# Acute respiratory distress syndrome (ARDS): An evidence-based management

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**Abstract**

Acute respiratory distress syndrome (ARDS) is a common acute respiratory failure problem in critically ill patients, with mortality rates of approximately 40.0% and causing long term morbidity in survivors. ARDS has been defined as Berlin definition and may modify in resource constrained settings. Various etiologies can induce lung inflammation and leading to the diffuse pulmonary edema that defines ARDS. The main treatment consists of specific correct lung injury etiology and support in critical illness that must be undertaken simultaneously. Several supportive strategies which are lung-protective ventilation, prone positioning and neuromuscular blocking agent in order to facilitate mechanical ventilation show a significant reduction in mortality. Currently, ARDS management shifts toward prevention and early treatment which are likely to reduce the incidence and burden of this syndrome.

**Keywords:** acute respiratory distress syndrome, acute respiratory failure

## Introduction

Ashbaugh and colleagues first described acute respiratory distress syndrome (ARDS) in 1967. They found acute condition which developed rapidly in 12 patients with pulmonary edema from various predisposing events. These patients shared 2 common major clinical symptoms which were refractory hypoxemia and decreasing in lung compliance. In consequence of lung inflammation, a leakage of cells, protein and fluid from vessels to alveoli occurred while alveolar surfactant decreased. Such pathophysiology was defined as diffuse alveolar damage (Ashbaugh, Bigelow, Petty, & Levine, 1967). ARDS has been widely recognized from this study and its diagnostic criteria have been defined according to the better understanding of pathogenesis. This progress results in the development of an expanded definition of ARDS in 1988, the American-European Consensus Conference (AECC) in 1994, and the latest Berlin definition, developed in 2012, proposing 3 categories depending on severity of hypoxemia which are associated with mortality rates as shown in table 1 (Ranieri et al., 2012).

Although ARDS has been recognized for over 50 years and has definite diagnostic criteria, its epidemiology is unclear, and it carries a high mortality and morbidity burden. In this article, clinical data of ARDS epidemiology, prevention and current treatment are collected under evidence-based study design.

### Epidemiology

Worldwide incidence of ARDS is 1.5-79 per 100,000 population, varying in different regions depending on diagnosis and report cases (Brun-Buisson et al, 2004). Two most common risk factors of ARDS are pneumonia and sepsis; common risk factors are shown in table 2 (Bellani et al, 2016). Diagnosis complying with the Berlin definition may not be made generally, especially in low-income countries. Hence, it is underreported and has very low incidence. A study in Rwanda was done to modify the diagnosis criteria according with the Berlin definition with the provided resources, known as Kigali modification of Berlin definition: without requirement for positive end expiratory pressure, hypoxia cut-off of pulse oxygen saturation

ratio and inspired oxygen fraction ($SpO_2/FiO_2$) less than or equal to 315, and bilateral opacities on lung ultrasound or chest radiography. Severity of ARDS could not be categorized as in Berlin definition but it was found that more cases were diagnosed with ARDS; its incidence also significantly increased (Elisabeth et al., 2016). Another study in intensive care unit (ICU) in 50 countries, the period prevalence of ARDS was 10.4% of ICU patients, or 23.4% of ICU patients who required mechanical ventilation. Its incidence was 0.27-0.57 per ICU bed occupancy in a period of 4 weeks. A medical record review in the study revealed that only 60.2% of patients who met criteria of the Berlin definition were diagnosed with ARDS. Currently, the factors that lead detection and diagnosis of ARDS include: close attention of nursing and medical staffs; young patients; severe hypoxemia; history of having pneumonia or pancreatitis. Some patients with ARDS were not properly diagnosed and treated. This may be a result of its high mortality rate of 40.0%. The mortality rate is associated with severity categories: mild, moderate and severe of which 28-day mortality rates were 29.6, 35.2 and 40.9% respectively. The patients who survived and discharged from ICU usually had physical and mental effects. Six-month to 2-year follow-ups disclosed that most of the patients had decreased physical functions (physical SF-36 score), of which 22.0-24.0% developed post-traumatic stress disorder (Biehl et al., 2015), 26.0-33.0% had depression, 33.0-44.0% experienced anxiety attacks (Bienvenu et al., 2015) and 46.0-80.0% had cognitive dysfunction (Sensen, Braune, Heer, Bein, & Kluge, 2017).

**Table 1** ARDS Diagnosis criteria according to Berlin definition and Kigali modification of Berlin criteria

| Characteristics | Berlin definition, 2012 | | | Kigali criteria |
|---|---|---|---|---|
| Timing | Within 1 week of a known clinical insult | | | |
| Severity | Mild | Moderate | Severe | - |
| $PaO_2/FiO_2$ (mmHg) | 201-300 and | 101-200 and | $\leq$ 100 and | $SpO_2/FiO_2 \leq 315$ |
| PEEP/CPAP ($cmH_2O$) | PEEP/CPAP $\geq$ 5 | PEEP $\geq$ 5 | PEEP $\geq$ 5 | No PEEP requirement |
| 28-day mortality rate (%) | 29.6 | 35.2 | 40.9 | - |
| Cause of pulmonary edema | Not fully explained by cardiac failure or fluid overload (Need objective assessment, such as echocardiography, to exclude) | | | |
| Chest imaging | CXR or chest CT show bilateral opacity(edema) which should not be fully explained by effusions, lobar or lung atelectasis, or nodules or masses | | | CXR or lung U/S show bilateral pulmonary edema |

$PaO_2/FiO_2$: ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, $SpO_2/FiO_2$: ratio of pulse oximetric saturation to the fraction of inspired oxygen, PEEP: positive end-expiratory pressure, CPAP: continuous positive airway pressure, CXR: Chest x-ray, CT: computer tomography, U/S: ultrasonography, mmHg: millimeter of mercury.

**Prevention**

Though ARDS has been studied extensively and its treatment guideline is implemented, morbidity and mortality rates are still high. Therefore, concepts of prevention from its occurrence and complications are recognized and established. Established ARDS prevention is classified by its different epidemiology as (Hemang, Taylor, & Gajic, 2017):

1. Primary prevention: avoiding or reducing risk factors in patients who are unaffected by ARDS or unexposed to its risks. Preventions which are tentatively advantageous are: lowering risks of pneumonia development by giving influenza and/or pneumococcal vaccines in those with indication, restrictive transfusion of blood or its components to reduce the risk of transfusion associated lung injury, and following patient care guideline to prevent aspiration which may induce aspiration pneumonia, etc.

2. Secondary prevention: early identification of patients at high risk of ARDS before the development of the full syndrome. This can be made by ARDS prediction tools such as evaluation of patients with lung injury using a studied checklist or Lung Injury Prediction Score (LIPS) as demonstrated in table 3 (Gajic et al., 2011). In observational study over 8-year period, identification of hospitalized patients at risk together with avoidance of additional risks of iatrogenic exposures such as high tidal volume (Vt), fluid over-replacement, unnecessary transfusion and inadequate septic control. These strategies were found to significantly reduce the hospital incidence of ARDS (Guangxi et al., 2011).

3. Tertiary prevention: avoiding and lowering complications or negative health effects in those with ARDS by following treatment guidelines to increase survival, restore mental and physical health, and promote quality of life after illness. The prevention may include proper ventilation appliance to reduce ventilator-induced lung injury (VILI), reducing ventilation duration by frequent evaluation and weaning off, rehabilitation with physical therapy, using guideline to lower risk of delirium, prevention of nosocomial infections, and palliative treatment of other systems. These cares should be performed regularly or assigned in a daily checklist (Hemang et al., 2017).

**Treatment**

Treatment of ARDS consists of specific correct lung injury etiology: giving proper antibiotics to treat pneumonia, controlling infection in septic patients, and supportive treatment without complications or with minimal effects to other organs.

**Ventilation in ARDS**

Ventilation is a supportive treatment to alleviate ARDS symptoms in order to promote enough gas exchange. The followings are evidence-based ventilation practice guidelines:

**Non-invasive support**

Initial approach in selected patients with ARDS, non-invasive support can be given, along with close monitoring, are sufficient to avoid more invasive support, intubation. From recent study, Frat and colleagues (2015) found that in case of hypoxemia where ratio of partial pressure of arterial oxygen and fraction of inspired oxygen ($PaO_2/FiO_2$) less than or equal to 300 mmHg, and without hypercarbia; it was found that ventilation using high-flow nasal cannula (HFNC) could improve survival, compared with those with facemask non-invasive ventilation (NIV). In case of inability to use NIV, it may be due to severity of pathology, patient noncompliance or technical problem using interface. In comparison of effectiveness of various types of interfaces, it was found that helmet NIV in ARDS ($PaO_2/FiO_2 \leq 250$ mmHg) gave a

favorable result and helped decrease chance of intubation better than facemask NIV did (Patel, Wolfe, Pohlman, & Kress, 2016).

There are supporting data about NIV in mild to moderate ARDS, using HFNC or helmet NIV. Patients with mild to moderate ARDS in which NIV with HFNC or helmet NIV were applied were more cooperative and technical problem was lesser, comparing to using NIV with other devices. Indicators of favorable response of the patients to the devices are: improved oxygenation, slower respiratory rate and better resting. Those with unstable conditions while applying NIV have rapid shallow breathing where rapid shallow breathing index (RSBI) is above 105 breaths/minute/liter, or deep breathing where tidal volume is over 9.5 milliliter (ml)/kilogram (kg) of predicted body weight (PBW). These indices can predict the failure of assisting ventilation. Dyspnea or high tidal volume can provoke irrelevant trans-pulmonary pressure (PL) which increases risk of lung injury (Patel et al., 2016). Other techniques should be considered.

**Table 2** Common risk factors of acute respiratory distress syndrome (ARDS)

| Direct lung-injury risk factors | Indirect lung-injury risk factors |
|---|---|
| Pneumonia | Non pulmonary infection |
| Aspiration | Non cardiogenic shock |
| Pulmonary contusion | Multiple trauma |
| Inhalation injury | Blood products transfusion |
| Pulmonary vasculitis | Pancreatitis |
| Near drowning | Major burn |

**Table 3** Lung injury prediction (LIP) score

| Predisposing Conditions | LIP scores |
|---|---|
| Shock | 2 |
| Aspirate | 2 |
| Pneumonia | 1.5 |
| Sepsis | 1 |
| High risk surgery* | |
| Aortic vascular | 3.5 |
| Cardiac | 2.5 |
| Acute abdomen | 2 |
| Spine | 1 |
| High-risk trauma | |
| Traumatic brain injury | 2 |
| Inhalation injury | 2 |
| Near drowning | 2 |
| Lung contusion | 1.5 |
| Multiple fractures | 1.5 |
| Risk modifiers | |
| $FiO_2$ > 0.35 (> 4 liter/minute) | 2 |

**Table 3** (Cont.)

| Predisposing Conditions | LIP scores |
|---|---|
| Dyspnea (respiratory rate > 30breaths/minute) | 1.5 |
| Acidosis (pH < 7.35) | 1.5 |
| Alcohol abuse | 1 |
| Obesity (BMI > 30 kilogram/meter$^2$) | 1 |
| Low serum albumin level | 1 |
| During chemotherapy session | 1 |
| $SpO_2$ < 95% | 1 |

*In emergency surgery, add on 1.5 marks, LIP: lung injury prediction score, BMI: body mass index, $SpO_2$: oxygen saturation by pulse oximetry. LIP points $\geq$ 4 marks considered as at risk of acute lung injury or acute respiratory distress syndrome with sensitivity 69.0% and specificity 78.0%

**Invasive Mechanical Ventilation (IMV)**

Conditions of most patients with ARDS usually deteriorated in dyspnea as well as hypoxemia, or unstable vital signs. IMV is usually selected in most cases, despite life-saving, it could be complicated by ventilation-induced lung injury (VILI). In ARDS, the size of functional alveoli in varying regions are non-homogeneous, depending on whether pulmonary edema taken place in the regions. As a result, overall respiratory volume and lung compliance diminished, so-called "baby lung" (Gattinoni et al., 2016). Mechanical ventilation is to assist or control breathing with tidal volume expanding by pressure gradient (trans pulmonary pressure; PL), but raising stress to the lung surface can lead to lung damage or baro-trauma. In general, PL is calculated from a difference between airway plateau pressure (Pplat) and pleural pressure (Ppl). Total volume of alveoli in unstressed condition is functional reserve capacity (FRC). During inhalation, Vt expands lung volume from resting stage; strain rises, making change to lung morphology. Excessive strain may result in lung injury, called volume-trauma. Strain is associated with fraction between Vt and FRC (Strain = Vt/FRC). In the regions where alveoli are closed or having low volume, they may repetitively open and close, responding to the respiratory cycle. Stress and shear produced in the regions, resulting from repetitive closing and opening of the alveoli, may cause a damage to the lungs, called atelec-trauma (Henderson, Chen, Amato, & Brochard, 2017). VILI that occurs during respiration triggers production of inflammatory mediators in injured regions, then they will be released into blood circulation, resulting in multiple organ dysfunction syndrome, so-called bio-trauma. When it happens, survival rate becomes poor (Curley, Laffey, Zhang, & Slutsky, 2016).

**Lung-Protective Ventilation**

Lung-protective ventilation is ventilation with Vt less than 6 ml/kg PBW, thought to be the same volume as baby lung. It is applied in any patients with ARDS to decrease strain and maintain Pplat to not over 30 centimeter of water ($cmH_2O$), aiming for stress reduction to prevent VILI. It can significantly lower mortality rate (Brower, et al. 2000). At present, there is a tendency to encourage ultra-protective ventilation by cutting down Vt to 4 ml/kg PBW, and Pplat not to over 25 $cmH_2O$, in order to prevent VILI as much as possible (Retamal et al., 2013). Closing of alveoli (atelectasis) may occur in ventilation with lower Vt, and gas exchange might be insufficient, resulting in hypoxemia. It, however, could be corrected with higher positive end-expiratory pressure (PEEP) to retain opening of alveoli. Hypercapnia may also be found, but could be

corrected by carbon dioxide washout with extracorporeal techniques, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal membrane carbon dioxide removal ($ECCO_2R$) to assist in ultra-protective ventilation (Fanelli et al, 2016). Concerning occurrence of inhomogeneous aeration in ARDS, using PBW value to predict Vt is questioned whether it is relevant to actual Vt the patients should have, depending on individual's functional size of the lung. Therefore, it may be insufficient to prevent VILI. Vt is directly proportional to respiratory system compliance (Crs), while in patients with assist ventilation, Crs is inversely proportional to ventilator driving pressure ($\Delta P$) as in the following equations:

$\Delta P = Pplat - PEEP$

$Crs = Vt / \Delta P$

It was also found that the ventilation in patients with ARDS whose $\Delta P$ was over 15 $cmH_2O$ was related to significantly higher mortality rate (Amato et al., 2015).

As aforementioned, Pplat should not exceed 30 $cmH_2O$ to avoid too high PL which may lead to VILI. In the present clinical practice, absolute PL can be derived from the equation:

PL = Pplat – Ppl

while Ppl can be replaced with pressure measured with esophageal manometer at the right position. PL is stress on alveoli

(PL = stress) and is directly proportional to lung elastance (EL) and strain; hence,

PL = EL x strain.

It is acknowledged that PL not over 22-23 $cmH_2O$ during expiration can lower incidence of VILI (Talmor et al., 2008).

**PEEP and Lung Recruitment**

Lung recruitment is opening lung technique by using transient high inspiratory airway pressures within 1-2 minutes to open the closed alveoli to be able to exchange gas, while applying appropriate PEEP helps keep opened alveoli open. With these, occurrence of atelec-trauma is lowered (Suzumura, Amato, & Cavalcanti, 2016).

In lung-protective ventilation, alveoli are prone to be closed, so high PEEP is needed to correct hypoxemia, and it also can reduce $FiO_2$ use. Applying PEEP in case of recruitable lung does not elevate Pplat; on another hand, it helps lower $\Delta P$ (Pplat – PEEP) and prevent VILI; survival is also improved. Nevertheless, in case of non-recruitable lung with opened alveoli, using high PEEP may lead to alveolar over-distension which may induce VILI. In this group of patients, Pplat and $\Delta P$ rise when adding PEEP (Goligher et al.,2014).

It was also found that higher PEEP which helped correct hypoxemia did not improve overall survival of ARDS (Kasenda, et al. 2016); in some studies, it even raised mortality rate (Cavalcanti et al, 2017).

The proportion of potentially recruitable lung in ARDS remarkably varies. It was also strongly associated with the response to PEEP (Gattinoni et al, 2006). There was a study revealing that approximately 50% of all patients with ARDS gained benefits from lung recruitment together with high PEEP application (Grasso et al, 2005). These patients were classified as PEEP responders. On the contrary, high PEEP application in non-responders may increase intra-thoracic pressure and pulmonary vascular resistance, possibly followed by right ventricular and circulatory failures. Lung recruitment and using high PEEP in ARDS should be considered corresponding to patients' response. Among responders, PEEP level should be just sufficient to open alveoli

without over-distension, to reach optimal respiratory system compliance and lessen $\Delta P$ without impact to circulatory system. Limitation of PL during expiration can be used to indicate optimal level of PEEP (Talmor et al, 2008).

## Modes of Ventilation

### Conventional Modes

Generally, ventilator modes used in setting of ARDS include volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV). Both modes give equivalent results (Rittayama et al., 2015). According to expert opinion, Vt can be set to comply with lung-protective ventilation where respiratory mechanics and $\Delta P$ are measurable in VCV. This is practical to evaluate patients, particularly in the early stage of illness. While in PCV, Vt cannot be guaranteed, but patients tend to feel more comfortable as inspiratory flow rate can be given corresponding to their requirement, promoting optimal synchrony between their respiratory effort and ventilator. This is practical when they are encouraged to breathe or while weaning from mechanical ventilation (Chiumello et al., 2017).

### Non-Conventional Ventilator modes

Other modes of ventilation studied in ARDS include high frequency ventilation and airway pressure release ventilation (APRV). High frequency ventilation uses low volume of Vt and more frequent ventilation is exploited to keep peak inspiratory pressures (PIP) and PL low, expected to promote gas exchange and prevent VILI.

There are some reports of use of high frequency oscillator ventilation (HFOV) that indicates Vt and high frequency percussive ventilation (HFPV) that determines PIP. It was found that gas exchange was improved but mortality rate was unchanged (Sud et al., 2016), or even higher in some studies (Meade et al., 2017) . Hence, this technique is not yet recommended as a guideline of ventilation in patients with ARDS but considered as an alternative in case of very severe hypoxemia ($PaO_2/FiO_2 \leq 64$ mmHg) that does not well respond to other techniques (Meade et al., 2017).

Airway pressure release ventilation (APRV) is another technique which allows spontaneous breathing by using 2 levels of continuous positive airway pressure (CPAP): high and low. High CPAP (high P) is selected in alveolar recruitment while low CPAP (low P) boosts alveolar ventilation by airway pressure reduction. Administration of APRV together with lung-protective strategy in patients with ARDS is expected to improve their ventilation-perfusion (V/Q) matching. Spontaneous breathing in optimal ventilation can cut use of sedatives and muscle relaxants, owing to synchrony between patient's respiratory effort and ventilator. Not only airway pressure decreases, but pressure in the thoracic cavity also lowers, leading to an increase in venous return and cardiac output (Mireles, & Kacmarek, 2016). Until now, however, there are not enough data to support that the use of APRV would lower mortality rate in patients with ARDS (Gonzalez et al, 2010). In addition, there is a tendency of increasing in the number of days that patients require ventilatory support (Maung, & Kaplan, 2011).

**Targets of treatment in patients with ARDS**

**Arterial $O_2$ tension ($PaO_2$)**

Optimal $PaO_2$ or arterial oxygen saturation ($SaO_2$) in ventilation which gives best results are still unclear. Prolonged hypoxemia may affect neurocognitive function in survivors (Mikkelsen et al, 2012). On the other hand, hyperoxemia ($PaO_2 \geq 120$ mmHg) in critically ill patients has a negative impact on survival rate (Girardis et al, 2016). Hyperoxia is also an independent risk factor and has a direct relationship with ventilator-associated pneumonia. Maintaining level of $PaO_2$ or $SaO_2$ in ARDS can be done by adding inspired oxygen concentration ($FiO_2$) and/or leveling up PEEP. However, from the evidence, prolonged administration of high ratio of $FiO_2$ may produce pulmonary $O_2$ toxicity from oxidative stress which may end up with lung inflammation or VILI. Applying $FiO_2$ of over 0.6 may increase risk of additional inflammation in existing lung pathology as of patients with ARDS (Neil, Aggarwal, & Roy, 2014). Most studies of ventilation in ARDS suggested optimal level of oxygenation at $PaO_2$ of 55-80 mmHg or $SaO_2$ of 88-95% (Brower et al., 2000). Even so, $PaO_2$ and $SaO_2$ upper target limits are usually seen most patients as most physicians focus on complications of hypoxia rather than risk of hyperoxia.

**Arterial $CO_2$ Tension ($PaCO_2$)**

Hypercapnia with or without respiratory acidosis in ARDS has pros and cons. It has anti-inflammatory effect (Curley, Hayes, & Laffey, 2011), assists with circulation in certain regions and encourages the matching of V/Q, as well as oxygen transport to the cells; while it deteriorates alveolar fluid clearance as well as cellular wound healing, and may cause acute cor-pulmonale (Mekontso et al., 2009). Moderate respiratory acidosis is an independent factor which improves 28-day mortality (Kregenow, Rubenfeld, & Hudson, 2006); while $PaCO_2$ of over 50 mmHg is an independent factor that increases mortality (Nin et al., 2017). This a paradoxical outcome. Currently, permissive hypercarbia is acceptable in low lung volume protective ventilation but safety data are still limited. Recommended $PaCO_2$ level in ARDS is that can maintain blood pH at 7.30-7.40 (Peter, Salvatore, & Alain, 2017).

**Extracorporeal Lung Support (ECLS)**

ECLS is a type of cardiopulmonary bypass by circulating blood back and forth between patient and the machine which acts as a lung to eliminate $CO_2$ or add $O_2$, aimed to correct hypercarbia and hypoxemia. ECLS techniques administered to patients with ARDS are extracorporeal membrane oxygenation (ECMO) and extracorporeal $CO_2$ removal devices ($ECCO_2R$).

Extracorporeal membrane oxygenation (ECMO) is a technique where ECMO pump is used to generate high blood flow for oxygenation. In general, veno-venous (VV) ECMO is widely used but in case of coexisting cardiac failure, veno-arterial (AV) ECMO may be chosen.

Extracorporeal $CO_2$ removal devices ($ECCO_2R$) is a bypass without using a pump. Low blood flow is enough for $CO_2$ removal. It is mostly used to correct hypercarbia during administration of lung protective or ultra-protective lung ventilations (Alain, Antonio, & Marco, 2017).

Indication to use ECMO is different in each study. Mostly, it was selected to use in severe ARDS where other ventilation techniques were not applicable, or to use together with ultra-protective lung ventilation under consideration of risks and benefits (Fanelli et al., 2016). It was found that administration of VV ECMO from

the beginning in patients with severe ARDS was able to lower mortality rate, but extend durations of ventilation and hospitalization. Because of its potential complications, operation by specialists is advisable.

**Prone Positioning**

Prone positioning has beneficial effects on redistribution of lung densities, recruitment of collapsed alveoli and stress redistribution, which might improve oxygenation and prevent VILI. In those whose $PaO_2/FiO_2$ was less than 150 mmHg, prone positioning for at least 16 hours per day during ventilation was able to improve oxygenation and lower mortality rate (Guerin et al., 2013). Its contraindications include: open wound on the abdomen, injury or fracture of vertebral column, increased intracranial pressure and unstable blood circulation. Prone positioning should be done under care of experienced and specialized personnel.

**Neuromuscular Blocking Agents**

Administration of neuromuscular blocking agents during lung-protective ventilation is able to facilitate the synchrony between patient's respiratory effort and ventilator to avoid dyspnea, high $\Delta P$ and VILI as a consequence (Guervilly et al., 2017).

In moderate to severe ARDS ($PaO_2/FiO_2$ <150 mmHg), administration of neuromuscular blocking agent, cisatracurium, within the first 48 hours helped reduce 28-day mortality rate and incidence of barotrauma significantly, without decrease in muscle power referring to medical research council muscle power scale (Papazian et al., 2010).

Data of use of neuromuscular blocking agents, other than cisatracurium, are still unclear. Consideration should be made when using neuromuscular blocking agents containing steroids, such as vecuronium, as they delay recovery of neuromuscular function after discontinuation (Prielipp et al., 1995) and may aggravate muscle weakness (Sessler, 2013).

## Medical Treatment

Medical treatment does not clearly affect the mortality rate, and may add side effects to the patients; therefore, it is not recommended in general; but some agents expected to have positive physiological effects have been studied:

Inhaled nitric oxide; selective pulmonary vasodilators, lowers pulmonary hypertension and may temporarily correct hypoxemia; but it may cause methemoglobinemia or acute renal failure (Gebistorf et al., 2016).

Corticosteroids; they have anti-inflammatory effect on the lung injury. Even though methylprednisolone is unable to prevent ARDS, it may help improve oxygenation in ARDS caused by pneumonia without effect on the mortality rate (Peter et al., 2008). In some studies, mortality rate is likely to increase when methylprednisolone is started 2 weeks after the onset of ARDS (Steinberg et al., 2006).

Aspirin and Statins; they can prevent vessel injury, thought to also be able to prevent lung vessel damage which may cause pulmonary edema and ARDS. However, there is no evidence to support use of aspirin or statins, in terms of ARDS prevention (Xiong et al., 2016).

**Fluid Restriction**

Fluid restriction to keep central venous pressure (CVP) below 4 mmHg and pulmonary artery occlusion pressure (PAOP) less than 8 mmHg, is able to increase ventilator and ICU free days without increase in other organ failures, while mortality rate is unchanged (Grissom et al., 2015).

**Nutritional Support**

A selection of enteric tropic feeding within the first 6 days after onset of ARDS or early administration of full calorie enteral nutrition have no effect on the mortality rate. However, enteric tropic feeding has less gastrointestinal intolerance (Rice, Wheeler, & Thompson, 2012). Whereas anti-oxidants provide no clear benefits (Raghavendran et al., 2008).

## Conclusion

ARDS has been recognized and studies for over 50 years, its mortality rate is still high. It also has an extensive physical impact on the survivors. This may be because some patients are under- or misdiagnosed, and receive improper treatments. At present, The Berlin definition or other modified criteria, implemented depending on existing resources, should be focused to look after the patients at risk. Treatments that may decrease the mortality rate include: lung-protective ventilation which should be administered in every patient with ARDS, Prone positioning during ventilation and/or use of neuromuscular blocking agents in ARDS with severe hypoxemia ($PaO_2$/Fi $O_2$<150 mmHg). Concepts of prevention now become accentuated. Various prevention guidelines are effective to prevent ARDS or alleviate its severity.

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