Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Endothelial-Epithelial Crosstalk Drives Alveolar-Capillary Barrier Dysfunction in ARDS

Juan Shi, Menglu Qiu, Siqi Han, Xulong Liu

Department of Pediatrics, Chengdu Fifth People's Hospital, Chengdu, Sichuan, 611130, People's Republic of China

Correspondence: Juan Shi, Department of Pediatrics, Chengdu Fifth People's Hospital, No. 33 Mashi Street, Liucheng Town, Wenjiang District, Chengdu, Sichuan, 611130, People's Republic of China, Email 18280108672@163.com

Abstract: The alveolar-capillary barrier (ACB) is essential to maintain the function of gas exchange. Acute respiratory distress syndrome (ARDS), is a critical disease characterized by complex etiology and significant clinical heterogeneity. ARDS is pathologically defined by the impairment of ACB integrity, fundamentally driven by maladaptive between alveolar epithelium and pulmonary endothelium that disrupt their coordinated barrier functions. This article systematically reviews the damage mechanism in ARDS, aiming to provide novel theoretical basis and research direction for clinical therapy optimization strategies and prognosis evaluation of ARDS.

Keywords: acute respiratory distress syndrome, alveolar-capillary barrier, alveolar epithelial cells, pulmonary vascular endothelial cells, mechanism, dysfunction

Acute respiratory distress syndrome (ARDS) is characterized by high morbidity,[1] high mortality[2,3] and clinical management complexity, threatening human health and life. Injury of the alveolar-capillary barrier (ACB) is the core pathological hallmark of ARDS, affecting the entire course of disease development and progression.[4] ARDS has a significant clinical heterogeneity with multiple pathogeneses, including viral pneumonia, sepsis-induced systemic inflammation, and severe infection by COVID-19.[5] ARDS is classified into different subphenotypes: hyperinflammatory and low-inflammatory, direct injury and indirect injury.[6,7] The direct pulmonary insults predominantly target alveolar epithelial integrity, whereas indirect injury mechanisms primarily involve endothelial dysfunction within the pulmonary vasculature. The cellular injury converge to disrupt the structural and functional integrity of the pulmonary epithelial and vascular endothelial barriers, pivotal to gas exchange and vascular homeostasis, which finally causes edema and cascade reaction of pulmonary inflammation, promoting progression of ARDS. At present, supportive therapies are the main therapeutic approaches for ARDS, which is difficult to clinical management and associated with risk of complications.[8] This article provides a systematic synthesis of the pathogenic role of ACB damage in ARDS, elucidating its multifaceted contributions to disease pathophysiology (Figure 1). A conceptual framework was established for developing targeted therapeutic interventions and refining prognostic biomarkers to enhance risk stratification and personalized management paradigms.

Alveolar-Capillary Barrier in ARDS

Alveolar-capillary barrier (ACB), air-blood barrier, is the central structure ensuring gas exchange efficiency in the lungs, with important functions of restricting the entry of liquids and macromolecules into the alveolar cavity.[9] ACB consists of multiple layers, including alveolar liquid layer, alveolar epithelial cells (AEC), pulmonary capillary endothelial cells (EC) and basement membrane between AECs and ECs. The AECs and pulmonary vascular ECs are the kernel structures of ACB. Under normal conditions, highly efficient gas exchange interfaces are formed through tight connections with alveolar and adjacent capillaries, enabling oxygen-carbon dioxide diffusion in the alveolar cavity and capillary blood. In

https://doi.org/10.2147/JIR.S577885
Received: 3 November 2025
Accepted: 23 April 2026
Published: 12 May 2026

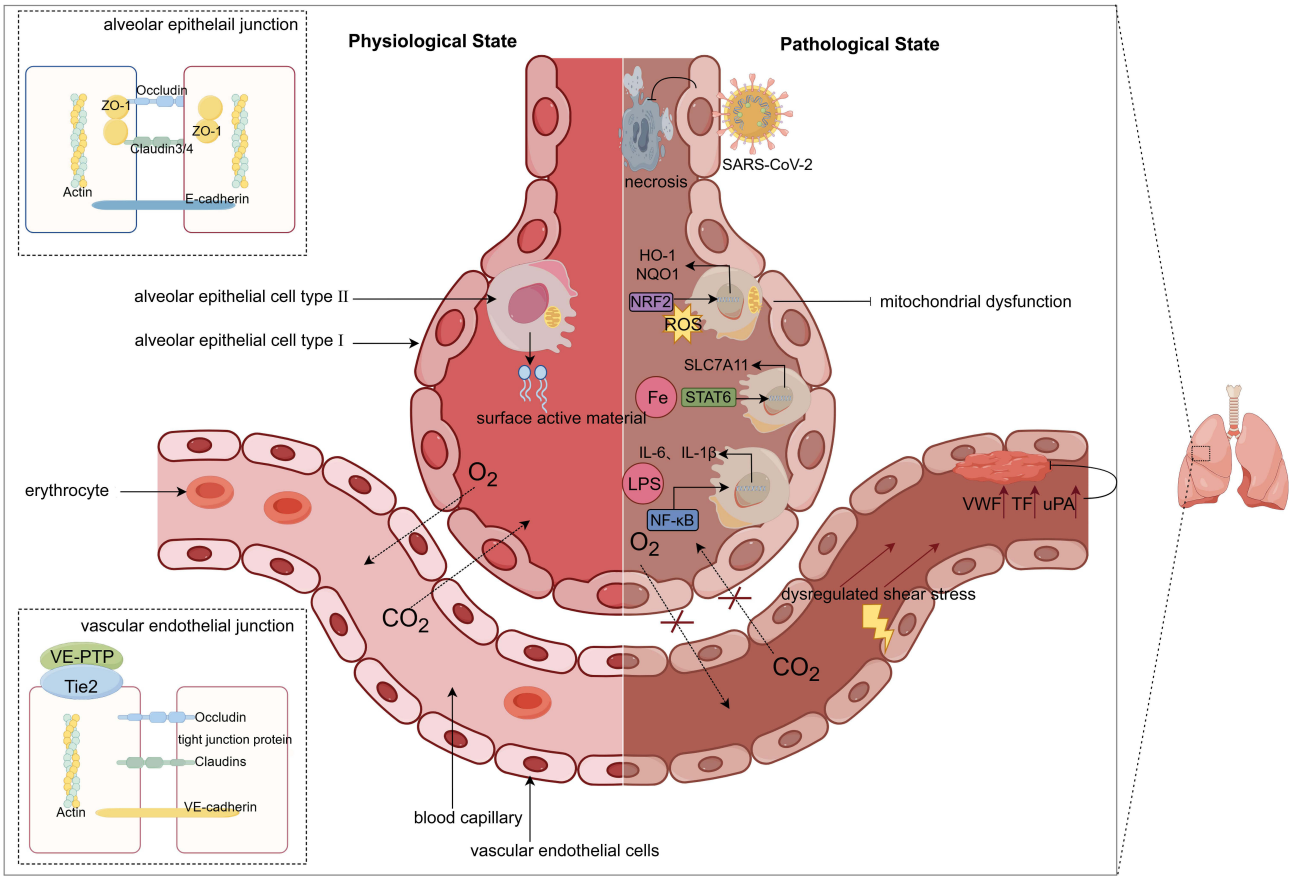

Figure 1 Schematic diagram of alveolar-capillary barrier disruption mechanisms in ARDS. The alveolar-capillary barrier is composed of alveolar epithelial cells (type I and type II) and pulmonary vascular endothelial cells, connected by tight junctions and adherens junctions. Under physiological conditions (upper left panel), alveolar epithelial tight junctions contain occludin, claudin 3/4, and ZO-1, while vascular endothelial junctions are maintained by VE-cadherin, occludin, claudins, and VE-PTP/Tie2 signaling (lower left panel). Type II alveolar epithelial cells produce surfactant and express protective molecules including HO-1 and NQO1 via NRF2 signaling. Under pathological conditions in ARDS (right panel), multiple insults converge to disrupt barrier integrity: (1) Direct injury from SARS-CoV-2 induces epithelial necrosis and inflammatory responses; (2) Oxidative stress and mitochondrial dysfunction in type II cells generate ROS, activating STAT6 and NF-κB pathways with subsequent release of IL-6 and IL-18; (3) Endothelial cells subjected to dysregulated shear stress and inflammatory mediators undergo junctional disassembly, with release of VWF, TF, and uPA; (4) Erythrocytes extravasation and iron accumulation via SLC7A11 further exacerbate oxidative damage. These coordinated disruptions of both epithelial and endothelial compartments lead to alveolar-capillary barrier failure, the hallmark of ARDS pathogenesis.

addition, the selective permeability of ACB plays a key role in maintaining alveolar fluid balance and lung immune homeostasis.

Respiratory viral infections cause extensive cell death in the lung epithelium and result from both direct viral action and exuberant immune response. Lytic bacteriophages induce the secretion of antiviral and proinflammatory cytokines from respiratory epithelial cells. Direct pulmonary insults, such as severe pneumonia (bacterial, viral, including SARS-CoV-2), aspiration of gastric contents, inhalation injury, and pulmonary contusion, initially target the alveolar epithelial layer. In these settings, pathogens or toxic substances directly damage type I and type II AECs, disrupting tight junctions, reducing surfactant production, and denuding the epithelial basement membrane. Indirect pulmonary insults, including sepsis,[10] severe pancreatitis,[11] major trauma (such as acute brain injury and traumatic thoracic injury),[12–14] and massive transfusion,[15] primarily affect the pulmonary vascular endothelium through circulating inflammatory mediators. Pathogens or damage-associated molecular patterns (DAMPs) in the bloodstream activate endothelial cells via pattern recognition receptors, inducing adhesion molecule expression, junctional disruption, and glycocalyx shedding.

While the initial insult may preferentially target either the epithelial cells or endothelial cells, damage to both cellular compartments ultimately occurs as inflammation propagates across the barrier. Whether epithelial-first in direct injury or endothelial-first in indirect injury is a key trigger for ACB dysfunction. This damage triggers a series of pathophysiological changes, including diminished gas exchange efficiency, heightened vascular permeability leading to fluid leakage,

and impaired lung liquid clearance, which further induce pulmonary edema and respiratory failure, and develop into ARDS. Consequently, preserving the structural and functional integrity of ACB is indispensable for pulmonary physiological competence and pathogenesis.

Barrier Integrity Disorder

Intercellular Junction Disruption

It is key to maintain the normal junction and adhere intercellular to adjust function stability of ACB. Synergistic effect of vascular endothelial cadherin (VE-cadherin) and tyrosine kinase receptor Tie2 maintains complete structure of pulmonary endothelial barrier. In the progress, VE-cadherin can stabilize the intercellular junction by forming homodimers.[16] Tie2 can adjust the function of pulmonary endothelial barrier via combination with angiopoietin (Ang),[17,18] which is regulated by vascular endothelial protein tyrosine phosphatase (VE-PTP). VE-PTP binds tightly to Tie2 and regulates its signaling, thereby maintaining the stability of the pulmonary endothelial barrier. The structural stability of the pulmonary vascular endothelial barrier is partially regulated by the endothelial glycocalyx layer, and significant endothelial glycocalyx shedding is found in ARDS caused by influenza syndrome.[19] Preserving the structural integrity of the vascular endothelial glycocalyx layer has been shown to reduce microvascular leakage and alleviate experimentally induced acute pulmonary damage in rats.[20]

The key to maintain integrity of alveolar epithelial barrier is cooperation of E-cadherin and tight junction (TJ), including Occludin, zonula occludens-1 (ZO-1) and claudin proteins.[21,22] Abnormal expression and function of these proteins destroy the junctions inter AECs and enhance the paracellular transport, which is a critical pathogenesis of ARDS. Analogous to vascular endothelium, the glycocalyx lining epithelial surfaces exert an integral regulatory function in preserving barrier integrity across alveolar epithelial compartments. Studies have found that the alveolar epithelial glycocalyx detachment in ARDS can aggravate the destruction and decrease of Occludin, Claudin-4 and ZO-1, further increasing the epithelial permeability.[23] It has significant protective effect on integrity of alveolar epithelial barrier to regulate the expression of Occludin, Claudin3/4 and E-cadherin.[24–26] Pharmacological modulation of these junctional complexes demonstrates therapeutic potential for controlling paracellular permeability and mitigating ARDS progression.

Mechanical Stress Damage

Hemodynamic disturbances characterized by dysregulated shear stress variations play a pivotal role in endothelial pathophysiological mechanisms during ARDS progression. Under homeostatic hemodynamic conditions, adaptive shear stress can improve the release of NO from endothelial cells, maintain vasodilation and inhibit inflammatory. However, lower flow shear stress is found in ARDS due to impaired pulmonary vascular function and blocked venous return, leading to endothelial dysfunction, reduced NO release, enhanced inflammatory response and increased endothelial permeability. Endothelial cell barrier function weakened under blood flow disturbance environment, resulting in large amount of albumin and low-density lipoprotein leakage.[27,28] In contrast, high shear stress can promote VE-PTP polarization, modulate Tie2 signaling, enhance endothelial barrier function, and reduce vascular leakage.[29] Change of flow shear stress has effects of amplifying signal in vascular endothelial injury of ARDS through interaction between mechanical signal transduction and molecular pathway. Therefore, there may be critical potential in monitoring dynamic changes of shear stress in progress of ARDS, and exploring therapeutic strategies that target relevant signaling pathways.

Endothelial-Epithelial Crosstalk in Alveolar-Capillary Barrier Dysfunction

The alveolar-capillary barrier is not a structural assembly of epithelial and endothelial layers but a dynamic functional unit maintained by bidirectional communication between these two cell types. In ARDS, disruption of this intercellular crosstalk exacerbates barrier injury and perpetuates disease progression through multiple interconnected mechanisms (Figure 2).

Epithelial cells actively regulate endothelial function through secret factors. Alveolar epithelial cells produce vascular endothelial growth factor (VEGF), a key signaling molecule that promotes endothelial cell survival, proliferation, and vascular branching,[30] thereby maintaining microvascular integrity adjacent to the alveolar epithelial cells. Epithelial-

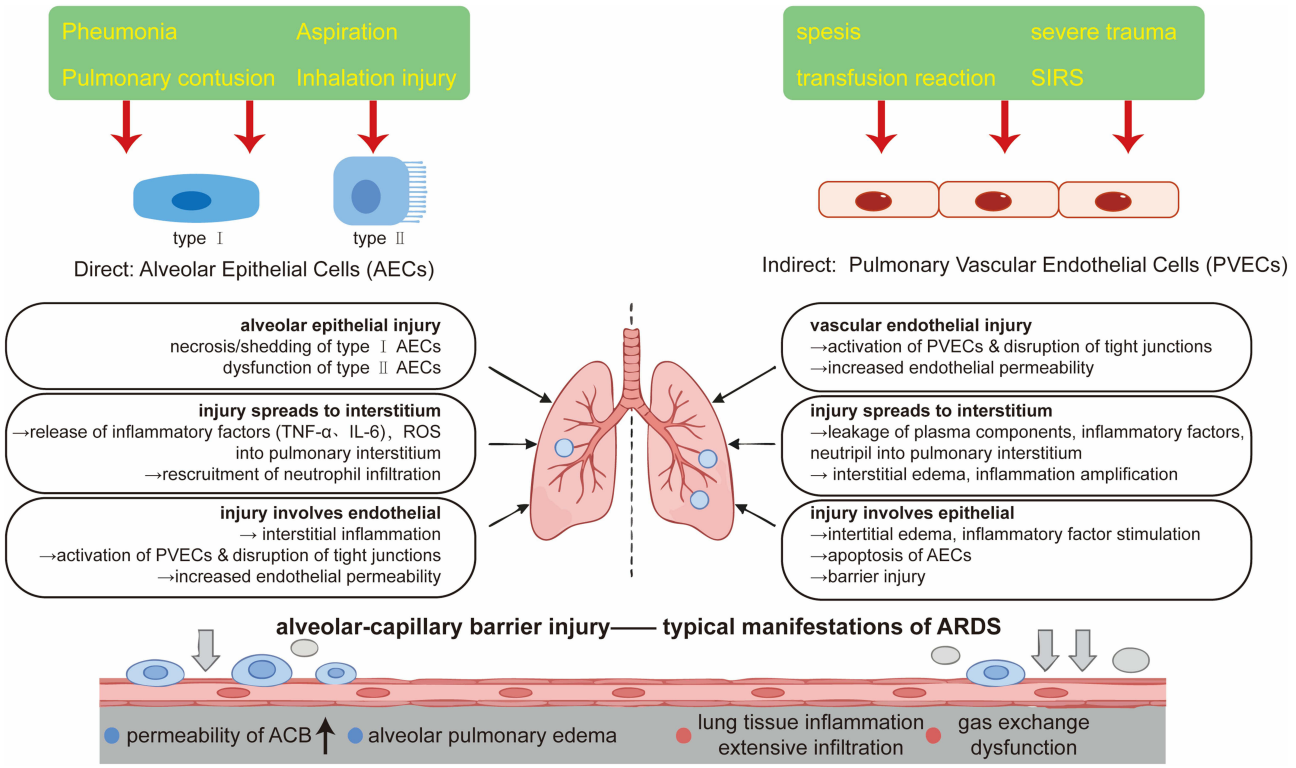

Figure 2 Etiology-specific patterns of alveolar-capillary barrier injury in ARDS. Schematic comparing direct versus indirect pulmonary insults. Left (Direct injury): Pulmonary pathogens/toxins (pneumonia, aspiration) initially target alveolar epithelial cells (AECs), disrupting tight junctions and inducing cell death. Inflammation propagates across the basement membrane to activate endothelial cells—an "outside-in" pattern. Right (Indirect injury): Circulating mediators (sepsis, pancreatitis) primarily activate endothelial cells, causing glycocalyx shedding, adhesion molecule upregulation, and junctional destabilization. Secondary signals involve alveolar epithelium—an "inside-out" pattern. Bottom: Both pathways converge on alveolar edema, hyaline membrane formation, and impaired gas exchange.

secreted angiopoietin-1 (Ang-1) binds to Tie-2 receptor on endothelial cells and regulated their growth.[31] Ang-1 deficiency may reduce vascular endothelial cell signaling to alveolar epithelial cells.[32] Under pathological conditions, the secretome of epithelial cells exposed to cigarette smoke significantly enhances inflammation level, apoptosis and permeability of microvascular endothelial cells.[33]

Conversely, endothelial cells modulate epithelial behavior through paracrine signals. Vascular endothelial cells secrete angiocrine factors through paracrine, and interact with adjacent epithelial cells to form vascular microenvironment and regulate lung regeneration and fibrosis.[34,35] Following repeated alveolar injury, dysregulated repair processes lead to pulmonary fibrosis, which induces endothelial cell reprogramming and increased vascular permeability. This fibrotic endothelial phenotype in turn exacerbates epithelial injury and inflammation, establishing a vicious cycle of tissue damage and aberrant repair.

Beyond separate signaling axes, both cell types engage in extensive reciprocal communication through shared mediators. Epithelial cells and endothelial cells secrete multiple cytokines, chemokines, growth factors, and lipid mediators, and regulate the proliferation, apoptosis, permeability, and inflammatory response of each other through paracrine signaling. In ARDS, inflammatory stimulation leads to an imbalance in this bidirectional paracrine network, forming an "inflammation amplification cycle" that intensifies barrier damage. It highlights the need for therapeutic strategies that target both cellular compartments simultaneously.

Inflammation Storms and Immune Disorder

Partial and systematic inflammatory is a core pathogenesis of ARDS. Multiple pathogenic factors can induce excessive inflammatory response, leading to ACB damage and increased permeability, promoting inflammatory mediator extravasation, and then amplifying pro-inflammatory signals, aggravating pulmonary inflammatory damage, forming a vicious cycle of injury and inflammation mutually promoting, promoting ARDS disease progression.

In the early stage, inflammatory mediator extravasation caused by ACB damage promotes neutrophils to release many harmful mediators. DAMPs stimulate the formation of neutrophil extracellular traps (NETs) that can amplify inflammatory signals, promote macrophage polarize to the M1 phenotype,[36] induce inflammasome activation and pyroptosis,[37] promote platelet aggregation and thrombosis formation.[38] Toxic components like histone proteins of NETs would damage epithelial and endothelial cells.[39] All above can aggravate lung tissue damage and block gas exchange.

Neutrophils are recruited mainly by alveolar macrophages (AMs), which perceive injury signals through pattern recognition receptors and present spatiotemporal-dependent phenotypic shifts. Different polarization phenotypes have different regulatory effects on inflammation in ARDS. M1 macrophages release pro-inflammatory factors and neutrophil chemoattractants (like IL-1β, IL-6 and TNF-α), resulting in progressive inflammation and lung injury. When converting to M2 anti-inflammatory phenotypes, anti-inflammatory factors are produced, which can remit the inflammatory cascade in ARDS and promote alveolar proliferation.

In ARDS, multiple signaling pathways are key to regulating the inflammatory response, such as nuclear transcription factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), toll-like receptor (TLR4) and NLR family pyrin domain containing 3 (NLRP3).[40–43] Rational regulation of these signals could alleviate alveolar epithelial injury and relieve ARDS. In the pathophysiological microenvironment of inflammation, activated NF-κB drives the coordinated upregulation of inflammatory mediators, chemokines and adhesion factors at both transcription and translation levels, thereby amplifying the inflammatory cascade. MAPK pathway (comprising ERK, JNK, and p38) affects alveolar epithelial cell damage by integrating inflammatory signals. For instance, influenza A virus (IAV) infection can promote p38 phosphorylation and inhibit ERK phosphorylation, to intensify the release of inflammatory mediators and ARDS progression.[44] Studies indicate that synergistic inhibition of NF-κB/ERK/p38 signal pathway activation effectively attenuates pathological disruption of the alveolar epithelial barrier.[24] In addition, active TLR4/MyD88 signaling axis triggers pyroptosis induced by NLRP3/Caspase-1 pathway and aggravated epithelial injury, suggesting potential therapeutic targets for pulmonary inflammatory injury.[45,46]

Pulmonary vascular endothelial damage is associated with inflammation in ARDS. Pathogens, inhalation injuries, ischemia reperfusion and other factors stimulate pulmonary vascular endothelial cells, which become activated by inflammatory signals (such as TNF-α, IL-1β and IL-6) and transition to pro-inflammatory, pro-coagulant and oxidative stress-enhanced phenotypes.[47,48] Active endothelial cells increase the expression of angiopoietin-2 (Ang-2) and adhesion molecules (such as IVAM-1 and VCAM-1), contributing to leukocyte recruitment and pulmonary microvascular inflammatory infiltration. Severe pulmonary inflammation induces endothelial homeostasis disruption, inflammatory mediator infiltration and pro-inflammatory factors production, while concurrently stimulating endothelial cell apoptosis. Progressive disintegration of barrier architecture destabilizes the endothelial barrier, thereby exacerbating ARDS progression toward irreversibility.

Oxidative Stress and Mitochondrial Dysfunction

ARDS-related pathologic factors induce massive production of reactive oxygen species (ROS) and dysregulation of redox-sensitive signaling cascades. ROS stimulates ECs to overexpress adhesion factors and pro-inflammatory factors, which compromises vascular integrity. During the early phase, the cytoprotective Nrf2-ARE axis undergoes activation, in which Nrf2 nuclear translocation regulates the transcription and translation of antioxidant-enzyme genes (such as superoxide dismutase and heme oxygenase 1). This mechanism clears ROS to preserve endothelial barrier homeostasis.[49]

Excess ROS accumulation induces mitochondrial dysfunction and triggers mitochondria-mediated apoptosis in alveolar epithelial cell type II (AEC II). AEC II apoptosis initiates intercellular junctional widening that destabilizes epithelial barrier integrity, concomitantly suppressing both biosynthetic pathways and regulated secretory mechanisms essential for pulmonary surfactant homeostasis. Dutra et al[50] identified mitochondrial dysfunction as a central pathogenic mechanism of ARDS. Notably, extracellular vesicles (EVs) derived from mesenchymal stromal cells (MSCs) significantly relieve alveolar epithelial barrier injury through attenuating mitochondrial dysfunction and restoring mitochondrial respiration function, suggesting that ROS reduction through enhanced antioxidant capacity represents a viable therapeutic strategy for ARDS-associated lung injury.

Mitochondrial dysfunction in AECs and vascular ECs triggers aberrant mitochondrial DNA (mtDNA) release, a key contributor to ARDS progression. Studies reveal that LPS binds to TLR4 in sepsis-induced ARDS, activating AMs to trigger mitochondrial oxidative stress and DNA damage, which induces pathological mtDNA release. This liberated mtDNA initiates a cascade inflammatory responses, damaging both alveoli and capillaries again, establishing an oxidative stress-injury-inflammation cycle.[51]

In conclusion, anti-oxidative agents mitigate oxidative damage by inhibiting ROS signal transduction and restoring mitochondrial function, emerging as promising therapeutic strategies for ARDS. Targeting Nrf2/ARE signal pathway to enhance antioxidative defence, exogenous intervention to repair mitochondrial function, and targeting TLR4 to inhibit mtDNA release represents novel research approaches for future clinical therapy.

Multiple Cell Death Patterns

In ARDS, death of AECs and vascular ECs is the primary pathological characteristic of ACB injury. This progress involves multiple patterns including apoptosis, necroptosis, ferroptosis, pyroptosis and others. Different cell death mechanisms differentially govern inflammatory cascade progression and ACB injury patterns across ARDS subphenotypes. Apoptosis is a classical form of AECs death in ARDS. Apoptosis does not trigger significant inflammatory responses, while the accumulation of apoptotic cells damages the integrity of the epithelial barrier, exacerbating lung injury in ARDS. In endothelial cells, the caspase-dependent apoptosis pathway and iNOS/NADPH oxidase-dependent signaling are critical regulators of apoptosis.[52] Necroptosis is usually accompanied by the release of inflammatory factors, amplifying local inflammatory response and tissue damage. During the exudative phase of ARDS, necroptosis of epithelial cells is particularly prominent. Studies confirmed that inhibition of necroptosis induced by SARS-Cov-2 in the alveolar epithelial cell effectively alleviates the inflammatory responses, attenuates lung damage, and boosts survival rates in mice.[53]

Ferroptosis constitutes a metabolically driven necrotic death modality, mechanistically driven by intracellular iron accumulation and lipid peroxides. Emerging evidences reveal the role of ferroptosis in ARDS. Yang et al[54] reported that signal transducer and activators of transduction 6 (STAT6) is a key regulator for ferroptosis. STAT6 can suppress p53 acetylation and restore the transcription and expression of solute carrier family 7 member 11 (SLC7A11) through competitive binding with CREB-binding protein (CBP), thereby inhibiting ferroptosis in AECs and keeping their homeostasis in acute lung injury. In addition, a drug screening study for ARDS revealed that dipyridamole significantly suppressed ferroptosis in alveolar epithelial cells in different ARDS models by modulating SOD1/CREB1/HO1 signaling axis.[55] Furthermore, within cytokine storm microenvironments, the expression of lipid peroxidation markers in pulmonary vascular endothelial cells is markedly elevated, confirming ferroptosis during endothelial barrier disintegration.[56]

Pyroptosis mediated by Gasdermin family proteins is inflammation-dependent. Modulating caspase-3/Gasdermin E pathway can significantly inhibit alveolar epithelial cell pyroptosis induced by H1N1 and relieve lung injury.[57] Similarly, preventing endothelial cell pyroptosis to maintain endothelial cell integrity presents a considerable efficacy in ARDS therapy. Bypass pathway delivers the mtDNA from abnormal release to endothelial cells, activating NLRP3 inflammasome and triggering pyroptosis mediated by Gasdermin D.[58] Notably, endothelial cell pyroptosis mediated by caspase-11 is a prominent symbol for pulmonary endothelial barrier dysfunction, which may be a promising therapeutic target.[59] Additionally, released inflammatory mediators (such as IL-1β and IL-18) during pyroptosis promote vascular leakage by neutrophil recruitment through positive feedback mechanisms,[60] and establish a vicious circle "inflammation-barrier damage".

Clinical Transformation and Therapeutic Strategies

Mechanism Limitation of Current Therapies

Conventional therapeutic approaches for ARDS remain limited by pathological mechanisms. The therapeutic landscape for ARDS has undergone a paradigm shift, transitioning from supportive care to precision, such as targeted biologics and cellular resuscitation strategies (Figure 3).

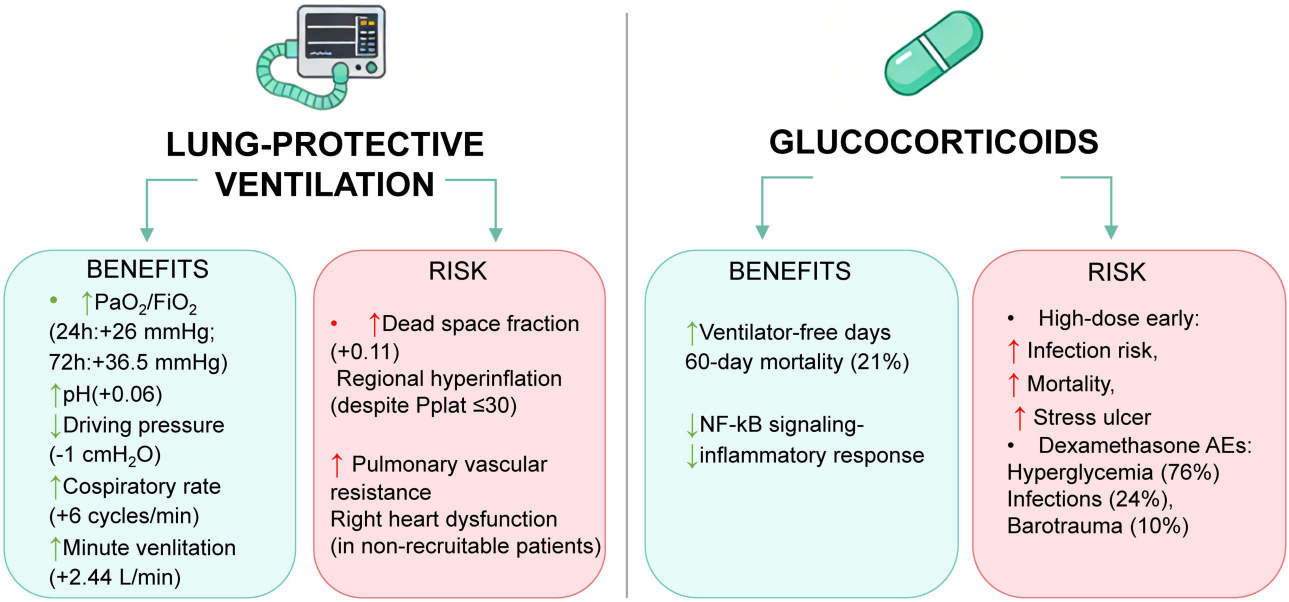

Figure 3 Dual effects of therapeutic interventions on alveolar-capillary barrier dynamics. Comparison of benefits and risks of lung-protective ventilation and glucocorticoids. Lung-protective ventilation (left) improves gas exchange, reduces driving pressure and increases conspiratory rate. However, dead space fraction increases; inappropriately set PEEP elevates pulmonary vascular resistance, risking right heart dysfunction in non-recruitable patients. Glucocorticoids (right) increased ventilator-free days and reduced 60-day mortality; suppress NF-κB and inhibits inflammatory response. However, high-dose early regimens increase infection risk/mortality; dexamethasone AEs (adverse events) include hyperglycemia (76%), infections (24%), barotrauma (10%).

Lung-Protective Ventilation Strategies

Low tidal volume (6 mL/kg) ventilation (LTVV) reduces mechanical injury but does not reverse the barrier damage that already occurred.[61] Overall mortality in patients with ARDS remains as high as 30–40% despite even lung-protective ventilation strategies. Under protective ventilation strategies, lung hyperinflation may still occur even if Pplat ≤30 cm H_2O. Furthermore, inappropriately set PEEP can induce pulmonary vascular resistance, raising the risk of right heart dysfunction particularly in volume-depleted non-recruitment patients.[62]

Clinical studies have demonstrated the physiological benefits of LTVV. In a randomized controlled trial,[63] the physiological changes in ARDS patients were observed after 24 h of TLVV. Significantly increased PaO_2/FiO_2 (Δ26 mm Hg, $P < 0.05$) and pH (Δ0.06, $P < 0.05$) confirm improved gas exchange. The decrease in driving pressure (Δ1 cm H_2O, $P < 0.05$), increase in respiratory rate (Δ6 cycles/min, $P < 0.05$), total minute ventilation (Δ2.44 L/min, $P < 0.05$), respiratory system compliance (Δ3.56 mL/cm H_2O, $P < 0.05$), and estimating dead space fraction (Δ0.11, $P < 0.05$) indicate the success of lung protection strategies. Teng et al[64] reported that after 72 h of LTVV, ARDS patients showed a marked increase in oxygenation index (PaO_2/FiO_2, Δ36.5 mm Hg, $P < 0.001$) and partial pressure of oxygen (PaO_2, Δ13.6 mm Hg, $P < 0.01$).

Glucocorticoids

Glucocorticoids suppress inflammatory responses by inhibiting NF-κB signaling, though their efficacy in ARDS remains controversial. In rapid progression of ARDS, high-dose and short-course regimens (eg, prednisolone 20mg/kg intravenous infusion over 24–48h or equivalent dexamethasone pulse therapy) are applied, which indicate uncontrolled progression of ARDS and adverse events such as increased infection risk and mortality, stress ulcer and others.[65] In contrast, several clinical randomized cohort studies reported that low-dose glucocorticoid application significantly decreased mortality, improved hypoxemia and lung compliance, shortened vasoactive drug administration without increasing infection complications.[66–69] A multicenter randomized controlled trial further substantiated these findings by comparing dexamethasone with placebo in ARDS patients.[70] Patients receiving dexamethasone had a significantly higher mean number of ventilator-free days (95% CI 2.57–7.03, $P < 0.0001$) and lower mortality (21%, $P < 0.001$) at 60 days than patients in the control group. However, dexamethasone-treated patients experienced a higher incidence of

Table 1 Novel and Potential Therapies for the Treatment of ARDS and Targeted Mechanisms

Therapeutic Strategies	Targeting Agents	Mechanisms/Effects
Barrier repairment	Mesenchymal stromal cells (MSCs)	Alleviating acute lung injury through homing, differentiation, immune and inflammatory regulation, and release of exosomes; IL-6 and IL-8 levels ↓, lung injury score ↑;[71] claudin-4 ↑ and maintenance of epithelial barrier[72]
	Fibroblast growth factor (FGF10)	Activating the receptor FGFR2, and driving ACE proliferation and promoting alveolar epithelial repair;[73] preventing alveolar epithelial barrier disruption and inflammatory injury[74]
Anti-inflammation and immune regulation	IL-6 receptor antagonist (tocilizumab)	Blocking IL-6 signaling and decreased 28-day mortality in COVID-19 related ARDS[75]
	NETs inhibitors (DNase I)	Targeting NETs by degrading extracellular DNA and reducing pulmonary edema; reducing alveolar leakage and suppressing pneumonia in sepsis-induced ARDS[76]
Antioxidant & mitochondrial protection	N-acetylcysteine (NAC)	Eliminating phlegm and relieving acetaminophen poisoning; effective in patients with high oxidative stress, no effect on improved overall survival[77]
	Mitochondrial targeted antioxidant (SS-31)	Modulating mitochondrial function and MAPK signaling pathway; alleviating pneumonia by reducing mitochondrial dysfunction and lung injury;[78] to be clinical validated

adverse events, including hyperglycemia (76%), infections (24%), barotrauma (10%). These findings underscore the critical importance of strict patient stratification and dose optimization in glucocorticoid therapy for ARDS.

Novel Therapies Targeting Mechanisms

Important advances have been made in therapeutic strategies targeting alveolar-capillary barrier injury, including barrier repairment, anti-inflammation and immune regulation, antioxidant and mitochondrial protection. These strategies provide new directions for the treatment of acute respiratory stress syndrome by reducing lung injury, inhibiting inflammatory response and improving alveolar epithelial function through different mechanisms (Table 1).

Conclusion

Central pathological mechanism of ARDS is ACB damage, involving barrier structure disruption, mechanical stress imbalance, inflammatory storm, oxidative stress and multi-modal cell death. The clinical heterogeneity of ARDS arises from direct injury primarily targeting the alveolar epithelium and indirect injury affecting vascular endothelial cells. Furthermore, bidirectional crosstalk between epithelial cells and endothelial cells creates an inflammation amplification cycle that indicates barrier dysfunction. Traditional supportive therapies cannot reverse the disruption of barrier structure and function, though able to alleviate partial symptoms of ARDS. Lung-protective ventilation improves oxygenation and mechanics but may increase dead space fraction; glucocorticoids suppress inflammation, while their efficacy depends critically on timing and dosage. This clinical limitation suggests the necessity for targeted intervention of pathological mechanisms. At present, targeted intervention strategies have made some progress, including barrier repairing by MSCs and exosomes, regulating ferroptosis and pyroptosis and others, showing significant clinical transformation potential. Nevertheless, there is difficulty of study on clinical heterogeneity and spatiotemporal dynamics of ARDS. It can focus on different mechanisms of ACB damage, integrate multi-component data to construct ARDS molecular type system; optimize treatment scheme, explore synergistic effects of anti-inflammatory, antioxidant and barrier repair, and joint intervention strategies; construct typing system based on biomarkers, and promote individualized medication. It is promising to break through the current treatment dilemma and realize ARDS precision treatment by multidisciplinary intersection and basic-clinical deep docking.

Consent for Publication

This paper has not been published elsewhere in whole or in part. All authors have read and approved the content and agree to submit for consideration for publication in the journal.

Acknowledgments

Figure 1 was created with Figdraw.

Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. JS was mainly responsible for the conceptualization, investigation, writing-original draft, and writing-review and editing of the paper. MLQ contributed primarily to the study design writing-original draft, writing-review and editing and project administration of the manuscriptpaper. SQH & XLL mainly contributed to the acquisition of data, analysis and interpretation, writing-original draft and visualization of the paper.

Funding

The authors declare that no funds were received during the preparation of this paper.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

References

1. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788–800. doi:10.1001/jama.2016.0291
2. Huang X, Zhang R, Fan G, et al. Incidence and outcomes of acute respiratory distress syndrome in intensive care units of mainland China: a multicentre prospective longitudinal study. *Critical Care*. 2020;24(1):515. doi:10.1186/s13054-020-03112-0
3. Khemani RG, Smith L, Lopez-Fernandez YM, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *Lancet Respir Med*. 2019;7(2):115–128. doi:10.1016/S2213-2600(18)30344-8
4. Esquivel-Ruiz S, González-Rodríguez P, Lorente JA, Pérez-Vizcaíno F, Herrero R, Moreno L. Extracellular vesicles and alveolar epithelial-capillary barrier disruption in acute respiratory distress syndrome: pathophysiological role and therapeutic potential. *Front Physiol*. 2021;12:752287. doi:10.3389/fphys.2021.752287
5. Alipanah-Lechner N, Hurst-Hopf J, Delucchi K, et al. Novel subtypes of severe COVID-19 respiratory failure based on biological heterogeneity: a secondary analysis of a randomized controlled trial. *Critical Care*. 2024;28(1):56. doi:10.1186/s13054-024-04819-0
6. Calfee CS, Janz DR, Bernard GR, et al. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. *Chest*. 2015;147(6):1539–1548. doi:10.1378/chest.14-2454
7. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014;2(8):611–620. doi:10.1016/S2213-2600(14)70097-9
8. Li L, Xing F, Fu Q, Song Q, Li S, Liu J. Progress of research on treatment of sepsis-induced acute lung injury. *Chin J Nosocomiol*. 2024;34:149–155.
9. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Prim*. 2019;5(1):18. doi:10.1038/s41572-019-0069-0
10. Qiao X, Yin J, Zheng Z, Li L, Feng X. Endothelial cell dynamics in sepsis-induced acute lung injury and acute respiratory distress syndrome: pathogenesis and therapeutic implications. *Cell Commun Signal*. 2024;22(1):241. doi:10.1186/s12964-024-01620-y
11. Farooq U, Abbasi AF, Tarar ZI, Chaudhary AJ, Kamal F. Understanding the role of frailty in local and systemic complications and healthcare resource utilization in acute pancreatitis: findings from a national cohort. *Pancreatology*. 2024;24(1):6–13. doi:10.1016/j.pan.2023.12.001
12. Frisvold S, Coppola S, Ehrmann S, Chiumello D, Guérin C. Respiratory challenges and ventilatory management in different types of acute brain-injured patients. *Critical Care*. 2023;27(1):247. doi:10.1186/s13054-023-04532-4
13. Seder DB. Implications of structural brain injury in ARDS. *Neurocrit Care*. 2024;40(1):40–41. doi:10.1007/s12028-023-01824-z
14. Carrié C, Rieu B, Benard A, et al. Early non-invasive ventilation and high-flow nasal oxygen therapy for preventing endotracheal intubation in hypoxemic blunt chest trauma patients: the OptiTHO randomized trial. *Critical Care*. 2023;27(1):163. doi:10.1186/s13054-023-04429-2
15. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 2019;133(17):1840–1853. doi:10.1182/blood-2018-10-860809
16. Yang K, Fan M, Wang X, et al. Lactate induces vascular permeability via disruption of VE-cadherin in endothelial cells during sepsis. *Sci Adv*. 2022;8(17):eabm8965. doi:10.1126/sciadv.abm8965
17. Li Y, Liu P, Zhou Y. Activation of angiopoietin-Tie2 signaling protects the kidney from ischemic injury by modulation of endothelial-specific pathways. *J Am Soc Nephrol*. 2023;34(6):969–987. doi:10.1681/ASN.0000000000000098
18. Zhang Y, Liu J, Zou T, et al. DPSCs treated by TGF-β1 regulate angiogenic sprouting of three-dimensionally co-cultured HUVECs and DPSCs through VEGF-Ang-Tie2 signaling. *Stem Cell Res Ther*. 2021;12(1):281. doi:10.1186/s13287-021-02349-y
19. Benatti MN, Fabro AT, Miranda CH. Endothelial glycocalyx shedding in the acute respiratory distress syndrome after flu syndrome. *J Intensive Care*. 2020;8:72. doi:10.1186/s40560-020-00488-7
20. Ding C, Tuo J, Cao J, et al. Xuebijing injection inhibits the degradation of pulmonary vascular endothelial calyx to improve acute lung injury induced by severe heatstroke. *Med J Chin PLA*. 2023;48:1387–1394.

21. Kuo W-T, Odenwald MA, Turner JR, Zuo L. Tight junction proteins occludin and ZO-1 as regulators of epithelial proliferation and survival. *Ann N Y Acad Sci*. 2022;1514(1):21–33. doi:10.1111/nyas.14798
22. Raya-Sandino A, Lozada-Soto KM, Rajagopal N, et al. Claudin-23 reshapes epithelial tight junction architecture to regulate barrier function. *Nat Commun*. 2023;14(1):6214. doi:10.1038/s41467-023-41999-9
23. Li J, Qi Z, Li D, et al. Alveolar epithelial glycocalyx shedding aggravates the epithelial barrier and disrupts epithelial tight junctions in acute respiratory distress syndrome. *Biomed Pharmacothe*. 2021;133:111026. doi:10.1016/j.biopha.2020.111026
24. Sim TY, Harith HH, Tham CL, et al. The protective effects of a synthetic geranyl acetophenone in a cellular model of TNF-α-induced pulmonary epithelial barrier dysfunction. *Molecules*. 2018;23(6):1355. doi:10.3390/molecules23061355
25. Short KR, Kasper J, van der Aa S, et al. Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions. *Europ Resp J*. 2016;47(3):954–966. doi:10.1183/13993003.01282-2015
26. Wan C, Yang D, Kong M, et al. Protective effect and molecular mechanism of Pudilan anti-inflammatory oral liquid on lung injury in mice infected with the influenza A virus. *J of China-Japan Frienship Hosp*. 2024;38:338–344+320+385.
27. Chiu -J-J, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiol Rev*. 2011;91(1):327–387. doi:10.1152/physrev.00047.2009
28. Ghim M, Alpresa P, Yang S-W, et al. Visualization of three pathways for macromolecule transport across cultured endothelium and their modification by flow. *Am J Physiol Heart Circulatory Physiol*. 2017;313(5):H959–h973. doi:10.1152/ajpheart.00218.2017
29. Shirakura K, Baluk P, Nottebaum AF, et al. Shear stress control of vascular leaks and atheromas through Tie2 activation by VE-PTP sequestration. *EMBO Mol Med*. 2023;15(4):e16128. doi:10.15252/emmm.202216128
30. Lorenc P, Sikorska A, Molenda S, Guzniczak N, Dams-Kozlowska H, Florczak A. Physiological and tumor-associated angiogenesis: key factors and therapy targeting VEGF/VEGFR pathway. *Biomed Pharmacothe*. 2024;180:117585.
31. Chiang WC, Huang YC, Fu TI, et al. Angiopoietin 1 influences ischemic reperfusion renal injury via modulating endothelium survival and regeneration. *Mol Med*. 2019;25(1):5. doi:10.1186/s10020-019-0072-7
32. Chen Chunyuan WL. Progress on the mechanism of microRNA in bronchopulmonary dysplasia. *Int J Pediatr*. 2026;53:16–20
33. Seenak P, Nernpermpisooth N, Kumphune S, et al. Secretome profiling of human epithelial cells exposed to cigarette smoke extract and their effect on human lung microvascular endothelial cells. *Sci Rep*. 2024;14(1):13740. doi:10.1038/s41598-024-64717-x
34. Chen X, Wang H, Wu C, et al. Endothelial H(2)S-AMPK dysfunction upregulates the angiocrine factor PAI-1 and contributes to lung fibrosis. *Redox Biol*. 2024;70:103038. doi:10.1016/j.redox.2024.103038
35. Ma J, Zhang L, Zhang X, et al. Inhibiting endothelial Rhoj blocks profibrotic vascular intussusception and angiocrine factors to sustain lung regeneration. *Sci Trans Med*. 2024;16(762):eado5266. doi:10.1126/scitranslmed.ado5266
36. Yu J, Fu Y, Gao J, et al. Cathepsin C from extracellular histone-induced M1 alveolar macrophages promotes NETosis during lung ischemia-reperfusion injury. *Redox Biol*. 2024;74:103231. doi:10.1016/j.redox.2024.103231
37. Li H, Li Y, Song C, et al. Neutrophil extracellular traps augmented alveolar macrophage pyroptosis via AIM2 inflammasome activation in LPS-induced ALI/ARDS. *J Inflamm Res*. 2021;14:4839–4858. doi:10.2147/JIR.S321513
38. Middleton EA, He X-Y, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. 2020;136(10):1169–1179. doi:10.1182/blood.2020007008
39. Saffarzadeh M, Juenemann C, Queisser MA, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PLoS One*. 2012;7(2):e32366. doi:10.1371/journal.pone.0032366
40. Zhou M, Meng L, He Q, Ren C, Li C. Valsartan attenuates LPS-induced ALI by modulating NF-κB and MAPK pathways. *Front Pharmacol*. 2024;15:1321095. doi:10.3389/fphar.2024.1321095
41. Millar MW, Fazal F, Rahman A. Therapeutic targeting of NF-κB in acute lung injury: a double-edged sword. *Cells*. 2022;11(20):3317.
42. Wang Y, Wang Y, Ma J, et al. YuPingFengSan ameliorates LPS-induced acute lung injury and gut barrier dysfunction in mice. *J Ethnopharmacol*. 2023;312:116452. doi:10.1016/j.jep.2023.116452
43. Wu Q, Zhou M, Chen Y, et al. Bletilla striata polysaccharides protect against ARDS by modulating the NLRP3/caspase1/GSDMD and HMGB1/TLR4 signaling pathways to improve pulmonary alveolar macrophage pyroptosis. *J Ethnopharmacol*. 2024;319(Pt 3):117361. doi:10.1016/j.jep.2023.117361
44. Li G, Tian T, Wang L, Xu S, Yang W. Andrographolide improves influenza A virus induced lung epithelial cells injury via regulating p38 and ERK phosphorylation. *Chin J Virol*. 2024;40:476–483.
45. Wen R, Zhang T, Yang N, Liu C. Recent research on pyroptosis in sepsis-induced myocardial depression. *Chin J Contemp Pediatr*. 2024;26:774–781.
46. Xu H, Shan B, Shan Y, Sun X, Yang Q. Effect of Guangchenpi volatile oil on lipopolysaccharide-induced inflammation through regulating TLR4/MyD88/NLRP3/Caspase-1 signaling pathway in pulmonary epithelial cells and their spectrum-effect relationship. *Drug Eval Res*. 2025;48:28–37.
47. Wang L, Tang Y, Tang J, et al. Endothelial cell-derived extracellular vesicles expressing surface VCAM1 promote sepsis-related acute lung injury by targeting and reprogramming monocytes. *J Extracell Vesicles*. 2024;13(3):e12423. doi:10.1002/jev2.12423
48. Jiang J, Huang K, Xu S, Garcia JGN, Wang C, Cai H. Targeting NOX4 alleviates sepsis-induced acute lung injury via attenuation of redox-sensitive activation of CaMKII/ERK1/2/MLCK and endothelial cell barrier dysfunction. *Redox Biol*. 2020;36:101638. doi:10.1016/j.redox.2020.101638
49. Wang L, Zhang X, Xiong X, et al. Nrf2 regulates oxidative stress and its role in cerebral ischemic stroke. *Antioxidants*. 2022;11(12):2377. doi:10.3390/antiox11122377
50. Dutra Silva J, Su Y, Calfee CS, et al. Mesenchymal stromal cell extracellular vesicles rescue mitochondrial dysfunction and improve barrier integrity in clinically relevant models of ARDS. *Europ resp J*. 2021;58(1):2002978. doi:10.1183/13993003.02978-2020
51. Long G, Gong R, Wang Q, Zhang D, Huang C. Role of released mitochondrial DNA in acute lung injury. *Front Immunol*. 2022;13:973089. doi:10.3389/fimmu.2022.973089
52. Gill SE, Rohan M, Mehta S. Role of pulmonary microvascular endothelial cell apoptosis in murine sepsis-induced lung injury in vivo. *Respir Res*. 2015;16(1):109. doi:10.1186/s12931-015-0266-7
53. Komiya Y, Kamiya M, Oba S, et al. Necroptosis in alveolar epithelial cells drives lung inflammation and injury caused by SARS-CoV-2 infection. *Biochim Biophys Acta Mol Basis Dis*. 2024;1870(8):167472. doi:10.1016/j.bbadis.2024.167472

54. Yang Y, Ma Y, Li Q, et al. STAT6 inhibits ferroptosis and alleviates acute lung injury via regulating P53/SLC7A11 pathway. *Cell Death Dis*. 2022;13(6):530. doi:10.1038/s41419-022-04971-x
55. Chen X, Shen J, Jiang X, et al. Characterization of dipyridamole as a novel ferroptosis inhibitor and its therapeutic potential in acute respiratory distress syndrome management. *Theranostics*. 2024;14(18):6947–6968. doi:10.7150/thno.102318
56. Shen K, Wang X, Wang Y, et al. miR-125b-5p in adipose derived stem cells exosome alleviates pulmonary microvascular endothelial cells ferroptosis via Keap1/Nrf2/GPX4 in sepsis lung injury. *Redox Biol*. 2023;62:102655. doi:10.1016/j.redox.2023.102655
57. Wei Z, Gao R, Sun Z, et al. Baicalin inhibits influenza A (H1N1)-induced pyroptosis of lung alveolar epithelial cells via caspase-3/GSDME pathway. *J med virol*. 2023;95(5):e28790. doi:10.1002/jmv.28790
58. Wu YT, Xu WT, Zheng L, et al. 4-octyl itaconate ameliorates alveolar macrophage pyroptosis against ARDS via rescuing mitochondrial dysfunction and suppressing the cGAS/STING pathway. *Int Immunopharmacol*. 2023;118:110104. doi:10.1016/j.intimp.2023.110104
59. Cheng KT, Xiong S, Ye Z, et al. Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. *J Clin Invest*. 2017;127 (11):4124–4135. doi:10.1172/JCI94495
60. Xian H, Watari K, Sanchez-Lopez E, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. *Immunity*. 2022;55(8):1370–1385.e1378. doi:10.1016/j.immuni.2022.06.007
61. Fielding-Singh V, Matthay MA, Calfee CS. Beyond low tidal volume ventilation: treatment adjuncts for severe respiratory failure in acute respiratory distress syndrome. *Crit Care Med*. 2018;46(11):1820–1831. doi:10.1097/CCM.0000000000003406
62. Cappio Borlino S, Hagry J, Lai C, et al. The effect of positive end-expiratory pressure on pulmonary vascular resistance depends on lung recruitability in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2024;210(7):900–907. doi:10.1164/rccm.202402-0383OC
63. Zou X, Zhang H, Wu Y, et al. Physiologic comparison of airway pressure release ventilation and low tidal volume ventilation in ARDS: a randomized controlled trial. *Chest*. 2025;167(2):453–465. doi:10.1016/j.chest.2024.08.050
64. Teng Z, Li Y, Yan Z, Zhuang C, Zhang C. Observation on the curative effect of airway pressure release ventilation in the treatment of patients with acute respiratory distress syndrome. *Chin J Diffic and Compl Cas*. 2022;21(7):706–710.
65. Meduri GU, Annane D, Confalonieri M, et al. Pharmacological principles guiding prolonged glucocorticoid treatment in ARDS. *Intensive Care Med*. 2020;46(12):2284–2296. doi:10.1007/s00134-020-06289-8
66. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *New Engl J Med*. 2006;354(16):1671–1684.
67. Meduri GU, Marik PE, Chrousos GP, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med*. 2008;34(1):61–69. doi:10.1007/s00134-007-0933-3
68. Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. *J Intensive Care*. 2018;6:53. doi:10.1186/s40560-018-0321-9
69. Li G, Chen D, Gao F, et al. Efficacy of corticosteroids in patients with acute respiratory distress syndrome: a meta-analysis. *Ann Med*. 2024;56 (1):2381086. doi:10.1080/07853890.2024.2381086
70. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267–276. doi:10.1016/S2213-2600(19)30417-5
71. Lv H, Chen W, Xiang AP, Zhang Q, Yang Y, Yi H. Mesenchymal stromal cells as a salvage treatment for confirmed acute respiratory distress syndrome: preliminary data from a single-arm study. *Intensive Care Med*. 2020;46(10):1944–1947. doi:10.1007/s00134-020-06122-2
72. Ren Q, Xu Y, Xu L, Lu Y, Zheng Y. Hypoxic bone marrow mesenchymal stem cell-derived exosomal lncRNA XIST attenuates lipopolysaccharide-induced acute lung injury via the miR-455-3p/Claudin-4 axis. *Int Immunopharmacol*. 2023;125(Pt A):111066. doi:10.1016/j.intimp.2023.111066
73. Yuan T, Volckaert T, Redente EF, et al. FGF10-FGFR2B signaling generates basal cells and drives alveolar epithelial regeneration by bronchial epithelial stem cells after lung injury. *Stem Cell Rep*. 2019;12(5):1041–1055. doi:10.1016/j.stemcr.2019.04.003
74. Lin L, Yang L, Wang N, et al. FGF10 protects against LPS-induced epithelial barrier injury and inflammation by inhibiting SIRT1-ferroptosis pathway in acute lung injury in mice. *Int Immunopharmacol*. 2024;127:111426. doi:10.1016/j.intimp.2023.111426
75. General Office of National Health Commission. COVID-19 diagnosis and treatment protocol (trial version 9). *J Cardivasc Pulmon Dis*. 2022;41:449–457.
76. Du Y, Chen Y, Li F, Mao Z, Ding Y, Wang W. Genetically engineered cellular nanovesicle as targeted DNase I delivery system for the clearance of neutrophil extracellular traps in acute lung injury. *Adv Sci*. 2023;10(32):e2303053. doi:10.1002/advs.202303053
77. Zhen J, Chen W, Sheng B, Zhao L, Zang X, Ma Y. Clinical trial of inhaled acetylcysteine solution in the treatment of elderly patients with acute respiratory distress syndrome undergoing mechanical ventilation. *Chin J Clin pharmacol*. 2020;36:2982–2985.
78. Yang D-Q, Zuo Q-N, Wang T. Mitochondrial-targeting antioxidant SS-31 suppresses airway inflammation and oxidative stress induced by cigarette smoke. *Oxid Med Cell Longev*. 2021;2021(1):6644238. doi:10.1155/2021/6644238