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REVIEW ARTICLE
ACUTE RESPIRATORY DISTRESS SYNDROME- A CONCISE CLINICAL REVIEW

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ABSTRACT:
Acute Respiratory Distress Syndrome (ARDS) is a challenging and deadly disease faced by critical care specialists. The literature concerning ARDS has been increasing for the last 12 years and there are now many options available to treat this disease. However, not all of these options work and some may even be harmful to patients. The purpose of this paper is to provide the reader with a review of the new criteria for ARDS definition and to discuss the pros and cons of the various treatment options now available.

Introduction:
ARDS is a complex clinical syndrome that represents a consistent recognizable pattern resulting from a large variety of both infectious and noninfectious etiologies. Over the last 12 years there has been an increasing amount of research done concerning ARDS, from establishing better evidence based studies for treatment to improving the definition. The main objectives for this review will be to describe the New Berlin Criteria for ARDS as well as briefly describing the pros and cons of the various treatment options available. For more detailed reviews of etiology and pathogenesis, the interested reader is referred to the bibliography for further reading[1,2].

Epidemiology:
In general ARDS occurs in approximately 5% of in-hospital cases on mechanical ventilation with a clinical burden of approximately 200,000 cases per year in the U.S. However, this number varies from country to country. Using the American-European 1994 Consensus Conference statement (AECC) definition ARDS occurs as follows: 64.2-78.9 cases/100,000 person years in the U.S, 7.2 cases/100,000 person years in Spain, 34 cases/100,000 person years in New Zealand/Australia, and 17cases/100,000 person years in Northern Europe[3]. The explanation for this disparate incidence between different regions of the world remains unclear. This difference may partially be explained by variations in healthcare delivery systems and demographics[3]. Current trends would suggest that if there is no effective preventative treatment developed for ARDS, incidence rates may be expected to rise to by 50% by 2030 in the U.S. alone representing approximately 330,000 cases/year[4].

Mortality:
In the U.S. ARDS/ALI (Acute Lung Injury) results in approximately 74,000 deaths per year. To place this number in perspective, the ARDS mortality rate exceeds the mortality rates of other diseases such as breast cancer, HIV, and asthma in the U.S.[5]. Risk factors for increased mortality in ARDS are: increased dead space fraction (greater than 0.60), hypoxemia (PAO_2/FIO_2 under 100), pulmonary vascular alterations, poor lung compliance, shock, liver dysfunction, acute kidney injury, age over 60, and increased severity of illness scores[1]. Only a relative minority of ARDS patients die of refractory hypoxemia (13%-15%) [3].

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The mortality rate of ARDS has been decreasing. Using the ARDS Network trials 60 day mortality endpoint, ARDS has declined from 36% (1996-1997) to 26% (2004-2005), with the most recent ARDS Net trial showing a mortality of 22% despite higher incidences of shock and higher severity of illness scores [1]. This decrease in ARDS mortality has been ascribed to better compliance and increased usage of the ARDS Net protocol. However there appears to be a plateauing effect of this decreased mortality trend thus necessitating the discovery and testing of new treatment options and preventive measures.

Definition:

The need for a stable and reproducible definition for ARDS is obvious when designing and implementing single center or multi center trials. The description of the syndrome of ARDS is generally credited to the article by Ashbaugh and Petty published in 1967. However, it is likely that the disease was described earlier in the medical literature with Laennec describing a fatal case of idiopathic pulmonary edema, published in 1821. During the twentieth century diseases described as "wet lung, Da Nang lung and shock lung " were all various names describing what is now termed ARDS [3].

In 1988 Murray et al attempted to expand the definition of ARDS creating the Lung Injury Score (LIS) [6]. The LIS graded ARDS severity across 4 main domains. These are: Number of quadrants involved in the chest x-ray, P/F ratio, PEEP, and lung compliance. Each domain is scored between 0-4 (Table I). However this score was found to be too complicated to practically implement in the clinical setting. In 1994 the AECC definition was created [7]. This definition remained the definition for ARDS until the recently proposed Berlin Criteria.

The 1994 AECC definition for ARDS is as follows: 1) Acute in onset, 2) bilateral infiltrates on a frontal chest x-ray, 3) No clinical or hemodynamic (wedge greater than 18) signs of left atrial hypertension and finally 4) a PaO_2/FIO_2 ratio of less than 200. In addition, a new category of Acute Lung Injury (ALI), defined as points 1-3 with a PaO_2/FIO_2 ratio of 200-300 was created. The need for the new definition of ALI was felt to be necessary in order to incorporate the range of clinical severity seen with ARDS. However there were several issues identified with the AECC 1994 definition. These are: 1) No clear cut definition of "acute", 2) the chest x-ray definition has been found to have moderate to poor inter-observer reliability, 3) The PaO_2/FIO_2 ratio is not constant over a range of FIO2 and PEEP, 4) subsequent to the AECC definition elevated wedge pressures have been demonstrated in patients with ARDS and no congestive heart failure. This could be due to transmission of positive pressure from the ventilator and aggressive fluid resuscitation. And finally 5) there is evidence that the AECC criteria can result in under identification of ALI/ARDS [8]. Due to these limitations an international panel was created, tasked with refining and adjusting the AECC criteria. This resulted in the current definition of ARDS referred to as the Berlin Criteria (Table II).

The Berlin Criteria included several changes from the AECC criteria and initially minute ventilation (as a surrogate for dead space) and lung compliance were added. However, in a subsequent validation study of 4188 patients with ARDS from 4 multicenter datasets and 269 patients from 3 single center datasets, it was found that the criteria of lung compliance and

minute ventilation did not add to the predictive power of the definition and therefore these were removed from the final definition set [9]

The final definition of the Berlin Criteria is as follows: 1) Timing: defined as within one week of worsening respiratory symptoms or after a defined insult known to cause ARDS, 2) Chest x-ray: bilateral opacities not fully caused by effusions, nodules, or lobar/ lung collapse, 3) Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid over load. Objective assessment of hydrostatic edema if no risk factors of ARDS is found (echocardiography). Of note PCWP pressure was removed and finally 4) the criteria of ALI was removed and a minimum requirement of PEEP (greater than or equal to 5cmH$_2$O) was added and three categories of severity were created. These are: P/F ratio of 200-300 mmHg (mild), 100-200 mmHg (moderate), and finally less than or equal to 100 mmHg (severe).

Overall, the Berlin Criteria performed better than the AECC criteria for mortality prediction (p<.001). However, the Berlin Criteria Area under the Receiver Operating Curve (AUC) was only marginally better than the AECC AUC (0.577 versus 0.536), though this did reach statistical significance as described above. With better definitions for acuity, chest x-ray findings, removal of the PCWP, addition of a minimum PEEP value and the deletion of the ALI designation the Berlin Criteria attempted to compensate for the known deficiencies of the AECC Criteria.

Recently, using diffuse alveolar damage (DAD) as the pathological lesion of ARDS, the sensitivity and specificity of the Berlin Criteria was compared to autopsy findings of ARDS. The Berlin Criteria was found to perform well with autopsy findings of both mild and severe ARDS [10]. Further clinical studies are needed to better define the sensitivity and specificity of the Berlin Criteria for detecting ARDS and its clinical severity subgroups. However, at present, the Berlin Criteria is the new definition for ARDS.

Treatment:

Over the last twelve years there has been significant improvement in our understanding of what works, what may work and what doesn't work for the treatment of ARDS. This present section will provide an update review of these therapies.

ARDS Net Protocol:

Published in the New England Journal of Medicine in 2000, the ARDS Network study of using lower tidal volumes to ventilate patients with ARDS represented a major advance in the treatment of ARDS [11]. Presently the ARDS Net lower tidal volume strategy represents the standard of care for the treatment of ARDS receiving a level 1A recommendation in the most recent Surviving Sepsis Campaign Guidelines [12]. The ARDS net protocol built on a growing body of animal studies of ARDS [13]. These studies demonstrated that cyclic volume changes causing alveolar opening and closing (atelectrauma) as well as alveolar volume over distension in reaction to mechanically delivered tidal volumes (volutrauma) can cause ARDS de novo as well as worsen existing ARDS. Unfortunately, adherences to using the ARDS Net lower tidal volume protocol remain less than optimal. A recent study evaluating the effect of using the lower tidal volume strategy on two year ARDS mortality found only a 41% compliance rate of using a low tidal volume strategy. Adherence to the ventilator strategies of the ARDS Net protocol resulted in a 3% decrease in mortality over 2 years for each element adhered to [14]. For a

description of the ARDS Net protocol the interested reader is referred to the ARDS Net web address at www.ardsnet.org/system/files/Ventilator%20Protocol%20Card.pdf

Conclusion: At present the use of the ARDS Net protocol remains one of the definitive treatments for ARDS.

Fluid Strategy for ARDS

Starling's equation offers a physiological basis for fluid restriction in ARDS.

The equation is defined as follows: $Kf(Pc - Pi) - \sigma(\pi c - \pi i)$

where Kf is the filtration coefficient, Pc capillary hydrostatic pressure, Pi Interstitial hydrostatic pressure, σ reflection coefficient, πc Capillary oncotic pressure and πi is the Interstitial oncotic pressure.

Based on this equation alteration in the reflection coefficient is one of the issues reflecting capillary leak and non-cardiogenic edema generation. Animal models of ARDS have suggested that a lower Pc results in a decrease in edema generation [15,16]. Two major human trials evaluating a fluid restrictive strategy for ARDS have been conducted of which the ARDS Net Fluids and Catheter Therapy Trial (FACTT trial) remains the largest multicenter trial to date [17,18] Both of these studies found no difference in the 28 day and 60 day mortalities respectively. Both studies found a significant increase in ventilator free days and less days spent in the ICU.

One of the possible untoward side effects of a fluid restrictive strategy and diuresis for ARDS is the potential for developing Acute Kidney Injury (AKI). A post hoc evaluation of the FACTT trial for AKI revealed that the occurrence of AKI was increased in the fluid liberal arm of the trial as well as a decreased survival rate in this group. Another post hoc study found that of the 306 patients in the FACTT trial that developed AKI within the first 48 hours of enrollment, those in positive fluid balance had a greater mortality. This study also found that a higher diuretic dose after AKI correlated with increased survival [18].

In addition in the same patient set as the FACTT study, it was demonstrated that the use of a Pulmonary Artery Catheter (PAC) was not necessary to treat ARDS when compared to the use of a CVP catheter [19].

Conclusion: At present a fluid restrictive strategy does not improve mortality in ARDS. However a fluid restrictive strategy can result in greater ventilator free days and fewer days spent in the ICU without compromising perfusion of other vital organs. The need of a liberal fluid strategy in the initial stages of ARDS with shock needs to continue balanced against a fluid restrictive strategy once the initial fluid resuscitation is completed. There is no role for the routine use of a PAC in the treatment of ARDS.

Corticosteroids and ARDS:

Pathologically ARDS goes through three overlapping phases of exudation, proliferation and fibrosis. The initial phase of ARDS is marked by intense inflammation with neutrophil influx and increased proinflammatory cytokine release. Thus, on a theoretical basis the application of corticosteroids should have a salutatory effect in decreasing this proinflammatory milieu and improve outcome in ARDS. Unfortunately clinical trials have had mixed results. In evaluating the role of corticosteroids for ARDS it is important to know the etiology of the ARDS under study. For example corticosteroids remain as suggested therapy for a multitude of non-infectious causes of ARDS such as acute interstitial pneumonia, hypersensitive pneumonitis, sarcoidosis, fat embolism, and post bone marrow transplant alveolar hemorrhage syndrome. However when

corticosteroid use has been studied in large scale clinical trials, incorporating all comers with ARDS, corticosteroids have not been shown to improve mortality. The ARDS net phase III trial is the largest of these clinical trials [20]. Patients with unresolved ARDS greater than day 7 were enrolled. The study found the following: 1) no survival advantage using steroids, and 2) subgroup analysis showed increased mortality and neuromuscular weakness in the patients that received their initial dose of low dose methylprednisolone (0.5-1mg/kg/day) beyond day 14. Recently a study conducted in 55 patients who received early methylprednisolone for ARDS had statistically significant shorter duration of mechanical ventilation, an improvement in the LIS, and lower intensive care unit mortality when compared to the control group. Also lower levels of interleukin-6 and increased levels of protein c were found on days 3 and 7 in the treatment arm[21].

Conclusion: At present the routine use of corticosteroids for the treatment of ARDS cannot be recommended. The use of corticosteroids in early severe ARDS and in fibrosing ARDS (before day 14) may be considered but the literature is not strong enough yet to make a firm recommendation.

PEEP and ARDS:

To date there have been 3 large scale clinical trials evaluating different PEEP strategies in ARDS. The Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury trial (ALVEOLI) compared high PEEP to low PEEP strategy for ALI. The Expiratory Pressure Study Group (EXPRESS) trial studied the effect of low PEEP to a recruitment PEEP strategy for creating the high PEEP group in patients with ALI. Finally the Lung Open Ventilation Study (LOV) used a PEEP level (higher or lower) based upon an oxygenation scale. Recently these 3 studies were analyzed in a meta-analysis that concluded that a higher PEEP strategy improved survival in the subset of patients who had ARDS. In contrast the use of high PEEP in patients with ALI without ARDS conferred no survival benefit and may actually harm patients with ALI [22].

Conclusion: At present a high PEEP strategy should be considered for use in patients with ARDS. High PEEP strategies should be avoided in patients with ALI or with mild ARDS as defined in the Berlin Criteria.

Prone Positioning:

From the earlier studies done of CT scans of the chest in patients with ARDS, it became apparent that though the disease may appear diffusely homogenous on chest x-ray on CT scan there was a gravity dependent distribution of ARDS. As patients in an ICU lie supine this distribution of ARDS was seen in the dorsal portions of the lung. Prone positioning a patient involves placing the patient on their stomach rather than back. Theoretically this should result in better gravity dependent perfusion of the relatively "normal" ventral lung and better ventilation of the dorsal lung.

However, until recently studies using prone positioning as a therapy for ARDS have not demonstrated any survival benefit. One large study actually reported an increased incidence of ET-tube displacement, and pressure sore development using prone positioning [23]. Recently a multi-center prospective trial using prone positioning for patients with severe ARDS (defined as a PAO_2/FIO_2 ratio of less than 150 mmHg) demonstrated an almost 50 % reduction in 28 day mortality (Supine 32.8% mortality versus 16% in the prone group)[24].

Conclusion: At present prone positioning is not recommended for routine use in ARDS. It should be considered rescue therapy for patients with a PAO_2/FIO_2 ratio of less than 150 mmHg [24,25]. Using prone positioning requires local expertise (both nursing and physician) to properly care for a pronated patient. Given the general lack of availability and resource requirements of other "heroic" maneuvers such as ECMO, high frequency oscillation, and nitric oxide in Pakistan, prone positioning may represent the only simple and readily available rescue maneuver that can realistically be performed here. This technique of prone positioning should be considered for use especially with the recent New England Journal of Medicine article demonstrating a significant survival benefit for patients with severe ARDS

Extra-Corporeal Membrane Oxygenation (ECMO)

First studied in the 1970s, ECMO use for ARDS was viewed as non-beneficial. However, during the H1N1 outbreak in 2009 groups in Australia and New Zealand reported good outcomes using ECMO to treat ARDS from H1N1 [26]. Of the 68 patients who received ECMO there was a 75% survival rate. Subsequently a prospective trial was done in the UK called CESAR (conventional ventilator support versus ECMO for severe adult respiratory failure). This study found that at 6 months the mortality and disability of the 90 patients that received ECMO was better than the control arm of usual ventilation (37% versus 53%, p=0.03). However this study has been criticized for 2 main reasons. 1) Twenty two patients randomized to the ECMO arm did not receive ECMO therapy, and 2) there was no specification as to what type of ventilator treatment (i.e. ARDS Net protocol) the control arm should receive [27].

Newer devices are being developed such as veno-venous ECMO, pumpless interventional lung assist (iLA) and ECMO-R (extra corporeal carbon dioxide removal) [28]. These newer devices may play a role in the future treatment of severe early ARDS. At present though, with standard ECMO use there is still a high risk of bleeding (54%) and a 9% chance of intracranial hemorrhage [3].

Conclusion: In the future Extra-Corporeal Oxygenators and CO_2 removal devices may help in the treatment of severe ARDS. At present its role in the treatment of ARDS remains investigational.

IV Beta Agonists:

The use of beta agonists in the treatment of ARDS makes some theoretical sense as beta agonists have been shown to be helpful in lung water clearance. However a recent multi-center trial called the Beta Agonists in Lung Injury Trial (BALTI 2) study demonstrated that IV beta agonist use in ARDS was associated with poor patient tolerance, was unlikely to be beneficial, and may actually pose some harm to the patient [29].

Conclusion: IV beta agonists should not be used as part of the treatment for ARDS.

High Frequency Oscillation Ventilation (HFOV)

Theoretically the use of HFOV should be useful in ARDS. If 6cc/kg works then using even lower tidal volumes at 6cc total/per breath should further limit lung trauma with mechanical ventilation. Unfortunately this has not been borne out in human trials. The Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial and the Oscillation in ARDS (OSCAR) trial results were recently published [30,31]. The OSCILLATE trial found that the application of HFOV resulted in greater deaths in the treatment arm and the study was terminated early. The OSCAR trial found no statistical significance in mortality between the treatment and control groups. In

both the OSCAR and OSCILLATE trials patients on HFOV had higher usage of sedation and neuromuscular paralysis then the control patients.

Conclusion: At present the use of HFOV cannot be recommended for routine use in ARDS. At best, HFOV may be considered as a rescue maneuver for patients with severe ARDS.

Neuromuscular Blockade Agents (NMBA):

NMBA use in ICU patients can result in prolonged paralysis from critical illness polyneuropathy, and critical illness myopathy. As awareness of this side effect of NMBA grew there was a movement away from their routine use in ARDS. The recent publication of the ACURASYS Study has started to change the prevalent opinion of avoiding NMBA use in patients with ARDS This study used cisatracurium besylate for 48 hours in the initial treatment of ARDS versus placebo [32]. The study found that the use of cisatracurium improved the adjusted 90 day survival for patients with severe ARDS (P/F ratio less than 120). The study found no difference in the development of ICU paresis between the two groups.

Conclusion: Presently the routine use of NMBAs for the treatment of ARDS cannot be recommended. The use of NMBA in patients with severe early ARDS (P/F ratio less than 120) may be considered.

Inhalation Therapies:

Nitric Oxide (NO): Nitric Oxide is a gas that when inhaled results in a decrease in pulmonary vascular pressures and improves V/Q matching. A recent Cochrane analysis of 14 trials using NO for the treatment of ARDS found no survival benefit, no change in ventilator free days and no change in ICU or hospital length of stay [33]. There is a temporary reduction in FIO_2 requirements. In addition an increased incidence of renal dysfunction was also found in the Cochrane analysis.

Iloprost: As an inhaled prostanoid, Iloprost's physiological results are similar to NO. Recently a published study demonstrated that in 20 patients with ARDS and pulmonary hypertension (defined either by ECHO or PAC) the use of Iloprost resulted in a statistically significant improvement in PaO2 [34].

Conclusion: Though not associated with improvement in mortality, the use of inhaled pulmonary vasodilators may be considered for rescue therapy to then allow other aspects of ARDS care to be implemented. However, at present these agents cannot be recommended for routine use in ARDS treatment.

Conclusion: Though there have been improvements in the management and mortality of ARDS, this disease still remains a challenging and deadly syndrome faced by critical care specialists. Adherence to the ARDS Net protocol remains the mainstay of therapy. Ongoing studies may help to better clarify new treatment options as well as improve our understanding of the exact role that existing therapies may have in the future. At present given the resource limitations of many of the above described therapies here in Pakistan, consideration should be given to the creation of prone positioning protocols to treat patients with severe ARDS. At present the Berlin Criteria and its severity scale, are the criteria that should be used to define ARDS.

References:

1) Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122(8):2731-2740

2) Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P et al. Early Identification of Patients at Risk of Acute Lung Injury. Am J Respir Crit Care Med 2011;183:462-470

3) Walkey AJ, Summer R, Ho V, Alkana P. Acute respiratory distress syndrome:epidemiology and management approaches. Clinical Epidemiology 2012:4 159-169

4) Rubenfeld GD, Caldwell E, Peabody E,Weaver J, Martin D, Neff M et al. Incidence and Outcomes of Acute Lung Injury. N Eng J Med 2005;353(16): 1685-93.

5) Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet 2010;375:1339-1346

6) Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138(3):720-723

7) Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L et al: Report of the American-European consensus conference on ARDS: definitions, mechanisms relevant outcomes and clinical trial coordination. Intensive Care Med 1994;20(3): 225-232

8) Raneri VM, Rubenfeld GD, Thompson BT: Defining ARDS: do we need a mandatory waiting period? Intensive Care Med. 2013 Apr;39(4):775-8

9) Raneri VM, Rubenfeld GD, Thompson BT et al: Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-2533

10) Thille AW, Esteban A, Fernandez-Segoviano P, Rodriguez JM, Aramburu A, Penuelas O et al Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with autopsy
Am J Respir Crit Care Med. Epub January 31, 2013: doi:10.1164/rccm.201211-19810C

11) [No authors listed.] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Eng J Med. 2000;342(18):1301-1308

12) Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Jaeschke et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.Critical Care Medicine 2013: 41(2) 580-637

13) Dreyfuss D, Saumon G: Ventilator-induced Lung Injury Lessons from Experimental Studies Am J Respir Crit Care Med 1998;157: 294-323

14) Needham DM, Colantuoni E, Mendez-Tellez PA, Dingas VD, Sevransky JE, Dennison Himmelfarb CR, et al: Lung protective mechanical ventilation and two year survival in patients with acute lung injury:prospective cohort study. BMJ Epub 2012;344:e2124 doi: 10.1136/bmj.e2124

15) Laine GA, Allen SJ, Katz J et al: Effect of systemic venous pressure elevation on lymph flow and lung edema formation. J Appl Physiol 1986;61:1634-1638

16) Allen SJ, Drake RE, Katz J et al: Elevation of superior vena caval pressure increases extravascular lung water following endotoxemia: J Appl Physiol 1987;62:1006-1009

17) Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 1992;145:990-998

18) [No authors listed] Comparison of Two Fluid-Management Strategies in Acute Lung Injury. The Acute Respiratory Distress Syndrome Clinical Trials Network. N Eng J Med. 2006;354:2564-2575

19) [No authors listed] Pulmonary-Artery versus Central Venous Catheter to Guide Treatment of Acute Lung Injury. The Acute Respiratory Distress Syndrome Clinical Trials Network. N Eng J Med 2006;354:2213-2224

20) [No authors listed] Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome. The Acute Respiratory Distress Syndrome Clinical Trials Network. N Eng J Med 2006;354:1671-1684

21) Seam N, Meduri GU, Wang H et al. Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early acute respiratory

22) Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD et al Higher vs Lower Positive End-Expiratory Pressure in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome. Systemic Review and Meta-analysis. JAMA 2010;303(9):865-873

23) Guerin C, Gaillard S, Lemasson S, Ayzac L, Girad R, Beuret P et al Effects of Systemic Prone Positioning in Hypoxemic Acute Respiratory Failure JAMA 2004;292:2379-2387

24) Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T et al Prone Positioning in Severe Acute Respiratory Distress Syndrome N Engl J Med. 2013 Jun 6;368(23):2159-68.

25) Sud S, Friedrich, Taccone P et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systemic review and meta-analysis. Intensive Care Med 2010;36(4):585-599

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

27) Combes A, Bacchetta M, Brodie D, Muller T, Pellegrino V. Extracorporeal membrane oxygenation for respiratory failure in adults. Curr Opin Crit Care 2012;18:99-104

28) Terragni P, Maiolo G, Ranieri. Role and potentials of low-flow CO_2 removal system in mechanical ventilation. Curr Opin Crit Care 2012;18:93-98

29) Smith FG, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W et al. Effect of Intravenous B-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicenter, randomized controlled trial. Lancet 2012 Jan 21;379(9812):229-235

30) Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. N Eng J Med 2013 Feb 28;368(9):795-805.

31) Young D, Lamb S, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-Frequency Oscillation for Acute Respiratory Distress Syndrome. N Eng J Med 2013 ;368(9):806-13

32) Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. N Engl J Med 2010;363:1107-1116

33) Afshari A, Brok J, Moller AM, Wetterslev. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD002787. doi: 10.1002/14651858.CD002787.pub2.

34) Sawheny E, Ellis AL, Kinasewitz GT. Iloprost Improves Gas Exchange in Patients with Pulmonary Hypertension and ARDS. Chest 2013; 144(1):55-62.

Table I: Lung Injury Score

	0	1	2	3	4
Chest X-ray: number of quadrants involved	None	1	2	3	4
PAO_2/FIO_2 Ratio	≥ 300	225-299	175-224	100-174	≤ 100
PEEP cmH_2O	≤ 5	6-8	9-11	12-14	≥ 15
Lung Compliance ml/cm H_2O	≥ 80	60-79	40-59	20-39	≤ 19

Table II: AECC and Berlin Criteria

	AECC	Berlin Criteria
Timing	Acute Onset	Within 1 week of known clinical insult or worsening Respiratory Symptoms
Chest X-ray	Bilateral Infiltrates	Bilateral opacities: Not explained by effusions collapse, or nodules
Origin of Edema	Pulmonary Artery Wedge pressure <18 mmHg or no clinical signs of Left Atrial Hypertension	Not of cardiac origin or fluid overload. Objective measurement in the absence of risk factors
Oxygenation PAO_2/FIO_2 Ratio		
Mild	PAO_2/FIO_2 ratio of 200-300 mmHg	200-300 with PEEP or CPAP $\geq$ 5 cmH_2O
Moderate	Acute Lung Injury (ALI)	100-200 with PEEP $\geq$ 5cmH_2O
Severe	$\leq$ 200mmHg (ARDS)	$\leq$ 100 with PEEP $\geq$ 5 cmH_2O