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Editorial

ARDS: Advances in Therapeutic Management

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Acute Respiratory Distress Syndrome (ARDS) by the latest Berlin definition agreed that ARDS is "a type of acute diffuse, inflammatory lung injury, to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (ie, edema, inflammation, hyaline membrane, or hemorrhage)" [1]. ARDS mortality remains high despite new advances in therapy. ARDS accounts for 10.2% of Intensive Care Unit (ICU) admissions in fifty different countries [2].

Sepsis is the leading cause of ARDS. With the new clinical definition for sepsis, it remains to be seen how the new guidelines could impact the analysis of the data, especially sepsis-induced ARDS, with the inclusion of the quick Sequential Organ Failure Assessment (qSOFA) score. For diagnosing sepsis in a patient, at least two qSOFA criterions must be met: altered mental status, RR > 22/min, systolic blood pressure < 100 mmHg [3]. These parameters were taken from one million electronical records to find the variables that predict organ failure with a life-threatening dysregulated host response of the body to an infectious process. Initial Systemic Inflammatory Response Syndrome (SIRS) parameters were arbitrarily selected in an effort to use a guidance tool for diagnosis. There have been reports of septic patients that do not fulfill the SIRS nor the qSOFA criteria. However, the merit of quantification and demystifying the art of medicine are important approaches to know the variables involved in the syndrome.

In the 2012 Berlin classification, ARDS was separated into three different groups: mild, moderate and severe. Mortality and severity were proportional in the classification system [1]. In particular, severe ARDS carries a high mortality, and is the group that had promising interventions in recent randomized controlled trials to be discussed in this editorial. After the Positive End Expiratory Pressure (PEEP) maneuver was first published in 1967 for improving oxygenation, the lung protective strategy was established in 2000, reducing the tidal volume to prevent lung damage in severe ARDS [4-7].

At the end of the spectrum of treatment in ARDS is the use of Extracorporeal Membrane Oxygenation (ECMO). With the introduction of ECMO in 2009, refractory ARDS patients now have an average previously had a very high hospital mortality rate now have a survival rate of 55 - 65% [8].

An expert group of investigators recommend the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score on the basis of a large cohort with external validation. The RESP score objectives are to benchmark outcomes, to interpret variation in practice and to inform clinicians and families of the possible outcomes for severe ARDS patients treated with ECMO. It may be calculated at the following site: www.respscore.com. The RESP score may help future studies determine when, how and on whom to perform ECMO [8].

Recently, lung protective maneuvers are utilized using the ECMO to decrease the tidal volume in the management of ARDS in multiple referral centers [8]. In a recent publication, the value of driving pressure measurement was found to be the only predictor of survival of multiple physiological variables in patients with ECMO and ARDS despite achieving lower plateau pressures, tidal volume size, PEEP, driving pressure levels, respiratory rate, minute ventilation, higher arterial PaO_2/FIO_2, higher arterial PH and lower $PaCO_2$ levels. Higher age, male gender and lower body mass index were independently associated with mortality [8].

A previous study showed correlation with mortality with higher driving pressure values (Driving pressure= Plateau pressure-PEEP) [9]. Manipulation of tidal volume and PEEP to achieve a low driving pressure improving ARDS survival outcomes has to be demonstrated. Airway pressure release ventilation (APRV) to allow small tidal volumes and keep functional ventilation is a modality used by many centers who treat ARDS that makes sense but its effects in mortality need to be validated by RCT [10].

Besides ventilator management, fluid restriction conservative strategy like the one found in the Fluid and Catheter Treatment Trial (FACCT) had been correlated with decreased mechanical ventilation days and ICU length of stay without a change in 60 day mortality [11]. Low aldosterone levels correlates with improved fluid resuscitation outcomes and mortality with the plasma analysis of the FACCT trial patients [12].

ARDS subphenotypes respond differently to randomized fluid management strategy. The latent class model the hyperreactive phenotype 2 had higher IL-6, IL8, soluble TNF levels with high prevalence of shock, lower serum bicarbonate and a higher prevalence of sepsis compared to the subphenotype [1]. Fluid management strategy had significantly different effects on 90-day mortality in the two subphenotypes; mortality in subphenotype 1 was 26% with fluid conservative strategy vs 18% with fluid liberal, while mortality in subphenotype 2 was 40% with fluid conservative strategy versus 50% in fluid liberal [13]. Interestingly, the subphenotype 2 had fewer ventilator days and multiple organ dysfunction days but higher mortality and showed good response to a high level of PEEP [14]. It seems that personalized medicine is coming to ARDS.

Deresuscitation negative fluid balance approach with diuretics or renal replacement therapy after initial successful resuscitation efforts is a logical step toward achieving homeostasis after critical illness. A recent meta-analysis showed decrease in ICU length of stay and ventilator free days in ICU in ARDS but its effect on mortality remain unanswered in that particular study [15]. Positive fluid balance is associated with higher mortality in sepsis.

A different population of ARDS are the hematological patients. Better survival is associated with recovery of neutropenia and early detection of the microbial agent [16]. A novel approach of a helmet Noninvasive Positive Pressure Mechanical Ventilation (NPPV) improved the mortality in immunocompromised patients avoiding intubation. Helmet NPPV was superior to face mask NPPV with less complications and better tolerance in ARDS [17]. Intubation is associated with increase mortality in this population increasing ventilator associated pneumonia events.

Pharmacologic agents play a special role in ARDS [18]. Sedatives, opiates, paralytic agents, antimicrobial agents are used by necessity in mechanically ventilated patients in a non-specific way. Linezolid clearance increased by 82% in ARDS patients raise concerns of super infection with *Staphylococcus aureus* and *streptococcus pneumonia* in around 25% of reported influenza pneumonia cases [19,20]. Methicillin Resistant *Staphylococcus aureus* (MRSA) prevalence is increasing the international community. Long term mental and physical impairment in mechanically ventilated patients and superiority of non-benzodiazepine regimens is well known [21-23]. Optimization of non-specific and antimicrobial pharmacotherapy is an issue that should be addressed as the number of survivors increase in the future.

The evidence of other approaches used in the past has not be encouraged in several guidelines in the international community by the data in terms of survival improvement [24,25]. The following interventions are examples of lack of survival benefit in adult patients: inhaled nitric oxide, High Frequency Oscillation Ventilation (HFOV), systemic corticosteroids, statins, beta adrenergic receptor agonists and specific nutritional supplementation with some arguments left for discussion about the benefits in ICU length of stay and ventilator free days in some cases. Specifically, nitric oxide studies showed an increase incidence of acute renal failure and the use of renal replacement therapy [26-32].

There are several trials underway that include interferon beta, cell based therapies (mesenchymal/stromal stem cell therapy) and other biological agents [33,34]. A discovery of a new family of Stretch-Activated-ion Channels (SAC) identify a link between mechanotransduction molecules and Ventilator Induced Lung Injury (VILI) as a potential therapeutic target for ARDS [35].

As the number of survivors of ARDS increase, probably newer complexities are going to be seen. The evolution of ARDS management is a direct consequence of new discoveries in management of sepsis, specific interventions in mechanical ventilation with extracorporeal circulation and pharmacotherapy. Promising biological therapies are being the target of several phases in clinical trials as an expected approach to decrease the mortality and mental disability caused by ARDS.

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