ARDS: Pathobiology, Current Management & Emerging Regenerative Medicine Research

A Medical Affairs Review

Disease Biology • Current Clinical Management • Translational Science • Emerging Regenerative Approaches

Breathe Biologics, Inc.

Medical Affairs | Pulmonary Medicine Resource

Executive Summary

Acute respiratory distress syndrome (ARDS) is a heterogeneous, life-threatening form of acute respiratory failure characterized by severe pulmonary inflammation, disruption of the alveolar-capillary barrier, increased pulmonary permeability, noncardiogenic pulmonary edema, impaired gas exchange, and hypoxemia.

ARDS may develop following a variety of direct and indirect pulmonary insults, including pneumonia, sepsis, aspiration, trauma, and other systemic inflammatory conditions.

Despite advances in critical care, contemporary ARDS management remains centered largely on supportive strategies designed to maintain oxygenation while minimizing additional ventilator-associated and systemic injury.

The biological complexity of ARDS has stimulated investigation of therapeutic strategies capable of influencing multiple components of lung injury simultaneously.

Among these approaches, mesenchymal stromal/stem cell (MSC)-based therapies have attracted scientific interest because experimental research suggests potential immunomodulatory, paracrine, endothelial-protective, epithelial-supportive, and tissue-repair activities.

These approaches remain investigational. Their clinical safety and efficacy for ARDS must be established through appropriately designed controlled clinical trials.

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1 | Understanding ARDS

A Syndrome of Acute Lung Injury

ARDS is not a single disease. It represents a clinical syndrome that may arise from multiple initiating insults converging on common pathways of acute pulmonary injury.

Important precipitating conditions include:

- Pneumonia
- Sepsis
- Aspiration of gastric contents
- Severe viral respiratory infection
- Major trauma
- Pancreatitis
- Inhalational injury
- Transfusion-associated lung injury
- Other severe systemic inflammatory insults

The resulting biological response can involve simultaneous injury to the pulmonary endothelium, alveolar epithelium, immune system, and extracellular matrix.

The Alveolar-Capillary Barrier

Normal gas exchange depends on an exceptionally thin interface between the pulmonary circulation and alveolar airspace.

This interface consists principally of:

Pulmonary capillary endothelium → interstitial compartment → alveolar epithelium

During ARDS, inflammatory and vascular injury increase permeability across this barrier.

Protein-rich fluid can enter the alveolar space, surfactant function may become impaired, alveoli may collapse, lung compliance may decline, and oxygen transfer becomes increasingly compromised.

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2 | Pathobiology of ARDS

From Inflammatory Injury to Respiratory Failure

ARDS involves interacting biological processes rather than a single molecular abnormality.

1. Initiating Injury

A pulmonary or systemic insult activates innate immune and inflammatory pathways.

2. Immune Activation

Neutrophils, macrophages, monocytes, platelets, and other immune components participate in the inflammatory response.

3. Cytokine and Mediator Signaling

Pro-inflammatory signaling contributes to amplification of pulmonary and systemic inflammation.

4. Endothelial Dysfunction

Pulmonary vascular endothelial injury can increase vascular permeability and promote movement of fluid and proteins into lung tissue and alveolar spaces.

5. Epithelial Injury

Damage to alveolar epithelial cells can impair barrier integrity, surfactant homeostasis, and alveolar fluid clearance.

6. Pulmonary Edema

Failure of the alveolar-capillary barrier contributes to protein-rich pulmonary edema and impaired gas exchange.

7. Dysregulated Repair

Recovery requires resolution of inflammation together with restoration of endothelial and epithelial integrity.

In some patients, abnormal repair responses may contribute to fibroproliferation and persistent pulmonary dysfunction.

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3 | The Central Role of the Alveolar-Capillary Microenvironment

The pathophysiology of ARDS can be viewed as disruption of an integrated pulmonary microenvironment.

Healthy Lung

Intact endothelium
↓
Controlled permeability
↓
Intact alveolar epithelium
↓
Effective fluid clearance
↓
Efficient oxygen exchange

ARDS

Inflammatory activation
↓
Endothelial injury
↓
Barrier disruption
↓
Alveolar flooding and epithelial injury
↓
Impaired oxygen exchange
↓
Respiratory failure

This interconnected biology helps explain why targeting a single inflammatory mediator has historically been challenging in a heterogeneous syndrome such as ARDS.

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4 | ARDS Is Biologically Heterogeneous

Patients meeting clinical criteria for ARDS may have substantially different underlying biology.

Differences may include:

- Etiology of lung injury
- Magnitude of systemic inflammation
- Degree of endothelial injury
- Degree of epithelial injury
- Pulmonary versus extrapulmonary origin
- Timing of presentation
- Host immune response
- Comorbidities
- Genetic susceptibility
- Stage of injury and repair

Research has increasingly examined whether biological phenotypes or subphenotypes may identify patient populations with different prognoses or treatment responses.

This heterogeneity represents both a challenge and an opportunity for future precision approaches to ARDS.

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5 | Current Management of ARDS

Protect the Lung While Treating the Cause

Current management generally combines treatment of the precipitating condition with evidence-based supportive critical care.

Lung-Protective Ventilation

Mechanical ventilation strategies seek to provide adequate gas exchange while limiting additional ventilator-induced lung injury.

Limiting excessive tidal volumes and airway pressures is an important component of ARDS management.

Positive End-Expiratory Pressure

PEEP can help maintain alveolar recruitment and improve oxygenation.

Current clinical guidance supports consideration of higher PEEP without prolonged lung recruitment maneuvers in appropriate patients with moderate-to-severe ARDS.

Prone Positioning

Prolonged prone positioning is recommended for patients with severe ARDS and can improve ventilation-perfusion matching while reducing regional mechanical stress.

Corticosteroids

Contemporary clinical guidelines support corticosteroid use in ARDS under appropriate clinical circumstances, although patient selection, timing, agent, and dosing remain clinical considerations.

Neuromuscular Blockade

Neuromuscular blocking agents may be considered in selected patients with early severe ARDS.

VV-ECMO

Venovenous extracorporeal membrane oxygenation may provide rescue support for carefully selected patients with severe ARDS refractory to conventional management.

Treatment of the Underlying Cause

Management must simultaneously address the precipitating condition—for example, antimicrobial therapy and source control when infection is responsible.

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6 | The Remaining Therapeutic Gap

Supportive care has improved substantially.

However, supportive interventions primarily seek to maintain physiological function and prevent additional injury while the underlying pulmonary damage resolves.

There remains scientific interest in therapies capable of directly modifying the biological processes responsible for ARDS.

Potential therapeutic objectives include:

Control excessive inflammation

Protect endothelial integrity

Restore epithelial barrier function

Enhance alveolar fluid clearance

Promote resolution of inflammation

Support physiological tissue repair

Limit maladaptive remodeling

A therapy capable of coordinating several of these biological activities could represent a fundamentally different therapeutic concept from conventional single-target pharmacology.

Whether such an approach can translate into meaningful clinical benefit remains an important research question.

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7 | Regenerative Medicine in Acute Lung Injury

From Cell Replacement to Paracrine Biology

Early concepts of regenerative cell therapy often emphasized replacement of damaged cells.

The scientific understanding of MSC biology has evolved.

Current evidence suggests that many biological effects attributed to MSCs occur predominantly through **paracrine and cell-to-cell signaling** rather than durable engraftment and direct replacement of pulmonary tissue.

Potential mediators include:

- Soluble proteins
- Cytokines
- Chemokines
- Growth factors
- Extracellular vesicles
- Exosomes
- Lipid mediators
- Regulatory RNAs
- Mitochondrial transfer and other intercellular processes

This has led to a broader concept of regenerative medicine:

Modifying the injured tissue environment sufficiently to permit endogenous repair.

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8 | MSC Biology and ARDS

A Multi-Pathway Investigational Strategy

Preclinical and translational literature has identified several interconnected activities through which MSCs may influence acute lung injury.

Immune Modulation

MSC signaling has been reported to influence:

- Macrophage activity
- Neutrophil responses
- T-cell function
- Innate immune signaling

- Pro- and anti-inflammatory mediator balance

Cytokine Regulation

MSC-associated paracrine activity may modify inflammatory signaling rather than simply suppressing the immune system globally.

Endothelial Protection

Experimental studies suggest potential effects on endothelial barrier integrity and pulmonary vascular permeability.

Epithelial Support

MSC-derived factors have been investigated for their potential to support alveolar epithelial survival and recovery.

Alveolar Fluid Clearance

Restoration of epithelial transport and barrier function may facilitate removal of pulmonary edema fluid from alveolar spaces.

Remodeling Regulation

Experimental research is evaluating whether MSC signaling can influence fibroblast activity, extracellular-matrix deposition, and other pathways involved in maladaptive repair.

These biological activities should be regarded as mechanistic rationale rather than proof of clinical benefit.

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9 | A Proposed Regenerative Framework

A useful conceptual model for regenerative investigation in ARDS is:

IMMUNE MODULATION

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CYTOKINE CONTROL

↓

ENDOTHELIAL STABILIZATION

↓

EPITHELIAL REPAIR

↓

ALVEOLAR FLUID CLEARANCE

↓

REMODELING CONTROL

↓

RESTORATION OF THE ALVEOLAR-CAPILLARY MICROENVIRONMENT

↓

POTENTIAL FUNCTIONAL RECOVERY

These processes are highly interconnected and should not be interpreted as a proven sequential mechanism.

Rather, they represent biological pathways under investigation across the MSC field.

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10 | Clinical Translation of MSC Therapy

MSC-based therapies have progressed from experimental models into human clinical investigation.

Clinical programs have evaluated MSCs derived from multiple tissue sources, including:

- Bone marrow
- Adipose tissue
- Umbilical cord tissue
- Placental and perinatal tissues

Studies have also varied substantially in:

- Cell-manufacturing methods
- Donor characteristics
- Culture conditions
- Passage number
- Cryopreservation
- Potency
- Dose
- Administration schedule
- Patient population

- ARDS etiology
- Disease severity
- Timing of intervention

These differences are scientifically important.

MSC products should not be assumed to be biologically or clinically interchangeable.

Cell source, manufacturing process, potency characteristics, formulation, dose, and clinical population can potentially influence biological activity and clinical performance.

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11 | What Has Clinical Research Shown?

Early clinical trials and aggregate analyses have generally supported the feasibility of intravenous MSC administration in critically ill populations.

The clinical efficacy question remains unresolved.

Some studies and meta-analyses have reported encouraging signals involving mortality, inflammatory biomarkers, oxygenation, or other outcomes, whereas other studies have not demonstrated definitive clinical benefit.

Differences in cell products, manufacturing, viability, dose, patient selection, ARDS phenotype, and study design complicate cross-trial interpretation.

Accordingly, larger and rigorously controlled clinical trials remain necessary.

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12 | Biomarkers and Pharmacodynamic Research

Biomarkers may play an increasingly important role in understanding both ARDS biology and response to investigational therapy.

Inflammatory Biology

Candidate markers include:

- IL-6
- TNF-associated pathways
- IL-8
- Interferon-associated signaling
- Other inflammatory cytokines and chemokines

Endothelial Injury

Research has evaluated markers associated with pulmonary vascular injury and permeability.

Epithelial Injury

Markers reflecting alveolar epithelial damage may provide insight into the severity and biological character of lung injury.

Pharmacodynamic Biomarkers

For regenerative therapies, biomarkers may potentially help answer several questions:

Did the therapy engage the intended biological pathway?

Did systemic inflammatory signaling change?

Were endothelial or epithelial injury pathways altered?

Can biological responders be distinguished from nonresponders?

Can biomarkers identify patients most likely to benefit?

These questions remain areas of active investigation.

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13 | Toward Precision Regenerative Medicine

The future of regenerative therapy for ARDS may depend on more than demonstrating that a cell product has biological activity.

The larger question may be:

Which therapy, for which biological ARDS phenotype, at which stage of disease?

Future clinical development may increasingly integrate:

Clinical phenotype

+

Inflammatory biomarkers

+

Endothelial and epithelial injury markers

+

Cell-product potency

+

Timing of administration

+

Clinical outcomes

Such strategies could potentially help move the field from broadly applied cell therapy toward biologically informed regenerative medicine.

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14 | Key Translational Challenges

Several important questions remain unresolved across the MSC field.

Product Characterization

What biological attributes define a therapeutically active MSC product?

Potency

Which assays best predict relevant biological activity?

Manufacturing

Can biological consistency be maintained across clinically meaningful manufacturing scale?

Dose

What cell dose and administration schedule provide optimal biological activity?

Timing

At what stage of ARDS is intervention most likely to influence disease biology?

Patient Selection

Should regenerative therapies target all ARDS patients or biologically defined subgroups?

Etiology

Can results from one form of ARDS be generalized to pneumonia-, sepsis-, aspiration-, trauma-, or other etiologies?

Biomarker Validation

Which biomarkers meaningfully demonstrate target engagement or predict clinical response?

Clinical Efficacy

Most importantly, can biological activity translate into improvements in outcomes that matter to patients?

These questions require prospective clinical investigation.

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15 | The Emerging Research Landscape

Regenerative medicine research in ARDS is expanding beyond conventional MSC administration.

Investigational areas include:

- MSC-based cellular therapies
- Extracellular vesicles
- Exosome-based approaches
- Cell-free secretome products
- Cellular preconditioning
- Bioengineered MSCs
- Gene-modified cells
- Biomaterial-assisted delivery
- Precision biomarker strategies
- Combination regenerative approaches

Each technology presents distinct scientific, manufacturing, regulatory, and clinical-development challenges.

None should be considered established therapy for ARDS without adequate clinical evidence and appropriate regulatory authorization.

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16 | Medical Affairs Perspective

ARDS represents an unusually compelling challenge for translational medicine.

Its biology encompasses inflammation, vascular permeability, epithelial dysfunction, pulmonary edema, immune dysregulation, and tissue repair.

This complexity may partly explain why development of effective disease-modifying pharmacotherapy has proven difficult.

Regenerative approaches offer a different scientific paradigm.

Rather than targeting a single receptor or inflammatory mediator, some regenerative platforms are being investigated for their potential to influence multiple components of the injured pulmonary microenvironment.

The biological rationale is compelling.

The translational challenge is equally substantial.

Ultimately, the value of regenerative medicine in ARDS will depend upon reproducible manufacturing, validated biological potency, appropriate patient selection, well-characterized pharmacodynamic activity, and—most importantly—evidence of clinically meaningful benefit from rigorous controlled trials.

Key Takeaways

ARDS is a heterogeneous syndrome, not a single disease.

Endothelial injury, epithelial damage, inflammatory dysregulation, pulmonary edema, and abnormal repair interact to produce severe respiratory failure.

Current treatment remains predominantly supportive.

Lung-protective ventilation, prone positioning and selected adjunctive interventions remain central to evidence-based management.

Regenerative medicine introduces a different therapeutic concept.

MSC research suggests the possibility of influencing inflammation, barrier integrity, tissue repair, and remodeling through coordinated paracrine signaling.

MSC products are not interchangeable.

Cell source, manufacturing, potency, formulation, dose, and clinical context matter.

Clinical efficacy remains to be established.

Early clinical research provides a foundation for continued investigation but does not establish regenerative cell therapy as standard treatment for ARDS.

Biomarkers may become increasingly important.

Integration of biological phenotyping, pharmacodynamic measurements, and product potency may help advance precision approaches to regenerative medicine.

Selected Scientific References

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3. Horie S, McNicholas B, Rezoagli E, et al. Cell-based therapies for acute respiratory distress syndrome: Where are we now? *Am J Respir Crit Care Med.* 2024;209:789–801.

4. Wang F, Xie C, Wang X. Mesenchymal stem cell therapies for ARDS: translational promise and challenges. *Stem Cell Res Ther.* 2025;16:504.

5. Additional peer-reviewed literature should be incorporated into the final Medical Affairs reference list covering ARDS epidemiology, endothelial and epithelial biology, prone positioning, lung-protective ventilation, ARDS phenotypes, MSC clinical trials, extracellular vesicles, and regenerative medicine.

Important Medical & Scientific Information

This material is intended for scientific and educational purposes.

Regenerative and cell-based therapies discussed in this review are investigational for ARDS unless otherwise specifically identified as approved by the applicable regulatory authority.

Discussion of biological pathways, mechanisms, biomarkers, preclinical findings, or emerging therapeutic strategies should not be interpreted as evidence of established clinical safety or efficacy.

This resource does not provide medical advice and is not intended to replace independent clinical judgment or applicable clinical practice guidelines.

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