological analysis of lung tissue obtained with an open lung biopsy.\(^{(8)}\) The other half showed one among a number of heterogeneous diseases (Figure 1), some of them with a specific treatment in the case of being diagnosed (e.g., pneumonia, pulmonary embolism or carcinomatous lymphangitis). Second, the effect of DAD on ARDS outcome was demonstrated in post-mortem and living patients. Lorente et al.\(^{(11)}\) analyzed 150 autopsies from patients with ARDS and found that the presence of DAD was associated with a lower age, lower ratio of partial oxygen pressure and inspiratory fraction (\(P_{a}O_{2}/FiO_{2}\)), and lower respiratory dynamic compliance, as well as a higher punctuation in the sequential organ failure score (SOFA) scale.

Of paramount importance was the fact that the cause of death was associated with the histological finding (in patients without DAD, refractory shock was the main cause of death in 55% and refractory hypoxemia in 5%; in contrast, in patients with DAD, refractory shock was the main cause of death in 29% and refractory hypoxemia in 25%). Similar differences were found between patients with ARDS and DAD versus ARDS with histological pneumonia. Cardinal-Fernández et al.\(^{(9)}\) analyzed 350 living patients with ARDS and open lung biopsy. They found that, although no differences were observed in the severity of the patients with and without DAD (\(P_{a}O_{2}/FiO_{2}\), and SOFA punctuation were similar on the day that the ARDS diagnosis and open lung biopsy were performed), mortality in patients with DAD was almost double than in patients without DAD (OR 1.81; IC95% 1.14 - 2.86). Kao et al.\(^{(10)}\) found that DAD was an independent risk factor for hospital mortality in living patients with ARDS (OR 3.55; IC95% 1.38 - 9.12). Finally, given that pneumonia
(viral and bacterial) is the second most frequent histological finding in patients with ARDS (Figure 1), it has been postulated that DAD and histological pneumonia could be considered together, with the aim to increase the correlation between clinical and pathological findings.\(^\text{17}\)

Although inconclusive, several facts argue against this proposal: (a) from a pathological point of view, DAD and pneumonia constitute two different entities that may exist independently from each other, (b) the microbiological rate of isolation differs in both entities, (c) the clinical evolution and the cause of death are different\(^\text{11}\) and (d) the mortality rate is also different.\(^\text{10}\) However, all of these differences do not exclude the possibility that some physiopathological pathways may be present in both entities and might explain why some pharmacological treatments may improve both conditions (see below).

**How can diffuse alveolar damage be diagnosed?**

Based on the previously described evidence, it appears necessary to recognize the subgroup of patients with ARDS and DAD with the aim to define a clinical-pathological entity,\(^\text{3,11,16,19}\) to increase the correlation between clinical and histological findings and to develop personalized pharmacological treatments (see below).\(^\text{20-22}\) Currently, the only model to estimate the probability of presenting DAD in patients with ARDS has been developed and validated in autopsies, and its accuracy is just moderate (area under receive operative curve 0.74, IC95% 0.65 -0.82).\(^\text{11}\) Likewise, the most frequent procedure to diagnose the DAD is performing an open lung biopsy, which is a risky procedure reserved for centers with demonstrated experience. Open lung biopsy is only recommended in two scenarios: (a) when there is high suspicion of curable etiology, less invasive procedures (e.g., bronchoalveolar lavage, blood samples and CT scan) are inconclusive and the risk of empirical therapy is too high and/or (b) when it is considered necessary to identify the fibro-proliferative phase (towards the end of the first week of evolution) to prescribe steroids.\(^\text{15,23,24}\)

The problem of diagnosing the gold standard is common to numerous diseases (e.g., myocardial infarction, neurodegenerative diseases and osteoporosis) and can be resolved using surrogate biomarkers. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or biological responses to a therapeutic intervention.\(^\text{25}\) A surrogate endpoint is "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."\(^\text{25}\)
The most common types of biomarkers are based on measuring clinical parameters or molecules. Imaging techniques have also been successfully used as surrogate biomarkers. In recent years, the combination of structural (e.g., computer tomography or nuclear magnetic resonance) with functional (e.g., positron emission tomography) imaging techniques has determined the appearance of a new kind of biomarker called functional imaging, which allows for the understanding of how physiological (or physiopathological) processes occur in a specific structure of the body.

A surrogate biomarker for DAD should have particular characteristics such as: (a) high accuracy for the diagnosis of DAD as well as ruling out any other diseases that may mimic the ARDS (this statement determines that the discovery and validation of a surrogate biomarker for DAD has to be performed using pathological findings); (b) high precision (the result can not vary if the same sample is analyzed several times using the same technique and the same laboratory conditions); (c) reflect the stage of the DAD evolution; (d) correlate the amount of parenchyma with DAD and (e) with the response of a specific treatment for DAD.

Finally, each kind of biomarker presents specific requirements. For example, if it is a molecule, it should be (a) present in minimally invasive samples (e.g., blood, urine or bronchio-alveolar lavage); (b) simple (e.g., a unique molecule with different levels of cut-off); (c) measurable with laboratory equipment available in average hospitals; (d) able to allow results to be obtained in a brief period of time; and (e) easily interpreted by physicians at the bedside. In addition, if it is a causal factor for DAD, it is more relevant because it could also be considered a therapeutic target. If the biomarker is an imaging technique, it should (a) be able to be performed with minimal displacement of the patient; (b) in a short period of time; (c) allow for the maintenance of all treatment and monitoring and (d) avoid the use of contrast that could harm the patient.

At this moment, N-terminal-peptide type III procollagen (NT-PCP-III) appears to be the most plausible surrogate biomarker for the fibro-proliferative phase of patients with ARDS. Forel et al. conducted an elegant study which included 32 consecutive patients presenting non-resolving, moderate or severe ARDS and open lung biopsy. In the study, they assessed the NT-PCP-III in serum and bronchioalveolar lavage as a surrogate biomarker of the fibro-proliferative phase in patients with ARDS. They found that the NT-PCP-III, measured 3 days (median) before the open lung biopsy, was higher in patients with ARDS with fibro-proliferation than in ARDS without fibro-proliferation (area under ROC was 0.90 [95%CI 0.80 - 1.00] for bronchioalveolar lavage and 0.75 [95%CI 0.57 - 0.92] for serum).

Why have almost all pharmacological treatments tried on acute respiratory distress syndrome failed?

A drug is usually defined as any chemical substance that affects the functioning of living things and organisms (e.g., bacteria, fungi, or viruses). Likewise, a drug target is “a molecular structure (chemically definable by at least a molecular mass) that will undergo a specific interaction with chemicals that we call drugs because they are administered to treat or diagnose a disease. The interaction has a connection with the clinical effect(s).”

On the other hand, clinical trials are a type of experiment designed to answer a specific question related to biomedical or behavioral intervention, including new treatments, protocols or medical devices. Currently, under the term “ARDS” in the international database Clinical Trials, 58 studies (drugs 41, cell therapy 7 and biological therapy 10) appeared, including 8376 patients (Tables 1 and 2).

For ARDS, no pharmacological treatment other than early paralyzation and prolonged steroids are routinely used at the bedside. This reality certainly demonstrates that we can identify targets and effective treatments in preclinical studies. However, we are unable to transfer the benefits to “real patients.” In this context, we have to keep in mind that “clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population,” since drugs exert their effect on specific targets, and obviously the target has to be present in the cohort in which the drug is tried on. In other words, you can only lump patients who carry the same target. If not, you have to split them into subgroups of patients that carry the same target. Using this point of view, if only half of the patients with ARDS present DAD, and if most of the targets have been identified in animal models (in which the histology was considered as the gold standard), the high number of failing pharmacological treatments applied to ARDS cannot be a surprise.

The term enrichment refers to the “prospective use of any patient’s characteristic to select a study population in which the detection of a drug effect (if one is present) is more likely than it would be in an unselected population.” Here, the great interest lies in biomarkers,
### Table 1 - Studies based on pharmacologic treatment attempted in patients with acute respiratory distress syndrome and registered in a clinical trial database[28]

| Type intervention | NCT Number | Drug | Title of the study | Sponsor or collaborators | Patients enrolled |
|-------------------|------------|------|--------------------|--------------------------|-------------------|
| Drug              | NCT01504867 | Acid acetilsalicic | LIPS-A: Lung Injury Prevention Study with Aspirin | Ognjen Gajic/Beth Israel Deaconess Medical Center/Montefiore Medical Center/Vanderbilt University/Mayo Clinic | 400 |
| Drug              | NCT01653937 | Acid acetilsalicic | The Effect of Aspirin on Reducing Inflammation in Human in Vivo Model of Acute Lung Injury | Belfast Health and Social Care Trust/The Intensive Care Society United Kingdom/Northern Ireland Clinical Trials Unit/Queen's University, Belfast | 33 |
| Drug              | NCT00112164 | Activated protein C | Activated Protein C to Treat Acute Lung Injuries | University of California, San Francisco/National Heart, Lung, and Blood Institute (NHLBI) | 90 |
| Drug              | NCT02106975 | Ascorbic acid | Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury | Virginia Commonwealth University/National Heart, Lung, and Blood Institute (NHLBI) | 170 |
| Drug              | NCT01434121 | Ascorbic acid | Ascorbic Acid (Vitamin C) Infusion in Human Sepsis | Virginia Commonwealth University | 24 |
| Drug              | NCT01050699 | Dexmedetomidine | Sleep Intervention During Acute Lung Injury | University of Arizona/National Heart, Lung, and Blood Institute (NHLBI) | 90 |
| Drug              | NCT00351533 | Fish oil | A Phase II Randomized Trial of Fish Oil in Patients with Acute Lung Injury (ALI) | University of Washington/National Heart, Lung, and Blood Institute (NHLBI)/American Thoracic Society/Acute Respiratory Distress Syndrome Foundation/American Society for Parenteral and Enteral Nutrition | 90 |
| Drug              | NCT01335932 | Ganciclovir/Valganciclovir | Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure | Fred Hutchinson Cancer Research Center/National Heart, Lung, and Blood Institute (NHLBI)/Genentech, Inc. | 160 |
| Drug              | NCT01713309 | Heparin binding protein | Heparin Binding Protein in Patients with Acute Respiratory Failure Treated with GCSF (Filgrastim) | Helsinki University Central Hospital/The Swedish Research Council | 59 |
| Drug              | NCT02425579 | Inhaled carbon monoxide | Safety Study of Inhaled Carbon Monoxide to Treat Acute Respiratory Distress Syndrome (ARDS) | Weill Medical College of Cornell University/Bingham and Women's Hospital/Massachusetts General Hospital/Duke University | 48 |
| Drug              | NCT00605696 | Insulin | Evaluating the Effectiveness of Early Insulin Therapy in People at Risk for Developing Acute Lung Injury/Acute Respiratory Distress Syndrome | National Heart, Lung, and Blood Institute (NHLBI) | 90 |
| Drug              | NCT01096771 | Intravenous lipids | The Effect of Intravenous Lipids on Lung Function in Acute Respiratory Distress Syndrome (ARDS) | Methodist Research Institute, Indianapolis | 14 |
| Drug              | NCT01938079 | Ketamine | Pharmacokinetic Alterations During ECMO | Columbia University | 20 |
| Drug              | NCT0159510 | Methylene blue & nitric oxide | Studies of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome | Northern State Medical University/Helse Nord | 28 |
| Drug              | NCT00655928 | N-acetylcysteine | Modulation of Lung Injury Complicating Lung Resection | Imperial College London/Royal College of Physicians/Royal Brompton & Harefield NHS Foundation Trust | 47 |
| Drug              | NCT01573715 | Neuromuscular blocking agents | Effects of Neuromuscular Blocking Agents (NMBA) on the Alteration of Transpulmonary Pressures at the Early Phase of Acute Respiratory Distress Syndrome (ARDS) | Assistance Publique Hopitaux De Marseille | 40 |
| Drug              | NCT00299650 | Neuromuscular blocking agents | Systematic Early Use of Neuromuscular Blocking Agents in ARDS Patients | Assistance Publique Hopitaux de Marseille/GlaxoSmithKline | 340 |
| Drug              | NCT02509078 | Neuromuscular blocking agents | Reevaluation of Systemic Early Neuromuscular Blockade | Massachusetts General Hospital/National Heart, Lung, and Blood Institute (NHLBI) | 1408 |
| Drug              | NCT00036082 | Neutrophil elastase inhibitor | A Phase II Study to Determine the Efficacy and Safety of Sivelestat in Subjects with Acute Lung Injury | Eli Lilly and Company | 600 |
| Drug              | NCT00219375 | Neutrophil elastase inhibitor | Study of Sivelestat Sodium Hydrate in Acute Lung Injury (ALI) Associated with Systemic Inflammatory Response Syndrome (SIRS) in Japan | Ono Pharmaceutical Co. Ltd | 649 |

Continue...
### Table: Drug Interventions and Studies

| Type of intervention | NCT Number | Drug | Title of the study | Sponsor or collaborators | Patients enrolled |
|----------------------|------------|------|--------------------|--------------------------|-------------------|
| Drug | NCT01391481 | Perfluorocarbon inhaled | Perfluorocarbon (PFC) Inhalation Treatment of Acute Lung Injury/Acute Respiratory Distress Syndrome | Chinese PLA General Hospital/The Second Artillery General Hospital/The 306 Hospital of People’s Liberation Army/First Hospitals affiliated to the China PLA General Hospital/General Hospital of Chinese Armed Police Forces/Beijing Shijitan Hospital/Air Force | 200 |
| Drug | NCT02370095 | Prostacyclin analogue | Treprostinil Sodium Inhalation for Patients at High Risk for ARDS | --- | 20 |
| Drug | NCT01274481 | Prostacyclin analogue | Iloprost Effects on Gas Exchange and Pulmonary Mechanics | University of Oklahoma/Actelion | 84 |
| Drug | NCT00455767 | Protein inhibitor of human neutrophil elastase | Safety and Efficacy Study of Deplestat in Acute Respiratory Distress Syndrome (ARDS) Patients | Debispharm International SA | 43 |
| Drug | NCT01597635 | Recombinant human angiotensin converting enzyme type 2 | The Safety, Tolerability, PK and PD of GSK2586881 in Patients with Acute Lung Injury | GlaxoSmithKline | 200 |
| Drug | NCT00996840 | Selective inhibitor of p38 alpha (MAPK) | SB-881233 IV for Subjects at Risk of Acute Lung Injury or ARDS | GlaxoSmithKline | 90 |
| Drug | NCT02166853 | Sevoflurane | Effects of Sevoflurane on Gas Exchange and Inflammation in Patients with ARDS (SEGA Study) | University Hospital, Clermont-Ferrand | 745 |
| Drug | NCT01619280 | Sodium nitroprusside | Safety Study of Nebulized Sodium Nitroprusside in Adult Acute Lung Injury | Mount Sinai Hospital, Canada | 400 |
| Drug | NCT00979121 | Statins | Statins for Acutely Injured Lungs from Sepsis | National Heart, Lung, and Blood Institute (NHLBI) | 200 |
| Drug | NCT00562835 | Steroids | Steroids in Patients with Early ARDS | Catholic University of the Sacred Heart | 100 |
| Drug | NCT01284452 | Steroids | Efficacy of Hydrocortisone in Treatment of Severe Sepsis/Septic Shock Patients with Acute Lung Injury/Acute Respiratory Distress Syndrome (ARDS) | Mahidol University | 197 |
| Drug | NCT00290602 | Steroids | Early Low Dose Steroid Therapy of Acute Respiratory Distress Syndrome | National Cancer Center, Korea | 400 |
| Drug | NCT01783821 | Steroids | LIPS-B: Lung Injury Prevention Study with Budesonide and Beta | Mayo Clinic/Stanford University/Beth Israel Deaconess Medical Center/University of Arizona/ National Center for Research Resources (NCRR) | 61 |
| Drug | NCT02819453 | Steroids | Corticosteroid Mediates Acute Respiratory Distress Syndrome | Shanghai Pulmonary Hospital, Shanghai, China | 20 |
| Drug | NCT00127985 | Steroids | 6-Methyl-Prednisolone for Multiple Organ Dysfunction Syndrome | Hospital Universitario Principe de Asturias | 240 |
| Drug | NCT00742482 | Surfactant | Efficacy and Safety of 3 Doses of HL10 Given at Fixed Time Intervals Compared to Standard Therapy | LEO Pharma | 418 |
| Drug | NCT01462279 | Thiamine | Effect of Thiamine on Oxygen Utilization (VO2) in Critical Illness | Beth Israel Deaconess Medical Center/American Medical Association | 20 |
| Drug | NCT02895191 | Urinary trypsin inhibitor | The Safety and Dose Response Relationship of Ulinastatin for Acute Respiratory Distress Syndrome (ARDS) | Techpool Bio-Pharma Co., Ltd./The First Affiliated Hospital of Guangzhou Medical University | 60 |
| Drug | NCT00004494 | Vasoactive intestinal peptide | Phase I Study of Vasoactive Intestinal Peptide in Patients with Acute Respiratory Distress Syndrome and Sepsis | Stony Brook University/State University of New York/FDA Office of Orphan Products Development | 18 |
| Drug | NCT02468531 | Xenon anesthesia | The Clinic Trial on Protection of Xenon Anaesthesia Against Perioperative Acute Lung Injury for Standford an Acute Aortic Dissection | Beijing Anzhen Hospital | 80 |

Studies with one (NCT01814896 [lipid emulsions]) or not registered patients (NCT00030121 [recombinant human atrial natriuretic polypeptide], NCT00431379 [tissue plasminogen activator], NCT01713956 [inhaled saline], NCT02113725 [adrenocorticotropic hormone analogue] and NCT01196428 [simvastatin]) were not included in the table. NR - not reported.
| Type of intervention | NCT number     | Intervention                                      | Title of the study                                                                 | Sponsor or collaborators                                                                 | Patients enrolled |
|----------------------|---------------|---------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------|
| Cell therapy         | NCT02804945   | Mesenchymal stem cells                            | Mesenchymal Stem Cells (MSCs) for Treatment of Acute Respiratory Distress Syndrome (ARD) in Stem Cell Transplant Patients | M.D. Anderson Cancer Center                                                                | 50                |
| Cell therapy         | NCT01775774   | Mesenchymal stem cells                            | Human Mesenchymal Stem Cells For Acute Respiratory Distress Syndrome                | Michael A. Matthay/National Heart, Lung, and Blood Institute (NHLBI)/Massachusetts General Hospital/Stanford University/University of Pittsburgh/University of Minnesota - Clinical and Translational Science Institute/University of California, San Francisco | 69                |
| Cell therapy         | NCT02097641   | Mesenchymal stem cells                            | Human Mesenchymal Stem Cells For Acute Respiratory Distress Syndrome (START)        | Michael A. Matthay/National Heart, Lung, and Blood Institute (NHLBI)/Massachusetts General Hospital/Stanford University/University of Pittsburgh/University of Minnesota - Clinical and Translational Science Institute/Ohio State University/University of Cal | 60                |
| Cell therapy         | NCT02215811   | Mesenchymal stem cells                            | Treatment of Severe Acute Respiratory Distress Syndrome with Allogeneic Bone Marrow-derived Mesenchymal Stromal Cells | Karolinska University Hospital/Karolinska Institutet                                    | 10                |
| Cell therapy         | NCT02444455   | Mesenchymal stem cells                            | Human Umbilical-Cord-Derived Mesenchymal Stem Cell Therapy in Acute Lung Injury     | Affiliated Hospital to Academy of Military Medical Sciences/Ivy Institute of Stem Cells Co. Ltd | 20                |
| Cell therapy         | NCT02112500   | Mesenchymal stem cells                            | Mesenchymal Stem Cell in Patients with Acute Severe Respiratory Failure             | Asan Medical Center                                                                      | 10                |
| Cell therapy         | NCT02611609   | Stem cells derived from bone marrow               | A Phase 1/2 Study to Assess MultiStemÂ® Therapy in Acute Respiratory Distress Syndrome | Athyrsys, Inc/Athersys Limited/Cell Therapy Catapult                                     | 36                |
| Biological therapy   | NCT01902082   | Adipose-derived mesenchymal stem cells            | Adipo-derive Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome          | Shaoxing Second Hospital                                                                 | 20                |
| Biological therapy   | NCT01438853   | Anti-TF antibody                                  | Effects of TNX-832 (Sunol cH36) in Subjects with Acute Lung Injury/Acute Respiratory Distress Syndrome | Altor Bioscience Corporation/Genentech, Inc./Tanox                                         | 18                |
| Biological therapy   | NCT00879606   | Anti-tissue factor antibody                       | Anti-TF Antibody (ALT-836) to Treat Septic Patients with Acute Lung Injury or Acute Respiratory Distress Syndrome | Altor Bioscience Corporation/National Heart, Lung, and Blood Institute (NHLBI)             | 150               |
| Biological therapy   | NCT00233207   | Chimeric CD14 antibody                            | IC14 Antibodies to Treat Individuals with Acute Lung Injury                        | National Heart, Lung, and Blood Institute (NHLBI)                                        | 13                |
| Biological therapy   | NCT00201409   | Granulocyte macrophage colony-stimulating factor  | A Randomized Trial of GM-CSF in Patients with ALI/ARDS                              | University of Michigan | National Heart, Lung, and Blood Institute (NHLBI) | 132               |
| Biological therapy   | NCT02595060   | Granulocyte macrophage colony-stimulating factor  | Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) Inhalation to Improve Host Defense and Pulmonary Barrier Restoration | Savara Inc.                                                                              | 45                |
| Biological therapy   | NCT02095444   | Human menstrual blood cells                       | Using Human Menstrual Blood Cells to Treat Acute Lung Injury Caused by H7N9 Bird Flu Virus Infection | S-Evans Biosciences Co., Ltd/First Affiliated Hospital of Zhejiang University              | 20                |
| Biological therapy   | NCT02622724   | Interferon beta-1a                                | Efficacy and Safety of FP-1201-Iyo (Interferon Beta-1a) in Patients Having Acute Respiratory Distress Syndrome (ARDS) | Faron Pharmaceuticals Ltd                                                                 | 300               |
| Biological therapy   | NCT00789685   | interferon-beta-1a                                | Safety, Tolerability and Preliminary Efficacy of FP-1201 in ALI and ARDS. Phase VII | Faron Pharmaceuticals Ltd                                                                 | 37                |
| Biological therapy   | NCT01627613   | Peptide mimicking the lectin-like domain of TNF   | Study in Intensive Care Patients to Investigate the Clinical Effect of Repetitive Orally Inhaled Doses of AP301 on Alveolar Liquid Clearance in Acute Lung Injury | Apeptico Forschung und Entwicklung GmbH                                                   | 40                |
present in minimally invasive samples, such as serum, urine or bronchoalveolar lavage, to surroget the diagnosis of DAD.

As previously mentioned, only early paralyzation and prolonged steroid therapy may be considered effective pharmacological treatment for severe ARDS. We hypothesize that this positive result may be related to the fact that they exert their effect over targets present in several entities that may mimic the ARDS. For that reason, it is possible to lump these entities in a clinical trial. Specifically, in the case of early paralyzation, the targets could be (a) the reduction in lung injury arising from ventilator desynchrony, (b) the attenuation of biotrauma and (c) limited expiratory muscle function, which reduces the respiratory system collapse and derecruitment. In addition, a recent experimental study suggests that neuromuscular blockers may inhibit the nicotinic pathway and induce an anti-inflammatory effect.

For all of the above reasons, although not definitively, the most plausible mechanism to explain the beneficial effect of early paralyzation on ARDS outcome is the attenuation of mechano-transduction related to lung injury (Figure 2). This is non-specific to ARDS patients and may also benefit all subjects who require mechanical ventilation. On the other hand, the effectiveness of steroids in ARDS may be explained by at least three reasons: (a) the potent down-regulation of inflammatory and fibroproliferative pathways; (b) the benefit of steroids in pneumonia (this is the second most common histological pattern in patients with ARDS); and (c) other specific diseases that may mimic ARDS (e.g., acute eosinophilic pneumonia, diffuse alveolar hemorrhage from vasculitis, cryptogenic organizing pneumonia, acute hypersensitivity pneumonitis and pneumocystis jiroveci pneumonia).

![Figure 2 - Mechano-transduction related lung injury.](image)

**CONCLUSION**

Every intensivist should know that diffuse alveolar damage is present in only half of patients with acute respiratory distress syndrome. Based on recent discoveries, diagnosing diffuse alveolar damage is not merely an academic exercise because its effects on acute respiratory distress syndrome outcome have been demonstrated. At this moment, the only way to diagnose diffuse alveolar damage is to perform an open lung biopsy. However, recently, several efforts have been performed to identify a surrogate biomarker that would allow us to diagnose diffuse alveolar damage without the risk of open lung biopsy. Currently, N-terminal-peptide type III procollagen appears to be an accurate surrogate biomarker for the fibro-proliferative phase of acute respiratory distress syndrome. In coming years, it will be of paramount importance to validate N-terminal-peptide type III procollagen in a large cohort of patients with acute respiratory distress syndrome, as well as to seek out other molecular or imaging biomarkers able to surrogate the diagnosis of diffuse alveolar damage.
RESUMO

A síndrome do desconforto respiratório agudo é um desafio para o intensivista. A característica principal desta doença aguda é o dano alveolar difuso, presente em cerca de metade dos pacientes com a síndrome. É claro que o suporte respiratório à síndrome do desconforto respiratório agudo tem melhorado gradualmente nas últimas décadas. É também evidente que todos estes procedimentos são benéficos, já que reduzem a lesão pulmonar e mantêm o paciente vivo. Isto deve ser interpretado como uma estratégia de ganho de tempo, até que o fator desencadeante ou de risco causal melhor, assim como a tempestade inflamatória diminua e o pulmão se cure. Por outro lado, todos - exceto dois tratamentos farmacológicos (bloqueadores neuromusculares e esteroides) - são incapazes de melhorar o desfecho da síndrome do desconforto respiratório agudo. A hipótese de que os resultados farmacológicos negativos podem ser explicados pela heterogeneidade histológica da síndrome do desconforto respiratório agudo tem sido apoiada pelas recentes demonstrações de que a síndrome com dano alveolar difuso tem características clínico-patológica específica. O dano alveolar difuso é um diagnóstico patológico, e a biópsia pulmonar a céu aberto (a técnica mais comum para obtenção de tecido pulmonar) tem efeitos colaterais graves, sendo necessário que se desenvolvam biomarcadores substitutos para o dano alveolar difuso. O objetivo desta revisão é discutir três tópicos relacionados à síndrome do desconforto respiratório agudo: o relacionamento entre a síndrome do desconforto respiratório agudo e o dano alveolar difuso; como o dano alveolar difuso pode ser representado no quadro clínico; e como o enriquecimento pode melhorar os resultados de estudos clínicos farmacológicos realizados com pacientes com a síndrome e com dano alveolar difuso.

Descritores: Síndrome do desconforto respiratório agudo; Dano alveolar difuso; Tratamento farmacológico; Biomarcadores substitutos

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-23.
2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(6):788-900.
3. Cardinal-Fernández P, Poy C, Kao KC. ARDS: Time to “separate the wheat from the chaff”. J Crit Care. 2016;34:31-2.
4. Tonelli AR, Zein J, Adams J, Ioannidis JP. Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 studies. JAMA. 2016;315(4):376-87.
5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526-33.
6. Esteban A, Fernández-Segoviano F, Frutos-Vivar F, Aramburu JA, Nájera L,Rubenfeld G, ND, Caldwell E, et al. Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Am Intern Med. 2004;141(6):440-5.
7. Pinheiro BV, Muraoka FS, Assis RV, Lamin R, Pinto SP, Ribeiro PJ Jr, et al. Accuracy of clinical diagnosis of acute respiratory distress syndrome in comparison with autopsy findings. J Bras Pneumol. 2007;33(4):423-8.
8. Cardinal-Fernández P, Bajwa EK, Dominguez-Calvo A, Menéndez JM, Papazian L, Thompson BT. The presence of diffuse alveolar damage on open lung biopsy is associated with mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Chest. 2016;149(5):1155-64.
9. Guerin C, Bayle F, Leray V, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(6):788-900.
10. Kao KC, Hu HC, Chang CH, Hung CY, Chiu LC, Li SH, et al. Diffuse alveolar damage associated mortality in selected acute respiratory distress syndrome patients with open lung biopsy. Crit Care. 2015;19:228.
11. Lorente JA, Cardinal-Fernández P, Muñoz D, Frutos-Vivar F, Thille AW, Jaramillo C, et al. Acute respiratory distress syndrome in patients with and without diffuse alveolar damage: an autopsy study. Intensive Care Med. 2015;41(11):1921-30.
12. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277-304. Erratum in Am J Respir Crit Care Med. 2002;166(3):426.
13. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Nadel JA, Robbins Jill, Selman M, Wells AU, Behr J, Boursos D, Brown KK, Colby TV, Collard HR, Coriell CR, Cottin V, Crestani B, Drent M, Duddon RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez F, Nadel JA, Protzko S, Raghu G, Richeldi L, Saveriati N, Swigris J, Valeyre D, ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(8):733-48.
14. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38(10):1573-82.
15. Papazian L, Calfee CS, Chiumello D, Luyt CE, Meyer NJ, Segeluch H, et al. Diagnostic workup for ARDS patients. Intensive Care Med. 2016;42(5):674-85.
16. Cardinal-Fernández P, Esteban A, Thompson BT, Lorente JA. ARDS: lessons learned from the heart. Chest. 2015;147(1):7-8.
17. Thompson BT, Matthay MA. The Berlin definition of ARDS versus pathological evidence of diffuse alveolar damage. Am J Respir Crit Care Med. 2013;187(7):675-7.
18. Sarmiento X, Almirall J, Guardiola JJ, Mesalles E, Labarta L, Mate JL, et al. [Study on the clinicopathological correlation in the secondary acute respiratory distress syndrome]. Med Intensiva. 2011;35(1):22-7. Spanish.
19. Cardinal-Fernández P, Correge E, Villanueva J, Rios F. Acute Respiratory Distress: from syndrome to disease. Med Intensiva. 2016;40(3):169-75.
20. Walkey AJ. Unreliable syndromes, unreliable studies. Ann Am Thorac Soc. 2016;13(7):1010-1.
21. Prescott HC, Caffee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. Am J Respir Crit Care Med. 2016;194(2):147-55.
22. Thompson BT, Guérin C, Esteban A. Should ARDS be renamed diffuse alveolar damage? Intensive Care Med. 2016;42(5):653-5.
23. Palakshappa JA, Meyer NJ. Which patients with ARDS benefit from lung biopsy? Chest. 2015;148(4):1073-82.
24. Wong AK, Walkey AJ. Open lung biopsy among critically ill, mechanically ventilated patients. A metaanalysis. Ann Am Thorac Soc. 2015;12(8):1226-30.
25. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89-95.
26. Forel JM, Guervilly C, Hraiech S, Voillet F, Thomas G, Somma C, et al. Type III procollagen is a reliable marker of ARDS-associated lung fibroproliferation. Intensive Care Med. 2015;41(1):1-11.
27. Imming P, Sinning C, Meyer A. Drugs, their targets and the nature and number of drug targets. Nat Rev Drug Discov. 2006;5(10):821-34.
28. Clinical Trials [Internet]. [cited 2016 Jan 9] Available from: https://clinicaltrials.gov/  
29. Food and Drug Administration. Guidance for industry, enrichment strategies for clinical trials to support approval of human drugs and biological products. Available from: http://www.fda.gov/downloads/drugs/guidancecompliancregulatoryinformation/guidances/ucm332181.pdf. Accessed 09/05/16
30. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Amal JM, Perez D, Sehgiboyan JM, Constantin JM, Courant P, Lefranc JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107-16.
31. Meduri GU, Bridges L, Shih MC, Manik PE, Siemieniuk RA, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients’ data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med. 2016;42(5):829-40.
32. Schwarz MI, Albert R. “Imitators” of the ARDS: implications for diagnosis and treatment. Chest. 2004;125(4):1530-5.
33. Guérin C, Thompson T, Brower R. The ten diseases that look like ARDS. Intensive Care Med. 2015;41(6):1099-102.
34. Fanelli V, Morita Y, Cappello P, Ghazarian M, Sugumar B, Delsedime L, et al. Neuromuscular blocking agent cisatracurium attenuates lung injury by inhibition of nicotinic acetylcholine receptor-α1. Anesthesiology. 2016;124(1):132-40.
35. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Maret E, Beausser M, Gutton C, Lefranc JY, Allacouichic B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369(5):428-37.
36. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci MO, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308(16):1651-9.
37. Torres A, Sibilia D, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015;313(7):677-86.
38. Thompson BT, Ranieri VM. Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: no. Intensive Care Med. 2018;42(5):921-3.