


Respiratory Therapy Peculiarities for Acute Respiratory Distress Syndrome in Children with Sepsis: A Narrative Review

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Abstract

Respiratory therapy for acute respiratory distress syndrome (ARDS) is a crucial link to the positive outcome of treatment in patients in the intensive care unit (ICU). A particular category of patients is children with ARDS and concomitant septic processes in the body. Difficulties arise in the successful intensive care of such patients due to the peculiarities of formulating clear diagnostic criteria for co-occurring pathological processes and the anatomical and physiological features of the respiratory system in children. It should be emphasized that artificial lung ventilation (ALV) in children with ARDS is not entirely unambiguous, and the currently available protocol for "protective" ventilation in children with ARDS entails many complications that aggravate the course of sepsis. This review aims to study current recommendations for diagnosing sepsis and acute respiratory distress syndrome in children, the features of the generally accepted mechanical ventilation protocol in children with ARDS, and possible ways to improve its effectiveness. The article reflects the epidemiology, current definitions, and diagnostic methods of pediatric sepsis and ARDS, as well as the peculiarities of ventilation in children with ARDS.

Keywords: Pediatric Sepsis, Pediatric Sepsis Diagnosis, Pediatric Acute Respiratory Distress Syndrome, Artificial Lung Ventilation, Intelligent Mode, Adaptive Support Ventilation (ASV).

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Introduction

Acute respiratory distress syndrome is one of the intensive care unit's most challenging pathologies to diagnose and treat. A recent study by PARDIE (Pediatric acute respiratory distress syndrome: incidence and epidemiology) reports an occurrence of 3.2% amid children accepted to the ICU. The death rate amid those patients who were ventilated is 6.1% (1).

Considering the structure of the causes of ARDS in children, we can distinguish between pulmonary causes, which directly damage the lungs, and extrapulmonary causes,

which act indirectly. The leading etiologic factors are pneumonia (35%), aspiration (15%), sepsis (13%), conditions close to drowning (9%), concomitant heart disease (7%), and other clinical conditions (21%). Infectious etiologies, including sepsis and pneumonia, account for about half of these (2) (Figure 1).

Diagnosis and treatment of ARDS and sepsis in pediatric practice are still primarily challenging. This is due to differences in the interpretation of diagnostic criteria resulting from the polymorphism of clinical manifestations of sepsis

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↑What is "already known" in this topic:

Pediatric acute respiratory distress syndrome (PARDS) is a common and dangerous complication of sepsis in children. Adult diagnostic criteria and respiratory support protocols (Berlin definition, ARDS Network protocol) do not take into account the anatomical and physiological characteristics of children. The current PALICC consensus recommends lung-protective ventilation; however, its use in sepsis remains controversial due to the high risk of complications.

→What this article adds:

This narrative review confirms that the PALICC criteria are significantly more accurate than the Berlin criteria in stratifying mortality risk in children with PARDS. Furthermore, the article highlights that standard ventilation protocols can worsen sepsis and suggests considering intelligent modes, such as ASV, as a promising avenue for improving treatment outcomes.

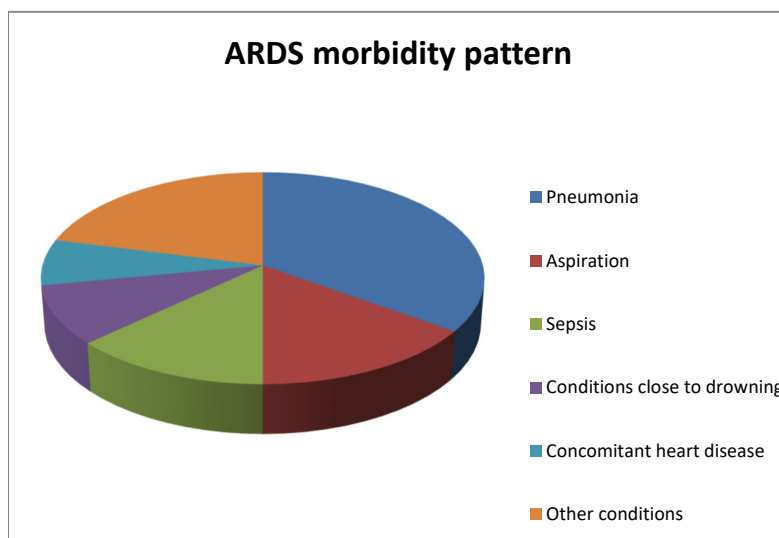


Figure 1. Describes the structure of the causes of ARDS in children

and acute respiratory distress syndrome in children of various age cohorts. It is also related to the anatomical and physiological features of the child's body systems, especially the respiratory and cardiovascular systems, and the inherent difficulty of identifying these criteria in comparison to those of adults. For a long time, the measures for pediatric sepsis and acute respiratory distress syndrome were excluded from the main recommendations published by sepsis and ARDS congresses, which were intended for adults. Respiratory therapy for ARDS in children with sepsis, as regulated by the Pediatric Acute Lung Injury Consensus Conference (PALICC), although covering its main directions, still leaves many questions for further research in this area.

Methods

A all-round literature survey was carried out in PubMed, Medline, and Scopus for a 10-year period from January 2015 to December 2024. The year 2015 was chosen as the starting point due to the publication of the new international guidelines of the Paediatric Acute Lung Injury Consensus Conference (PALICC), which replaced the 2012 Berlin definition of ARDS in pediatric practice. The following search string with Boolean operators was used: ("pediatrics sepsis" or "pediatric sepsis diagnosis") and ("acute respiratory distress syndrome in children" or "pediatric ventilation therapy" or "protective ventilation" or "artificial ventilation" or "intelligent mode" or "adaptive support ventilation" or "ASV"). The search was refined using filters such as article type (review, clinical trial, original article), the presence of an abstract, and the presence of a full-length article. Language restrictions were applied: only publications in English were comprised in the analysis because of the deficiency of high-quality translations and interpretations.

We focused on the pediatric population, defined as children aged 1 year (excluding neonates/preterm infants and children younger than 1 year) to 10 years. Exclusion criteria

were as follows: studies focusing exclusively on the adult population; case reports with fewer than 20 patients; conference abstracts without full-text access; and studies published before 2015. An initial search of all databases identified 98 records. After deletion copies and selection headings and abstracts, 58 articles were considered potentially eligible. Following full-text review, studies were subsequently excluded because they focused on the adult population, did not report primary clinical outcomes, or were published as conference abstracts. Ultimately, 19 articles were selected for final inclusion. These articles represent the most clinically relevant data on pediatric ventilation strategies for ARDS, pediatric sepsis, and modern intelligent modes as of 2025.

The principles of intensive therapy outlined in the protocol used in our country are not fundamentally different from the concept of ARDS treatment according to PALICC. There are protocols for the diagnosis and therapy of Acute Respiratory Distress Syndrome in grownups in the Republic of Kazakhstan. These measures include nutritional modification with an early transition to enteral feeding to reduce the risk of hospital-acquired pneumonia and other infectious outcomes. Secondly, the approach to implementing infusion therapy is also variable, with mandatory control of its adequacy at a level sufficient for tissue perfusion (3). As pulmonary capillary permeability increases in ARDS, fluid intake restriction should help reduce the severity of pulmonary edema. However, on the other hand, with decreased CVC, cardiac output decreases, oxygen delivery to the tissues deteriorates, and the detoxification process worsens, which is especially important during sepsis in the body.

Respiratory support protocol for ARDS (NIH ARDS Network), as outlined in the guidelines and used in Kazakhstan (3) (Table 1).

There is no unified protocol for diagnosing and treating pediatric ARDS in Kazakhstan. The intensive care

Table 1. The respiratory support protocol for ARDS (NIH ARDS Network)

| Parameter | Protocol |
|---|--|
| Ventilation mode | Volume assist-control |
| Respiratory volume | 6 mL/kg of proper body weight |
| Plateau pressure | 30 cmH ₂ O. |
| Respiratory rate/desired pH | 6-35/min; adjust to achieve a pH of 7.30 if possible. |
| Inspiratory flow, I:E | Adjust to achieve I:E ratio of 1:1-1:3 |
| Desired oxygenation level | PaO ₂ 80 mmHg or SpO ₂ 95% |
| FIO ₂ /PEEP combination (mmHg) | 0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1.0/18, 1.0/22, 1.0/24 |
| Respirator weaning | Tries to wean with pressure support at FIO ₂ /PEEP 0.40/8 |

Note. *SpO₂ – arterial blood O₂ saturation by pulse oximetry

protocol, including respiratory support for adult ARDS in Kazakhstan, is not fundamentally different from the protocol adopted worldwide, as it is based on the same global recommendations (NIH ARDS Network). In contrast to the respiratory therapy of pediatric ARDS according to PALICC, the local protocol includes additions in the form of a definition of the recommended mode of ventilation, a ratio of respiratory rate to desired pH, inspiratory flow rates, and FIO₂/PEEP combinations, as well as conditions for ventilator weaning (3).

Results

The 20 selected articles were synthesized into thematic areas to assess outcomes related to ventilation strategies, specific modes, and compliance with PALICC guidelines. Key findings and outcomes from the reviewed studies are summarized in Table 2, demonstrating the effect sizes and

evidence strength.

The analyzed studies demonstrate significant heterogeneity in study design (ranging from expert consensus to randomized controlled trials), age ranges within the pediatric spectrum (from neonates to adolescents), and underlying etiologic factors of ARDS. This variability limits the feasibility of direct meta-analysis for specific effect sizes. Despite this heterogeneity, all high-quality studies strongly suggest that partisanship to lung-protective ventilation principles is directly associated with elevated survival in children. Current data also confirm that the Berlin definition of ARDS underestimates illness severity in pediatric patients compared to the PALICC criteria, which are more sensitive to the anatomical and physiological characteristics of children's body systems. Furthermore, data on intelligent modes, such as ASV, are primarily derived from observational studies and systematic reviews. This

Table 2. Summary of key outcomes from selected studies on pediatric ARDS respiratory therapy

| Study (Author, Year) | Study Design | Population / Scope | Key Outcomes / Effect Sizes | Strength of Evidence |
|----------------------------|--------------------------|--------------------------|---|---|
| Khemani et al. (1) | Observational (PARDIE) | 145 PICUs / 955 children | 17% mortality with PALICC criteria. It is confirmed that Berlin criteria underestimate PARDS severity. | High-quality multicenter data. |
| Cheifetz (2) | Clinical Review | Pediatric patients | Advocates for VT of 6 mL/kg, high PEEP of 10-15 cm H ₂ O, and permissive hypercapnia with a pH of 7.15-7.30. | Expert consensus / Basis for practice. |
| PALICC Consensus (4) | Consensus Guidelines | International | Established Oxygenation Index (OI) for severity; OI > 16 correlates with 33% mortality. | Gold standard for PARDS definitions. |
| Prusakowski & Chen (5) | Clinical Review | Pediatric sepsis | Emphasizes the early recognition and aggressive fluid resuscitation in sepsis-induced PARDS. | Comprehensive clinical guidance. |
| Matics & Sanchez-Pinto (7) | Validation Study | 303 children | Validated pSOFA score demonstrated higher mortality in sepsis-associated dysfunction (12.1%). | Strong evidence for organ failure scores. |
| Roberts et al. (8) | Data Analysis | 2M+ measurements | Developed age-based MAP percentiles for more precise hemodynamic monitoring in children. | High-quality reference data. |
| Hagedoorn et al. (9) | Systematic Review | Pediatric guidelines | Identified significant variability in hypotensive thresholds across different sepsis protocols. | Critical analysis of clinical standards. |
| Davis et al. (10) | Practice Parameters | ACCM guidelines | Provided updated algorithms for hemodynamic support (fluid boluses and vasoactive agents). | International clinical standard. |
| Weiss et al. (11) | International Guidelines | Surviving Sepsis (SSC) | Integrated respiratory and hemodynamic goals for pediatric septic shock management. | High-level global recommendation. |
| Emr et al. (13) | Clinical Update | Pediatric sepsis | Analyzed the physiological differences between children and adults in sepsis-induced lung injury. | Pathophysiological synthesis. |
| Silvestre & Vyas (17) | Clinical Review | PARDS management | Highlighted the necessity of using pediatric-specific (PALICC) criteria rather than adult (Berlin) criteria. | Contemporary clinical review. |
| Orloff et al. (20) | State-of-the-art Review | PARDS trends | Evaluated adjuncts: prone positioning and neuromuscular blockade in severe cases. | Comprehensive therapeutic update. |

demonstrates the necessity for additional randomized controlled trials in children to define effective ventilation modes and parameters for this patient population.

The main provisions for respiratory therapy of pediatric ARDS are outlined in the general intensive therapy program for pediatric ARDS, created based on the Consensus Conference on Pediatric Acute Lung Injury (PALICC) (4).

The program recommends using low respiratory volumes during artificial ventilation (5-8 mL/kg for saved lung pliability and 3-6 mL/kg for low lung pliability). These actions aim to reduce the risks of barotrauma and volutrauma to initially damaged pulmonary parenchyma during ARDS due to high respiratory volume. However, this provision can be considered controversial regarding the occurrence of further complications. Hypoventilation resulting from ventilation with reduced respiratory volume leads to hypoxemia and worsens hypoxia in ARDS (4). PALICC recommendations also include high PEEP (positive end-expiratory pressure) in the range of 10-15 cmH₂O. It is not difficult to agree with this statement because PEEP prevents expiratory airway closure. Since PEEP increases lung volume at the end of exhalation, already partially inflated lungs require less volume and energy to inflate during the inspiration phase. Other benefits of PEEP, such as opening collapsed or unstable alveoli, improving the ventilation-perfusion ratio, reducing intrapulmonary shunting, and improving pulmonary compliance, are pathogenetically effective in ARDS and have a positive impact on the disease course (4). Also quite controversial is the recommendation for using acceptable hypercapnia in patients with ARDS, which implies maintaining the acid-base equilibrium pH between 7.15 and 7.30. Respiratory acidosis resulting from hypoventilation leads to an undesirable negative inhibitory

effect on the CNS, subsequently making weaning from the ventilator much more difficult (4).

Definition of sepsis and septic shock in children

To form an effective program of respiratory therapy for sepsis-associated ARDS in children, it is necessary to identify sepsis and stratify the degree of risk of organ dysfunction as soon as possible because, to date, the medical community faces a lack of a unified interpretation of its diagnostic criteria in children.

The description of pediatric sepsis arose through the endeavors of the experts from the Society for Critical Care Medicine (SCCM), working with the American College of Critical Care Medicine (ACCM). In 2002, ACCM, in partnership with the Society of Critical Care Medicine, created the initial guidelines for pediatric sepsis; the distinctions in handling pediatric and neonatal sepsis compared to grown-ups were emphasized. Global definitions of systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and organ impairment in pediatric care were established in 2002 by attendees of the International Pediatric Sepsis Consensus Conference. Updated ACCM suggestions regarding septic shock were established in 2007 and rely upon the finest existing contemporary literature and specialist input on treating sepsis and septic shock in neonatal and pediatric practice (5, 6).

According to these guidelines, the systemic inflammatory response (SIR) in children differs from that in adults in that it requires the establishment of two criteria, including one change in body temperature or leukocyte count (Table 3) (5, 6).

Hence, a clear understanding of the reference values of clinical and laboratory parameters characteristic of each age category is necessary for accurately detecting SIR and

Table 3. Signs of systemic inflammatory response in children

| No | |
|----|---|
| 1 | Internal body temperature (rectal or oral) above 38.5 °C or below 36 °C |
| 2 | Tachycardia |
| 3 | Tachypnea |
| 4 | Abnormally high or low white blood cell counts for this age group (>10% immature neutrophils) |

Note: references used in this table (5, 6).

Table 4. Reference values of clinical and laboratory parameters of SIR in children of different age groups

| Age group | Tachycardia | Brachycardia | RR | Leucocytes quantity | Hypotension (SBP) |
|------------------------|-------------|--------------|-----|---------------------|-------------------|
| From birth to one week | >180 | <100 | >50 | >34 | <59 |
| 1 week-1 month | >180 | <100 | >40 | >19.5 or <5 | <79 |
| 1 month-1 year | >180 | <90 | >34 | >17.5 or <5 | <75 |
| 2-5 years | >140 | - | >22 | >15.5 or <6 | <74 |
| 6-12 years | >130 | - | >18 | >13.5 or <4.5 | <83 |
| 13-18 years | >110 | - | >14 | >11 or <4.5 | <90 |

Abbreviation: SBP - systolic blood pressure, RR - respiratory rate. Note: Data from Refs. (7-9).

Table 5. Clinical findings suggestive of infection in children

| No | |
|----|--|
| 1 | Petechiae or purpura and hemodynamic disorder/instability |
| 2 | Lightning-fast purpura |
| 3 | Fever, cough, hypoxemia, pulmonary infiltrates, and leukocytosis |
| 4 | Fever or hypothermia, protrusion or stiffness of the occipital muscles, and irritability. |
| 5 | Fever, unstable temperature, unstable glucose levels, and irritability (in newborns and premature infants) |
| 6 | Temperature instability and seizure (in newborn). |
| 7 | Rash with rapid migration, fever, pain, and leukocytosis. |
| 8 | Abdominal bloating, fever, and leukocytosis |
| 9 | Recognizable infection-mediated clinical syndromes (e.g., infectious-toxic shock) or infectious skin lesions |

Note: references used in this table (7, 10, 11).

sepsis in children (Table 4) (5).

Sepsis in children suggests SIR criteria amidst a known or suspected infection (bacterial, viral, etc.), the signs of which are listed in Table 5. Severe sepsis in children is considered to be a sign of sepsis combined with the development of cardiovascular failure, ARDS, or organ dysfunction in at least two body systems (kidneys, liver, CNS, etc.). Septic shock in children is sepsis with cardiovascular dysfunction, accompanied by signs of organ and tissue perfusion disorders. Signs of tissue and organ hypoperfusion include:

- 1) Cool extremities
- 2) Pallor or marbling of the skin
- 3) Decreased peripheral pulse
- 4) Significant differences between central and peripheral pulses.
- 5) Instantaneous capillary filling time or prolonged capillary filling time of more than 2 seconds.
- 6) Altered levels of consciousness from baseline or irritability.
- 7) Decreased diuresis (<0.5 mL/kg/h) (7, 10-12).

Once a diagnosis of sepsis has been made, timely prediction of sepsis outcomes in children should also be conducted using the Pediatric Sequential Organ Failure Assessment (pSOFA) scale (Table 6) (7, 11, 14).

The highest sepsis mortality rate is observed in children with decreased cardiac output (13). In contrast to adults, interpreting tachycardia in sepsis as a compensatory mechanism is more diagnostically meaningful because the younger the child, the higher their baseline HR. Tachycardia as a compensatory mechanism has a very time-limited effect because an increase in HR alone cannot provide adequate cardiac output. In addition, under conditions of low cardiac output, compensatory generalized peripheral vasoconstriction occurs in response to decreased cardiac output. The left ventricular-post-load increases, leading to left ventricular heart failure, and microcirculatory disturbances of the type of 'cold' shock occur in pediatric practice. This pathophysiological mechanism explains the high

effectiveness of inotropic drugs in children with severe sepsis and septic shock. The course of the septic process in children demonstrates the rapid development of cardiac dysfunction and vasoregulation disorders, which explains the emphasis on inotropic support in the intensive care program for sepsis (14).

ARDS course peculiarities in children with sepsis

Acute respiratory distress syndrome (ARDS) often accompanies the pathological sepsis process and occurs in the child's body first. This tendency is connected, firstly, with the anatomical and physiological features of the respiratory tract in children, and secondly, it is associated with the essential functions of the lungs.

The type of breathing in young children is mainly diaphragmatic-abdominal. In children under five years of age, the diaphragm is high, and the ribs are connected to the spine horizontally, almost at right angles, which reduces respiratory volume and predisposes to hypoxia in early development. The diaphragm in newborns cannot contract as rapidly and powerfully as in older children and has less capacity for recovery when fatigued. The chest, especially in a newborn, is constantly in a state of inhalation, which, combined with weak respiratory muscles, explains the small amplitude of chest excursions and shallow breathing. The stretchiness of lung tissue decreases with age due to the development of elastic structures, making ventilation in older children more effective. The number of alveoli in a newborn is significantly lower than in an adult. During the first two years of life, the most intensive formation of new alveoli occurs. The growth of alveoli ends by the age of 8 years. The size of a newborn's alveoli is four times smaller than that of an adult's, leading to an increased need for oxygen (almost two times more) than an adult. Children's lungs during the first two years are rich in connective tissue, abundantly supplied with blood, and elastic tissue is poorly developed, making them less airy and more full-blooded than those of adults. These factors predispose individuals to the development of emphysema and atelectasis.

Table 6. Diagnostic scale for multi-organ dysfunction in children with sepsis (pSOFA)

| № | Criteria | Points | | | | |
|-------------|------------------------------------|---------|---------|--------------|--------------------|---------------------|
| | | 0 | 1 | 2 | 3 | 4 |
| 1 | PaO ₂ /FiO ₂ | ≥400 | 300-399 | 200-299 | 100-199 | 100 |
| | SpO ₂ /FiO ₂ | ≥292 | 264-291 | 221-264 | 148-220 | 148 |
| 2 | Thrombocyte | ≥150 | 100-149 | 50-99 | 20-49 | <20 |
| 3 | Bilirubin, mg/dL | <1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | ≥12 |
| 4 | Average blood pressure | | | | | |
| | Less than 1 month. | ≥46 | <46 | Dopamine or | Dopamine >5 | Dopamine >15 |
| | 1-11 months | ≥55 | <55 | Dobutamine 5 | μg/kg/min or | μg/kg/min or |
| | 1-2 years | ≥60 | <60 | μg/kg/min | adrenaline, | adrenaline, |
| | 2-5 years | ≥62 | <62 | | noradrenaline ≤0.1 | noradrenaline > 0.1 |
| | 5-12 years | ≥65 | <65 | | μg/kg/min | μg/kg/min |
| 12-18 years | ≥67 | <67 | | | | |
| 5 | Glasgow Coma Scale | 15 | 13-14 | 10-12 | 6-9 | <6 |
| 6 | Creatinine, mg/dL | | | | | |
| | Less than 1 month. | <0.8 | 0.8-0.9 | 1.0-1.1 | 1.2-1.5 | ≥1.6 |
| | 1-11 months | <0.3 | 0.3-0.4 | 0.5-0.7 | 0.8-1.1 | ≥1.2 |
| | 1-2 years | <0.4 | 0.4-0.5 | 0.6-1.0 | 1.1-1.4 | ≥1.5 |
| | 2-5 years | <0.6 | 0.6-0.8 | 0.9-1.5 | 1.6-2.2 | ≥2.3 |
| | 5-12 years | <0.7 | 0.7-1.0 | 1.1-1.7 | 1.8-2.5 | ≥2.6 |
| 12-18 years | <1.0 | 1.0-1.6 | 1.7-2.8 | 2.9-4.1 | ≥4.2 | |

Note: reference used in this table (7, 11, 14).

Regarding the relationship between lung function and the development of ARDS in sepsis, its barrier function involves neutralizing biologically active substances, inflammatory mediators, and hormones circulating in the body. In sepsis, large amounts of inflammatory mediators are released into the systemic bloodstream, damaging the pulmonary capillaries' endothelium, which makes them porous and permeable to fluid in the lumen of pulmonary alveoli. Accumulating fluid in the alveoli in ARDS causes edema and, consequently, thickening of the alveolocapillary membrane, leading to disruption of oxygen transport and carbon dioxide elimination. Areas of airless lungs arise, and the pulmonary parenchyma loses its elasticity and extensibility. Acute respiratory failure with hypoxemia and subsequent development of tissue hypoxia and hypercapnia occurs inevitably, as even a high oxygen content in the inhaled air mixture will not be able to overcome the resulting barrier, and the elimination of carbon dioxide will also be problematic.

Due to changes in surface tension, surfactant stabilizes alveoli during inhalation, protecting them from overstretching, and during exhalation, protecting them from recession. Fluid in the alveoli and the thickening of the alveolocapillary membrane destroy the surfactant lining the alveoli from the inside. Therefore, the pathological course of ARDS is characterized by the recession of many alveoli with the formation of areas of pulmonary atelectasis, which cannot fully resolve due to a progressive decline in pulmonary surfactant functionality.

A vital role in acute respiratory distress syndrome is played by the local immune protection of the lungs in sepsis due to bacterial and viral invasion. In conditions of damage and edema of the alveolar-capillary membrane, the protective function of mucus containing class A and G immunoglobulins is lost. Thus, the immunological ability of the lungs to resist the infectious agent is diminished since they have antiviral and opsonin activity, i.e., they prepare the foreign agent for phagocytosis and other mechanisms of absorption and destruction (15).

The occurrence of ARDS against the background of severe sepsis and septic shock is also associated with the so-called "crisis of microcirculation." This is because peripheral vasospasm is initially replaced by paresis and the opening of arteriovenular shunts. Progressive blood stasis leads to the liquid part of the blood releasing into the extracellular space and disturbances in blood rheology and significant clotting. The formed microthrombi migrate into the pulmonary vasculature through the small circle of circulation, and generalized microthrombization of the overall vascular bed leads to the development of DIC syndrome. The body's response to the activation of several links of typical pathological processes leads to a general inflammatory response with simultaneous activation of leukocytes, phagocytosis, and inflammatory mediators, resulting in the development of a "cytokine storm." A "vicious circle" occurs in the mechanisms of inflammatory mediators' release. The immediate release of interleukins -1, -6, -8 by macrophages and endothelial cells leads to the aggregation and adhesion of leukocytes to the vascular wall. In response, free oxidation radicals and proteases are released, which

destroy the endothelium and lead to an even greater re-release of proinflammatory cytokines. Under these conditions, the increasing "mediator storm" leads to further progressive damage to the alveolar-capillary membrane of the lungs and aggravation of the course of ARDS.

PALICC guidelines for ARDS in children

Acute respiratory distress syndrome is linked with a high death rate in children in the ICU. As in the case of pediatric sepsis, until recently, there were also no clear diagnostic criteria for pediatric ARDS. The PALICC consensus was established to surpass the constraints of the Berlin Conference on ARDS definitions, which determined its criteria for adults only.

A 2016-2017 international prospective cross-sectional observational study (PARDIE) involving 145 pediatric intensive care units from 27 countries demonstrated the high prevalence of pediatric ARDS and high mortality in the ICU. This study also clearly revealed the lack of informativeness of the Berlin Conference criteria on ARDS in children. Namely, 95% of patients had complete data for analysis, with a mortality rate of 17% according to PALICC criteria. In contrast, only 32% of patients meeting the Berlin criteria had a mortality rate of 27%. Depending on the severity of hypoxemia, the mortality rate was similar among children on noninvasive ventilation with mild to moderate ARDS (10-15%), but higher for patients with severe ARDS (33%). The mortality rate of patients with ARDS on noninvasive ventilation (50%) who were subsequently intubated was 25%. Using the PALICC-derived ARDS criteria definition, the severity of the condition six hours after diagnosis more reliably differentiated mortality in the ICU than when ARDS was diagnosed according to the Berlin Conference. According to the PARDIE study, the PALICC definition identified more children with ARDS than the Berlin Conference definitions. The severity criteria improved mortality risk stratification, mainly when used six hours after diagnosing ARDS in children (1).

Our findings confirm that the Berlin definition of ARDS underestimates the severity of the course of ARDS in children and differs in its detection of only the high-risk group of children.

In addition, individuals with ARDS who underwent noninvasive ventilation displayed elevated instances of intubation and death and ought not to be categorized as having mild ARDS, as indicated by the Berlin Conference.

The Pediatric Consensus Conference on Acute Pulmonary Injury (PALICC) published in 2015 a framework for the definition, diagnosis, and specificities of intensive care for pediatric ARDS. Unlike previous ARDS conferences focused on adults, PALICC offers specific management for pediatric patients with ARDS and priorities for future research. A vital aspect of the PALICC definition is that there are no age gradations for diagnosing ARDS. The PALICC definition, however, does not encompass causes of acute hypoxemia specific to the perinatal period or linked to congenital abnormalities. Unlike previous definitions used for adults, the PALICC definition removes the requirement for bilateral pulmonary infiltrates observed on imaging studies. This exclusion is based on the absence of strong evidence

demonstrating a difference in patient outcomes between those with unilateral and bilateral pulmonary parenchymal involvement. The PALICC conference eliminated the term 'acute lung injury.' It recommended that the severity of ARDS be stratified based on the degree of reduction in oxygenation, which defines one of the degrees of severity of the disease course: mild, moderate, or severe. In contrast to the Berlin conference, according to which the degree of hypoxemia was determined by the ratio of partial oxygen tension in arterial blood to the fraction of oxygen in the inhaled air ($\text{PaO}_2/\text{FiO}_2$) (Table 7), the determination of the same index according to PALICC is based on the determination of the oxygenation index (OI) ($\text{FiO}_2 \times \text{average airway pressure} \times 100 / \text{PaO}_2$) and the oxygen saturation index (OSI) ($\text{FiO}_2 \times \text{average airway pressure} \times 100 / \text{SpO}_2$). A mild degree is defined at OI 4-8 (OSI 5-7.5), a moderate degree at OI 8-16 (OSI 7.5-12.3), and a severe degree at OI >16 (OSI >12.3) (Table 8). At the same time, the percentage of mortality when exceeding the mark of 16 indexes of oxygenation is 40% (17).

The definition and criteria for ARDS in Pediatric Practice (PARDS) were created based on the Pediatric Acute Lung Injury Consensus Conference (PALICC) (17).

Respiratory therapy for ARDS in children

Mechanical ventilation is unquestionably the main element of respiratory therapy for acute respiratory distress in children. Rapid decompensation of the central systems of the child's organism, primarily the respiratory system, is inevitable in this disease process affecting the lungs, aggravated by the negative impact of the ongoing septic process.

Artificial lung ventilation in ARDS aims to prevent the damaging effects on the lungs caused by mechanical ventilation. These complications arise due to excessive force

applied to the lungs, resulting in the overstretching of the pulmonary parenchyma. Therefore, PALICC recommends respiratory therapy within the concept of 'protective ventilation.'

The goals of protective ventilation are: to prevent excessive stretching of the pulmonary parenchyma, which can lead to volutrauma and barotrauma; to minimize cyclic opening and closing of alveoli (atelectotrauma); and to minimize the impact of biochemical mediators on the lung. Abrupt fluctuations in transpulmonary pressure due to inspiratory effort may lead to further progression of the pathological process in the lungs. In ARDS, lung volume and pressure changes can exacerbate the initial lung injury. High respiratory volumes and high transmural vascular pressure cause a further increase in vascular wall permeability, leading to worsening alveolar edema (negative pressure pulmonary edema).

Some evidence confirms that the Berlin PARDS definition underestimates the severity of the course of ARDS in children and emphasizes only the high-risk group of children. It has been found that ARDS occurs in approximately 3% of children admitted to the ICU, with a subsequent course associated with 17% mortality. The criterion for determining the severe course of ARDS in children proposed by PALICC is the measurement of the saturation oxygenation index rather than the ratio of the partial pressure of oxygen in arterial blood to the fraction of inhaled oxygen ($\text{PaO}_2/\text{FIO}_2$ ratio). In addition, children with ARDS who received noninvasive ventilation were found to have high rates of subsequent intubation and mortality and should not be regarded as having a mild course of ARDS, as suggested by the Berlin definition (PARDS) (2, 4).

The definition and criteria for ARDS in Pediatric Practice (PARDS) were created based on the Pediatric Acute Lung

Table 7. Berlin Criteria for ARDS

| No | |
|----|---|
| 1 | Acute onset, lasting less than one week of illness |
| 2 | Bilateral infiltrates (pleural effusion, collapsed lung, and nodules must be excluded). |
| 3 | Pulmonary edema (exclusion of respiratory failure and fluid overload) |
| 4 | Oxygenation index: mild $\text{PaO}_2/\text{FiO}_2$ 200-300, moderate $\text{PaO}_2/\text{FiO}_2$ 100-200, severe $\text{PaO}_2/\text{FiO}_2 < 100$ |

Note: reference used in this table (18).

Table 8. PALICC Criteria in Pediatric ARDS

| Age | Exclude children with perinatal lung disease |
|--------------------------|---|
| Timeline | Within seven days of an established clinical event |
| Origin of the edema | Not related to heart disease |
| Chest radiography | Infiltrates correspond to pulmonary parenchyma lesions. |
| Oxygenation | Noninvasive ventilation: Full-face mask with bi-level ventilation or CPAP > 5 cmH ₂ O $\text{PaO}_2/\text{FiO}_2 < 300$ OI $\text{SpO}_2/\text{FiO}_2 < 264$ OSI Invasive ventilation: Mild degree $4 < \text{OI} < 8.5 < \text{OSI} < 7.5$ Medium degree $8 < \text{OI} < 16, 7.5 < \text{OSI} < 12.3$ Severe degree $\text{OI} > 16, \text{OSI} > 12.3$ |
| "Blue" heart disease | Standard criteria above, chest radiography, and hypoxia are not explained by cardiac disease. |
| Chronic lung disease | Standard criteria above, as well as pulmonary imaging associated with new infiltrates and acute worsening of oxygenation from baseline. |
| Left ventricular failure | The standard criteria above new infiltrate on the CXR and acute worsening of oxygenation are not explained by left ventricular failure. |

Note: references used in this table (4, 16, 17).

Injury Consensus Conference (PALICC).

There is no reliable data on the benefits of using different ventilation modes in children with ARDS. Thus, PALICC cannot provide clear recommendations on standard ventilation modes that could be used in the respiratory therapy of pediatric ARDS. The PALICC Consensus Conference recommended additional studies to estimate the influence of ventilatory strategies on the clinical outcomes of pediatric ARDS (2, 4, 16, 17, 19).

It is also worth noting that there is no evidence of a target respiratory volume during mechanical ventilation for pediatric patients with ARDS. Routinely, 6 mL/kg for respiratory volume during mechanical ventilation appears in the recommendations for adult patients. Several studies have shown an opposite correlation between respiratory volume and mortality in children and infants. For children older than one year, studies have shown no significant association between respiratory volume values (even when values were 6 mL/kg or 10 mL/kg of ideal body weight) and mortality or days without mechanical ventilation (2, 4, 16, 17, 19).

PALICC recommendations state that for children on a ventilator, the exposed respiratory volume should be within the physiologic respiratory volume range according to the child's age and body weight (i.e., 5-8 mL/kg of ideal body weight), given the degree of lung damage and respiratory compliance. Respiratory volume should be 3-6 mL/kg of body weight for children with severe pulmonary parenchymal damage and 5-8 mL/kg for patients with relatively intact respiratory compliance (2, 4, 16, 17, 19).

Lower respiratory volumes can reduce overstretching and overexpansion of the lungs, thereby reducing alveolocyte damage and preventing interstitial pulmonary edema and the re-release of proinflammatory cytokines. However, the heterogeneity of localization and volume of the area of pulmonary parenchyma damage in ARDS leads to several difficulties in mechanical ventilation according to the protocol of protective ventilation, especially in children with sepsis. A frequent complication of this approach to respiratory support, which affects the positive outcome of therapy, is alveolar hypoventilation, with subsequent development of hypoxemia, which aggravates the overall course of sepsis and contributes to its further progression.

Moreover, several studies prove a linear relationship between mortality and PIP (peak inspiratory pressure) value, i.e., peak inspiratory pressure. A peak inspiratory pressure of 28 cmH₂O is recommended, with an acceptable increase of 29-32 cmH₂O for children with increased thoracic flexibility (2, 4, 16, 17, 19).

Two of the three studies on using high PEEP parameters in adults demonstrated low mortality rates in patients with severe ARDS but showed no efficacy in patients with milder ARDS. Due to the lack of reliable data on the use of high PEEP during mechanical ventilation, PALICC recommends its use in the range of 10-15 cmH₂O. Additionally, attention should be paid to the limitation of peak inspiratory pressure when setting the upper limit of PEEP reference values (2, 4, 16, 17, 19).

It is significant to note that improving systemic oxygenation in patients with ARDS does not correlate with

improved disease outcomes. It was shown that the group of patients with a low respiratory volume of 6 mL/kg in ALV had a high survival rate. However, they also had lower mean oxygen saturation than those patients whose respiratory volume was 12 mL/kg. A probable interpretation is that improved oxygenation may demand tighter ventilatory parameters, leading to ventilator-associated pulmonary complications and adverse outcomes. The PALICC Conference states that in mild ARDS, using PEEP of 10 cmH₂O, the target saturation value should be 92-97%. For patients with more severe ARDS with a PEEP of 10 cmH₂O, a "permissive" hypoxemia approach is recommended, in which the patient's saturation is acceptable to be maintained between 88-92% (2, 4, 16, 17, 19).

Allowable hypercapnia, also part of the protective ventilation program, involves keeping the pH between 7.15 and 7.30. However, as in the case of permissive hypoxemia, an individual decision is required when using these approaches, as their use involves a risk of complications and has several contraindications. These include acute intracranial pathology, such as intracranial hypertension, clinically significant pulmonary hypertension, strong arterial hypertension, congenital heart disease, and marked ventricular dysfunction with hemodynamic instability (2, 4, 16, 17, 19).

Thus, the standard protocol for pulmonary protection strategies in ARDS includes low respiratory volumes, high PEEP greater than 10 cmH₂O, and Pplateau of 28 cmH₂O or less. All these parameters aim to avoid excessive stretching of lung tissue, which can lead to the development of barotrauma, volutrauma, and secondary interstitial pulmonary edema. One of the leading problems during lung ventilation in children with ARDS is the synchronization of ventilator operation with the patient's external respiratory apparatus. Attempts at self-inspiration under pressure-controlled mandatory ventilation have shown that the use of muscle relaxants has not proven effective in mechanical ventilation in children with ARDS, as there are difficulties in weaning from artificial ventilation (2, 4, 16, 17, 19).

Discussion

Thus, respiratory therapy for ARDS in children with sepsis requires a comprehensive approach, taking into account the complications arising from the use of the standard protocol for mechanical ventilation in children with sepsis. These complications, which further aggravate the course of sepsis, make the possibility of a positive outcome of ARDS therapy negligible. It is necessary to improve the approach to artificial lung ventilation by revising it in favor of using an intelligent mode of Adaptive Support Ventilation (ASV), as solely isolated prosthetic external respiration through mechanical ventilation is not sufficient for the successful resolution of ARDS in children with sepsis. The reason lies in the very close relationship between the emergence, further progression, and positive outcome of the course of ARDS and the main links of sepsis pathogenesis.

Conclusion

An analysis of existing approaches to respiratory therapy in children with acute respiratory distress syndrome

(ARDS) secondary to sepsis has demonstrated the challenges faced by intensive care physicians in managing this patient population. Difficulties in defining diagnostic criteria for sepsis and ARDS, the structural and functional features of the child's respiratory system, and the aggravation of the overall pathological process in the child's body by the combined effects of sepsis and ARDS lead to the underutilization of the potential of respiratory therapy in the intensive care of ARDS and sepsis in children. Further research utilizing modern mechanical ventilation capabilities is needed to optimize approaches to respiratory therapy for ARDS secondary to sepsis in children.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

D.M.: Conceptualization, Data curation, Visualization, Investigation, Data Analysis, Writing—Original Draft; N.M.: Visualization, Data Analysis; S.Sh.: Supervision, Conceptualization; Zh.S.: Supervision, Conceptualization; Y.K.: Conceptualization, Data Analysis. All authors have read and agreed to the published version of the manuscript.

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AI Use Statement

During the preparation of this work, the authors used Google Gemini in a limited capacity to assist with the technical organization of data into table and to perform minor language polishing of the drafts for better readability. All core ideas, interpretations, and data verification were performed manually by the authors, who take full responsibility for the final content.

References

1. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE): An International, Observational Study. *Lancet Respir Med*. 2019;7:115–28. doi:10.1016/S2213-2600(18)30344-8.
2. Cheifetz IM. Pediatric ARDS. *Respir Care*. 2017;62(5):718–31. doi:10.4187/respcare.05591.
3. Respiratory distress syndrome in an adult (J80). Diagnostic and Treatment Protocol of Republic of Kazakhstan.

4. The Pediatric Acute Lung Injury Consensus Conference Group. Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations From the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428–39. doi:10.1097/PCC.0000000000000350.
5. Prusakowski MK, Chen AP. Pediatric Sepsis. *Emerg Med Clin North Am*. 2017;35(1):123–38. doi:10.1016/j.emc.2016.08.008.
6. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.
7. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA Pediatr*. 2017;171(10):e172352. doi:10.1001/jamapediatrics.2017.2352.
8. Roberts JS, Yanay O, Barry D. Age-Based Percentiles of Measured Mean Arterial Pressure in Pediatric Patients in a Hospital Setting. *Pediatr Crit Care Med*. 2020;21(9):e759–e768. doi:10.1097/PCC.0000000000002495.
9. Hagedoorn NN, Zachariasse JM, Moll HA. A comparison of clinical paediatric guidelines for hypotension with population-based lower centiles: a systematic review. *Crit Care*. 2019;23(1):380. doi:10.1186/s13054-019-2653-9.
10. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med*. 2017;45(6):1061–93. doi:10.1097/CCM.0000000000002425.
11. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatr Crit Care Med*. 2020;21(2):e52–e106. doi:10.1097/PCC.0000000000002198.
12. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762–74. doi:10.1001/jama.2016.0288.
13. Emr BM, Alcamo AM, Carcillo JA, Aneja RK, Mollen KP. Pediatric Sepsis Update: How Are Children Different? *Surg Infect (Larchmt)*. 2018;19(2):176–83. doi:10.1089/sur.2017.316.
14. Bulatova YY, Maltabarova NA, Zhumabayev MB, Li TA, Ivanova MP. Modern Diagnostics of Sepsis and Septic Shock in Children. *Electron J Gen Med*. 2020;17(4):em216. doi:10.29333/ejgm/7879.
15. Griffiths MJD, McAuley DF, Perkins GD, Barrett N, Blackwood B, Boyle A, et al. Guidelines on the Management of Acute Respiratory Distress Syndrome. *BMJ Open Respir Res*. 2019;6(1):e000420. doi:10.1136/bmjresp-2019-000420.
16. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA Pediatr*. 2017;171(10):e172352. doi:10.1001/jamapediatrics.2017.2352.
17. Silvestre C, Vyas H. Paediatric Acute Respiratory Distress Syndrome (PARDS). *Paediatr Child Health*. 2021;31(7):229–32. doi:10.1016/j.paed.2021.03.001.
18. Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology. *Pediatr Crit Care Med*. 2015;16(5 Suppl 2):S23–S40. doi:10.1097/PCC.0000000000000432.
19. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*. 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.
20. Orloff KE, Turner DA, Rehder KJ. The Current State of Pediatric Acute Respiratory Distress Syndrome. *Pediatr Allergy Immunol Pulmonol*. 2019;32(1):35–44. doi:10.1089/ped.2019.0999.