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Acute respiratory distress syndrome in the pediatric age: an update on advanced treatment

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Abstract: Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome that lacks definitive treatment. The cornerstone of management is sound intensive care treatment and early anticipatory ventilation support. A mechanical ventilation strategy aiming at optimal alveolar recruitment, judicious use of positive end-respiratory pressure (PEEP) and low tidal volumes (VT) remains the mainstay for managing this lung disease. Several treatments have been proposed in rescue settings, but confirmation is needed from large controlled clinical trials before they be recommended for routine care. Non-invasive ventilation (NIV) is suggested with a cautious approach and a strict selection of candidates for treatment. Mild and moderate cases can be efficiently treated by NIV, but this is contra-indicated with severe ARDS. The extra-corporeal carbon dioxide removal ($ECCO_2$ R), used as an integrated tool with conventional ventilation, is playing a new role in adjusting respiratory acidosis and CO_2. The proposed benefits of $ECCO_2$ R over extra-corporeal membrane oxygenation (ECMO) consist in a reduction of artificial surface contact, avoidance of pump-related side effects and technical complications, as well as lower costs. The advantages and disadvantages of inhaled nitric oxide (iNO) are better recognized today and iNO is not recommended for ARDS and acute lung injury (ALI) in children and adults because iNO results in a transient improvement in oxygenation but does not reduce mortality, and may be harmful. Several trials have found no clinical benefit from various surfactant supplementation methods in adult patients with ARDS. However, studies which are still controversial have shown that surfactant supplementation can improve oxygenation and decrease mortality in pediatric and adolescent patients in specific conditions and, when applied in different modes and doses, also in neonatal respiratory distress syndrome (RDS) of preemies. Management of ARDS remains supportive, aimed at improving gas exchange and preventing complications. Progress in the treatment of ARDS must be addressed toward the new paradigm of the disease pathobiology to be applied to the disease definition and to predict the treatment outcome, also with the perspective to develop predictive and personalized medicine that highlights new and challenging opportunities in terms of benefit for patient's safety and doctor's responsibility, with further medico-legal implication.

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Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome with a complex pathology and mechanisms of disease that still remains without a definitive and efficacious treatment. ARDS is less frequent in infants and children than in adults and the severity of respiratory failure is lower. The judicious use of positive end-respiratory pressure (PEEP), fraction of inspired oxygen (FiO_2) and tidal volumes (VT) in the last decade has made of ARDS a rarely seen condition in today's modern pediatric ICUs.

The cornerstone of management is correct intensive care treatment. Early anticipatory management may improve outcomes, avoid side effects and complications, and increase survival.

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Treating the primary cause (e.g., sepsis, pneumonia), minimizing the risk of multiple organ failure (MOF) and dysfunction and ventilator-induced lung injury (VILI) are essential.

Recently, ARDS was given a new definition under the Berlin Definition of ARDS Statement and has been classified into three exclusive categories on the basis of the degree of hypoxemia, thereby eliminating the acute lung injury (ALI) terminology: Mild (200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg), Moderate (100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg), and Severe (PaO_2/FiO_2 ≤ 100 mm Hg)[1].

Four ancillary variables [severity of chest radiograph, PEEP ≥ 10 cm H_2O, compliance of the respiratory system (C_{rs}) ≤ 40 mL/cm H_2O, corrected expired volume per minute (VE_{corr}) ≤ 10L/min)] in addition to the oxygenation index (OI) are suggested for the evaluation of severe ARDS, even though these variables do not contribute to the prognostic for survival[2].

The Berlin Definition is not a prognostic tool but can be of help, despite several limitations, in that a common classification may be useful for evaluating not only severity and patient prognosis, but also to facilitate the definition of therapeutic strategies predicated on severity.

The most important change in the management of adult ARDS has been the adoption of lower VT strategies and suitable PEEP levels to prevent VILI and improve survival[3-5].

A similar body of literature does not exist in infants and children and ventilation strategies in these age groups are predicated on the experience matured in adults. An attempt to carry out a similar study in children has failed and revealed inconsistent mechanical ventilation practices and the use of adjunctive therapies in patients with ALI[6-7].

Similarly, a low VT strategy can be considered a milestone in the study of ventilation for ARDS and acute respiratory failure in the pediatric age. A VT ≤ 6-7 mL/kg, high PEEP level (a minimum of 2-3 cm H_2O over the upper lower inflection point of the volume/pressure curve) for keeping terminal bronchioles patent and improving functional residual capacity (FRC) and a high respiratory rate according to minute volume (if possible by maintaining $PaCO_2$ ≤ 45 mm Hg) can be used as has been proposed for adult patients.

The risk of low VT ventilation is that of reducing tidal volume, hypoventilation and that only dead space ventilation can be produced while the increased respiratory rate is not able to normalize minute volume and eliminate CO_2 (hypercapnia development). Increase in $PaCO_2$ (permissive hypercapnia) is acceptable - instead of increasing tidal volume or peak inspiratory pressure (PIP) - but $PaCO_2$ should remain ≤ 50-55 mm Hg to be on the safe side. Minute ventilation can be reduced by lower tidal volumes as long as $PaCO_2$ is balanced by serum bicarbonate levels to determine a pH above 7.20. A safe pH level in the pediatric age remains one unresolved issue and, crucially, in the premature neonate and infant setting where an increased risk of brain hemorrhage exists[8-9].

Acidosis may be protective, by reducing cellular stress and may be beneficial for avoiding acute organ injury (i.e. MOF). Hypercapnic acidosis may also down-regulate inflammatory cell activity and inhibit xanthine oxidase, thus reducing oxidant stress[10].

Permissive hypercapnia is suggested as a protective ventilation strategy but the real benefits on cardiac output improvement, reduction of the artery-venous difference and of lactate production remain unconfirmed.

1 Atelectasis

The finding that mechanical ventilation can lead to atelectasis in normal lung during anesthesia is not recent. Several studies have shown that 85%-90% of patients with normal lung develop atelectasis during anesthesia, but this finding is difficult to recognize by conventional chest X-ray imaging[11].

The development and origin of atelectasis have not been fully investigated among mechanically

ventilated children undergoing intensive care. The experience gained from anesthesia can be used in evaluating atelectasis appearance, especially if the child remains in the supine position, sedated and paralyzed. Atelectasis formation has been demonstrated in dependent lung areas after 15 minutes of anesthesia, muscle paralysis and intermittent positive pressure ventilation in children[12].

Several complications have been linked to atelectasis. A reduction in functional residual capacity (FRC), the development of hypoxemia and the need to increase FiO_2 (increase in oxygen toxicity risk) and surfactant inhibition that can lead to alveolar instability and increased permeability. Atelectasis can increase macrophages activity in producing IL-1 and TNF-α (with concurrent risk of MOF)[13].

Moreover, atelectasis and pneumonia may be considered together because the changes associated with atelectasis may predispose to pneumonia[14].

Recruiting maneuvers have been proposed to resolve atelectasis, improve oxygenation and re-opening of non-ventilating lung areas[15-16].

Various types of recruiting maneuvers have been described: the application of sigh during lung protective strategy, with three consecutive sighs per minute at 45 cm H_2O of plateau pressure for one hour in patients ventilated with a protective strategy, sustained lung inflations, decremental PEEP titration. However, there is a need for large-size, controlled clinical trials to confirm their efficacy, safety, and side effects. The method used to apply the recruitment maneuver may influence both their efficacy and potential for complications. Although recruitment maneuvers compromise respiratory and hemodynamic conditions transiently, serious long-term complications seem to be rare[17]. The long-lasting effects of recruiting maneuvers on arterial blood gases are contradictory[18].

Several questions remain unresolved regarding performing recruitment: (1) which peak pressure level is ideal, (2) for how long sustained inflation must be maintained at the end of inspiration, (3) which level of PEEP is useful for keeping the recruited lung open[11, 15].

In neonates, infants and small children, no study has so far indicated the most appropriate recruitment method to be applied without creating lung barotrauma. It is reasonable to suggest a 5-8 cm H_2O increase over preset PIP and sustained distention for 8-10 seconds[15]. In case of lung pathology with unilateral prevalence, selective bronchial intubation and recruitment of the pathologic lung may be used with the aim of re-opening the atelectasis/consolidated lung and protecting the less pathologic lung from over-distension[19].

Bedside monitoring of alveolar recruitment (or derecruitment) has entered the clinical area and should improve in the close future the ventilatory management of patients with ARDS. Because it is noninvasive and easily repeatable, bedside trans-thoracic lung ultrasound appears as the most promising semi-quantitative technique for evaluating the recruited lung areas and which have maintained patency[20].

Lung recruitment must be followed by adequate ventilation strategies to prevent collapse of re-opened lung. The suggested treatment is the application of PEEP level to maintain the alveoli open (keeping PEEP above the lower inflection point on a pressure-volume curve, i.e. Pflex), improve oxygenation and oxygen transport and avoid provoking hemodynamic complications. PEEP optimization may lead to lung protection via mechanisms other than alveolar recruitment, e.g. by avoiding surfactant depletion and disruption occurring at low end-expiratory lung volumes[21].

We do not have a clear idea about which level of PEEP is “best”, but surely any level that can avoid repeated lung collapse and maintain alveolar patency is clearly desirable[22]. The follow-up of ARDS NET demonstrated that survival was similar with high and low PEEP, and that improvement in outcome was strictly connected to “low tidal volume strategy”[23].

Setting PEEP still remains a “compromise” that allows improvement in oxygenation and oxygen

transport while avoiding hemodynamic complications. Decremental PEEP titration to determine the level of PEEP required to maintain an open lung after lung recruitment is a suggestive technique but it needs further confirmation to be recommended in clinical practice[24-25].

2 Prone positioning

Prone positioning has been proposed for improving oxygenation, respiratory mechanics, alveolar inflation and ventilation distribution, for homogenizing pleural pressure gradient and limiting lung over inflation. Prone positioning may be helpful in increasing lung volume, reducing the amount of atelectatic lung areas in the dependent lung and in facilitating the drainage of secretions[26-27].

With the prone position, pulmonary densities redistribute from the dependent lung regions, whereas in the supine position (proximal to the spine) they redistribute to the dependent lung regions (next to the sternum). The prone position reverses alveolar inflation and ventilation distribution, due to the reverse of hydrostatic pressure overlying the lung parenchyma, reverses the pressure resulting from the weight of the heart and changes in chest wall shape and mechanical properties. On return to the supine position, the alveoli in the dorsal regions may remain open because of PEEP resulting in a persistent response[28].

A recent Cochrane review showed that the prone position was significantly superior to the supine position in terms of oxygenation. Placing infants and children in the prone position may thus improve respiratory function. In this review, the benefits of prone positioning appear to be most relevant to infants because this age group has been more investigated[29].

The inefficacy of the prone position is probably due to delays in its application (the lung is consolidated and cannot be re-opened) and may also derive from an incorrect definition of the duration of the prone position. Keeping a patient for 12 hours in the prone position, as suggested by some studies, may induce alterations similar to those connected with the supine position. Depending on the early development of atelectasis in ventilated patients, prone positioning and mobilization must be started as soon as possible in order to improve its efficacy.

There are children who do not respond to undergoing prone positioning as well as adults do. This lack inefficient response may be due to the type of lung pathology they suffer from and delays in their treatment. In these cases, selective lung recruitment before prone positioning must be considered to improve prone positioning efficacy.

3 Non-evidence based treatments

3.1 Non-invasive ventilation

Despite controversial, sometimes far from encouraging, results from large studies which should have induced clinicians to a prudent attitude and a strict selection of patients to treat, non-invasive ventilation (NIV) is increasingly used in the ICU in patients with ALI/ARDS. Published data are contradictory and are of difficult evaluation. In general, these studies are case reports or retrospective, uncontrolled, small size clinical studies with a remarkable quantity of case mixing and an unclear definition of the inclusion and exclusion criteria[30].

In the last five years, various reviews have been published which attempted to throw light on the real possibilities of NIV in acute respiratory failure (ARF). All these studies conclude that greater caution should be exercised in the use of NIV for those patients among whom NIV cannot bring an actual benefit[31].

3.1.1 Continuous positive pressure airway ventilation

From the time of the earliest report at the beginning of the 1970s, the application of continuous positive pressure airway ventilation (CPAP) has been proposed to open under-ventilated alveoli and increase functional residual capacity (FRC), thereby decreasing the right-to-left intrapulmonary shunt and improving lung

mechanics[32]. CPAP has been widely used and has met with considerable success in pediatric setting outcomes, chiefly among premature newborns with or without idiopathic respiratory distress syndrome (IRDS)[33-34].

In patients with mild ARDS, CPAP can increase oxygenation, reduce dyspnea, and respiratory muscle unloading. CPAP alone improves gas exchange but does not unload the respiratory muscles. Non-invasive positive pressure ventilation (NIPPV) provides a better response in these conditions by unloading the muscles and relieving dyspnea. By lowering left-ventricular transmural pressure in patients with congestive left-heart failure, positive airway pressure may induce left-ventricular afterload reduction without compromising the cardiac index[35].

3.1.2 Non invasive positive pressure ventilation

Non invasive positive pressure ventilation (NIPPV) is frequently applied in patients with clinical and radiographic evidence of lung disease, supplemented with a FiO_2 of greater than 50%. The rationale of NIPPV use in adults is the possibility of reducing the work of breathing, improving gas exchange, reducing the need for endotracheal intubation and of infection, and increasing survival[36].

While indicating the possible use of NIV, a real "chorus" of experts continues to claim that, first and foremost, the necessity of immediate or early intubation must be categorically excluded before starting to think of NIPPV[37-38]. The delay in intubation may expose the patient to the risk of cardiac arrest during intubation - if the patient is severely hypoxic and difficult to oxygenate prior to initiate the maneuver- and to the necessity of applying more invasive procedures for treating a worsened pathology.

NIPPV can be used early in mild and in early moderate forms of ARDS. Published experience has largely been limited to the adults where it has been proposed as first line treatment in ARDS, even though it has been demonstrated that NIPPV reduces the need to intubate while failing to decrease mortality significantly[37].

A high rate of failure suggests caution in its use in ALI/ARDS, including early initiation, intensive monitoring, and prompt intubation if signs of failure develop. NIPPV must be used very carefully in mixed cases, the timing of ETI must be anticipatively recognized in order to avoid delayed intubation when needed and must be used selectively[38]. In hypoxic patients, it is safe not to prolong NIPPV if no rapid improvement occurs (the one hour test).

NIV must be preferentially applied in ICU or in departments where safe and prompt intubation can be carried out. In moderate ARF, NIV should be used with caution, depending on patient's age, work of breathing and onset and severity of symptoms. In the hypercapnic patient, there is a high rate of inefficacy because NIPPV increases gas exchange, though not survival[38].

3.1.3 High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) has been proposed in the rescue treatment of ARDS when conventional ventilation has failed in infants and children. HFOV may be thought of as the ultimate high-PEEP, low-tidal-volume strategy. Because of the extremely small tidal volumes used, HFOV minimizes repetitive opening and closing and possibly reduces VILI, if the lung is sufficiently recruited. Because of the extremely high respiratory rates, carbon dioxide can be maintained at satisfactory levels.

There are at present no sufficient data to confirm its advantages in the treatment of ARDS over conventional ventilation using a protective lung strategy.

Most of the experience in the use of HFOV is derived from uncontrolled studies and case reports in which improvement in oxygenation and safety were demonstrated. In many of these studies, unfortunately, HFOV is compared to large tidal volume, low respiratory rate and low PEEP and not to a "low tidal volume strategy". One small-size randomized controlled trials has shown that HFOV is as safe and effective as conventional mechanical ventilation but does not improved survival[39].

In adult patients, the interest in using HFOV could decrease in the wake of the publication of two recent multicenter, randomized trials. The first demonstrated that a HFOV strategy with high mean airway pressures led to more deaths than did a conventional mechanical ventilation strategy that used relatively high PEEP levels[40]. The second study did not find a major difference in outcome between HFOV and conventional mechanical ventilation[41].

The data obtained from adult studies can raise some perplexity and concern regarding the ventilation of infants and children with HFOV, even though at present we currently have no specific data in these patient populations. Future studies are needed to assess whether HFOV, used under optimal conditions, with an especial regard for indication and timing using the best oscillator settings can have a major effect on patient outcomes[42].

3.2 Extracorporeal carbon dioxide removal

Extracorporeal gas exchange, and extracorporeal membrane oxygenation (ECMO) in particular, was extensively studied in the 1970s. Enthusiasm for these methods waned after a large, prospective trial of ECMO showed no improvement in outcome compared with conventional therapy. Some successes have revived interest in ECMO in recent years. Several case reports and series have described patients who seemed to have survived because ECMO was used after conventional therapy had failed. Nonetheless, ECMO is currently used primarily by few centers which have the necessary resources, expertise, and an interest to develop the technique further[43].

The extracorporeal carbon dioxide removal ($ECCO_2$ R) concept, used as an integrated tool with conventional ventilation, is playing a new role in adjusting respiratory acidosis consequent to tidal volume reduction in a protective ventilation setting[44-45].

Pumpless extracorporeal lung assist therapy (i.e. interventional lung assist, or iLA), makes use of a low resistance gas exchange membrane (lung assist device - LAD) is interposed between two cannulas that are connected via short tubing to establish an arterio-venous shunt into the femoral vessels. The gas phase is located inside, while blood passes outside a hollow-fiber system. Gas exchange takes place alongside a semi- permeable membrane. It is driven by the partial pressure gradient of carbon dioxide and oxygen between blood and the gas phase, which is connected to an oxygen supply (12-13 L/min). Blood flow through the tubing and gas exchange membrane is solely determined by the difference between arterial and venous blood pressure[46].

The proposed advantages of $ECCO_2$ R compared to ECMO are the reduction of artificial surface contact, the avoidance of pump-related side effects and technical complications and reduced operating costs[47].

The methodology appears interesting but requires more studies and investigation in the pediatric age[48]. Concerns are connected to the use of large-caliber catheters for maintaining a sufficient flow. The positioning of a large catheter could occlude femoral vessels and cause severe peripheral vascular thrombosis.

3.3 Inhaled nitric oxide

The use of inhaled nitric oxide (iNO) has been proposed in the treatment of severe lung diseases including ARDS over the past 15 years to reduce pulmonary hypertension and pulmonary hypoxic vasoconstriction, as it may improve ventilation of the lung and possibly reduce the need for a ventilatory support setting and favors oxygenation by reducing FiO_2, thereby limiting the toxicity of high-dose oxygen.

After the initial enthusiasm triggered by the use of iNO in ALI and ARDS, the benefits and drawbacks of this treatment are now better appreciated. Improvement in ventilation and reduction of FiO_2, the two main benefits obtained by various researchers have been questioned in a Cochrane Review which failed to show a statistically significant effect on the mortality rate and on the transiently improved oxygenation in hypoxemic respiratory failure among

children and adults treated with iNO[49].

The risks and benefits of iNO treatment are now better understood. Apart from the well-established indications in neonatal persistent pulmonary hypertension (PPHN) and in heart disease (especially for patients prior to cardiac surgery and/or following cardiac repair), the risks of toxicity both for patients and in the immediate environment (including medical staff) are well demonstrated, as is the absolute necessity of vigilant and accurate monitoring to avoid severe side effects. Particular attention has been paid to the possibility of inducing iNO dependency with prolonged ventilator weaning and of the toxic effects of iNO on exogenous pulmonary surfactant which can both negatively impact treatment[50].

iNO cannot be recommended for ARDS and ALI in children and adults. iNO results in a transient improvement in oxygenation but does not reduce mortality and may even be harmful[51].

3.4 Surfactant supplementation

Multiple surfactant abnormalities have been described in patients with ARDS[52]. Alterations in surfactant composition and function are believed to result from the actions of a variety of mediators, including oxygen radicals, proteases, lipases, bioactive lipids, and serum proteins. Abnormal surfactant function renders some lung units prone to collapse, which results in much of the inspired tidal volume being directed toward more compliant, non-atelectatic areas of the lung. Uninjured portions of the lung may then become over-distended and injured if ventilator settings are not adjusted accordingly. Alveolar instability also may result in cyclical atelectasis (with reference to lung units that open with inspiration and close with exhalation), which may cause shear forces that additionally exacerbate lung injury. Exogenous surfactant supplementation could theoretically ameliorate many of these problems.

Several randomized trials of adults have found no clinical benefit of various surfactants at doses and with treatment modalities identical to those administered to premature newborns with RDS and adults with ARDS, respectively[53]. Other studies, on the contrary, found that surfactant supplementation improves oxygenation and significantly decreases mortality in pediatric patients[54 -56].

The second trial by Willson and colleagues did not confirm earlier positive data reported by the same group. In this new study, it was shown that surfactant supplementation did not improve ALI/ARDS outcomes. This failure was correlated to an insufficient dosage and to the modality of administration of the surfactant and to the failure to recruit the lung during supplementation[57].

It is unlikely that the use of surfactants as appropriate in premature infants (by bolus administration and in high doses) is the best modality of supplementation later in infancy and childhood, or to adults, as the aetiology of surfactant deficiency differs in these age groups. In actual fact, surfactant deficiency in the premature newborn with RDS results from pneumocyte type II alveolar immaturity while ARDS in infants and children mainly develops from the impaired production and inactivation of surfactant. For these reasons, it may be that other modalities of supplementation, such as bronchoalveolar lavage (BAL), could meet with more success as surfactant is supplied when the surfactant inhibitors which are present in the lungs have been mostly removed already[58-60].

The supplementation of surfactant remains a fascinating tool in the treatment of ARDS in infants and children when surfactant deficiency is suspected. Larger studies are necessary to explore different modalities of surfactant supplementation (such as BAL and aerosol) and assess dosage for various lung pathologies and in different age groups in pediatrics. A big boost to our knowledge of surfactant application could materialize when its compassionate use in the final stage of lung pathology is finally abandoned and early application becomes routine practice. The high cost of this therapy currently represents a real barrier to research and clinical applications.

3.5 Adjunctive treatments

Adjunctive treatments play an important role in the treatment of ARDS. Improvements in care (bronchosuctioning, sedation, muscle paralysis), patient mobilization and secretion removal appear to be very helpful as is a reduction in fluid intake[61].

Recently, two interesting studies suggested new ideas in the treatment of severe lung pathology. Temperature preconditioning in the first of these studies and protection from the dissemination through the airways of the lung pathology in the second could play an important role in ameliorating treatment and improving outcomes in adult patients with severe lung pathology.

The first study suggests that the maintenance of appropriate thermoregulation is essential for normal lung cellular functioning. Heat exposure occurring simultaneously with high pressure ventilation accentuates VILI. Suzuki et coll. found that moderate (33-35 °C) hypothermia can attenuate the adverse response in models of VILI induced by mechanical forces and by pre-existing inflammation[62].

The second study highlights how the artificially ventilated lung easily spreads disease from one area to another if treatment is not targeted or adequate. Ventilatory support over-distends the lungs while allowing the repetitive opening and closure of the alveoli and thus facilitates bacterial translocation and spread from the alveoli to the blood stream. The author suggests that greater care should be exercised in ventilating these patients in order to avoid these risks[63]. Similar studies are currently lacking form the pediatric literature and ought to be investigated.

4 Final considerations

Substantial progress has been made to advance out understanding of the basic mechanisms of ARDS and to optimize clinical management. Despite this progress, our knowledge of how to predict the evolution of the disease prior to severe symptoms, improve disease definition and classification, and target novel and new treatments in a more personalized manner still remains inadequate.

Currently, mechanical ventilation strategies aiming at optimal alveolar recruitment with the judicious use of PEEP and low tidal volumes remain the mainstay of the management of respiratory failure in children. As in many others areas of pediatric critical care, clinicians must await new data and trials to use this methodology in on a daily basis in routine care[64].

The management of ARDS remains supportive, is aimed at improving gas exchange and preventing complications while the underlying disease that precipitated ARDS is treated. Potential ARDS-specific therapies (new ventilation strategies and drugs) have been studied but they have not been hitherto shown to improve clinical outcomes and thus cannot be recommended for routine care.

The improvement in survival we are currently witnessing is probably due to a better overall treatment of patients and to greater attention being paid to the ventilation method used. There is no single method of treating all ARDS patients. The treatment must be modulated according to the age of the patient and to the severity of the lung pathology, taking into account that supportive and adjunctive therapies can be extremely important in improving the final outcome.

Patient mobilization (e.g. by prone positioning) in order to recruit dependent lung areas and avoid the retention of secretions, the use of methods to naturally or artificially improve cough to eliminate secretions more easily, the early application of ventilatory support and the reduction of deep sedation and muscle paralysis which blunt cough reflexes and allow secretion accumulation in dependent lung areas are taking on a fundamental role[50,65].

Advances in molecular biology provide new ground-works for defining pulmonary diseases and their severity. Specific molecular markers have proved useful in the diagnosis of lung pathologies such as cystic fibrosis, infections, etc, and it is probable that in the near future similar markers will be developed also

for ARDS[66-67].

Our future challenge must be to investigate pathobiology across systems and levels, from one organ to another and from molecular processes and signatures to expression of clinical symptoms across patients and populations. A new paradigm is needed in traditional disease definitions that will relate phenotypic traits to fundamental biologic processes instead of relying on the end point expression of clinical symptoms[68].

Progress must be addressed toward an integrated and system view of disease pathobiology that may be applied to disease definition and predict treatment outcome[69-70] , also with the perspective to develop predictive and personalized medicine that highlight new and challenging opportunities in terms of benefit for patient's safety and doctor's responsibility, with further medico-legal implication[71-72].

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附中文概要（儿童急性呼吸窘迫综合征的治疗进展）

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急性呼吸窘迫综合征（ARDS）是一种具有复杂病理和发病机制的异质性综合征，目前仍没有一个明确和有效的治疗对策。根据低氧血症程度，ARDS 分成三类：轻度（200 mm Hg < 氧合指数≤ 300 mm Hg）、中度（100 mm Hg < 氧合指数≤ 200 mm Hg）、严重（氧合指数≤ 100 mm Hg）。治疗 ARDS 的基础是正确的重症监护治疗。早期管理可以改善预后，避免副作用和并发症，并提高存活率。治疗诱因（如败血症、肺炎），最大限度地减少多器官功能衰竭（MOF）、功能障碍和呼吸机相关性肺损伤（VILI）的风险在治疗过程中是至关重要的。

低潮气量（VT）策略是通气治疗在 ARDS 和急性呼吸衰竭研究中的一个里程碑。目前成人 ARDS 患者的通气治疗策略包括：VT ≤ 6~7 mL/kg、保持终末细支气管功能的高 PEEP 水平，提高功能残气量（FRC）和每分通气量相关的呼吸频率。与此同时，低 VT 通气亦有一定风险：潮气量降低、通气不足，增加呼吸频率时无法纠正每分通气量，二氧化碳无法消除，产生死腔通气。机械通气可引起肺不张，继而导致多种并发症，尤其是肺炎的发生。功能残气量（FRC）的减少，低氧血症的发展，氧中毒风险的增加和表面活性剂的抑制，均可导致肺泡的不稳定性和通透性的增加。对此，多种肺复张方式如持续性肺膨胀等，可以有效地解决肺不张，改善氧合及未通气肺区域的复张。肺复张后必须继续予以足够的通气策略，以防止肺萎陷的再发。其治疗原则是 PEEP 的应用，它可维持肺泡开放，改善氧合和氧的运输，避免刺激产生血液动力学并发症。

另外，研究表明俯卧位可有效地改善氧合、呼吸力学、肺泡充气等，促使胸腔压力梯度的平均化和限制肺过度充气。最新的 Cochrane 系统评价认为，俯卧位的氧合能力显著优于仰卧位。因此，把婴儿和儿童置于俯卧位，可改善其呼吸功能。

目前，对于使用无创通气（NIV）治疗 ARDS 这一观点仍有争议。NIV 可有效治疗轻度和中度患者，但它是重症 ARDS 的禁忌。持续正压气道通气（CPAP）治疗则已广泛应用，并在儿科，尤其是伴或不伴特发性呼吸窘迫综合征（IRDS）的早产患儿中应用成效显著。无创正压通气（NIPPV）可用于轻度和中度 ARDS 的早期治疗，既可减少呼吸功，改善气体交换，又可减少气管插管的感染几率，从而最终提高患者的生存率。研究表明，高频振荡通气（HFOV）可运用于在 ARDS 抢救治疗期间使用常规通气失败的婴儿和儿童。目前，体外二氧化碳清除（ECCO2 R）具有了新作用，即调节保护性通气期间潮气量降低导致的呼吸性酸中毒。相比起体外膜肺氧合（ECMO），ECCO2 R 优点是减少人工表面接触，避免泵相关的副作用和技术相关的并发症，降低运行的成本。其缺点则是大导管的定位可能会堵塞股血管，造成严重的周围血管栓塞。

吸入性一氧化氮（iNO）可以改善肺通气。它降低治疗时的氧浓度，从而限制了高浓度氧的毒性。但目前研究表明 iNO 虽然可导致一过性的氧合改善，但并不降低病死率，相反可能是有害的，因此在儿童和成年人 ARDS/ 肺损伤（ALI）中并不推荐使用 iNO。ARDS 患者存在着多种表面活性剂异常现象。表面活性剂的异常功能易引起一些肺单位的崩溃，继而肺正常部分可因过度扩张而受伤。肺泡的不稳定亦可能导致周期性肺不张。尽管几个试验发现补充各种表面活性剂在成年 ARDS 治疗上并无临床益处，但它仍是患有 ARDS 的婴儿，尤其是表面活性剂缺乏患儿的治疗方案之一。

与此同时，相应的护理治疗，如镇静、肌麻痹、分泌物的吸除等，在 ARDS 的治疗中亦发挥着重要作用。适当的维护体温调节，避免人工通气期间肺泡内细菌移位和蔓延，也是必不可少的治疗措施。

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