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REVIEW ARTICLE

Severe Bronchiolitis as a Cause of ARDS in Early Childhood. Pathophysiology and Strategies to Minimize Lung Injury

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ABSTRACT

Bronchiolitis is one of the most frequent acute diseases of the lower respiratory tract in infants worldwide, and Respiratory Syncytial Virus remains the most common and aggressive viral disease. The course of the disease is usually benign, but its severity may change by evolving into parenchymal disease. In the more severe cases, its clinical and radiological characteristics may be consistent with acute respiratory distress syndrome. Management of these cases includes admission to paediatric intensive care and invasive mechanical ventilation. This paper reviews the definition of paediatric and neonatal acute respiratory distress syndrome, which was primarily designed and validated for adults. The article investigates the pathophysiology of paediatric acute respiratory distress syndrome further, describing how damage to the alveolar-capillary units, surfactant inactivation and inflammation occurs. Mechanisms that contribute to acute lung injury, such as volutrauma, barotrauma, stress and strain, are illustrated in detail, and an overview of the strategies that may help minimize neonatal lung injury and optimize ventilatory support is provided. These strategies include lung-protective mechanical ventilation, surfactant treatment, inhaled nitric oxide, high frequency oscillatory ventilation, recruiting manoeuvres, prone position and neuromuscular blocking agents. The objective is to help clinicians understand the peculiar pathophysiology of severe bronchiolitis and so guide them in preventing or attenuating lung injury during treatment. As such, this paper aims to contribute to defining optimal treatment of severe cases of bronchiolitis.

Introduction

Bronchiolitis is one of the most frequent acute diseases of the lower respiratory tract in infants worldwide, and Respiratory Syncytial Virus (RSV) remains the most common and aggressive viral cause of bronchiolitis, particularly in young infants. In an epidemiological study on the incidence and predisposing factors for severe bronchiolitis conducted in 310 otherwise healthy term infants with a mean birth weight of 3.1±0.5 kg, 73.2% of them resulted positive for RSV, and this percentage increased to 84.6% when only the most severely ill infants were considered[1]. It is of note that while the American Academy of Pediatrics defines RSV bronchiolitis as an infection of infants in the first two years of life, in Europe the age range for bronchiolitis is considered between 0 and 1 year of age. This difference is not negligible in terms of epidemiology, risk factors for Paediatric Intensive Care Unit (PICU) admission or invasive mechanical ventilation, response to treatments and the estimated cost of hospitalization. The management of bronchiolitis is well-defined internationally, including the recommendation of respiratory and hydration support, with no indication for the use of albuterol, glucocorticoids, antibiotics, and epinephrine. However, these treatments are still widely used, which possibly indicates that the clinical picture of bronchiolitis is heterogeneous and also affected by age. Thus, the clinical practice of the most severe form of respiratory failure is far from being standardizable. The course of bronchiolitis, characterized by obstructive small airway disease with an increase in respiratory resistance, is usually benign, and most children recover with limited medical intervention. The chest x-ray demonstrates bilateral hyperinflation with perihilar infiltrates. The severity of the disease may change its clinical features by evolving into parenchymal disease in infants with high-risk factors, including RSV carriage, young age <1 month[1] and presence of co-morbidities (e.g., chronic pulmonary disease, congenital heart disease, immunodeficiency, neurologic disease)[2,3]. In this subgroup of infants, bronchiolitis is a frequent cause of hospitalization and in the more severe cases the clinical and radiological characteristics may be consistent with acute respiratory distress syndrome (ARDS)[4]. In this instance, the chest X-ray shows bilateral alveolar consolidation (Figure 1), and lung function tests reveal that the elastic component of the respiratory system rather than airway resistance is the main determinant of the super-imposed work of breathing (WOB)[4,5]. The presence of bacterial coinfection is also significantly associated with the development of ARDS[6]. By contrast, the role of epidemiological variables and environmental factors (e.g., passive smoking, crowded households) seems less likely[1]. The management of the severe form of bronchiolitis includes admission to PICU and mechanical ventilation.

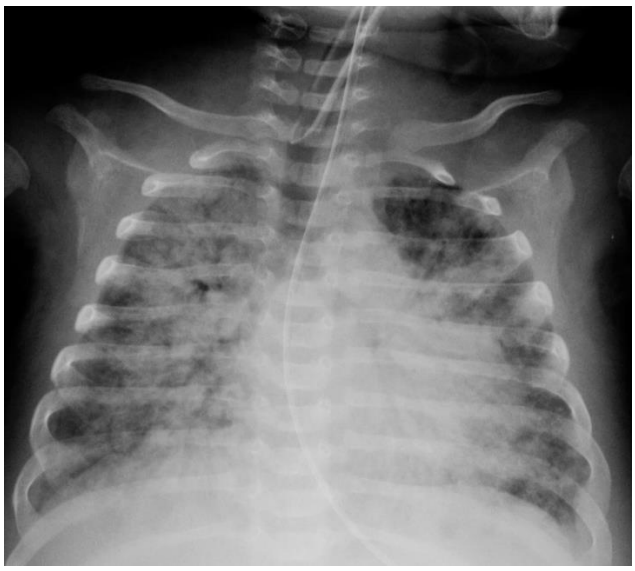

Figure 1. Typical chest X-ray of an infant affected by severe RSV restrictive disease and characterized by diffuse, bilateral and irregular infiltrates

Even in late preterm infants (i.e., born at a gestational age (GA) between 33^{+0} and 36^{+6} weeks), bronchiolitis may be characterized by a severe clinical picture. This group of infants has respiratory and innate immune systems that are not yet fully mature[7], and they are not always protected by RSV prophylaxis[2], two factors that explain why they are prone to more severe infections. In these infants, exposure to 21% oxygen represents a premature contact with a hyperoxic environment compared with that in utero, with the resulting inhibition of the activity of the Hypoxia-Inducible Factors, a class of transcription factors that play a critical role in lung development[8,9]. This issue has negative effects on the structure and function of the developing lung, which may lead to unfavourable consequences affecting respiratory health postnatally. Late preterm infants have lower functional residual capacity (FRC), decreased compliance, and smaller airway diameters than term infants. Moreover, alveoli are not completely mature until 36 weeks of GA[10-12]. Available data largely indicate that these infants are also predisposed to wheezing in infancy and early childhood and have more rehospitalizations[13].

Definition of paediatric and neonatal acute respiratory distress syndrome

ARDS is a life-threatening respiratory failure characterized by lung tissue inflammation, increased permeability to proteins across the pulmonary

endothelial and epithelial barriers and is described as a restrictive disease with reduced lung compliance caused by loss of surfactant function, atelectatic lung regions and accumulation of interstitial/alveolar plasma leakage[14]. Patients usually develop acute respiratory failure rapidly because of arterial hypoxemia, as well as impaired carbon dioxide excretion and elevated WOB.

In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed a specific definition of paediatric ARDS (PARDS) in order to overcome the limitations of various definitions, which were primarily designed and validated for adults (e.g., the 'Berlin definition' of ARDS)[15]. More recently, a definition of neonatal ARDS (NARDS) that is applicable from the perinatal period was issued by an expert consensus (i.e., the 'Montreux definition')[16]. Its aim is to increase clinical attention and research into mechanisms associated with ARDS that also occur in some severe neonatal respiratory disorders, excluding respiratory distress syndrome, transient tachypnoea, and congenital pulmonary anomalies. The variables considered for the diagnosis of PARDS and NARDS are:

- Timing: within 1 week of a known clinical insult (direct or indirect);
- Lung imaging: diffuse, bilateral, and irregular opacities or infiltrates, or complete opacification of the lungs;
- Origin of oedema: excluded hydrostatic oedema (cardiac failure or fluid overload);
- Oxygenation deficit: defined by oxygenation index (OI) in PARDS and NARDS[15,16], or by oxygenation saturation index (OSI) if arterial blood gas analysis values are not available in PARDS[15] (Table 1).

Table 1. Oxygenation deficit in PARDS and NARDS defined by OI* and OSI**

Mild	Moderate	Severe
$4 \leq OI < 8$	$8 \leq OI < 16$	$OI \geq 16$
$5 \leq OSI < 7.5$	$7.5 \leq OSI < 12.3$	$OSI \geq 12.3$

*$OI = ([FiO_2 \times \text{mean airway pressure (Paw)} \times 100]/PaO_2)$; **$OSI = ([FiO_2 \times Paw \times 100]/SpO_2)$

It is essential to distinguish between the direct (pulmonary) and indirect (extra-pulmonary) causes of PARDS. In infants, as well as in children and adults, the most frequent direct cause of PARDS is viral or bacterial pneumonia, followed by aspiration (e.g., gastric aspiration, meconium aspiration in newborns) and, less frequently, by near-drowning or inhalation of toxicants. The indirect causes of PARDS are primarily systemic infections followed by hypovolemic shock, generalized trauma, multiple transfusions, burn injury and other primary extra-pulmonary injuries[15,17]. Indirect forms of PARDS have substantial multi-organ pathologies that significantly affect long-term patient outcomes reducing the impact and effectiveness of pulmonary-based therapies.

Although the incidence of ARDS is relatively low from a population-based perspective, the severity of the illness is quite high, as demonstrated by its mortality rate of 24.0% to 33.7%[18,19]. The diverse underlying conditions and triggering diseases across the ages explain why PARDS shows a remarkable variability in epidemiology, prognosis, and management[19,20].

Pathophysiology of PARDS

PARDS is characterized by an initial injury that triggers cell-mediated mechanisms to release a cascade of a variety of mediators that alter the integrity and function of the cellular linings of the alveolar-capillary unit. Hyaline membranes, alveoli flooded with protein-rich oedema fluid, infiltrates of polymorphonuclear neutrophils, macrophages and erythrocytes are the leading histological hallmarks[17,22,23]. The net effect at cellular level is massive cell damage, alveolar denudation and sloughing of cell debris into the lumen of the alveolus.

The pathways by which surfactant activity can be compromised during PARDS are many and not yet fully understood. These include reduced surfactant synthesis by injured type II cells, dilution of surfactant material by oedema fluid, surfactant functional inhibition by plasma constituents, and increased breakdown by activated oxidative and hydrolytic pathways[24-27]. Each of these mechanisms may contribute to surfactant dysfunction to varying degrees in individual patients.

The degree of inflammation depends on the imbalance between pro- and anti-inflammatory cytokines, and a close interrelationship exists between inflammatory mediators and the coagulation cascade [28,29]. Factors that activate coagulation or inhibit fibrinolysis have been identified that produce platelet–fibrin thrombi in small pulmonary vessels[30,31]. This interplay occurs both in the alveolar compartment and in intra- and extravascular space leading to unresolved fibrin

deposits and alveolar hyaline membranes. On the clinical level, WOB increases for several reasons: surfactant depletion, alveolar collapse due to augmented surface tension, alveolar filling, cellular debris within the alveoli and increased airway resistance.

Over the past decades, pathology and computed tomography scans of ARDS lungs of adult patients have demonstrated uneven distribution of aerated areas and dense consolidated regions, with the remaining alveolar surface for gas exchange largely reduced. Gattinoni defined this condition as 'baby lung' because the alveolar surface available for gas-exchange has the lung-dimensions of that of a 5-6-year-old child[32]. The functioning part of this lung is considered to be as small as 25% of the physiological volume.

During mechanical ventilation, lung inhomogeneity is therefore characterized by the presence of three different areas (Figure 2):

- the aerated ventral areas (baby lung), which have the highest compliance (a);
- the intermediate areas of collapse, characterized by reversible lung closure, which are prone to cyclic recruitment-de-recruitment (b);
- the consolidated and atelectatic areas, which usually affect bilateral dependent zones, are characterized by irreversible lung closure (c).

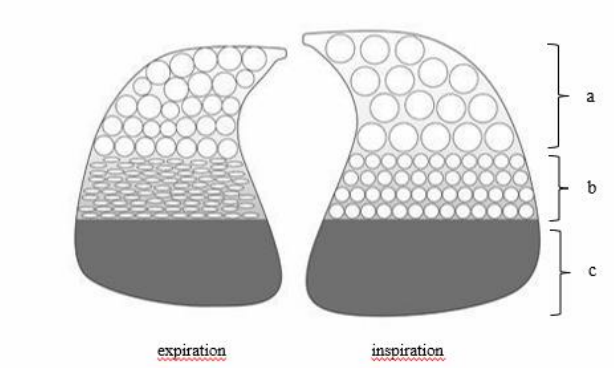

Figure 2. Schematic representation of lung parenchyma inhomogeneity in PARDS characterized by: (a) aerated ventral regions (baby lung), (b) regions prone to cyclic recruitment-de-recruitment and (c) regions of consolidation and atelectasis.

This condition results in much of the inspired tidal volume being directed towards the remaining and largely reduced open lung regions. Uninjured portions of the lung may then become over-distended (*volutrauma*) if exposed to excessive inflating pressures (*barotrauma*) with an increase in dead space and a risk of complications from air leaks. Alveolar instability also results in repetitive opening and closing of the collapsed areas during the respiratory cycle, which may cause shear forces that worsen the lung injury (*atelectrauma*). Moreover, a widened interstitial space between the alveolus and the vascular endothelium decreases oxygen diffusion, while collapsed alveoli result in a mismatch of ventilation-perfusion units and in right-to-left intra-pulmonary shunts leading to severe hypoxia. Severe pulmonary hypertension may also develop from hypoxia, hypercarbia, and small-vessel thrombosis and can result in increased right ventricular work, right ventricular dilatation and, eventually, in left ventricular outflow tract obstruction caused by intraventricular septal shifting toward the left ventricle. These changes may, in turn, decrease cardiac output and further reduce oxygen delivery to vital organs. For resolution, the dynamic interaction between inflammation, coagulation, restoration of water transport and cell function needs to be rebalanced and surfactant production restarted.

As is well known, lung-protective ventilation is based on limiting barotrauma (the pressure applied to the airways: Paw) and volutrauma defined as tidal volume (Vt) per ideal body weight (IBW). Recently, in addition to these parameters, the concepts of mechanical power, stress and strain have been introduced as more significant factors that contribute to acute lung injury[33,34]:

Mechanical power: Mechanical power is the amount of energy transferred from the mechanical ventilator to the lungs per unit of time and is expressed in joules per minute (J/cycle x cycles/min)[34]. The energy delivered per breath depends on which ventilatory parameters are set and is stored in part as elastic energy and is in part dissipated into the lungs. The risk of ventilator induced lung injury (VILI) from mechanical power depends not only on the amount of energy delivered by the mechanical ventilator to the respiratory system in the unit of time, but also on the lung size and the underlying lung disease. The energy transfer is less intense if the lungs have a large surface with uniform mechanical properties and is much higher if the ventilated area of the lungs is reduced (baby lung) as they are partially atelectatic with uneven mechanical properties. Depending on the amount of mechanical power, the alterations to the lung parenchyma may range from mechanical rupture of the lung skeleton to an inflammatory reaction.

Stress: this term defines the forces tending to cause extension from resting state. Paw is the pressure required to distend not only the lung but also the chest wall to the same extent. The transpulmonary pressure (P_{TP}) is the real pressure at which alveoli are stressed and is calculated as the difference between airway and pleural pressures (Paw-P_{PL}).
P_{TP} depends on (Figure 3):

- active inspiratory efforts (a);
- the relationship between lung and chest wall elastance (b).

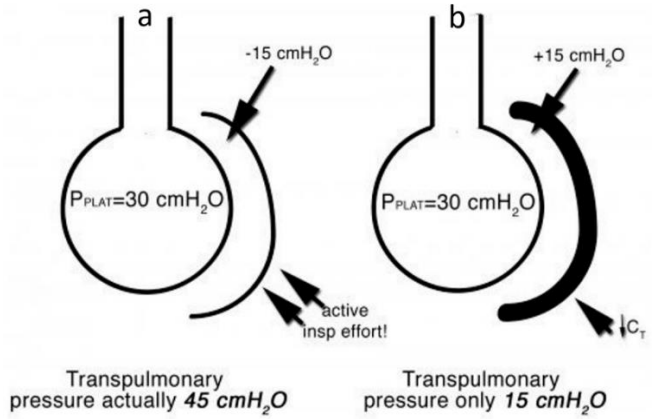

Figure 3. Transpulmonary pressure (P_{TP}) is the difference between airway and pleural pressures (Paw-P_{PL}). During mechanical ventilation its value depends on (a) the balance between Paw and active inspiratory efforts of the patient and (b) between Paw and the mechanical properties (elastance) of the chest-wall

The P_{PL} should be taken into consideration especially in the case of patients who are very dyspnoeic because the high P_{TP} generated by strong spontaneous breathing efforts favours negative-pressure pulmonary oedema and can worsen lung injury by patient self-inflicted lung injury (P-SILI), which appears to be closely correlated with the patient's excessive respiratory work[35]. The oesophageal pressure (P_{ES}) is considered the most effective surrogate for P_{PL}. In the case of patients on controlled mechanical ventilation, the measurement of oesophageal pressure is used for the evaluation of P_{TP}, which is an effective indicator of the dynamic stress to which the lungs are subjected: targeting transpulmonary pressure means "personalizing" the ventilatory settings[36]. In patients with spontaneous breathing, oesophageal pressure is a good indicator of the work exerted by the respiratory muscles and is therefore an effective indicator of respiratory effort[37].

Strain: this term defines the change in lung volume relative to its resting position, defined as Vt + positive end expiratory pressure (PEEP) volume/FRC (Vt + PEEP volume/FRC). Strain can be differentiated in dynamic strain, which is the change in lung volume in relation to initial volume (Vt/FRC + PEEP volume), and in static strain, which corresponds to the change in volume determined by PEEP. Dynamic strain is the most harmful for the lung, which means that it is the size of the lung that is being ventilated that is important, not the size of the Vt/kg itself. A volume of 6 mL/kg is normal for a well expanded lung, but it corresponds to 24 mL/kg in a lung where 25% of its volume is participating in gas exchange. When the ventilated lung reaches its maximal volume, i.e. total lung capacity (TLC), stress and strain increase abruptly; if the distension increases further, exceeding the tensile properties of the collagen, the pulmonary fibroelastic skeleton may be disrupted triggering a secondary inflammatory response (*biotrauma*)[38]. However, experimental data have demonstrated that harmful values of end-inspiratory stress and strain are rarely reached in clinical practice and damage has been reported with values well below the upper limit. This means that, in addition to stress, strain and baby lung, other factors such as a lung inhomogeneity and the presence of stress raisers in the lung parenchyma must be taken into account. *Stress raisers* or *concentrations* are sites in a structure where the stress is significantly greater than in the surrounding regions[39]. Stress concentrations occur locally at the interface between closed and open lung units, where lung injury is augmented by cyclic opening and closing of airway and pulmonary units. These areas, characterized by irregularities in geometry that cause an alteration in the flow of stress, are subject to a concentration of the force applied to lung tissue during ventilation and this force may be amplified several times (Figure4).

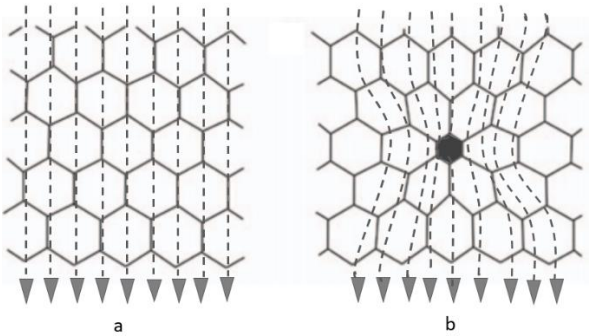

Figure 4. The open alveoli surrounding collapsed alveoli are subject to a concentration of the force applied to lung tissue during ventilation due to their mechanical interdependence. Stress and strain are minimized in homogeneously inflated alveoli (a), and increased in neighbouring atelectatic alveoli (b).

Mechanical ventilation: lung protective strategy

Positive pressure mechanical ventilation with supplemental oxygen is the cornerstone of treatment of severe hypoxemia, but careful attention must also be given to nutrition, sedation, analgesia, cardiopulmonary interactions and fluid balance.

The essential concept of lung-protective ventilation is the 'open lung strategy', characterized by the use of low Vt and facilitating its uniform distribution in well recruited lungs. The use of large tidal volumes (≥10 mL/kg) may cause a remarkable overdistention of the 'baby lung' resulting in loss of compliance. Based on these observations, the concept of VILI evolved during the 1990s, and VILI is now considered to continue the primary injury and sustain it (becoming secondary lung injury) following a similar histological and inflammatory pattern to that of the original ARDS. Current opinion is that secondary lung injury may be reduced using a strategy characterized by[17, 27,40]:

- Protective ventilation with low Vt: patient-specific Vt according to severity of disease should be considered. For example, Vt should be 3-6 mL/kg per IBW for those with reduced respiratory compliance, and closer to the expected or normal physiological range (5-8 mL/kg per IBW) for those with better preserved respiratory compliance.
- Decelerating flow: maintenance of airway pressure over time, i.e. the plateau pressure (P_{PLAT}), is more likely to inflate more difficult non-compliant lung units.
- P_{PLAT} ≤28 cmH_2O or ≤29-32 cmH_2O for patients with reduced chest compliance, as for example in the case of infants with hydrops, chest wall oedema, or abdominal distension.
- Airway driving pressure or delta pressure ($\Delta P = P_{PLAT}$ - PEEP) <13-15 cmH_2O. The driving pressure is the ventilation variable that best stratifies risk: decreases in ΔP owing to changes in ventilator settings are strongly associated with increased survival[19,41-43].
- Alveolar recruitment with 'best PEEP' (5-15 cmH_2O) in order to maintain FRC above closing volumes and to minimize repeated alveolar collapse and re-expansion. PEEP should be set according to an oxygenation target such as the protocol developed by the ARDS Network.[15,43]. This table recommends combinations of PEEP and FiO_2, such that both are increased or decreased in tandem as hypoxemia worsens or improves (Table 2). A multicentre, retrospective analysis of patients with PARDS demonstrated that patients had higher mortality when managed with lower PEEP relative to FiO_2 than that recommended by the ARDS Network[44]. Nevertheless, PEEP values >15 cmH_2O should be used with great caution, especially in younger infants, and applied only after other therapies to improve oxygenation have been considered. Unfortunately, definitive data do not exist to guide PEEP management for PARDS, and the optimal level is not yet well definable because 'lung recruitability' is extremely variable in this pulmonary disease. It is well known that alveolar overdistension increases both pulmonary vascular resistance and alveolar dead space, and thus worsens the intrapulmonary shunt. The right clinical strategy is to balance the cardiorespiratory effects of higher PEEP by determining the optimal relationship between increased pulmonary compliance, reduced dead-space ventilation, and satisfactory haemodynamics, while maintaining adequate oxygenation[15,18]. Optimal oxygen delivery may not occur at the point of maximal arterial oxygen content, because this may correspond to excessive mean intrathoracic pressure and, thus, lower cardiac output. Using a high level of PEEP, markers of oxygen delivery, pulmonary compliance and haemodynamics should be closely monitored. Cautious slow incremental or decremental PEEP recruitment steps may also be considered in those with severe oxygenation failure[15,44], but not by sustained inflation manoeuvres.

Table 2. Combinations of FiO_2 and PEEP according to ARDS Network Protocol

FiO_2	PEEP (cmH_20)
0.21-0.4	5
0.4-0.5	8
0.5-0.7	10
0.7-0.9	14
0.9-1	18
1	18-24

If the achievement of a normal pH and normal $PaCO_2$ requires respiratory support strategies that are potentially damaging to the lung, lower pH and higher $PaCO_2$ compared to normal levels should be tolerated to minimize this risk. Permissive hypercapnia is therefore acceptable to reduce Vt or P_{PLAT}, but $PaCO_2$ should remain ≤50-55 mmHg and balanced by serum bicarbonate levels to determine a pH above 7.20[15,27]. Adult data have demonstrated a significant improvement in mortality with this approach, which has also gained widespread acceptance in the paediatric field, although no large-scale randomized controlled trials (RCTs) have been performed to date. Unfortunately, there is no standardized guidance for

mechanical ventilation policy and supportive management of bronchiolitis once a child is admitted to PICU for bronchiolitis. This means that there are naturally occurring differences in the clinical management between PICU centres as well as difference in outcomes. Lately, the use of non-invasive ventilation has increased significantly with the aim of reducing the need of invasive mechanical ventilation. A retrospective analysis of more than 200,000 infants of less than 2 years of age admitted to the hospitals for bronchiolitis in United States from 2010 to 2019 showed that 19.3% were admitted to PICUs and that, while the use of non-invasive ventilation increased 7-fold from 2010 to 2019, the use of invasive mechanical ventilation did not significantly change over time suggesting that non-invasive ventilation was not a protective strategy to reduce the rate of mechanical ventilation[45]. Conversely, the use of non-invasive ventilation was unexpectedly associated with higher rates of cardiac arrest even after controlling for severity[46]. These higher rates could be explained by the fact that non-invasive ventilation may mask a progressive respiratory failure leading to cardiac arrest. This highlights both the need for appropriate cardiorespiratory monitoring during non-invasive ventilation and also the need to transfer to PICU patients at risk before their conditions worsens critically. These recent studies underline the need to conduct large prospective clinical trials on standardizing supportive care for children admitted to PICUs for bronchiolitis.

If adequate oxygenation and ventilation cannot be met with the lung protective strategy, the following therapeutic tools should be considered: exogenous surfactant, inhaled Nitric Oxide (iNO), High Frequency Oscillatory Ventilation (HFOV), recruitment manoeuvres, prone position, neuromuscular blocking agents (NMBA).

Surfactant treatment

It seems unlikely that surfactant use in infancy should follow the same strategy employed in premature infants characterized by administration of high doses by bolus, as the aetiology of surfactant deficiency differs significantly between these two groups of patients. In PARDS, the effects of surfactant with this mode of treatment are often only transient because it is rapidly inactivated, and repeated administrations are frequently needed for the treatment of severe respiratory failure[47-50]. Currently there are still few studies that have analysed the efficacy of surfactant in PARDS caused by bronchiolitis. Observational studies conducted in mechanically ventilated infants with viral pulmonary infection have demonstrated lower concentrations of surfactant lipids in broncho-alveolar lavage (BAL) fluids and endotracheal aspirates, which may be explained by viral invasion of type-II pneumocytes and altered regulation of the production of surfactant lipids[51-53]. Studies *in vivo* with stable isotopes showed that surfactant desaturated phosphatidylcholine is severely impaired in infants with bronchiolitis and severe respiratory failure[54]. A meta-analysis which included three small RCTs on a total of 79 participants suggested that the use of porcine surfactant for critically ill infants and children with bronchiolitis may reduce the duration of mechanical ventilation and the length of stay in PICU without any side effects[53]. Moreover, surfactant had favourable effects on oxygenation and elimination of CO_2. These data suggest a beneficial role for porcine surfactant in the treatment of viral respiratory infection when there are oxygenation disturbances, and the administration of surfactant at the onset of mechanical ventilation seems reasonable. The limited number of studies and the small cohorts of participants are the limitations of this review.

Many of the published trials have evaluated surfactant delivery in paediatric age via intratracheal instillation: a large quantity of surfactant is generally delivered by this route, which may be of benefit in counteracting the effect of surfactant inhibition. However, a large surfactant dose can also result in flooding of the central airways and in an increased airway resistance leading to worsening of hypoxemia. Moreover, uniform delivery of surfactant to both collapsed and expanded parts of the lung might improve atelectasis in affected regions but may be harmful in unaffected areas. An alternative is segmental administration by bronchoscopy[55,56]. However, this technique is not always easy to perform in clinical practice. BAL with saline-diluted surfactant is another mode of supplementation that may have greater efficacy since the endogenous surfactant pool is restored simultaneously with the removal of inhibitors and toxic agents from the alveoli[57,58]. A more recent trial was carried out in 14 Italian PICUs[59]. The protocol stipulated the administration of surfactant (50 mg/kg) in two separate doses: the first dose was used as a BAL and the second as supplementation. Sixty-nine children, age 0–24 months, affected by PARDS treated with exogenous porcine surfactant were enrolled, and RSV bronchiolitis represented one third of the cohort. A recruitment manoeuvre was performed after each administration (30 cmH_2O for 30 sec.) The results showed that the use of surfactant in its porcine form improves oxygenation, PO_2/FiO_2 ratio and pH without

adverse events for patients affected by moderate or severe respiratory failure. This study also supports the early use of surfactant as soon as the disease requires high-pressure mechanical ventilation and elevated FiO_2 or the use of non-conventional ventilation modes.

The type of surfactant used must be also considered. Various exogenous surfactants are available for clinical use: porcine (poractant alfa), bovine (calfactant), synthetic (lucinactant) surfactant. However, results varied when used *in vivo* for PARDS treatment.

Therefore, surfactant supplementation remains a great challenge in infants and children, but larger trials are necessary to test different modes of dosage, dilution and supplementation. Moreover, the inherent costs of surfactant preparations and the risk of inactivation urge the search for new synthetic surfactant preparations enriched with SP-B and SP-C proteins, that would be more stable and less expensive[60]. It is expected that this strategy will allow an early and no longer compassionate use of surfactant supplementation.

Inhaled Nitric Oxide

Hypoxemia in PARDS is caused mainly by a ventilation/perfusion mismatch with increased intrapulmonary shunting and pulmonary hypertension. Inhaled NO has been shown to be an ideal selective pulmonary vasodilator improving oxygenation and decreasing pulmonary arterial pressure. However, current data suggest that although iNO improves oxygenation in PARDS, it does not affect patient outcomes positively[61]. This conclusion is strengthened by the outcome of a meta-analysis of 604 children and adults with ARDS[62]. Moreover, an increased incidence of renal impairment in patients managed with iNO was reported. For these reasons iNO is not recommended for routine use in PARDS. However, its use may be considered in patients with documented pulmonary hypertension or severe right ventricular dysfunction. Its use may be considered also in selected cases of severe PARDS or as rescue therapy from extracorporeal membrane oxygenation (ECMO). Without clear positive effects its use should be discontinued[61,63].

High Frequency Oscillatory Ventilation

HFOV should be considered as an alternative ventilatory mode in hypoxic respiratory failure in patients in whom P_{PLAT} › 28 cmH_2O. With HFOV it is possible to ventilate the patient in the so-called "safe zone of the pressure/volume curve" preventing strain and stress: consequently, the main goals of lung protective ventilation may theoretically be achieved with this technique. A multicentre RCT compared the outcomes of adult patients affected by ARDS and treated with either the open-lung approach or HFOV[64]. The trial demonstrated that early application of HFOV does not reduce and may increase in-hospital mortality. Moreover, a recent multicentre trial on 328 paediatric patients reported that the use of HFOV was associated with increased 28-day mortality[65]. Thus, the use of HFOV in paediatric patients should be carefully considered only as rescue therapy and on an individual basis[15].

Recruiting manoeuvres

Lung recruitment is a strategy to increase P_{TP} briefly and to maximize the number of alveoli participating in gas exchange, which is usually achieved by slow incremental and decremental PEEP steps[15,66,67]. These interventions should be considered in children with early PARDS and severe hypoxemia, but the effects may be transitory. There is also the potential risk that some children will be non-responders to lung recruitment and that this manoeuvre may in fact simply overdistend already recruited alveoli. Moreover, the increase in intrathoracic pressure during the recruitment manoeuvre provokes a reduction in venous return and therefore in cardiac output. Additionally, overdistension of alveoli will increase the regional pulmonary vascular resistance and will subsequently decrease regional perfusion. The current evidence does not allow a consensus to be reached on which method is most effective, nor on which patients are most appropriate for lung recruitment manoeuvres: for these reasons their clinical use is still controversial. Nevertheless, bedside monitoring of alveolar recruitment by trans-thoracic lung ultrasound or electrical impedance tomography are increasing in clinical practice and in the near future they should become powerful tools for monitoring and measuring lung expansion in real time.

Prone position

Decreased lung compliance in patients with PARDS is the result of uneven distribution of P_{TP} with hyperinflation of nondependent (sternal) zones and collapse or consolidation of dependent (dorsal) ones, in which there is also an increased retention of interstitial fluid. Under the influence of gravity and a consequent reduction in the compression of the lungs by the heart, the prone position determines changes in the distribution of P_{TP} and pulmonary perfusion in the dependent lung regions. As such, it may be helpful both in reducing the extension of collapsed areas and in facilitating the drainage of secretions. In the prone

position, the application of PEEP or alveolar recruitment manoeuvres can distribute P_{TP} more homogeneously, leading to more uniform lung expansion[68-70]. This technique has good evidence for benefit in adults and is easier to apply in infants[71]. However, it is still rarely used in paediatric age[72], despite consensus-based recommendations to consider it in severe PARDS[61]. A Cochrane review published in 2012 concluded that prone positioning is significantly more beneficial than supine positioning in terms of oxygen saturation, arterial oxygen and thoracoabdominal synchrony[73]. In a more recent trial, 14 infants with a median age of 33 days and with severe bronchiolitis were randomized to receive 7 cmH_2O of continuous positive airway pressure (CPAP) for 1 hour in either the prone position or in the supine position, followed by 1 hour in the supine position or prone position respectively[74]. Flow and oesophageal, airway, gastric and transdiaphragmatic pressures, as well as the electrical activity of the diaphragm were simultaneously recorded; the results suggest a benefit of the prone position for infants with severe bronchiolitis requiring non-invasive ventilation by significantly decreasing the inspiratory effort and the metabolic cost of breathing.

Nevertheless, the prone position is not without problems: the patients are at increased risk of pressure ulcers at the contact points (especially on the face), obstruction or dislodgement of the endotracheal tube, and they may have an increased need of sedation or difficulties with enteral feeding. However, these adverse events probably occur mainly in PICUs whose personnel use prone positioning infrequently. Currently there is not enough evidence to recommend its use routinely in the paediatric field, but its employment must be considered in infants affected by severe PARDS[61].

Neuromuscular blocking agents

In PARDS, children must receive adequate sedation to improve their tolerance to mechanical ventilation. Simple and reliable pain/sedation scales appropriate for different ages should be used for monitoring and titrating to achieve sedation goals. In infants who produce intense inspiratory efforts, there is the risk of P-SILI due to deep swings in P_{TP} and, if sedation is not sufficient to achieve effective and protective synchronized ventilation, then paralysis with NMBA must be considered. These drugs should be used early in the course of PARDS and, if possible, for the shortest time necessary[15,18]. The harmful effect of NMBA, especially if associated with steroids whose routine use is not recommended, is the appearance of critical illness myopathy, a neuromuscular weakness that delays weaning, disturbs rehabilitation, and is associated with increased hospital and PICU stays as well as increased PICU death rates[75,76]. The beneficial effects of short-term use of NMBA in severe PARDS are:

- improvement in OI, PaO_2/FiO_2 and decreased mean Paw;
- reduced patient-ventilator asynchrony;
- minimization of barotrauma by prevention of P-SILI and active expiration;
- decreased lung inflammation and reduced oxygen consumption resulting from decreased WOB.

Conclusions

The cornerstone of the management of PARDS caused by severe bronchiolitis is the early and correct intensive care treatment and prevention of its side effects and complications. This strategy, based above all on lung protective strategies, may improve outcomes and increase survival. Neonatologists and paediatric intensivists treating these patients must be aware of the remarkable differences in pathophysiology between neonatal RDS and paediatric ARDS. The new definition of PARDS and NARDS may aid in both more uniform and earlier recognition of the disease and will be useful for clinical, epidemiological, and research purposes.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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