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REVIEW ARTICLE

Surfactants in Acute Respiratory Distress Syndrome in Infants and Children: Past, Present and Future

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Abstract There is a lack of definitive data on the effective management of acute respiratory distress syndrome (ARDS) in infants and children. The development and validation of the Berlin definition (BD) for ARDS and the Pediatric Acute Lung Injury Consensus Conference (PALICC) recommendations in children represented a major advance in optimizing research and treatment, mainly due to the introduction of a severe ARDS category. Proposed reasons for the lack of consistent results with surfactants in children and infants compared with neonates include different causes, type of lung damage (direct or indirect), timing and mode of administration as well as the type of surfactant used. Secretory phospholipase A2 plays an important role in inflammation and possible dysfunction of surfactants in ARDS. Bronchoalveolar lavage (BAL) with normal saline and surfactant allows the removal of inhaled material, the recruitment of non-ventilating areas and the maintenance of the surfactant pool size. BAL with diluted surfactant allows rapid absorption of the surfactant at the air/liquid interface, which blocks the progression of pathological lung disease and in turn disrupts the inflammatory cycle. Importantly, it is now recognized that the type of surfactant, the time of administration and the method of administration could all play an important role in the management of ARDS, and there is evidence that surfactant is effective and well tolerated in children and infants with ARDS.

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Key Points

ARDS is a multifactorial syndrome that causes significant morbidity and mortality in infants and children.

The BD can evaluate the severity of ARDS in children as shown by the decreased survival and reduced number of ventilation-free days in patients with severe ARDS compared with patients with mild and moderate ARDS.

Negative trial data have been published on the use of surfactants in infants/children with ARDS but it is important to evaluate every aspect of the selected treatment.

ARDS in infants and children is different from hyaline membrane disease—in children, as well as an underlying surfactant deficiency, there is inhibition/inactivation of endogenous surfactant. In these patients, removal of inhibitors should be performed before administration of exogenous surfactant.

The type of lung damage first needs to be established: exogenous surfactant therapy is useful in patients with direct lung injury.

BAL with normal saline and surfactant may show a synergistic therapeutic effect that allows the removal of inhaled material, the recruitment of non-ventilating areas and the maintenance of surfactant pool size. BAL using a diluted surfactant solution followed by supplementation of exogenous surfactant with regular instillation has been effectively adopted in clinical trials.

The timing, dosage and type of surfactant used are of paramount importance. The earlier treatment is begun the greater the chance of a positive outcome.

There are reliable real-world data showing poroctant alfa is effective and well tolerated in children/infants with ARDS.

1 Introduction

Effective management of acute respiratory distress syndrome (ARDS), a pulmonary condition with overwhelming clinical consequences, remains elusive despite many years of ongoing research [1]. This is in part due to its complex pathogenesis and heterogeneous clinical features but also to the difficulties involved in conducting large-scale clinical trials, especially in paediatric patients. Intensity of scientific discussion surrounding the management of ARDS with surfactant iterates that it is an opportune time to review our current understanding. In this paper we discuss how the definition of ARDS has changed in recent years, outline the processes involved in the development of ARDS in infants and children, identify gaps in our knowledge and present available data on the use of surfactant.

2 Defining Acute Respiratory Distress Syndrome (ARDS)

A validated definition of ARDS is fundamental in designing clinical trials, assessing the benefits and risks of a given therapy, identifying subgroups of patients who may benefit from new therapies, and determining prognosis [2, 3]. Since its first description in the 1960s, considerable progress has been made in the understanding and management of ARDS. The American–European Consensus Conference (AECC) in 1994 defined acute lung injury (ALI) as respiratory failure of acute onset with a PaO_2/FiO_2 ratio $\leq$300 mmHg and ARDS as a PaO_2/FiO_2 ratio $\leq$200 mmHg [4]. Despite the fact that an 11-year-old and four teenagers were among the 12 patients initially reported by Ashburgh, the syndrome was termed ‘adult respiratory distress syndrome’ [2, 3]. The AECC later recommended that ‘adult’ be changed to ‘acute’ to accurately reflect the fact that the syndrome occurs in both adults and children.

In 2012, the Berlin definition (BD) addressed many of the limitations of the AECC [5–7]. Essentially, according to the new BD, ARDS was considered as a unique pathophysiological process and was described by timing, radiographic changes, origin of oedema and severity. It was classified as mild, moderate or severe according to the PaO_2/FiO_2 ratio. The ALI term was not included in the BD because it was not useful and frequently used inappropriately.

3 Berlin Definition of ARDS Validated for Adults: But What About Infants and Children?

It has long been recognized that ARDS in infants/children is different from that in adults, and both the AECC and BD have limitations when applied to children. The European Society for Paediatric Neonatal Intensive Care (ESPNIC) evaluated BD validity for a paediatric population, reporting that in ages between 30 days and 18 months. It is mainly due to the introduction of a ‘severe ARDS’ category [7, 8].

It is suggested that the BD can better describe the severity of ARDS in children in comparison with the AECC definition, as shown by the decreased survival in patients with severe ARDS compared with patients with mild or moderate ARDS [9]. A subsequent study confirmed that in patients aged up to 15 years old who have ARDS, the BD can identify a subgroup of patients with distinctly worse outcomes, as shown by the increased mortality and reduced number of ventilator-free days in the severe ARDS group. The authors concluded that BD must not be thought of as a prognostic tool, but should be used to optimize clinical assistance, research and health services planning in paediatric critical care [9].

Considering the lack of a paediatric-specific definition of ARDS and a paucity of robust clinical trials in this population, the Pediatric Acute Lung Injury Consensus Conference (PALICC), in an effort to initiate discussion regarding optimization and consistency of care for paediatric ARDS (PARDS), developed paediatric-specific definitions and recommendations on treatment and research priorities [10–12]. As in the BD, the onset of PARDS must occur within 7 days of a known clinical insult, and respiratory failure must not be fully explained by cardiac failure or fluid overload. To grade disease severity, the PALICC used the oxygenation index (OI) but if patients are under non-invasive support and arterial blood gas was not available, the oxygen saturation index (OSI) rather than the PaO_2/FiO_2 ratio was used. The introduction of OSI allows the application of a standardized definition to children without an arterial line [13]. According to a recent study, applying the PALICC definition more paediatric patients with ARDS may be identified and the mortality rate may be lowered except for the more severe group [14]. Epidemiological data and animal studies suggest there are age-dependent differences in distribution, causes and peculiarity of ARDS, whereas the pathophysiology of ARDS does not change. It is important to understand the differences to identify new therapeutic interventions to prevent/modulate lung injury and improve repair [15].

4 Incidence of ARDS

The lack of an accepted validated definition for ARDS and the dearth of prospective studies mean that a wide range in the incidence is quoted in the literature. Before the availability of current definitions, the estimated incidence in the USA ranged from 50,000 to 190,000—nearly a fourfold difference [16]. In 2005 Rubenfled et al. [17], in a prospective cohort study to address some of these limitations, concluded that the incidence of ALI/ARDS in the USA was substantially higher (2.5–5 times for ALI and 2–40 times for ARDS) than previously considered. They estimated that in the USA there are 190,600 cases of ALI annually associated with a staggering 3.6 million hospital days.

While we know that ALI/ARDS occurs less often in children and infants, large numbers are nevertheless affected—in the USA an estimated 2,500–9,000 children have ARDS, contributing to 500–2,000 deaths each year [18]. If compared to adults ARDS in children shows a lower mortality, this is probably due to a more frequent infectious trigger. A prospective multicentre study in Australia and New Zealand using American–European Consensus Conference guidelines showed a population incidence of 2.95/100,000 in children under 16 years of age. While ALI accounted for just 2.2% of admissions to paediatric intensive care, mortality was high (35%) [19]. Similarly, a retrospective observational study in The Netherlands in children aged 0–16 years reported an incidence of 2.2 per 100,000 per year and a mortality rate of 20.4% [20]. The reported incidence of paediatric ARDS is lower compared to that in adults but data are underestimated because the AECC definition is used. ARDS is still an underdiagnosed and undertreated condition with high mortality and major social and economic costs. There is clearly a significant need for an improved therapeutic strategy for the management of paediatric patients with ARDS.

5 Mechanism of Surfactant Deficiency in ARDS

Natural pulmonary surfactant plays an essential role in lung physiology; it is responsible for lowering surface tension within the alveoli and maintaining the functional integrity of the distal airways. It is a phospholipoprotein formed and stored by type II alveolar cells. The main lipid component of surfactant, DPPC, reduces surface tension by covering the air–water interface of alveoli due to its hydrophilic head groups that stay in the water and its hydrophobic tails, which face towards the air. Lack of surfactant results in respiratory failure, secondary to atelectasis, alveolar flooding and severe hypoxaemia. Since the advent of exogenous surfactant replacement therapy, mortality from respiratory distress syndrome in neonates has been reduced by >50% [21]. Surfactant deficiency in hyaline membrane disease is well described, and it has also been recently suggested that other mechanisms promote the quantitative dysfunction of surfactant in the lungs of neonates causing an ARDS-like appearance. It is known that in the paediatric age group ARDS is due to a severe lung inflammation and to qualitative and quantitative surfactant deficiencies [22, 23]. Even though surfactant abnormalities in ARDS are not the primary pathogenic factors, surfactant deficiency, either in the presence or absence of type II

pneumocyte alterations, may result from primary or secondary inhibition/inactivation of pulmonary surfactant in the alveolar space [16, 24, 25]. Type II secretory phospholipases A2 (sPLA2) is an enzyme that plays a key role in this cascade, correlating with the clinical severity of patients [26]. An increased activity of sPLA2 has been detected in adult patients and in children affected by ARDS, confirming that its pathophysiology is the same across a range of ages. sPLA2 promotes inflammation and directly catabolizes surfactant phospholipids through the hydrolysis of dipalmitoil-phosphatydil-cholina (DDPC) [26–28]. Moreover, this enzyme causes the inactivation of exogenous surfactant [29].

Surfactant deficiency and inactivation will further induce alveolar collapse and pulmonary oedema, leading to the characteristic pathophysiology of ARDS. ARDS is associated with direct and indirect (systemic) pulmonary causes—for the former clinical trial evidence suggests that exogenous surfactant therapy shows greater efficacy while in the latter multi-organ pathology significantly affects long-term outcomes, reducing the effectiveness of pulmonary-based therapies such as exogenous surfactant. Surfactant dysfunction in ARDS is most prominent in the acute exudative phase of disease, and it is here where surfactant therapy has the greatest theoretical benefits [30].

6 Surfactant: The Solution to This Now Well-Defined Problem?

Despite the fact that surfactant deficiencies occur in patients with ARDS, trials of exogenous surfactant therapy in adults have had variable success in improving long-term outcomes. Only three specific interventions—the use of low tidal volumes, prone positioning and neuromuscular blockade early in the course of severe ARDS—have been shown to decrease mortality in adult patients with ARDS [25, 30, 31]. However, exogenous surfactant may improve outcomes in infants and children (Table 1) [32–48]. For almost a quarter of a century there have been reports of the benefits of exogenous surfactant in infants and children with acute respiratory failure or ARDS. One of the early studies by Auten et al. [39], in full-term neonates with respiratory failure associated with pneumonia and meconium aspiration syndrome, showed that intratracheal calf lung surfactant significantly improved oxygenation.

Table 1 Overview of case histories and clinical trials demonstrating the benefits of exogenous surfactant therapy in children/infants/babies with acute respiratory failure or acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) (adapted from Raghavendran [25])

Study	Patients (*N*)	Disease or syndrome	Surfactant	Outcomes
Fettah et al. [48]	Baby (1)	ARDS secondary to near drowning	Curosurf®	Rapid and persistent improvement after 2 doses of Curosurf® (100 mg/kg body weight, 1.25 ml/kg)
Willson et al. [45]	Children (110 enrolled)	ARDS	Infasurf®	No immediate improvement in oxygenation: study stopped at sponsor's request
Willson et al. [34]	Children (152)	ARDS from multiple causes	Infasurf®	Improved oxygenation and ventilation
Moller et al [38]	Children (35)	ARDS, multiple causes	Alveofact®	Improved oxygenation
Hermon et al. [36]	Children (19)	ARDS + post-op cardiac	Curosurf® or Alveofact®	Improved oxygenation
Herting et al. [37]	Children (8)	Pneumonia	Curosurf®	Improved oxygenation
Luchetti et al. [44, 46]	Infants (20 and 40)	RSV bronchiolitis	Curosurf®	Improved oxygenation
Tibby et al. [47]	Infants (19)	Respiratory syncytial virus bronchiolitis	Survanta®	More rapid improvement in oxygenation and ventilation indices over the first 60 h of ventilation
Lopez-Herce et al. [35]	Children (20)	ARDS + post-op cardiac	Curosurf®	Improved oxygenation
Willson et al [32, 33]	Children (29 and 42)	ARDS from multiple causes	Infasurf®	Improved oxygenation
Findlay et al. [43]	Infants (40)	Meconium aspiration	Survanta®	Improved oxygenation decreased pneumothorax and mechanical ventilation
Lotze et al. [40, 41]	Infants (28 and 328)	ECMO, multiple indications	Survanta®	Improved oxygenation, decreased ECMO
Khammash et al. [42]	Infants (20)	Meconium aspiration syndrome	bLES®	Improved oxygenation in 75% of patients

Similarly, intratracheal surfactant moderately improved oxygenation in children with secondary pulmonary pathology or systemic disease [35]. Following the positive results of a pilot trial, Willson et al. [32] conducted a prospective, randomized, controlled trial in 42 children (aged 1 day to 18 years) with hypoxaemic respiratory failure. Results showed intratracheal administration of calfactant was well tolerated and associated with a rapid improvement in oxygenation, earlier extubation and decreased requirement for intensive care [33]. The same group conducted a similar multicentre, randomized, placebo-controlled trial using a larger cohort (152) of patients with ARDS [34]. Endotracheal surfactant improved oxygenation and significantly decreased mortality (27/75 vs. 15/77 in the placebo and treated groups, respectively). There were no differences in long-term complications. In contrast with the previous trial, the duration of respiratory failure was not improved with calfactant with a mean duration of ventilation and length of hospital stay being similar in the two groups. The authors suggest this may be due to the disproportionate survival of marginal surfactant-treated patients and, paradoxically, increased survival may increase the need for prolonged supportive care. Post-hoc analysis demonstrated that improvements with surfactant occurred only in those patients with direct lung injury (pneumonia, aspiration or near drowning), and so it was decided to focus on a more homogeneous population of children with direct injury. 110 paediatric patients (aged from 37 weeks post-conception to 18 years) with direct ARDS were randomized to receive either surfactant or placebo (air) within 48 h of intubation and initiation of mechanical ventilation [45]. Unlike previous studies there appeared to be no improvement in oxygenation with surfactant administration. This was unexpected as only patients with direct lung injury (the subgroup that appeared to benefit most in the ad hoc analysis) were enrolled. The study was stopped early at the sponsor's request. The authors proposed three possible contributory factors for the lack of response: surfactant volume used was more concentrated, it was administered without a recruitment manoeuvre and instillation was performed in two rather than four aliquots with two rather than four position changes during administration. This study had an important bias because it evaluated oxygenation only with saturation in young patients where the amount of fetal haemoglobin is unpredictable. Moreover, a mixed adult-paediatric population was enrolled before the BD and PALICC definition were published. Jat and Chawla [49] reviewed three studies with a total of 79 patients on the use of surfactant therapy in the management of bronchiolitis in critically ill infants and concluded that surfactant had positive effects on the duration of mechanical ventilation, duration of time spent in the intensive care unit, oxygenation and carbon dioxide elimination. When the results of the Luchetti 1998 study were excluded (extreme heterogeneity of the study population), the duration of mechanical ventilation was significantly shorter in the surfactant group. No adverse events and no complications were reported. The authors concluded there is a need for large trials and cost-effectiveness data before the use of surfactant can be universally recommended in infants with bronchiolitis.

In summary, clinical trials (controlled and uncontrolled) reported that exogenous surfactant therapy could be beneficial in children and infants with ARDS/ALI without significant adverse long-term effects.

7 How to Explain this Dichotomy: What Should We be Doing in the Clinic?

Surfactant has proven efficacy in pre-term babies so why are results inconsistent in infants and children? Marraro et al. [50] outlined possible factors that could account for the inconsistent results. One possible reason is the different origins of lung pathologies—a deficiency of surfactant in preterm babies can be resolved by the administration of exogenous surfactant, but in infants and children in addition to reduced surfactant production there may also be inhibition/inactivation of any surfactant produced. In these patients it is necessary to first remove the inhibitors (for example, inflammatory mediators) before giving surfactant. A second reason could be the type of lung damage—we have seen that in patients with direct lung injury (for example bronchiolitis, near drowning) exogenous surfactant is effective in improving gas exchange and survival while patients with indirect lung injury do not show similar outcomes [51]. A third possible reason is the mode of administration of surfactant therapy. In recent years, there have been some experiences of alternative, less invasive methods of the administration of surfactant, but evidence supporting the most appropriate method does not exist. [52] Bronchoalveolar lavage (BAL) with normal saline and surfactant has the advantage of facilitating a synergistic effect that allows removal of inhaled material, the recruitment of non-ventilating areas and the maintenance of surfactant pool size. It may be that BAL with diluted surfactant allows rapid absorption of the surfactant at the air/liquid interface, which blocks the progression of pathological lung disease and in turn disrupts the inflammatory cycle [49, 53]. Timing of surfactant therapy may also be important: if treatment is started early there could be an improved chance of success, but definite timing has not been established [48]. Finally, it is now recognized that the type of surfactant used plays an important role [51]. Considering surfactant composition and the important role of sPLA2 on pathophysiology of lung damage in ARDS,

Table 2 Possible mechanisms and possible solutions for surfactant failure in paediatric acute respiratory distress syndrome (PARDS)

Possible mechanism	Possible solution
sPLA2 inactivation	Use of surfactant refractory to sPLA2 inactivation
Failure to remove PARDS triggers	Adoption of anti-inflammatory agents, antibiotics, anti-viral therapy
Lack of knowledge of effective dose/lavage ratio	Modification of ratio based on BAL studies
Lack of knowledge of effective dose	Modification of dose
Lack of knowledge of effective procedure	Use of bronchoscope and bronchoalveolar lavage
Composition of surfactant	Use of more effective one
Wrong timing	Start earlier the treatment
Poor ventilated lung areas	Lung recruitment by ventilation, bronchial toilette, prone position

also due to a surfactant inactivation, some strategies might be considered. For example, animal studies suggest the lung-protective effect of surfactant refractory to sPLA2 inactivation or the positive action of surfactant in directly inhibiting sPLA2. Moreover, surfactant might spread anti-inflammatory agents in an ARDS lung [54–56]. Table 2 shows the possible mechanisms for surfactant failure in PARDS.

8 Surfactant Administration Via Bronchoalveolar Lavage: The Way Forward?

BAL with diluted surfactant allows rapid absorption of surfactant at the air/liquid interface. Animal studies indicate that optimal results are obtained when BAL using a diluted surfactant solution was followed by a supplementation of exogenous surfactant with regular instillation [57]. This procedure allows better distribution of the exogenous surfactant in the lung, reduces the total amount of surfactant used and benefits from the detergent proprieties of surfactant as a safe and potent lavage solution. There is limited evidence from clinical trials in humans but surfactant BAL seems to act better than simple instillation as it uses a larger volume and has improved peripheral distribution especially in severely injured lungs. BAL removes inflammatory factors that inactivate surfactant and reduces the dosage of exogenous surfactant left in the lungs after lavage. There are several case reports describing BAL with diluted surfactant in ARDS children using either bronchoscope manoeuvres (older children) or direct tracheal lavages (smaller children) but no definitive data exist. Despite ARDS, the aetiologies were very different (sepsis, near drowning, trauma and aspiration syndrome), and all of them showed a rapid decrease of ventilator settings and improvement of lung mechanics after the treatment [58–60]. Unfortunately, insufficient data exist regarding many open questions on this therapeutic strategy. There is a lack of knowledge with regard to the best surfactant-lavage ratio, the adequate dosage after lavage, the best timing for administration of the treatment, the way to perform the procedure and how to ventilate the patient after treatment. More data are necessary to better understand BAL composition in animal models and in vivo patients of different ages in order to attain answers to these questions. Studies on this topic are difficult of perform in Pediatric Intensive Care Units due to the small numbers and the logistical aspects (necessity for laboratories and economic support). A standardized procedure and common guidelines for this topic are necessary.

Compliance with Ethical Standards

This article was written according to acceptable ethical standards.

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Conflict of interest A. Amigoni, A. Pettenazzo, V.Stritoni have no conflicts to declare. M. Circelli is an employee of Chiesi Farmaceutici Spa.

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