



Review Article

From Omics to Artificial Intelligence: Revolutionizing Sepsis-Induced Acute Respiratory Distress Syndrome Management

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Abstract

Background: Sepsis-induced acute respiratory distress syndrome (ARDS) represents a formidable challenge in critical care, marked by significant mortality and long-term morbidity among survivors. This study comprehensively reviewed the current advances in omics technologies, AI, and novel therapeutic approaches in sepsis-induced ARDS management.

Methods: The current literature on multi-omics approaches, advanced imaging modalities, biomarker development, and AI applications in sepsis-induced ARDS underwent investigation.

Results: Recent advances in high-throughput omics technologies (genomics, transcriptomics, proteomics, metabolomics, and epigenetics) have enabled detailed dissection of the molecular and cellular pathways underlying sepsis-induced ARDS. These approaches have facilitated the discovery of key biomarkers in blood, urine, and exhaled breath condensate, offering promise for earlier diagnosis, precise risk stratification, and targeted intervention. Concurrently, developments in advanced imaging modalities (e.g., HRCT, MRI, and PET) have enhanced the visualization of pulmonary injury, improved disease monitoring, and informed therapeutic decision-making. Novel therapeutic modalities (i.e., nanoparticle-based drug delivery, lung-targeted and anti-inflammatory therapies, microbiome modulation, and extracorporeal life support) are expanding the therapeutic armamentarium. Furthermore, the integration of AI and ML into critical care workflows is transforming sepsis-induced ARDS management, enabling sophisticated predictive modeling, real-time clinical decision support, and the harnessing of big data analytics for precision medicine.

Conclusion: The synergy between omics technologies, advanced imaging, and AI is catalyzing a paradigm shift toward personalized medicine in sepsis-induced ARDS, with the potential to improve survival rates and long-term outcomes. Overall, these interdisciplinary innovations are reshaping the landscape of sepsis-induced ARDS by enabling more nuanced patient phenotyping, individualized therapy, and dynamic monitoring.

Keywords: Sepsis-induced acute respiratory distress syndrome, Biomarkers, Omics technologies, Novel therapeutics, Artificial intelligence, Personalized medicine



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Introduction

Sepsis-induced acute respiratory distress syndrome (ARDS) represents a critical health condition that is characterized by severe respiratory impairments caused by an uncontrolled inflammatory response to infection. This condition imposes a substantial burden on public health and adversely affects the quality of life of patients, with high mortality rates and persistent complications among survivors (1). Consequently, advancing research and innovation is essential to enhance outcomes for individuals

impacted by sepsis-induced ARDS. Particularly, omics technologies have significantly transformed our comprehension of sepsis-induced ARDS by offering profound insights into its molecular underpinnings. Genomics, encompassing whole-genome sequencing and transcriptomics, facilitates the identification of genetic variations and gene expression profiles linked to ARDS onset and progression (2). In addition, proteomics allows for the quantitative examination of proteins and their post-translational modifications (PTMs), illuminating critical



signaling pathways and disease markers. Metabolomics offers an integrative perspective on metabolic profiles and the synthesis of signaling molecules, thereby providing crucial data on dysregulated metabolic pathways. Moreover, epigenetic studies, including DNA methylation and histone modification analysis, deepen our understanding of gene expression regulation and cellular behavior in ARDS (3).

Advanced imaging modalities, such as high-resolution computed tomography (HRCT), magnetic resonance imaging (MRI), and positron emission tomography (PET), are indispensable in diagnosing and evaluating sepsis-induced ARDS (4). HRCT enables detailed visualization of lung structure and function, along with the early detection of lung injury (5). Further, MRI provides comprehensive insights into lung perfusion, gas exchange, and the presence of pulmonary edema and inflammation. Furthermore, PET imaging allows for the assessment of inflammatory activity and disease progression through measuring cellular metabolic processes (6). Moreover, the discovery and validation of novel biomarkers are critical in the context of sepsis-induced ARDS. Biomarkers derived from blood, urine, and exhaled breath condensate (EBC) hold potential for early diagnosis, risk stratification, and monitoring of treatment responses (7). However, significant barriers to translating these biomarkers into clinical practice remain, underscoring the need for innovative strategies to incorporate them into routine care (8). Multiplexed diagnostics (e.g., combinatorial biomarker detection, digital polymerase chain reaction, and next-generation sequencing) demonstrate promise in enhancing diagnostic precision and accuracy (9).

Emerging therapeutic approaches for sepsis-induced ARDS include lung-targeted therapies, anti-inflammatory interventions, vasoactive agents, and extracorporeal life-support techniques, such as extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). Similarly, lung-targeted therapies, including inhalational corticosteroids, bronchodilators, and surfactant replacement therapy, aim to reduce inflammation while optimizing pulmonary function. Likewise, anti-inflammatory strategies involving corticosteroids, immunomodulatory drugs, and modulation of interleukins (IL), such as IL-6 and IL-10, offer potential for mitigating excessive immune responses. In addition, vasoactive agents, such as nitric oxide (NO) and prostacyclin analogs, aid in improving pulmonary circulation and oxygenation. It is noteworthy that ECMO and VADs provide critical life-saving support for patients experiencing severe respiratory and cardiac failure (10). The microbiome has emerged as a vital factor in the pathogenesis of sepsis-induced ARDS. Microbiome analysis, utilizing techniques such as 16S ribosomal RNA (*rRNA*) gene sequencing and shotgun metagenomics, elucidates the complex interactions between microbial communities and the host immune response. Further, microbiome-targeted interventions, including probiotics, prebiotics, fecal microbiota transplantation

(FMT), and antibiotics targeting microbial virulence factors, offer promising avenues for modulating the microbiome and reducing ARDS severity (11). Nanoparticle (NP)-based drug delivery systems present several advantages, such as targeted delivery to the lungs, improved bioavailability, and minimized side effects. However, challenges like optimizing NP properties and ensuring their safety and efficacy must be addressed to fully exploit their potential for treating sepsis-induced ARDS (12).

The optimization of mechanical ventilation strategies remains crucial for improving ARDS patient outcomes. Advanced ventilation modalities, including adaptive support ventilation and non-invasive ventilation (NIV), provide tailored respiratory assistance to enhance lung function (13). Other approaches, such as adjusting positive end-expiratory pressure (PEEP) levels and managing tidal volume and plateau pressure, help mitigate lung injury. Furthermore, the open lung strategy, incorporating lung recruitment maneuvers and high-frequency oscillation ventilation, has demonstrated efficacy in improving ventilation-perfusion matching and preserving lung function (14). Big data analytics play a pivotal role in synthesizing data from diverse sources, such as electronic health records (EHRs), clinical trials, and omics studies (15). Personalized treatment strategies and improved patient outcomes can be achieved by analyzing these extensive datasets. Nonetheless, challenges regarding data quality, consistency, privacy, and security must be resolved to realize the full potential of big data analytics in critical care research (16). Virtual reality (VR) rehabilitation has shown promise in managing sepsis-induced ARDS by promoting early mobilization and exercise, thereby reducing complications. Nevertheless, barriers (e.g., cost, availability, and patient acceptance of VR rehabilitation programs) must be addressed for broader implementation (17). Personalized medicine, encompassing genomic profiling through whole-genome sequencing and targeted gene panels, in addition to pharmacogenomics for predicting drug responses and adverse effects, has the potential to revolutionize ARDS management. Tailored treatment plans and prevention strategies based on precision medicine principles can optimize individual outcomes (18). The integration of artificial intelligence (AI) and machine learning (ML) holds transformative potential in critical care. Likewise, predictive modeling for patient outcomes and disease progression informs decision-making and resource allocation (19). AI-driven clinical decision support systems (CDSSs) provide real-time monitoring and set up alerts for timely interventions, while natural language processing (NLP) enhances patient communication and clinical text analysis, thereby enabling valuable data insights (20).

Root Causes of Sepsis-Induced Acute Respiratory Distress Syndrome Sepsis Pathogenesis

Pathogenesis describes the origin and progression of

a disease, encompassing the sequence of events that culminate in its clinical manifestation. It involves investigating the underlying causes, mechanisms, and processes that drive the onset and evolution of a specific disease or condition. In the context of sepsis, pathogenesis refers to the intricate interaction between host and microbial factors that contribute to the development of the disease. Sepsis arises from an unregulated host response to an invading microorganism, which can initiate a cascade of pathological events, ultimately resulting in organ dysfunction and mortality (21). The pathogenesis of sepsis is multifaceted and progresses through distinct stages. It begins with the entry of microorganisms into the body via portals such as wounds or the respiratory tract. This invasion activates the body's immune system, thereby triggering an inflammatory response characterized by redness, swelling, heat, and pain. The resulting inflammation can compromise the endothelium—the inner lining of blood vessels—by increasing its permeability and impairing blood flow. These effects contribute to tissue damage and the potential failure of critical organs (e.g., the kidneys, liver, and lungs) due to the unchecked inflammatory response (22). The systemic inflammatory response syndrome represents an extreme, body-wide inflammatory state that can escalate to multiple organ failure and death. As a severe and life-threatening complication of sepsis, septic shock is marked by critically low blood pressure, impaired oxygen delivery, and organ dysfunction despite adequate fluid resuscitation. Understanding the underlying mechanisms of sepsis pathogenesis has been pivotal in the development of therapeutic interventions, including the use of antimicrobials, vasopressors, and anti-inflammatory agents. Furthermore, advancements in early detection and management strategies have been instrumental in preventing the progression of sepsis to severe stages, such as septic shock and multi-organ failure (23).

Mechanisms of Sepsis-Induced Acute Respiratory Distress Syndrome

Sepsis-induced ARDS is a severe and frequently fatal complication of sepsis that is characterized by significant mortality. The systemic inflammation triggered by sepsis extends to the lungs, leading to damage to the alveolar-capillary membrane (24). This disruption compromises the barrier between airspaces and the bloodstream, allowing proteins and fluids to infiltrate the airspaces. Additionally, inflammation hampers lung function by limiting chest expansion, reducing lung compliance, and impairing oxygenation. Increased vascular permeability permits the entry of bacteria and inflammatory substances into the lungs, further exacerbating inflammation and tissue damage (25). A secondary consequence of sepsis (e.g., bacterial pneumonia) can amplify lung injury. Sepsis also induces a cytokine storm, characterized by excessive production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), IL-1 β , and IL-

6, aggravating tissue destruction in the lungs. Oxidative stress, a hallmark of sepsis, causes an imbalance between the generation of reactive oxygen species and the antioxidant defenses of the body, leading to cellular injury and inflammation. Dysregulated NO production results in excessive NO levels, further intensifying lung damage. In addition, elevated platelet-activating factor contributes to inflammation, platelet aggregation, and vascular constriction, further impairing lung function (26). Genetic predispositions may also heighten susceptibility to ARDS in sepsis patients, as variations in certain immune and inflammatory response genes can influence disease severity. Accordingly, gaining insights into these mechanisms is essential for the development of targeted therapeutic interventions (27).

Alveolar injury in sepsis-induced ARDS may arise from direct or indirect damage caused by bacteria, viruses, or other harmful agents. Such damage activates alveolar macrophages, which release inflammatory mediators (e.g., TNF, IL-6, and IL-8), thereby recruiting neutrophils and monocytes to the site of injury. These activated neutrophils exacerbate tissue damage by releasing toxic substances, further compromising the alveolar barrier. This disruption results in the flooding of the interstitial and alveolar spaces with fluids and inflammatory cells. The inflammatory cascade is perpetuated by cytokines released from macrophages and neutrophils, thereby amplifying tissue damage and inflammation. Ultimately, this process leads to the destruction of alveolar structures and the accumulation of fluids due to the compromised barrier function. A thorough understanding of this inflammatory cascade is vital for devising therapeutic strategies aimed at halting the progression of inflammation and preserving alveolar integrity (9). [Figure 1](#) illustrates the pathogenesis of sepsis-induced ARDS.

Risk Factors

ARDS can result from a variety of direct and indirect insults to the lungs. As a severe systemic infection, sepsis is a leading cause of ARDS, primarily through immune-mediated inflammation that affects lung tissue. Moreover, pneumonia, another major contributor to ARDS, leads to inflammation and fluid accumulation within the alveoli, impairing gas exchange. Further, traumatic injuries (e.g., those caused by accidents or falls) can initiate ARDS through several mechanisms, such as shock and the release of fat emboli. Likewise, surgical procedures, particularly in individuals with preexisting lung conditions, can provoke ARDS due to the added stress on already compromised respiratory systems. Extensive burns affecting large areas of the skin can induce a systemic inflammatory response that damages the lungs. Similarly, smoke inhalation inflicts direct harm on lung tissue from heat, toxins, and oxygen deprivation. Additionally, exposure to hazardous chemicals (e.g., industrial agents or pesticides) causes caustic damage to the lungs, further increasing ARDS risk (28).

Furthermore, substance overdoses, particularly with

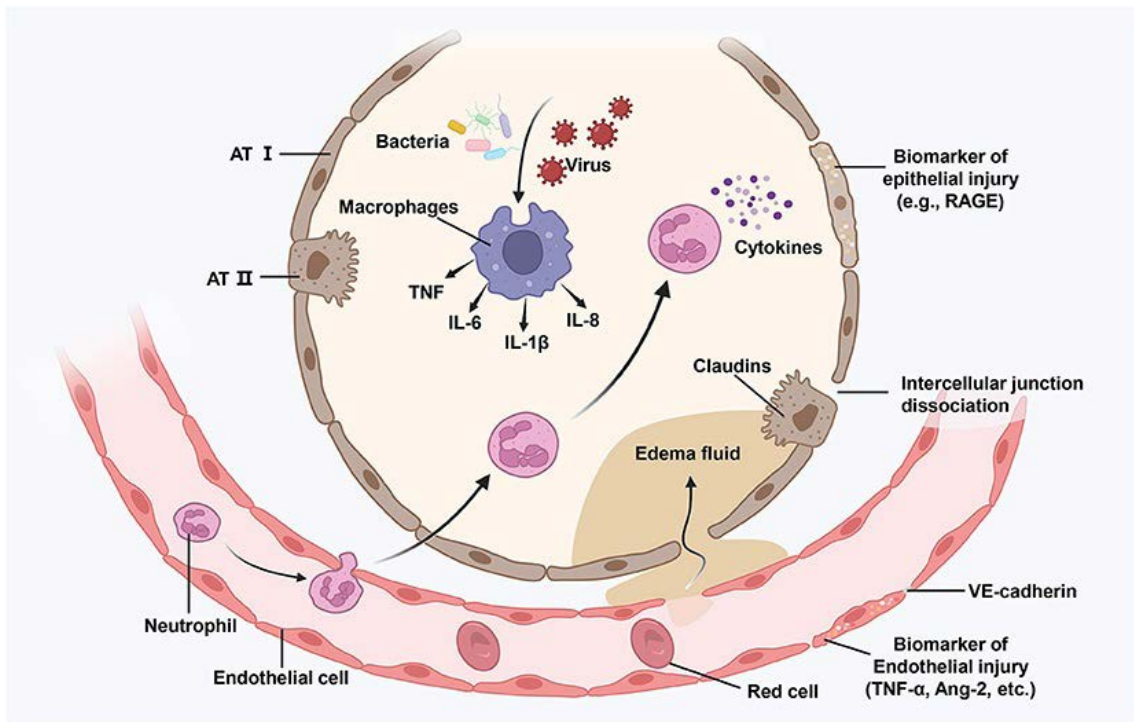


Figure 1. Pathogenesis of Sepsis-Induced Acute Respiratory Distress Syndrome. Reprinted under the terms of the Creative Commons Attribution License (CC BY) (9)

respiratory depressants (e.g., opioids and benzodiazepines), are strongly associated with ARDS due to their suppression of normal breathing. Chronic alcohol consumption and smoking contribute to oxidative stress, which progressively damages lung tissue over time. Older adults, especially those with chronic health conditions, face a heightened risk of ARDS due to age-related immune system decline and structural changes in the lungs. Similarly, premature infants are particularly vulnerable to ARDS because of their underdeveloped and fragile lung architecture (29). Additionally, individuals with chronic lung diseases (e.g., chronic obstructive pulmonary disease and cystic fibrosis) have compromised respiratory function, making them more susceptible to ARDS. Organ failure, including heart, liver, or kidney dysfunction, can lead to fluid overload, resulting in pulmonary congestion. Malnutrition weakens the immune system, whereas obesity exacerbates conditions like diabetes and sleep apnea, thereby placing additional strain on the lungs. Pregnancy, especially in the third trimester, alters immune responses and increases ARDS risk. Immunocompromised individuals (e.g., those with human immunodeficiency virus/acquired immunodeficiency syndrome) are also more prone to lung injuries and ARDS. However, ARDS can occasionally develop in the absence of identifiable risk factors, highlighting the importance of prompt evaluation when respiratory distress occurs (30).

Omics Technologies

Sepsis-induced ARDS remains a significant challenge in critical care medicine, although omics technologies have substantially advanced the understanding of the pathophysiological mechanisms underlying this condition.

Genomics

Genomic research, particularly through whole-genome sequencing, has facilitated the identification of genetic variations linked to sepsis-induced ARDS. Variants in genes involved in immune responses, inflammation, and lung function have been associated with an increased risk of developing ARDS. For instance, Richa et al reported that individuals carrying a specific variant in the *TLR4* gene were more likely to develop ARDS following sepsis (31). Additionally, transcriptomic analyses have unveiled changes in gene expression patterns in sepsis-induced ARDS patients. Research has shown that genes related to inflammation, immune responses, and apoptosis are differentially expressed in ARDS patients compared to healthy individuals. For example, the findings of one study revealed heightened expression of pro-inflammatory genes (e.g., *NF-κB* and *IL-1β*), along with reduced expression of anti-inflammatory genes (e.g., *IL-10*) in ARDS patients (32). Furthermore, integrative genomics approaches have clarified the relationship between genetic variations and gene expression changes in sepsis-induced ARDS. One such study identified variants in the *IL-6* gene that were associated with increased gene expression and elevated serum IL-6 levels in ARDS patients (33).

Proteomics

Quantitative proteomics has enabled the identification of protein abundance changes and PTMs in sepsis-induced ARDS. In addition, proteomic studies have uncovered dysregulated proteins involved in inflammation, oxidative stress, and cell signaling in ARDS patients (34). For example, Gong et al identified elevated levels of pro-inflammatory cytokines (e.g., TNF-α and IL-1β),

coupled with reduced levels of antioxidant proteins (e.g., superoxide dismutase) in ARDS patients (35). PTMs, which regulate protein function and activity, have also been investigated in the context of sepsis-induced ARDS (36). Yang et al reported dysregulated PTMs in proteins involved in inflammation, cell signaling, and lung function (37). For instance, Juanes-Velasco et al demonstrated increased levels of phosphorylated signal transducer and activator of transcription 3 (a transcription factor linked to inflammation) and decreased levels of acetylated histone H3 (a marker of chromatin relaxation) in ARDS patients (38).

Metabolomics

Metabolomic analyses have provided valuable insights into the metabolic disruptions that occur in sepsis-induced ARDS (Table 1). Alterations have been observed in metabolites associated with energy, amino acid, and lipid metabolism (39). For example, McClintock et al reported decreased glucose levels and elevated lactate levels in ARDS patients, suggesting impaired glucose metabolism (40). Likewise, Tian et al used metabolomics to explore the biogenesis and

metabolism of signaling molecules in sepsis-induced ARDS and found changes in neurotransmitter, hormone, and inflammatory mediator metabolism (41). For instance, Li et al concluded that ARDS patients exhibited increased levels of prostaglandin E2 (a pro-inflammatory mediator) and decreased levels of dopamine (a neurotransmitter involved in vasodilation) (42).

Epigenetics

Epigenetic mechanisms (e.g., histone modifications) play a critical role in regulating gene expression by altering chromatin structure, thereby influencing its accessibility to transcription factors, as presented in Table 2 (43). Some studies investigated histone modification changes in sepsis-induced ARDS (44). For example, Mailem and Tayo observed elevated levels of histone H3 lysine 9 trimethylation (H3K9me3), a marker of repressive chromatin, in the lung tissues of ARDS patients compared to healthy individuals. This increase in H3K9me3 was suggested to contribute to the silencing of genes involved in lung repair and regeneration (45). DNA methylation, another key epigenetic mechanism, involves the

Table 1. Analytical Techniques in Proteomics and Metabolomics for Sepsis-Induced ARDS Research

Omics Field	Analytical Techniques	Principle and Strengths	Main Contributions	Key Findings/Applications	References
Proteomics	Liquid chromatography–tandem mass spectrometry (LC-MS/MS)	- Separation of peptides/proteins by liquid chromatography, followed by identification and quantification via tandem mass spectrometry. - High sensitivity and specificity for protein profiling and PTMs.	- Quantitative and qualitative profiling of protein abundance - Identification of PTMs (e.g., phosphorylation and acetylation) - Discovery of disease biomarkers	- Elevated pro-inflammatory cytokines (e.g., TNF- α and IL-1 β) - Alterations in antioxidant proteins (e.g., superoxide dismutase) - PTMs, such as increased phosphorylated signal transducer and activator of transcription 3 and decreased acetylated histone H3	(34-36)
	Two-dimensional difference gel electrophoresis	- Differential labeling of protein samples with fluorescent dyes, separation by isoelectric focusing and SDS-PAGE - Quantitative comparison of protein spots	- Comparative analysis of protein expression between conditions - PTM analysis	- Identification of dysregulated proteins and PTMs associated with ARDS progression	(36,37)
	Matrix-assisted laser desorption/ionization-time of flight	Rapid ionization and mass analysis of proteins/peptides from tissue or serum samples with minimal preparation.	- High-throughput protein profiling - Identification of protein biomarkers	- Discrimination between healthy and ARDS patient proteomes	(38)
Metabolomics	LC-MS	Separation of small molecules by LC, detection by MS Suitable for a broad range of metabolites, including polar and non-polar compounds	- Comprehensive profiling of metabolites - Biomarker discovery - Pathway elucidation	- Detection of energy metabolism alterations: decreased glucose and increased lactate in ARDS - Changes in amino acid and lipid profiles	(39,40)
	LC-MS/MS (targeted and untargeted)	Tandem MS allows for structural elucidation and quantification of targeted or global metabolite sets	- Targeted quantitation of known metabolites - Untargeted discovery of novel metabolic changes	- Identification of metabolic pathways dysregulated in ARDS, such as increased prostaglandin E2 and decreased dopamine	(3,41, 42)
	Gas chromatography–mass spectrometry (GC-MS)	Volatile and semi-volatile metabolites are separated by GC and detected by MS Excellent for organic acids, fatty acids, and volatile organic compounds	- Profiling of volatile metabolites (e.g., in EBC) - Quantification of organic acids	- Elevated levels of volatile organic compounds and oxidative stress markers in ARDS patients' breath and fluids	(40,43)
	Nuclear magnetic resonance spectroscopy	- Non-destructive, quantitative analysis of metabolites based on magnetic properties of atomic nuclei - Highly reproducible	- Quantitative analysis of metabolite concentrations - Structural elucidation	- Identification of metabolic fingerprints distinguishing ARDS from controls - Validation of targeted biomarker candidates	(39)

Note. ARDS: Acute respiratory distress syndrome; PTM: Post-translational modifications; TNF- α : Tumor necrosis factor-alpha; IL: Interleukin; SDS-PAGE: Sodium dodecyl sulfate polyacrylamide gel electrophoresis; EBC: exhaled breath condensate.

Table 2. Omics Technologies in Sepsis-Induced ARDS Research: Techniques, Contributions, and Key Findings

Omics Technology	Key Techniques	Main Contributions to Sepsis-Induced ARDS Research	Examples of Findings
Genomics	- Whole-genome sequencing - Transcriptomics - Integrative genomics	- Identification of genetic variants associated with ARDS susceptibility - Analysis of gene expression patterns - Understanding gene-environment interactions	- TLR4 gene variant associated with increased ARDS risk - Increased expression of pro-inflammatory genes (NF- κ B and IL-1 β) - Decreased expression of anti-inflammatory genes (IL-10)
Proteomics	- Quantitative proteomics - PTMs analysis	- Measurement of protein abundance changes - Identification of dysregulated proteins - Analysis of protein modifications	- Increased levels of pro-inflammatory cytokines (TNF- α and IL-1 β) - Decreased levels of antioxidant proteins (superoxide dismutase) - Increased phosphorylation of signal transducer and activator of transcription 3 - Decreased acetylation of histone H3
Metabolomics	- Metabolite profiling - Signaling molecule analysis	- Identification of metabolic alterations - Analysis of signaling molecule biogenesis and metabolism	- Decreased glucose levels and increased lactate levels - Increased prostaglandin E2 levels - Decreased dopamine levels
Epigenetics	- Histone modification analysis - DNA methylation profiling	- Investigation of chromatin structure changes - Analysis of DNA methylation patterns	- Increased histone H3 lysine 9 trimethylation in lung tissue - Increased DNA methylation at the IL-8 gene promoter

Note. ARDS: Acute respiratory distress syndrome; TLR4: Toll-like receptor 4; IL: Interleukin; TNF- α : Tumor necrosis factor-alpha; PTMs, post-translational modifications.

addition of methyl groups to cytosine residues in CpG dinucleotides and regulates gene expression. Altered DNA methylation patterns have been observed in sepsis-induced ARDS (46). For instance, Vanhorebeek and Van den Berghe reported increased DNA methylation at the promoter region of the *IL-8* gene, which encodes a potent neutrophil chemoattractant. This hypermethylation was hypothesized to have a role in the overproduction of IL-8, thereby exacerbating lung injury in ARDS patients (47).

Advanced Imaging Techniques

These techniques are essential for diagnosing and managing sepsis-induced ARDS. These modalities provide detailed insights into lung structure, function, and pathophysiology, aiding in early detection, severity assessment, and treatment monitoring.

High-Resolution Computed Tomography

HRCT is a non-invasive imaging method that generates high-resolution images of lung parenchyma, thereby enabling detailed evaluation of lung structure and function. This method is widely used in diagnosing and monitoring sepsis-induced ARDS (48). Studies have highlighted the value of HRCT in identifying early lung injury. For example, research published in *Radiology* demonstrated that HRCT could detect subtle lung architectural changes (e.g., alveolar consolidation and ground-glass opacities) even before the clinical symptoms of respiratory failure become apparent. Similarly, Han et al revealed that HRCT could identify regions of the lung with impaired ventilation-perfusion matching, a key factor in ARDS pathogenesis (49). Additionally, HRCT provides information on lung function, including parameters like lung volume, air trapping, and gas diffusion. Likewise, Lee reported a strong correlation between HRCT-derived measures of lung volume and the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO₂/FiO₂)

ratio (an indicator of oxygenation status) in patients with sepsis-induced ARDS (50).

Magnetic Resonance Imaging

MRI uses magnetic fields and radio waves to produce detailed images of internal organs. This method has become increasingly valuable in studying lung diseases, including sepsis-induced ARDS. One of the key advantages of MRI is its ability to assess lung perfusion and gas exchange. Osawa et al concluded that MRI could accurately quantify lung blood flow and gas exchange, offering critical insights into sepsis-induced ARDS pathophysiology. MRI can also detect complications such as pulmonary edema and inflammation, which are common in ARDS (51). Furthermore, MRI provides functional information about lung tissue. For instance, Ge et al found that MRI-derived metrics of lung stiffness and strain were significantly correlated with the PaO₂/FiO₂ ratio, suggesting that MRI could be a useful tool for monitoring disease severity and treatment response in sepsis-induced ARDS (52).

Positron Emission Tomography Imaging

PET, a nuclear medicine imaging technique, visualizes cellular metabolic activity. It has been applied for studying inflammatory conditions, including sepsis-induced ARDS (53). PET imaging provides valuable insights into inflammatory responses and disease progression in ARDS. For example, some researchers used PET imaging to examine inflammation dynamics in mice with sepsis-induced ARDS, demonstrating its ability to monitor changes in inflammatory activity over time and to identify molecular targets for therapy (54,55). PET imaging is also useful for assessing treatment efficacy. A number of scholars evaluated PET imaging to monitor corticosteroid therapy in sepsis-induced ARDS patients, finding that it could detect changes in inflammatory activity and help

optimize drug dosages and treatment timing (56,57).

Biomarker Development

Identification of Novel Biomarkers

Blood and Urinary Biomarkers

Blood and urinary biomarkers have shown promise for the early detection and monitoring of sepsis-induced ARDS. These biomarkers include proteins, cytokines, chemokines, and metabolites altered during systemic inflammation and organ dysfunction (8). For instance, elevated levels of IL-6, TNF- α , and neutrophil gelatinase-associated lipocalin (NGAL) have been linked to sepsis-induced ARDS (58).

Exhaled Breath Condensate Biomarkers

EBC contains volatile and non-volatile compounds that reflect lung physiology and can potentially diagnose and monitor respiratory diseases, including sepsis-induced ARDS. Research has shown that the concentrations of NO, carbon monoxide, and hydrogen peroxide in EBC are altered in ARDS, highlighting their potential as biomarkers (59).

Validation and Clinical Implementation

While promising, translating biomarkers into clinical practice faces challenges, including (1) standardizing sample collection, storage, and analysis, (2) establishing reference ranges, and (3) addressing confounding variables (60). Cost-effectiveness, availability, and user-friendly assays are also critical for widespread adoption (61). Strategies to overcome these barriers include multicenter validation studies, analytical method harmonization, and biomarker incorporation into EHRs. Point-of-care testing and minimally invasive sampling methods can further enhance feasibility while reducing costs (62).

Multiplexed Diagnostics

Multiplexed diagnostic platforms enable simultaneous measurement of multiple biomarkers, thereby improving diagnostic accuracy and providing a more comprehensive understanding of disease mechanisms. For example, a multiplex immunoassay panel measuring IL-6, TNF- α , and NGAL has been developed to differentiate sepsis-induced ARDS from other ARDS causes (63). Emerging technologies (e.g., digital polymerase chain reaction and next-generation sequencing) allow highly sensitive detection of nucleic acid biomarkers. These tools have identified novel genetic markers associated with sepsis susceptibility and outcomes. Nonetheless, further research is required to assess their clinical utility (64).

Novel Therapeutic Approaches

Lung-Targeted Therapies

Inhalational corticosteroids, which have anti-inflammatory properties, are being investigated for sepsis-induced ARDS. Meng et al found improved survival in patients treated with these agents (65), though

larger trials are needed for confirmation. Bronchodilators (e.g., albuterol) have been used to relieve bronchospasm and reduce inflammation, with studies demonstrating improved lung mechanics but limited data on long-term outcomes. Surfactant replacement therapy, which supplements deficient endogenous surfactant, has shown contradictory results in different studies, necessitating further investigation (14,66).

Anti-Inflammatory Strategies

Corticosteroids and immunomodulatory drugs are utilized to modulate the inflammatory response in sepsis-induced ARDS. A meta-analysis revealed improved survival with corticosteroids, though evidence quality was low (67, 68). Drugs targeting cytokines such as IL-6 (e.g., tocilizumab) and IL-10 have shown promise, but their long-term safety and efficacy remain under investigation (69, 70).

Vasoactive Agents

NO donors and prostacyclin analogs have been explored for improving vascular function in sepsis-induced ARDS, though evidence on their efficacy is limited (71). In addition, endothelin receptor antagonists (e.g., bosentan) have shown benefits in pulmonary hypertension but require further study in ARDS (72,73).

Statins and Antioxidants

Statins, known for their anti-inflammatory properties, have demonstrated contradictory results in sepsis-related research. Some studies suggested improved outcomes, though evidence quality is low (74-75). Similarly, antioxidants like vitamins C and E have been investigated, but their effects on ARDS outcomes remain inconclusive (76).

Immunonutrition and Extracorporeal Membrane Oxygenation

Immunonutrition, involving nutrient supplementation to support immune function, has shown potential for reducing infections while improving outcomes in critically ill patients, though optimal protocols are unclear (77). ECMO has been used in severe cases of ARDS, with studies reporting benefits in younger patients without significant comorbidities (78).

Proning and Early Mobilization

Proning, or positioning patients on their stomachs, has improved gas exchange and survival in mechanically ventilated ARDS patients. However, its specific efficacy in sepsis-induced ARDS requires further research (79). Early mobilization has been linked to improved functional outcomes and reduced intensive care unit (ICU) stays, though optimal timing and intensity need clarification (80).

Non-Invasive Ventilation

NIV, which avoids intubation, has shown promise in

mild-to-moderate ARDS cases, reducing intubation rates while improving survival (81).

Microbiome Analysis in Sepsis-Induced Acute Respiratory Distress Syndrome

The Role of the Microbiome

The human microbiome, comprising trillions of microorganisms, plays a significant role in health and disease. Dysbiosis, or microbial imbalance, has been implicated in sepsis-induced ARDS (82). Alterations in the lung microbiome, including the overgrowth of pathogenic bacteria and reduced beneficial microbes, exacerbate inflammation, increase permeability, and impair lung function. Moreover, gut microbiome changes have been linked to sepsis and ARDS, underscoring the interconnectedness of microbiomes (83, 84). In health, the lung microbiome is dominated by *Firmicutes* and *Bacteroidetes*, with genera such as *Prevotella* and *Streptococcus* being the most prevalent. In disease, inflammation promotes pathogenic species such as *Proteobacteria*. Microbiome shifts correlate with disease severity, phenotypes, and outcomes, as illustrated in Figure 2 (85). Therefore, understanding these dynamics is key to identifying novel therapeutic targets for sepsis-induced ARDS.

Strategies for Analyzing the Microbiome

A range of techniques has been developed for investigating the microbiome, among which two are particularly prominent. *16S rRNA* gene sequencing targets the variable regions of the *16S rRNA* gene, facilitating the detection and quantification of diverse bacterial taxa.

In addition, this culture-independent method enables comprehensive profiling of microbial composition and diversity without necessitating the isolation of individual bacterial strains (86). On the other hand, shotgun metagenomics sequences fragmented DNA directly from environmental samples, thereby circumventing the need for prior taxonomic assumptions. This approach not only identifies the constituents of microbial communities but also elucidates their functional genes and potential virulence determinants. Both *16S rRNA* gene sequencing and shotgun metagenomics have been pivotal in characterizing microbiome alterations in various pathologies, including sepsis-induced ARDS. Using these methodologies, researchers have delineated distinctive microbial patterns in the pulmonary and gastrointestinal microbiomes that correlate with sepsis-induced ARDS, potentially paving the way for personalized therapeutic strategies tailored to individual microbiomic profiles (87).

Potential Interventions Based on Microbiome Analysis

Targeted modulation of the microbiome presents promising avenues for the therapeutic management of sepsis-induced ARDS. Some of the primary strategies are as follows:

Probiotics and Prebiotics

Probiotics are defined as live microbial supplements that confer health benefits to the host when ingested in sufficient quantities. In contrast, prebiotics are indigestible dietary fibers that selectively foster the proliferation and metabolic activity of beneficial gut bacteria. Both agents have been explored as interventions for sepsis-induced

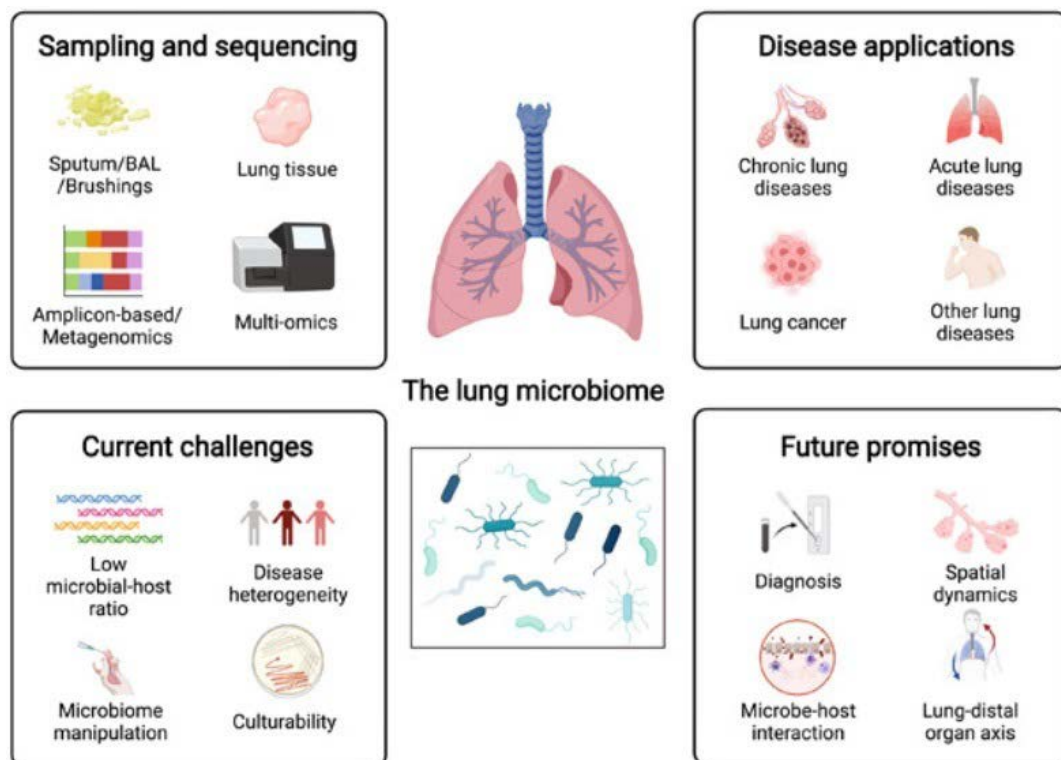


Figure 2. The Dynamic Lung Microbiome. Reprinted under the terms of the Creative Commons Attribution License (CC BY) (85).

ARDS, demonstrating favorable effects in preclinical animal models and early-phase clinical investigations (88).

Fecal Microbiota Transplantation

FMT entails the introduction of fecal material from healthy donors into the gastrointestinal tract of recipients, aiming to re-establish a balanced microbiota. Its efficacy and safety have been substantiated in conditions such as *Clostridioides difficile* infection. Further, its utility in sepsis-induced ARDS is under active investigation (89).

Antibiotics and Anti-Virulence Therapy

While broad-spectrum antibiotics remain a mainstay in sepsis management, escalating concerns over multidrug resistance necessitate alternative approaches. In this regard, anti-virulence therapies, which inhibit pathogenic mechanisms without exerting selective pressure for bacterial survival, offer a promising adjunct or alternative to conventional antibiotics (90).

Antimicrobial Stewardship

Effective management of sepsis-induced ARDS critically depends on the judicious application of antimicrobials, encompassing appropriate selection, dosing, and duration. Antimicrobial stewardship programs are essential for minimizing the emergence of resistant organisms and mitigating adverse effects (91). In this context, addressing antibiotic resistance requires a multifaceted approach that spans early diagnosis, evidence-based regimen selection, optimized pharmacokinetics, and vigilant monitoring for complications. Combination therapies, immunomodulation, stringent infection control, and public health education are integral components in this respect (92). Sustained efforts in research, surveillance, protocol refinement, and multidisciplinary collaboration are necessary to entrench a culture of stewardship, thereby

improving clinical outcomes, preserving antibiotic efficacy, and fostering responsible use on a systemic level (93).

The lung microbiome significantly influences local and systemic inflammatory responses in pulmonary disorders, such as ARDS. Notably, ARDS is characterized by the pulmonary enrichment of gut-derived bacteria, which serve as salient biomarkers. In critically ill patients, the disruption of the lung microbiome can amplify inflammatory cascades, thereby worsening prognoses. The migration of gut microbes to the pulmonary environment is increasingly recognized as a pathogenic mechanism in sepsis and ARDS, although the precise contribution of gut microflora to lung pathology remains incompletely understood (94). Early microbiome perturbations, including increased bacterial burden, overrepresentation of gastrointestinal taxa, and decreased microbial diversity, are associated with heightened ARDS susceptibility and prolonged dependence on mechanical ventilation. Baseline dysbiosis, potentially induced by environmental exposures (e.g., smoking), may also predispose to post-traumatic ARDS. Viral reactivation, particularly of the herpesviridae family, is frequently observed, reflecting complex, multifactorial drivers of microbial dynamics. Remarkably, ventilator-associated pneumonia is often characterized by the overgrowth of existing bacterial genera rather than the acquisition of new pathogens. While antibiotics target dominant organisms, they may concurrently exacerbate dysbiosis. Studies consistently reveal that the ARDS lung microbiome contains lower gastrointestinal tract bacteria, with their abundance correlating with disease severity (95). Figure 3 displays the mechanisms of lung microbiome disruption in ARDS.

Nanoparticle-Based Drug Delivery

Advantages of Nanoparticle-Based Drug Delivery

NP-mediated drug delivery systems offer several distinct

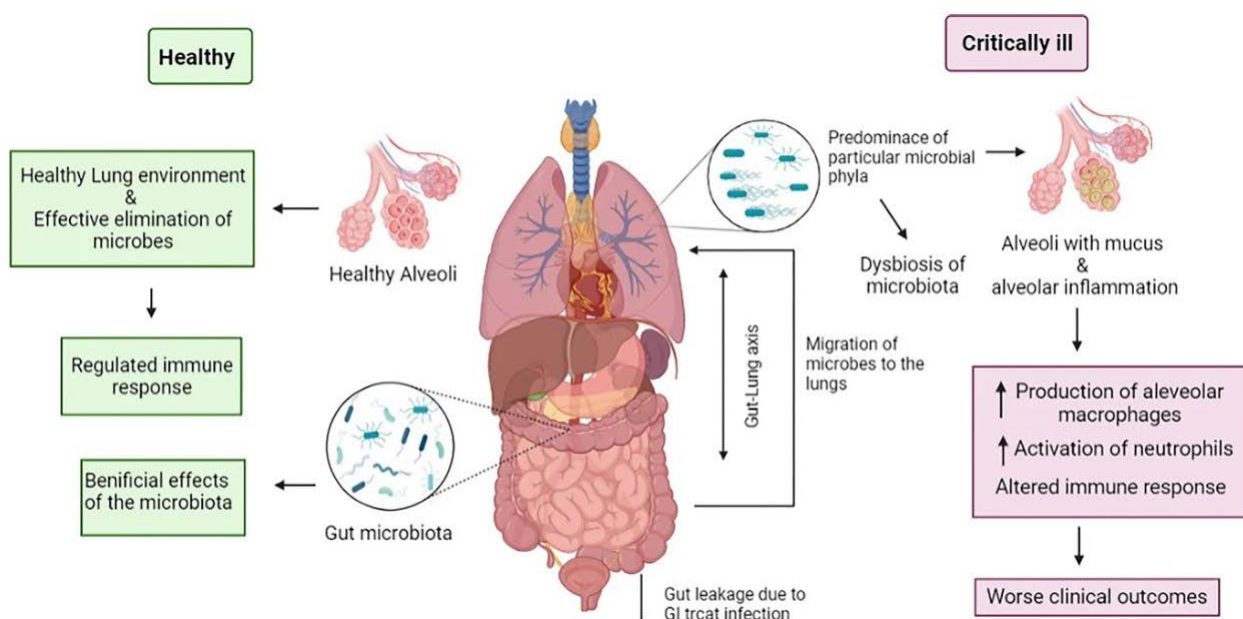


Figure 3. Mechanisms of Lung Microbiome Disruption in Acute Respiratory Distress Syndrome. Source. (95).

advantages (e.g., enhanced pharmacokinetic profiles, improved bioavailability, and attenuated systemic toxicity) over traditional modalities (96). These nanoscale vehicles can be precisely engineered to achieve targeted delivery to specific cellular or tissue sites, thereby maximizing therapeutic efficacy while minimizing off-target effects (97). Additionally, NPs can be formulated for controlled and sustained drug release, contributing to increased drug stability, extended half-life, and reduced dosing frequency (98).

Challenges and Limitations

Despite their promise, the clinical translation of NP-based drug delivery faces significant obstacles. Accordingly, achieving efficient and selective NP localization at the intended biological target remains challenging, particularly within the complex and heterogeneous architecture of lung tissue (66). Furthermore, the inherent physicochemical properties of certain NPs may elicit toxicological responses, including inflammation and cellular injury (99). Regulatory pathways for NP therapeutics are still evolving, thereby presenting additional barriers to widespread clinical adoption.

Applications in Sepsis-Induced Acute Respiratory Distress Syndrome

Sepsis-induced ARDS represents a critical condition with persistently high mortality despite advances in supportive care, underscoring the need for innovative therapeutic strategies. NP-based drug delivery holds substantial potential to enhance pulmonary drug targeting while reducing adverse effects. For instance, liposomal formulations have demonstrated improved pulmonary delivery in sepsis-induced ARDS cases. Moreover, NPs can be designed for the co-delivery of multiple pharmacological agents, potentially addressing the complex pathophysiology of sepsis through multifaceted mechanisms. Nonetheless, comprehensive research is required to establish the safety and efficacy profiles of these systems in clinical settings (100).

Optimization of Mechanical Ventilation in Sepsis-Induced Acute Respiratory Distress Syndrome

Protective ventilation protocols, incorporating low tidal volumes and tailored PEEP, are pivotal in minimizing ventilator-induced lung injury in ARDS patients. However, these strategies must be meticulously adapted for burn victims in order to prevent hypoventilation. The presence of inhalational injury exacerbates respiratory compromise via inflammatory responses, edema, and airway obstruction. Adjunctive supportive measures encompass bronchial hygiene, antimicrobial therapy for superimposed infections, and advanced rescue modalities for refractory hypoxemia. Ultimately, ARDS management in the context of burns necessitates a highly individualized strategy that accommodates the unique physiological and pulmonary pathophysiology of each patient (101).

Advanced Modes of Ventilation

Technologies such as adaptive support ventilation utilize the real-time assessments of lung mechanics and gas exchange to dynamically adjust ventilatory support, thereby optimizing oxygen delivery while reducing the risk of ventilator-associated injury. NIV offers respiratory assistance through external interfaces, obviating the risks associated with invasive airway management (102).

Strategies for Optimizing Mechanical Ventilation

Customizing PEEP and tidal volume settings according to lung-specific parameters allows for personalized mechanical ventilation, thereby enhancing oxygenation while minimizing the risk of barotrauma. The open lung approach employs alveolar recruitment maneuvers followed by adequate PEEP and low tidal volumes, ensuring sustained alveolar patency and minimizing the cyclical injury associated with repetitive collapse and re-expansion (103).

Open Lung Approach

To address atelectasis and optimize gas exchange in sepsis-induced respiratory failure, recruitment maneuvers transiently apply elevated pressures or tidal volumes to reinflate collapsed alveoli. High-frequency oscillatory ventilation achieves gas exchange via rapid oscillations, thereby enabling lower tidal volumes and reduced risk of ventilator-induced injury. These advanced ventilation modalities, in conjunction with the meticulous application of lung-protective strategies and open lung approaches, empower clinicians to effectively manage respiratory compromise in sepsis, thereby reducing morbidity and mortality (104).

Big Data Analytics in Sepsis-Induced Acute Respiratory Distress Syndrome

Integration of Data From Various Sources

The convergence of data from EHRs, clinical trials, and omics platforms has opened new frontiers in managing sepsis-induced ARDS. EHRs provide comprehensive patient profiles, encompassing demographic, comorbid, physiological, and laboratory data, which inform tailored management strategies (105). Clinical trials contribute critical insights into the efficacy and safety of emerging interventions, while omics technologies elucidate the molecular architecture and biomarker signatures underlying ARDS. Thus, integrating these heterogeneous datasets through sophisticated analytics and AI has the potential to revolutionize sepsis care (106).

Potential Insights and Benefits

Utilizing big data analytics enables the implementation of precision medicine in sepsis-induced ARDS, with interventions customized to individual patient risk factors and genetic backgrounds. Predictive modeling can anticipate disease progression, facilitating earlier intervention and more informed clinical decision-making.

Moreover, stratifying patients by risk allows for targeted preventive measures, ultimately reducing the incidence of ARDS, improving outcomes, and diminishing long-term healthcare impacts (20).

Challenges and Limitations

Realizing the transformative potential of big data analytics in sepsis-induced ARDS hinges on overcoming challenges related to data integrity, security, accessibility, and ethical stewardship. Ensuring algorithmic transparency and interpretability is vital for timely and actionable clinical insights. Human oversight remains essential to complement ML, fostering confidence and collaboration. The standardization of data sources, equitable access to analytics tools, and ongoing adaptation to new discoveries are crucial in this regard. It should be noted that success requires a holistic approach that balances data sharing with privacy, inclusivity, and responsible innovation, enabling equitable transformation of sepsis-induced ARDS management on a global scale (107).

Virtual Reality Rehabilitation

Benefits of Virtual Reality Rehabilitation

VR-based rehabilitation offers patients the opportunity to commence mobilization and physical therapy earlier than is often feasible with traditional modalities, potentially expediting recovery and enhancing clinical outcomes. VR provides a highly controlled and interactive environment, reducing the risk of rehabilitation-related complications, such as falls or secondary injuries. Furthermore, this immersive approach allows patients to safely and repetitively practice targeted movements and exercises, promoting functional improvement (108).

Challenges and Limitations

The widespread adoption of VR rehabilitation is impeded by the significant costs associated with acquiring and maintaining the necessary technology and software, which may be prohibitive for many healthcare institutions. Accessibility issues are further compounded in rural or underserved regions. Additionally, patient acceptance can present a barrier, as unfamiliarity with VR or skepticism regarding its effectiveness may deter participation. Sustaining patient motivation and adherence to VR-based protocols represents an additional challenge for clinical teams (109). Accordingly, an informed understanding of these benefits and limitations is essential for healthcare providers seeking to incorporate VR into rehabilitation programs and optimize patient outcomes.

Personalized Medicine in Sepsis-Induced Acute Respiratory Distress Syndrome

Precision medicine approaches offer transformative possibilities for the individualized management of sepsis-induced ARDS by enabling care that is holistically tailored to each patient's unique clinical, genetic, and environmental context. Incorporating natural and

traditional remedies that resonate with a patient's cultural values (e.g., herbal therapies, acupuncture, or meditation) may complement conventional anti-inflammatory and regenerative treatments (110). This integrative paradigm addresses the patient as a whole and fosters enhanced engagement and satisfaction with care. Leveraging detailed genomic, lifestyle, and environmental data further refines therapy selection, thereby allowing clinicians to anticipate and mitigate risks, such as those related to genetic predisposition or prior smoking history (66). It is noteworthy that identifying individuals at high risk for sepsis or ARDS through genetic screening enables proactive surveillance and early intervention strategies, potentially forestalling disease onset. In general, personalized medicine in this domain aims to deliver truly individualized, comprehensive care by aligning therapeutic interventions with the distinct risk profiles and needs of each patient, thereby improving prevention, outcomes, and the overall healthcare burden (111).

Artificial Intelligence and Machine Learning

AI and ML have emerged as transformative technologies in critical care, especially regarding the diagnosis and management of sepsis-induced ARDS. This literature review explored the burgeoning role of AI and ML in this context. Recent advances in these fields have introduced new opportunities to enhance the management of sepsis-induced ARDS (112). [Figure 4](#) illustrates two deployment models of the COMPOSER platform. In the evaluation phase (panel b), test data pass through a weighted input layer and an encoder to produce a new representation $H(2)$. Conformal prediction evaluates whether $H(2)$ matches the conformity standards established by the training set; the sample proceeds to the sepsis risk predictor if conformity is confirmed at a specified confidence level ϵ . In contrast, panel (c) demonstrates model deployment without conformal prediction, omitting this safeguard (113).

Predictive Modeling

Predictive modeling with AI and ML algorithms is poised to revolutionize medicine, especially in intensive care. These models can discern patterns and relationships beyond human capability by synthesizing vast datasets, encompassing EHRs, imaging, and laboratory findings. In addition, AI-driven analysis provides prognostic insights regarding survival, recovery likelihood, and ICU admission requirements (16). This information empowers clinicians to optimize triage, allocate resources effectively, and tailor treatment plans. Further, modeling the trajectory of sepsis-induced ARDS enables early identification of clinical deterioration or improvement, supporting timely and individualized intervention (19).

Clinical Decision Support Systems

AI-enhanced CDSSs offer real-time, evidence-based recommendations for diagnosis, therapy, and monitoring by integrating patient-specific data with current medical

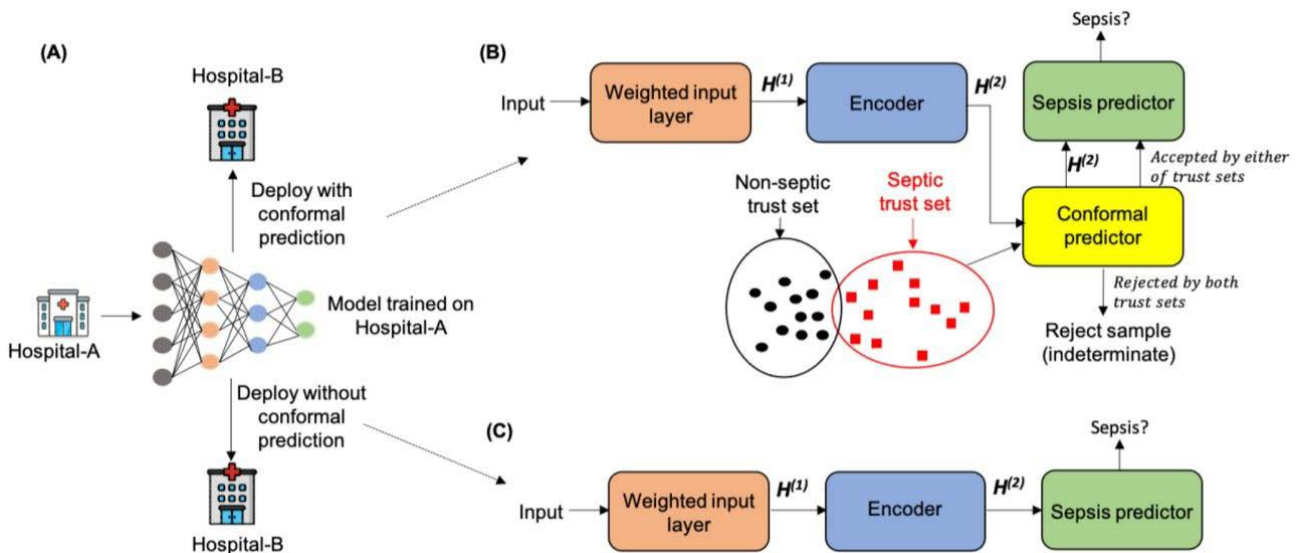


Figure 4. The Role of Artificial Intelligence and Machine Learning in Managing Sepsis-Induced Acute respiratory distress syndrome. Reprinted under the terms of the Creative Commons Attribution License (CC BY) (113).

knowledge. Furthermore, these systems can suggest diagnostic and therapeutic options adapted to each patient's needs, thereby reducing cognitive errors, improving operational efficiency, and streamlining clinical workflows. Moreover, continuous monitoring of vital signs and laboratory data enables prompt alerts for deviations or clinical deterioration, facilitating timely intervention and improved patient safety (114).

Natural Language Processing

NLP represents another frontier for AI and ML in healthcare, enabling the extraction of actionable insights from unstructured data sources (e.g., clinical notes and radiology reports). Additionally, NLP-powered chatbots can mediate communication among patients, families, and clinicians, addressing concerns and symptoms in real time, thereby enhancing engagement and satisfaction (115). By analyzing large corpora of clinical text, NLP can also uncover trends and patterns that inform quality improvement, risk stratification, and research. The integration of AI and ML into sepsis-induced ARDS management holds the potential to transform patient care, improve outcomes, and reduce costs, although challenges remain in their implementation and validation (116).

Conclusion

The integration of omics technologies, advanced imaging modalities, and biomarker discovery has yielded significant advances in understanding the complex pathophysiology of sepsis-induced ARDS, facilitating more accurate diagnosis and enabling the development of personalized treatment strategies. Emerging therapies, including lung-targeted interventions, anti-inflammatory agents, and microbiome modulation, demonstrate potential for improving clinical outcomes. Further enhancements have been achieved through optimized ventilation protocols and the application of big data analytics, AI, and ML,

all contributing to superior clinical decision-making. Nonetheless, key challenges persist, such as the need for larger-scale validation of new therapies, translation of biomarker findings to clinical practice, and the management of risks associated with NP-based delivery. In addition, the high costs and limited accessibility of some advanced technologies impede their widespread use, particularly in resource-constrained environments.

Recommendations

Several strategic recommendations are proposed to overcome current barriers and further progress in the management of sepsis-induced ARDS. First, there is an urgent need for robust, multicenter randomized controlled trials to establish the safety and efficacy of novel therapies across diverse populations. Second, efforts should be intensified to standardize and expedite the clinical translation of biomarker discoveries. Third, additional research is warranted to refine NP-based drug delivery systems, thereby enhancing their safety and specificity. Fourth, prioritizing the development of affordable and user-friendly advanced technologies will increase their adoption in varied healthcare contexts. Fifth, interdisciplinary collaboration should be promoted to integrate insights from omics, imaging, and clinical datasets, thus fostering the creation of comprehensive predictive models and individualized therapeutic plans. Finally, as AI and ML become more prevalent in clinical care, ethical considerations and the protection of patient privacy must remain paramount.

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Competing Interests

The author declares that he has no competing interests.

Ethical Approval

Not applicable.

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