Editorial

ARDS treatment strategies: after half a century do we still need guidelines?

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Acute respiratory distress syndrome (ARDS) is a very serious form of respiratory failure due to multifactorial causes whose mortality reaches up to 45%.

The ARDS's pathophysiological and anatomical characteristics result in severe refractory hypoxia to conventional treatment with oxygen and a collapse of large lung areas that thus can not participate in gaseous exchanges, greatly reducing the lung's compliance.

Various etiologies may induce an inflammatory process in the pulmonary parenchyma. In some patients, inflammation spreads throughout the lungs, leading to diffuse edema that causes severe ARDS (1). Dependent lung regions tend to collapse under the weight gain of the pulmonary parenchyma (2) and only non-dependent lung regions remain open for ventilation.

Non-ventilated, gas-free regions and reduced lung size are the two anatomical bases of the two major ARDS symptoms: oxygen-refractory to the inspired oxygen fraction (FiO_2) (3) and decreased pulmonary compliance (4).

Therefore, the main feature in ARDS is the development of a major inflammatory edema of the pulmonary parenchyma, which results in an important reduction in the respiratory exchange surface and an increase in the weight of the lung itself. Clearly, since there are multifactorial etiologies and different causes to determine ARDS, etiologic therapy is very complicated, and it is still important to remove the triggering causes.

Therefore, ARDS therapy remains a symptomatic therapy, but it also closes the pitfalls of the side effects of the therapy itself. Other non-specific treatments to fight lung inflammation have been ineffective both in terms of symptoms and impact on outcomes (5).

The hinges of the treatment are, on the one hand, mechanical ventilation in an attempt to improve gaseous exchanges, and on the other hand keep the lung open to avoid alveolar collapse.

As the presentation of ARDS is so heterogeneous, it becomes crucial to differentiate the etiology in order to carry out targeted treatment, and above all to identify the phase and severity of ARDS itself.

Various parameters were evaluated to differentiate the severity of ARDS, some based on hypoxia related to FiO_2, positive end-expiratory pressure (PEEP), ventilatory mechanics. Others are based on lung imaging (CT scan), measurement of extravascular lung water, etc.

An attempt to rationalize ARDS in a severity rating is given by the Berlin Classification (6) that foresees a mild, moderate, and severe ARDS differentiation based on the PaO_2/FiO_2 ratio <300, 200 and 100 with PEEP of 5 cmH_2O.

Based on the severity of ARDS, the treatment will be different from the point of view of ventilation strategies and the use of extracorporeal aids.

Despite extensive literature on ARDS both experimental and clinical, the effects of proposed therapies on mortality

are not comforting.

Some therapies are absolutely indispensable, such as mechanical ventilation, and others absolutely to be abandoned and avoided altogether.

In such a varied situation, attempting to fix, in a sequence of points, ARDS therapy is crucial in order to standardize the treatment and make it the same in any situation where ARDS is present with those severity characteristics.

The recent guideline (7) (an Official American Thoracic Society/European Society of Intensive Care Medicine/ Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome) seeks precisely to determine the priorities of ARDS treatment, identifying the therapies, according to EBM, that can positively modify the outcome of the patients.

In this guideline, a multidisciplinary panel conducted systematic reviews and meta-analyses of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology for clinical recommendations.

Scientists, gathered on several occasions, discussed the results of current literature on ARDS and described some of the findings of the literature as strong or weak, and therefore either strongly recommended, suggested or advised some therapies.

These therapies were conditioned by the clinical context and the individual patient and deserve special attention from the clinician.

The panel formulated and provided the rationale for recommendations on selected ventilatory interventions for adult patients with ARDS. Clinicians managing patients with ARDS should personalize decisions for their patients, particularly regarding the conditional recommendations in this guideline.

The strategy adopted in this guideline seems very clever as it focuses the reader's attention on some crucial questions about ARDS treatment.

The first question point is mechanical ventilation: how should it be protective?

The patient with ARDS is severely hypoxic due to inflammatory edema that causes intra-pulmonary shunt and pulmonary parenchyma collapse. Mechanical ventilation, through tidal volume and driving pressure, attempts to expand collapsed areas that, after inspiration, will tend to re-collapsed if no PEEP is applied. Pressure and volume, however, cause a change in stress and strain of the lung, a condition that can cause ventilation-induced lung injury (VILI) (8,9). At one time it was thought that this damage was related to the mechanical ventilator, but it is actually due to ventilation as soon as the energy load conditions on the lung are changed.

Indeed, a completely "safe" ventilatory strategy does not exist, and the support must be tailored to each single patient, based on hemodynamics, gas exchange, lung recruitability and respiratory mechanics (10).

Compared to traditional ventilation, the reduction in tidal volume resulted in a significant reduction in mortality, as shown in RCT trials.

For many years it has been said to reduce the tidal volume to 6 mL/kg, although this volume could increase stress on pulmonary parenchyma by causing VILI (11). In fact, the inhomogeneity of the lung parenchyma in ARDS, especially severe ARDS, greatly reduces the surface of the healthy lung and results in a reduction in the lung volume (baby lung as defined by Gattinoni). So, considering how much healthy lung (CT scan) the ARDS patient has, we should personally choose the right tidal volume to be delivered to the patient (12). This could be well below 6 mL/kg, as with recent ongoing trials. But an aggravation of ARDS damage to the lung is the pressure load, determined by high inspiratory pressure values (11).

This guideline recommends, as a strong indication, to administer a tidal volume between 4–8 mL/kg predicted body weight and a lower inspiratory pressure such as to determine a plateau pressure <30 cmH_2O (13).

Although the population with ARDS is heterogeneous and the severity of the disease is different, these low-tidal volume and low-inspiratory pressure treatments are indispensable if you want to try to reduce morbidity and mortality in the ARDS population.

This should probably be the first therapeutic step for an ARDS patient in any intensive care unit. In patients with ARDS, the recommended low tidal volume ventilation has a high level of evidence (1A).

The second question concerns the ARDS patient positioning

The prone position increases pulmonary homogeneity by combating gravitational forces with a more favorable matching between the lung and the chest wall (14).

The prone position of the patient with ARDS results in a gravitational movement of the pulmonary parenchyma

inflammation with the distribution of collapsed areas toward the most compliant lung parenchyma. This causes better lung recruitments with improved gaseous exchange and reduced pressure stress on the parenchyma. In other words, only the prone position reduces the pulmonary stress and strain with benefits on the patient's outcome.

This guideline strongly recommends the prone position for more than 12 h/d (15) in severe ARDS, while in mild to moderate ARDS the results about prone position are not conclusive and the decision is left to the physicians. A doctor's question is then for which patients and when to begin ventilation treatment with the patient in the prone position. Surely early pronation results in better results on the outcome and the inability to correct hypoxia with protective ventilation standards can be two valid triggers for prone positioning of the ARDS patient (16).

The pronation of the patient does not remove the risks that in the literature range from simple tracheal tube obstruction to the more serious pressure injuries. For these reasons, and especially for recommended long pronation periods, high care skills are required in the ICU.

The third question concerns high-frequency oscillatory ventilation

The results of the literature are controversial, the trials comprise few patients and in some cases there have been worsening of clinical conditions.

This does not prevent the physician from adopting high frequency oscillatory ventilation in selected cases, but the guideline strongly recommends not to use this ventilation strategy routinely in moderate or severe ARDS patients (17).

Thus, the literature provides at the moment three strong recommendations regarding the treatment of the patient with ARDS: two favorable (low-tidal volume and low inspiratory pressure and prone positioning) and one against (HFOV).

It's already a big step forward with ARDS's current varied therapy!

As far as the fourth and fifth questions are concerned, the issues are complex for two reasons: the results of the literature are not definitive, although consistent and the opinion of the individual participants in the drafting of the guideline has been controversial.

So with regard to the PEEP level to be delivered and the recruitment maneuvers, the suggestions are conditional and the physician will decide from time to time, case by case, how to apply these therapeutic measures.

The fourth question is: how much PEEP in the patient with ARDS?

PEEP increases the homogeneity of the lungs by preventing inter-tidal collapse and keeping the recruited pulmonary units open.

Although PEEP improves pulmonary atelectasis, retains the lungs recruited and thus reduces pulmonary stress and strain, many side effects are linked to PEEP, such as alveolar overdistention, increased dead space and intrapulmonary shunt, hemodynamic impairment related to preload decrease and pulmonary hypertension.

But what is the ideal PEEP value? In the literature there are many papers based on the concept that the best PEEP therapy is to prevent alveolar collapse without overdistending the healthy lung (18).

It should be remembered, however, that the increase in the value of PEEP, fundamentally linked to the best blood oxygenation, increases the plateau airway pressure >30 cmH_2O and this can increase the stress load and VILI.

The guideline panelists, despite some controversy linked to the different conclusions of the trials, suggest starting high-PEEP ventilation in a moderate or severe ARDS patient. Methods to improve the choice of PEEP level range from imaging (CT scan), ventilatory mechanics, and oxygenation upgrading, but all have some problems. Research, but there is a need for more comforting results from RCT trials, is focusing on transpulmonary plateau pressure measurement as an indicator for titration of PEEP.

The simplest clinical suggestion is to achieve the PEEP value that allows recruitment of the lungs with oxygen improvement to select PEEP-responder patients.

The fifth question concerns alveolar recruitment: should it always be done?

Various techniques are described to recruit the lung, such as the sigh (a high tidal volume intermittently delivered during ventilation), the extended sigh (a stepwise increase of PEEP or both PEEP and plateau pressure) and the sustained inflation (a static increase in airway pressure applied for 20–40 s) (19).

The goal of recruitment maneuvers, in all techniques used, is to apply a high transpulmonary pressure for an adequate time, so to expand the collapsed pulmonary lung zones. The recruitment maneuvers allow improved oxygenation for a variable period of time, with some hemodynamic and barotraumatic side effects; however, their

use has not shown per se to lead to a significant reduction in mortality (20).

Lung recruitment is defined as the enrollment of pulmonary units at a different level of inflation. In patients with ARDS, lung recruitability is very variable, ranging from 0–70% of the total lung weight as estimated by lung CT scan. Although pulmonary CT-scan is considered the gold standard for the measurement of lung collapse and recruitability, it requires the transport of the patient outside the ICU with associated worsening of the ventilatory and clinical condition and the use of X-rays. As an alternative lung ultrasound helps in estimating lung recruitability in the ICU, but only few studies confirm this finding.

The guideline panelist, despite some controversy linked to the side effects and to the different results, recommends using recruitment maneuvers in the ARDS patient, depending on the clinical condition of the patient.

Particular attention should be paid to the patient in shock or the patient with heart disease who may be severely affected by the recruitment maneuver.

The sixth question concerns the use of extracorporeal oxygenation: is that safe?

Despite some encouraging results related to the H1N1 epidemic campaign, there is no definitive data on the safety and positive outcome of treatment with ECMO (21).

The very high technology and skill needed for extracorporeal respiratory treatment requires the ECMO be performed in select high-volume ARDS therapy centers. This involves centralizing patients with severe ARDS and the patient's starting and arrival conditions from the periphery to the reference center may vary dramatically.

Perhaps, if we could better define VILI's predictive criteria, we would have effective triggers to initiate ECMO treatment instead of consolidated ARDS therapies.

Many other therapies in use in the patient with ARDS, both pharmacological and mechanical, should be explored in the light of promising ongoing trials.

Why after half a century is the mortality for ARDS still so high?

Most likely, we must strive to identify this syndrome very early, understand etiology, and perform personalized and titrated treatment to reduce complications and try to improve the outcome (22). The goal of this practical guide is to do what is surely to be done, ignoring speculations. Probably the application of measures such as transpulmonary pressure and driving pressure will allow identification of the best treatments for each individual patient. Driving pressure (**Δ**P) is calculated as the difference between plateau pressure and total PEEP, and can be measured quite easily using end-inspiratory and end-expiratory occlusions respectively.

A multilevel mediation analysis of individual pooled data from 2,365 ARDS patients included in four randomized controlled trials showed that **Δ**P was the ventilator variable associated most strongly with hospital survival. Any change in tidal volume or PEEP affected the outcome only when associated with a decrease in **Δ**P.

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Footnote

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