Recent advances in understanding NARDS, and the effect of the budesonide on the prevention of NARDS

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July 5, 2022

Abstract

Acute respiratory distress syndrome (ARDS) is an acute respiratory failure syndrome caused by non-cardiogenic pulmonary edema of various etiologies.[1](#ref-0001) When the fetus encounters asphyxia, acidosis, infection, meconium inhalation, et al. during childbirth, the inflammatory pathway will be activated. The systemic inflammatory response can remove pathogens, but the excessive inflammatory response will prompt pulmonary surfactant (PS) inactivation and increase the permeabilities of alveolar epithelial and endothelial cells, resulting in the accumulation of edema fluid in the alveoli and eventually leading to severe hypoxemia, respiratory distress and decreased lung compliance.[1,2](#ref-0001) Population-based studies in the United States, Australia, Europe, and New Zealand reported that the incidence of ARDS in children is 2.0-12.8 per 100000 person-years,[3](#ref-0003) and according to the interim report of the International Neonatal ARDS Multicenter Study, the mortality of neonatal ARDS (NARDS) is approximately 20%.[4](#ref-0004) Due to the high mortality of NARDS, the researchers try to explore potential new treatments to limit the incidence and mortality of NARDS. Systemic inflammatory response plays a significant role in the occurrence and development of NARDS, budesonide, a non-halogenated corticosteroid, has a potent local pulmonary anti-inflammatory effect, therefore, it may be an effective treatment option for NARDS. This article reviews the evolution of ARDS definition and diagnosis, pathophysiological mechanisms of NARDS, and gives an outlook on the application of budesonide in NARDS.

Introduction

The evolution of ARDS definition and diagnosis (Table. 1)

In an observational study of 272 adult patients receiving ventilator-assisted ventilation, Ashbaugh et al. found that some patients did not respond to conventional ventilator-assisted supportive treatment, and their clinical and pathophysiological changes were similar to those of infants with neonatal respiratory distress syndrome (nRDS), such as severe dyspnea, tachypnea (the average respiratory rate for all patients was 42 breaths per minute), cyanosis that did not respond to oxygen supplement, loss of lung compliance, and bilateral white lung changes on chest radiographs. And at autopsy in some patients, aggregation of alveolar macrophages and hyaline membrane formation could be seen microscopically in the lungs. From this, they first proposed the concept of acute respiratory distress syndrome (ARDS) in 1967.[5]

The American European Consensus Conference (AECC) on ARDS has made new recommendations on the definition, pathogenesis, diagnostic criteria, treatment, and future research directions of ARDS. For example, the committee proposed that ARDS specifically refers to acute respiratory distress syndrome, not adult respiratory distress syndrome, so the age limitation was removed. The AECC defined ARDS as an acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen ($PaO_2/FiO_2 \leq 200$ mmHg), with the pulmonary artery wedge pressure ≤ 18 mm, with bilateral infiltrates on the frontal chest radiograph. The AEEC proposed a new definition of acute lung injury (ALI) using similar criteria but with less severe hypoxemia ($PaO_2/FiO_2 \leq 300$ mmHg). The committee emphasized nitric oxide inhalation, tracheal gas

insufflation, perfluorocarbon-associated (partial liquid) ventilation, prostacyclin inhalation, anti-endotoxin immunotherapy, corticosteroids, and et al. may be effective in the treatment of ARDS. The committee also proposed new recommendations on the future research directions of ARDS such as linking cellular and humoral responses to physiological and clinical outcome measures, measuring long-term outcomes of ARDS in multiple ways such as the 2-month survival rate and the quality of life for survivors, and linking short-term outcomes such as changes in gas exchange to long-term outcomes such as functional status and mortality.[6,7]

In 2012, the European Society of Intensive Care Medicine convened an international panel of experts to revise the definition of ARDS. The Berlin definition proposed that the patients with ARDS were identified within 72 hours to 7 days. The Berlin definition retained bilateral infiltrates on the frontal chest radiograph as defining criteria for ARDS. The Berlin definition removed exclusion criteria for pulmonary artery wedge pressure ≥ 18 mm, because the patients with ARDS may also have hydrostatic edema in the form of heart failure or fluid overload, therefore, in the absence of risk factors, ARDS may also be diagnosed if the respiratory failure is not entirely explained by heart failure or fluid overload, and other objective assessment such as echocardiography was needed to rule out hydrostatic edema. The Berlin definition classified the severity of ARDS according to the degree of hypoxemia (mild ($200\text{mmHg} < PaO_2/FiO_2 \leq 300\text{mmHg}$), moderate ($100\text{mmHg} < PaO_2/FiO_2 \leq 200\text{mmHg}$) and severe ($PaO_2/FiO_2 \leq 100\text{mmHg}$)). The Berlin definition had a better predictive validity for mortality than the AECC definition, with an area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P < 0.001$).[8]

In 2015, Pediatric Acute Lung Injury Consensus Conference (PALICC) proposed new recommendations for the definition, epidemiology, and diagnosis of pediatric ARDS (PARDS). PALICC recommended using the oxygenation index (OI) ((FiO_2 × Mean airway pressure × 100) ÷ PaO_2) to define the everity of patients receiving invasive mechanical ventilation. If the OI is not available, we could use the oxygen saturation index (OSI) ((FiO_2 × Mean airway pressure × 100) ÷ SpO_2) to define the everity of patients receiving invasive mechanical ventilation. But for the patients receiving noninvasive, full face mask ventilation, we could use PF ratio (PaO_2 ÷ FiO_2) to diagnose PARDS. PALCC did not emphasize the bilateral infiltrates on chest imaging, this was different from the AEEC and Berlin definitions.[3] PALICC believed that children with preexisting chronic lung disease or cyanotic congenital heart disease may also develop ARDS if they fulfilled diagnostic criteria (acute onset, a known clinical insult, chest imaging supporting new-onset pulmonary parenchymal disease) and had an acute deterioration in oxygenation not explained by the underlying cardiac disease.[9] The use of PALICC criteria increases the number of patients diagnosed with PARDS and lowers the overall mortality rate.[10]

In 2017, an international, collaborative, multicenter, and multidisciplinary project proposed a consensus definition applicable to neonatal ARDS (NARDS). The Montreux definition applies to infants from birth until 44-week postmenstrual age (PMA) or until postnatal age 4-week (for neonates born after PMA 40 weeks) without congenital anomalies (such as pulmonary adenomatous malformation, sequestration, or diaphragmatic hernia), genetic disorders of the surfactant system, RDS and transient tachypnoea of the neonate. This definition defined NARDS as an acute onset (within one week) of hypoxemia from a known or suspected clinical injury, with diffuse, bilateral, irregular opacities, infiltrates, or complete opacification of the lungs on the radiographs and scans. The Montreux definition used the same OI as in the PALICC definition to define the severity of ARDS and emphasized the special role of perinatal factors, such as meconium aspiration syndrome, perinatal asphyxia, necrotizing enterocolitis. And the research on the associated risk factors, clinical epidemiology, characteristics of the clinical pathogenesis, treatment, and prognosis of NARDS and tne, and the applicability of the Montreux definition is ongoing.[10]

With the deepening of research, some scholars believe that NARDS can be superimposed on some more classic neonatal respiratory diseases, such as neonatal respiratory distress syndrome (NRDS), a neonatal idiopathic respiratory distress syndrome (NIRDS) that occurs due to insufficient synthesis and secretion of pulmonary surfactant (PS) because of the immature lung development. The combination of the two may lead to more serious clinical symptoms.[11] NIRDS is caused by primary PS system insufficiency,[12] while NARDS is caused by secondary PS system dysfunction.[13] The etiology of NIRDS is single, but NARDS is the result

of multi-factor interaction.[14] If NIRDS is not treated in time, dyspnea will progressively worsen, resulting in changes such as hypoxia, acidosis, atelectasis, and pulmonary vascular exudation. The inflammatory response is promoted, resulting in impaired PS system function, further aggravation of pulmonary edema and atelectasis decreased lung compliance, and worsening lung function. Due to the multi-factor interaction, respiratory failure will progress to multi-organ failure and finally causes NIRDS to superimpose NARDS. Therefore, the treatment of NARDS requires not only PS replacement therapy but also causal therapy and systemic supportive therapy, while the NIRDS can be easily solved by PS replacement therapy.[15,16] The "superposition" theory runs through the whole process of NARDS etiology, pathology, diagnosis, and therapy, it can more comprehensively and profoundly recognize and understand the essence of NARDS, which has a positive effect on the diagnosis and treatment of NARDS.

Based on the update of the above definitions, clinicians have a new understanding of the definition and diagnosis of NARDS. However, there are few large-sample clinical studies on NARDS. Since January 2018, the Chinese NARDS Collaborative Group and the International NARDS Collaborative Group have simultaneously launched their own multi-center cross-sectional surveys to investigate the epidemiology of NARDS and explore the applicability of the Montreux Criteria for the diagnosis of NARDS.[17] A single-center retrospective study using the "Montreux criteria" for the diagnosis of NARDS, reported that among the 204 reported cases of NARDS, 137 cases (67.2 %) were mild ARDS, 49 cases (24.0 %) were moderate ARDS, and 18 cases (8.8 %) were severe ARDS, the cure rate of NARDS was 79.9 %, and the death rate of NARDS was 20.1 %,[18] the NARDS mortality reported by this single-center retrospective study was similar to the mortality rate reported in an interim report of an international NARDS multicenter study.[4] While another single-center retrospective study of NARDS based on the "Montreux criteria" reported that the children with NARDS accounted for 2.46 % of children admitted to neonatal units during the same period, mild NARDS accounted for 41.4 %, moderate NARDS accounted for 37.3 %, severe NARDS accounted for 21.3 %, and the mortality rate was 9.6 %.[17] The difference in mortality between the two single-center studies may be due to differences in severity and gestational age among the children with NARDS included in the studies.

Pathophysiology and pathogenesis of ARDS (Figure 1)

ARDS is not merely a disease, but an involute clinical syndrome with a heterogeneous clinical phenotype.[19] Sine the concept of ARDS was first introduced by Ashbaugh et al. in 1967,[5] numerous valuable insights into the mechanism responsible for the pathophysiology and pathogenesis of ARDS have been presented. ARDS is caused by pulmonary and nonpulmonary factors such as asphyxia, sepsis, and meconium aspiration.[2] Regardless of the risk factors, dysregulated inflammation and increased lung endothelial and epithelial permeabilities, leading to diffuse alveolar injury, are critical in the development of ARDS.[1] The pathophysiological changes in ARDS can be divided into three consecutive phases, including the inflammatory phase, proliferative phase, and fibrotic phase.[20,21]

Initially, microbial products and cell injury-associated endogenous molecules will activate a variety of signal transduction pathways such as nuclear factor kappaB (NF-$\varkappa$B), mitogen-activated protein kinase (MAPK), nucleotide-binding oligomerization domains, leucine-rich repeats, and pyrin domain-containing signal transduction pathway 3 (NLRP3), toll-like receptors (TLRs), adrenergic receptors, and JAK/STAT signaling pathways.[22-24] During these processes, cells including polymorphonuclear neutrophils (PMNs), macrophages, vascular endothelial cells (VEC), and alveolar epithelial cells are involved. The PMNs, VEC, macrophages, and platelets can be activated to produce pro-inflammatory factors such as TNF-α, IL-1, IL-9, IL-8, IL-6, IL-10, interferons (IFNs), chemokines, reactive oxygen species, and leukocyte proteases, and all of these products will aggravate the lung injury.[25] The pro-inflammatory factors will lead to disruption of the endothelial basement membrane, the epithelial basement membrane, and the cell connections between alveolar endothelial and epithelial, therefore the lung microvascular barrier will be destroyed, resulting in interstitial and alveolar edema of pulmonary.[26] Meanwhile the inflammatory response will lead to the degradation of PS and the damage of type II alveolar cells, which will reduce the synthesis of PS, thus the secondary PS deficiency occurred and eventually led to the formation of hyaline membranes and alveolar collapse, causing refractory hypoxia.[2]

As the disease recovers, lung tissue enters a proliferative phase, the character of this phase is the recovery of type II alveolar epithelial cells, which is critical for survival, later the type II alveolar epithelial cells will differentiate into type I alveolar cells, establishing the functional epithelial layer. The regeneration of the functional epithelial layer allows the exudative fluid to be cleared into the interstitium, and alveolar architecture and function will be reestablished.[20]

The third stage is the fibrotic phase, including the failure to remove the alveolar collagen formed early in the injury process, coupled with the development of cystic changes, most children with severe ARDS will have significant fibrosis later in life, resulting in lung tissue permanent structural change.[21]

The use of budesonide in ARDS

In the complex pathophysiological mechanism of ARDS, the widely activated host immune response and inflammatory response play key roles in the occurrence and development of ARDS.[27]Budesonide has a wide range of anti-inflammatory and anti-host immune response effects, which can effectively reduce airway inflammation and promote airway remodeling. [28,29] Therefore, budesonide may be a potentially effective treatment for ARDS.

Pharmacology of budesonide

Budesonide, a non-halogenated corticosteroid, has potent glucocorticoid activity and weak mineralocorticoid activity.[30] Its corticosteroid activity is mediated through glucocorticoid receptors (GRs) presenting in the cytoplasm of most cells.[31]Budesonide is lipid-soluble and it can diffuse freely across cell membranes, it will produce both genomic and non-genomic effects when binding to GRs in the cytoplasm.[32] The genomic effects of budesonide are described below: 1) when budesonide bind to GRs, then the GRs conformational change occurs, which results in dissociation of anchoring chaperone proteins and exposure of nuclear localization signals, which allow the rapid translocation of the active GR-ligand complex into the nucleus.[33] GRs dimerize in the nucleus and bind directly to glucocorticoid response elements (GREs) in the promoters of the target genes to enhance the expression of genes,[34] which encode mitogen-activated protein kinase phosphatase-1 (MKP-1)[35], annexin-1 (Anx-1)[36] and glucocorticoid-induced leucine zipper (GILZ)[37], all of them will interfere inflammation-activated MAPKs to exert anti-inflammatory effects.[35] 2) GRs will interact with other transcription factors, such as nuclear factor kappa-B (NF-ϰB) and activator protein-1 (AP-1)[38-41], to suppress their ability to activate gene expression. NF-ϰB is activated by many pro-inflammatory stimuli and it is important for the expression of many inflammatory mediators, therefore the inhibition of NF-ϰB is a powerful anti-inflammatory mechanism.[42]Trans-inhibition of AP1 may also help suppress the expression of anti-inflammatory genes, but the mechanism appears to be different.[43] An animal research revealed that the combination of GRs and AP-1 will inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-responsive element (TRE), thereby exerting anti-inflammatory effects,[44] because activation of AP-1 and its subsequent binding to TRE is important in mediating the proinflammatory effects of many cytokines, growth factors, and proteases.[45] Meanwhile GRs will also interact with the signal transducer and activator of transcription (STAT), CCAAT/enhancerbinding protein (C/EBP) to exert an anti-inflammatory effect.[46] The non-genomic effects of budesonide typically manifest within seconds to minutes. The budesonide will embed into membranes, which alters cation transport across the plasma membrane and promotes mitochondrial proton leak,[47] which is an important part of cellular metabolism, involved in tissue thermogenesis and anti-reactive oxygen species. [48]

What's more, budesonide has been shown to induce pulmonary epithelial cells to differentiate into type II alveolar cells and produce PS, and type II alveolar cells can further differentiate into type I alveolar cells, alveolar-capillary membranes will be established and the effective gas exchange will be carried out.[49] And budesonide enhances the expression of surfactant protein (SP), especially surfactant protein B (SP-B), and epithelial sodium channel (ENaC), to promote lung maturation,[50,51] Increased synthesis of endogenous SP-B will decrease alveolar surface tension, resulting in increased alveolar area, therefore the lung function will be improved.

The advantages of budesonide

Noah H Hillman et al. reported that intratracheal administration of budesonide with PS improved lung physiology and decreased the level of pro-inflammatory cytokine responses in the lung, liver, and brain, the findings were consistent with those of another animal study.[52,53] It has been reported that intratracheal administration of budesonide with PS on the day of birth limited hyperoxia-associated disruption of lung function and structure in preterm rabbits.[54] In an observational study of 2 premature infants diagnosed with ARDS and receiving ventilator-assisted ventilation, Burak Deliloglu et al found that intratracheal administration of budesonide with PS can effectively improve pulmonary ventilation function and oxygenation index.[27] In a case-control study, T. Brett Kothe et al found that compared with the use of PS alone, the intratracheal administration of budesonide with PS can shorten the duration of mechanical ventilation. [55]

Budesonide can be rapidly taken up by the lung and can remain in the airways and lung parenchyma for a long time,[56] because most of the budesonide will be esterified intracellularly.[44,57,58] Budesonide ester has been shown to have no pharmacological activity, but it can be hydrolyzed by intracellular lipases to release free, pharmacologically active budesonide.[57,58] Therefore the anti-inflammatory effect of the budesonide can be prolonged. But fluticasone propionate and beclomethasone dipropionate do not produce fatty acid esters, this is why budesonide has a longer pharmacological action in airway tissue than other corticosteroids. [59] Meanwhile in a standard in vitro experiment, it is reported that compared with cortisol, budesonide has higher receptor affinity and local anti-inflammatory ability, the affinity of budesonide for the glucocorticoid receptor is 200-fold higher than cortisol, and the topical anti-inflammatory potency of budesonide is 1000-fold higher than cortisol.[30]

The side effects of budesonide

Studies have shown that the combination of budesonide and surfactant improves gas exchange, matures the lung, and reduces lung inflammation in animal models of respiratory distress syndrome (RDS).[50,51,60-63] However, the budesonide was detected in the plasma of premature infants and premature sheep that were given budesonide mixed with surfactant. Such systemic exposure may cause associated systemic side effects, therefore, close monitoring of the systemic effects of budesonide, including in the brain, is critical.[50,60,62,64] Therefore although administration of budesonide through the airway limits systemic exposure, the risk of systemic corticosteroid-related adverse effects including metabolic derangements, such as the development of the adrenal crisis, dyslipidemia, insulin resistance, glucose intolerance, caused by budesonide cannot be ignored.[65,66] Meanwhile it is shown that steroid use in the early postpartum period affects neurodevelopment, thus it is critical to understand the role of budesonide in neurodevelopment.[67] The inhaled budesonide has one of the longest safety records of the current commercially available ICS.[65] The study by Yeh et al. demonstrated that plasma levels of budesonide are low, but they did not explore its other systemic effects.[62] A review revealed that inhaled budesonide therapy only in very rare cases appears to be associated with an increased risk of adrenal crisis.[65] And in the developmental follow-up of an observational study of infants exposed to intratracheal budesonide for the reduction of BPD, the infants who received budesonide had similar fine and gross motor skills at 4–6 months corrected age (CA), similar muscle tone on physician exams at 6 months CA, similar scores at 18–22 months CA on the Bayley III, these findings are similar to those of Yeh and Bassler et al. Their studies confirmed that budesonide exposure did not affect nervous system development.[62,68,69] First of all, budesonide will be absorbed through the airways and it will rapidly dissolve into cellular lipids in the airways, there it will be rapidly and reversibly esterified by oleic and palmitic acids, and the budesonide esters have a low affinity for GR, thus no pharmacological effect will be exerted.[70,71] secondly, the systemic half-life of budesonide is much shorter than that of fluticasone propionate, the budesonide can be metabolized by members of the cytochrome P450 (CYP) 3A family of enzymes into a variety of inactive products in lung and liver microsomes, and finally cleaved to 16α-hydroxyprednisolone, thus the systemic exposure to budesonide can be minimized.[72]

The dose of budesonide

Yeh et al. proposed the dose of budesonide combined with intratracheal administration of PS to treat severe RDS based on the application of budesonide in childhood asthma, namely intratracheal instillation of a mixture of 0.25 mg/kg of budesonide and 100.00 mg/kg of PS, budesonide at this dose can exert effective

anti-inflammatory effect without inhibiting adrenal function and increasing adverse effects.[73] Studies have shown that using different doses of budesonide, such as 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg budesonide, there is no significant difference in the anti-inflammatory effect.[60] And a dose-escalation trial of budesonide in surfactant for prevention of bronchopulmonary dysplasia reported that even lower doses of budesonide can provide effective anti-inflammatory treatment with lower systematic risk.[74] But an animal research reported that lower doses of budesonide were not as effective as budesonide 0.25 mg/kg at decreasing lung inflammation. Meanwhile, the research found that in the group using 0.25 mg/kg budesonide, the amount of budesonide esters formed in the lungs accounted for about 40% of the total budesonide, whereas in the group using 0.1 mg/kg (14%) and 0.04 mg/kg (19%) budesonide, there were fewer budesonide esters formed, therefore the prolonged anti-inflammatory effects found by Yeh et al. may not occur at lower doses.[75] However, most of the studies were animal studies, and they only analyzed the short-term efficacy of different doses of budesonide, and the long-term effects of budesonide at different doses were not considered, so more clinical randomized controlled trials were needed to explore the short-term efficacy and long-term effects of different doses of budesonide.

The way of administration of budesonide

Budesonide aerosols, a budesonide inhalation suspension, developed to meet the drug delivery needs of infants and young children with persistent asthma, are the first inhaled corticosteroid approved for nebulizer administration.[76] Numerous placebo-controlled trials demonstrated the tolerability and efficacy of budesonide inhalation suspension.[77-79] Meanwhile previous studies have shown that surfactants can assist in the delivery of drugs in the lungs, such as antibiotics,[80,81]immunosuppressive drugs,[82]antioxidants[83,84], and other anti-inflammatory molecules,[85-87] therefore there are also studies using budesonide suspension combined with surfactant administered intratracheally.[62] A randomized controlled clinical trial reported that the intratracheal administration of budesonide with PS reduces the incidence of BPD, need for repeated doses of surfactant, duration of assisted ventilation, and hospitalization.[88] It is also reported that budesonide inhalation could decrease the RDS grades, Downes scores, serum IL-8 levels, and the duration of hospitalization of infants with RDS.[89] A meta-analysis suggested that early combined utilization of budesonide and PS by airway could shorten the duration of assisted ventilation, duration of invasive ventilation, and hospital stays of preterm infants with RDS. And its subgroup analysis based on the mode of budesonide administration (inhalation or intratracheal instillation) showed that reductions in mortality, duration of assisted ventilation, and hospital stay were primarily in the budesonide intratracheal instillation subgroup rather than the budesonide inhalation subgroup.[90] And an observational study reported that intratracheal instillation of the budesonide could significantly improve lung function, and reduce the duration of assisted ventilation and PS reuse.[91] First of all, intratracheal administration of budesonide with PS can ensure high initial pulmonary bioavailability, secondly, administering inhaled glucocorticoids to preterm infants is technically challenging and the effects are limited.[92] Meanwhile some scholars revealed that inhaled budesonide would increase the death rate of extremely preterm infants.[69] However the death rate or adverse physical or neurological outcomes of the extremely preterm infants using intratracheal administration of budesonide with PS were not increased.[62,73,93] Therefore intratracheal administration of budesonide with PS may be a better way of administration, but more well-designed randomized controlled trials with larger sample sizes and longer follow-up from all over the world ought to be conducted in the future.

As for the stability of budesonide/PS suspension, a study exploring the biophysical and chemical stability of budesonide combined with PS and the intrapulmonary distribution of the drug after intratracheal administration found that when the PS/budesonide concentration ratio was 50:1 or even as high as 160:1, the surface tension-lowering activity of PS was hardly affected, and the PS/budesonide mixtures with different concentration ratios were analyzed by high-performance liquid chromatography (HPLC) at 0, 1, 4, 8, 12, and 24 hours, and no new compounds were found, this indicated that PS/budesonide has certain chemical stability.[92]The intratracheal administration of budesonide with PS can ensure high initial pulmonary bioavailability, and also utilize the good diffusion properties of PS to promote the pulmonary distribution of budesonide. Research using Nano/PET digital scans technology to explore the distribution of budesonide in the lungs of rats found that PS promoted the distribution of budesonide in the peripheral lung. This is

consistent with the findings of Riccardo Zecchi et al. In the study, they used mass spectrometry imaging to analyze the distribution of PS/budesonide in lamb lungs, and they demonstrated that compared with the PS/saline group, the PS/budesonide group had a more uniform distribution of budesonide in the lung and more distribution in the peripheral lung.[94]

CONCLUSIONS

At present, the treatment for NARDS is mainly PS replacement therapy and ad adjunctive supportive therapy. Budesonide is a powerful local anti-inflammatory drug, and a large number of animal and clinical trials have demonstrated that the utilization of budesonide could reduce the incidence of BPD, duration of assisted ventilation, and hospitalization. Therefore, it is reasonable to suppose that budesonide may be an effective drug for the treatment of NARDS. This review summarizes the current state of research on the effects of budesonide in ARDS in terms of clinical aspects and related mechanisms; our findings may provide new insights for clinical application. However, questions remain regarding the possible mechanisms of budesonide in the treatment of NARDS. Further clinical and experimental data are still needed to demonstrate the safety and efficacy of budesonide in the treatment of NARDS.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the reviewers and editors of *Pediatric Pulmonology* . This article was supported by the National Natural Science Foundation of China (81571480); Luzhou Municipal People's Government-Southwest Medical University Science and Technology Strategic Cooperation Project (2020LZXNYDJ03) and the Major Science and Technology Project of Sichuan Provincial Science and Technology Department (22ZDYF147).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable—no new data is generated.

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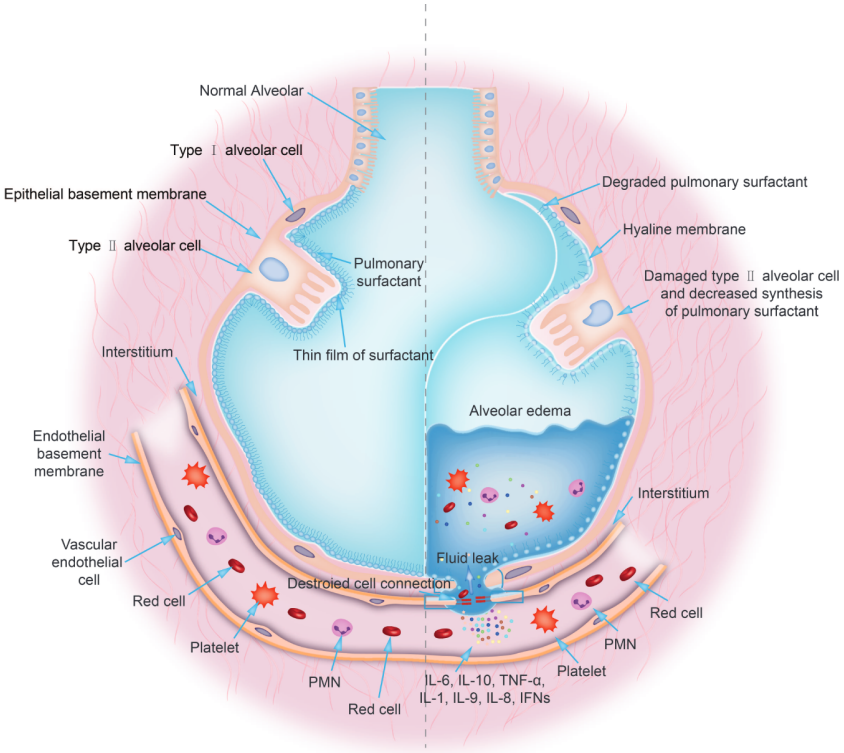

Figure 1. Microbial products and endogenous molecules associated with cellular damage will activate multiple signal transduction pathways. The polymorphonuclear neutrophils (PMNs), macrophages, vascular endothelial cells (VEC), and alveolar epithelial cells will be activated and produce pro-inflammatory factors such as TNF-α, IL-1, IL-9, IL-8, IL-6, IL-10, interferon (IFN), these pro-inflammatory factors will disrupt the endothelial basement membrane, the epithelial basement membrane, and the connections between alveolar endothelial and epithelial cells, leading to interstitial and alveolar edema. At the same time, the pro-inflammatory factors will lead to PS degradation and damage of type II alveolar cells, reduced PS synthesis, and secondary PS deficiency, which eventually leads to hyaline membrane formation and alveolar collapse, resulting in intractable hypoxia.

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