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Management of Acute Respiratory Distress Syndrome (ARDS): A Review of Current Ventilatory and Pharmacological Strategies

Jan Pielaciński [JP]

Samodzielny Publiczny Specjalistyczny Szpital Zachodni im. św. Jana Pawła II, ul. Daleka 11, 05-825 Grodzisk Mazowiecki, Poland

ORCID: https://orcid.org/0009-0007-0675-3037

E-mail: janpiel02@gmail.com

Szymon Pucyło [SP]

Miedzylesie Specialist Hospital in Warsaw, ul. Bursztynowa 2, 04-749 Warsaw, Poland

ORCID: https://orcid.org/0009-0007-0143-7115

E-mail: spucylo@gmail.com

Mateusz Nieczyporuk [MN]

First Department of Internal Medicine, Szpital Bielański im. ks. Jerzego Popiełuszki,

Cegłowska 80, 01-809 Warsaw, Poland

ORCID: https://orcid.org/0009-0002-0196-0946

E-mail: mateusz.nieczyporuk@wp.pl

Martyna Skweres [MS]

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland

ORCID: https://orcid.org/0009-0003-1228-7918

E-mail: martynaskweres7@gmail.com

Gabriela Piotrowska [GP]

Central Clinical Hospital, Medical University of Warsaw, Stefana Banacha 1a, 02-097, Warsaw

ORCID: https://orcid.org/0009-0001-5840-0942

E-mail: gabrysiapiotrowska@wp.pl

Katarzyna Ceglarz [KC]

Praski Hospital of the Transfiguration of the Lord, al. "Solidarności" 67, 03-401 Warsaw, Poland

ORCID: https://orcid.org/0009-0001-2003-0659

E-mail: cegkat123@gmail.com

Aleksander Rudnik [AR]

LUX MED Sp. z o.o., Szturmowa 2, 02-678 Warsaw, Poland

ORCID: https://orcid.org/0009-0003-1325-5694

E-mail: aleksanderrudnik2@gmail.com

Kinga Sikora [KS]

Faculty of Medicine, University of Rzeszow, al. Rejtana 16c, 35-959 Rzeszów

ORCID: https://orcid.org/0009-0005-7201-2742

E-mail: kinga97317@gmail.com

Abstract

Introduction and Purpose. Acute Respiratory Distress Syndrome (ARDS) is a severe inflammatory lung condition associated with high mortality. Despite advances in intensive care, optimal management remains a challenge. This review synthesizes current ventilatory and pharmacological strategies, emphasizing precision medicine to improve outcomes.

Material and Methods. A comprehensive literature search was conducted using PubMed and Google Scholar, focusing on ARDS management studies published since 2015. Keywords included "ARDS," "mechanical ventilation," "prone positioning," "pharmacological therapy," and "precision medicine."

Brief Description of the State of Knowledge. Lung-protective ventilation, utilizing low tidal volumes and prone positioning, significantly reduces mortality in ARDS. Positive end-expiratory pressure (PEEP) optimization and extracorporeal membrane oxygenation (ECMO) serve as adjunct strategies in severe cases. Pharmacological approaches, including early corticosteroid administration and neuromuscular blocking agents, show selective benefits, particularly in hyperinflammatory ARDS phenotypes. Novel therapies, such as mesenchymal stem cells, IL-1β inhibitors, and machine learning-assisted ventilation strategies, represent promising future directions.

Conclusions. ARDS management is evolving toward a personalized, phenotype-driven approach integrating ventilatory and pharmacological strategies. Despite significant advances, challenges remain in optimizing corticosteroid use, PEEP titration, and ECMO application.

Future research should focus on biomarker-driven therapies and artificial intelligence-assisted ventilation to enhance patient outcomes and reduce mortality.

Keywords: Acute Respiratory Distress Syndrome, lung-protective ventilation, prone positioning, pharmacological interventions, ARDS phenotypes

Introduction and objective

Acute Respiratory Distress Syndrome (ARDS) remains a critical challenge in intensive care medicine, characterized by life-threatening hypoxemia and inflammatory lung injury. Defined by the 2012 Berlin criteria and expanded in the 2021 Global Definition to include non-intubated patients and resource-limited settings, ARDS affects 10.4% of ICU admissions globally, with mortality rates ranging from 34.9% to 46.1% depending on severity and etiology [1]. Its pathophysiology involves a triphasic cascade of alveolar-capillary barrier disruption, cytokine-driven inflammation, and fibroproliferation, with emerging evidence highlighting distinct mechanisms in COVID-19-associated ARDS, such as preserved lung compliance despite profound hypoxemia [2]. Despite advancements in lung-protective ventilation strategies including low tidal volumes (4–8 mL/kg PBW) and prone positioning, which reduce mortality by 22% and 16%, respectively—optimal management requires integration of pharmacological interventions such as early corticosteroids (15% mortality reduction) and phenotype-targeted therapies [3]. This review synthesizes the latest evidence to evaluate current ventilatory and pharmacological strategies, address persistent challenges in implementation, and explore the paradigm shift toward precision medicine approaches in ARDS management.

Material and methods

A comprehensive literature review was conducted using two primary databases: PubMed and Google Scholar. The search focused on articles related to ARDS management, published from 2015 onwards. Key search terms included "ARDS," "mechanical ventilation," "lung-protective strategies," "prone positioning," "pharmacological interventions," and

"personalized medicine in ARDS". Additional terms were used to capture specific aspects of ARDS management, such as "ECMO," "corticosteroids in ARDS," and "ARDS phenotypes".

Pathophysiology of ARDS

Acute Respiratory Distress Syndrome (ARDS) is characterized by a triphasic pathophysiological process involving alveolar-capillary barrier disruption, inflammatory cascade activation, and fibroproliferation. The exudative phase initiates with diffuse alveolar damage due to increased permeability of the alveolar-capillary membrane, allowing protein-rich fluid influx into alveoli and impairing gas exchange [4, 5, 6]. This phase is driven by cytokine release (e.g., IL-1β, IL-18) and neutrophil-mediated injury, where activated neutrophils release reactive oxygen species, proteases, and extracellular traps that amplify inflammation via NLRP3 inflammasome activation [5]. Concurrently, endothelial and epithelial injury particularly to type I alveolar cells, which constitute 90% of the alveolar epithelium reduces fluid clearance and exacerbates edema. The proliferative phase follows, marked by attempts to restore alveolar integrity through fibroblast proliferation and type II pneumocyte-mediated surfactant production. In severe cases, a fibrotic phase ensues, characterized by irreversible lung remodeling.

Regarding COVID-19-associated ARDS, it demonstrates distinct features such as primarily targeting pulmonary endothelial cells via ACE2 receptors, causing endothelial dysfunction, microthrombosis, and perfusion dysregulation without significant epithelial damage [6]. This results in preserved lung compliance despite profound hypoxemia ("silent hypoxemia") and increased dead space ventilation due to pulmonary vascular microthrombi. Unlike classical ARDS, which often involves reduced lung volume and compliance from combined epithelial-endothelial injury, COVID-19 ARDS maintains near-normal lung mechanics early in the disease course. Both forms, however, share hallmark inflammatory pathways, including cytokine storms and coagulation activation, though COVID-19 exhibits heightened thrombotic risks (18% vs. 3% in classical ARDS) [6, 7].

Ventilatory Strategies

Mechanical ventilation remains the cornerstone of ARDS management, with strategies evolving to prioritize lung protection and minimize ventilator-induced lung injury (VILI). The

foundation of these approaches is lung-protective ventilation, characterized by low tidal volumes (4–8 mL/kg predicted body weight (PBW)) and plateau pressure limitation (<30 cmH2O). This strategy has demonstrated a significant 22% reduction in mortality compared to traditional higher volume ventilation, underscoring its critical importance in ARDS care. The concept of "baby lung" in ARDS, where only a fraction of the lung remains aerated and functional, emphasizes the need for these protective strategies to prevent overdistension and further injury to the limited healthy lung tissue [8, 9, 10].

Prone positioning has emerged as a pivotal intervention, particularly in moderate-to-severe ARDS (PaO2/FiO2 ratio less than 150 mmHg). This technique enhances oxygenation through multiple mechanisms: redistributing ventilation to dorsal lung regions, reducing dependent alveolar collapse, and improving ventilation-perfusion matching. When applied early during ARDS and maintained for extended periods (≥12–16 hours daily), prone positioning has been shown to reduce mortality by 16%. The physiological benefits extend beyond immediate oxygenation improvements, including more homogeneous distribution of lung stress and strain, potentially mitigating VILI. [11, 12]

Positive end-expiratory pressure (PEEP) optimization remains a crucial yet complex aspect of ARDS ventilation. Higher PEEP levels (typically 10–20 cmH2O) aim to improve functional residual capacity, prevent cyclical alveolar collapse (atelectrauma), and enhance oxygenation. However, the optimal PEEP setting varies among patients and even within different lung regions of the same patient. Advanced techniques for PEEP titration include esophageal manometry to estimate transpulmonary pressure and electrical impedance tomography for real-time assessment of regional ventilation distribution. These methods allow for more personalized PEEP settings, balancing the benefits of alveolar recruitment against the risks of overdistension. [8, 10, 13]

The concept of driving pressure (<14 cm H2O) has gained prominence as a key target in ventilation management, showing stronger correlations with survival than tidal volume alone. Driving pressure, calculated as the difference between plateau pressure and PEEP, serves as a surrogate for the strain applied to the functional lung tissue. Minimizing driving pressure while maintaining adequate ventilation represents a delicate balance in ARDS management. [8, 13]

Advanced recruitment strategies, such as open-lung recruitment maneuvers, involve transiently increasing inspiratory pressure (40–60 mbar) to recruit collapsed alveoli. While these maneuvers can improve oxygenation and lung mechanics in some patients, their routine use remains controversial due to uncertain mortality benefits and potential risks of barotrauma

and hemodynamic instability. The effectiveness of recruitment maneuvers often depends on the underlying ARDS etiology and the individual patient's lung recruitability.

Advanced Ventilatory Approaches

Extracorporeal Membrane Oxygenation (ECMO) serves as a rescue therapy for severe ARDS refractory to conventional ventilation, enabling ultra-protective ventilation by offloading gas exchange and reducing ventilator-induced lung injury (VILI). Recent evidence demonstrates that increasing ECMO blood flow (targeting mixed venous oxygen saturation [SvO_2] >80%) reduces pulmonary artery pressure (30 ± 5 mm Hg vs. 34 ± 6 mm Hg at lower flows) and cardiac output (7.9 vs. 9.2 L/min), improving right ventricular workload without altering ventilation-perfusion mismatch. ECMO's role extends to bridging patients to recovery or definitive interventions, such as surgical management of ARDS complications (e.g., ruptured pulmonary hydatid cysts). However, outcomes depend on center expertise, with high-volume centers reporting lower mortality (39% vs. 62.5%) [14, 15].

High-Frequency Oscillatory Ventilation (HFOV) employs rapid oscillations (3–15 Hz) and tidal volumes ≤1–4 mL/kg to minimize alveolar overdistension while maintaining constant mean airway pressure (mPaw) for lung recruitment. Despite theoretical advantages in reducing VILI, clinical trials show conflicting mortality benefits, leading to restricted use in refractory hypoxemia or as a rescue strategy. HFOV's efficacy hinges on precise mPaw titration to balance oxygenation (FiO_2 <0.6) and hemodynamic stability, though its active expiratory phase risks air trapping in heterogeneous ARDS lungs [16, 17].

Recruitment Maneuvers (RMs) and Open Lung Strategies aim to reverse atelectasis through transient increases in transpulmonary pressure (40–60 cmH_2O for 30–40 seconds) followed by optimized PEEP. Stepwise RMs, combining incremental PEEP adjustments with constant driving pressure, are preferred over sustained inflation to mitigate barotrauma and hemodynamic compromise. While RMs improve oxygenation in recruitable lungs (PaO_2/FiO_2 increase of 50–100 mmHg), their mortality benefit remains unproven, particularly in non-focal ARDS phenotypes with fluid-filled alveoli. Current guidelines recommend RMs only in hemodynamically stable patients under close monitoring, paired with PEEP ≥10 cmH_2O to sustain alveolar stability [18, 19].

Table 1: Ventilatory Strategies in ARDS Management

Strategy	Description	Outcome
Lung-protective ventilation	Low tidal volumes (4-8 mL/kg PBW), plateau pressure <30 cmH2O	22% reduction in mortality
Prone positioning	≥12-16 hours daily, for PaO2/FiO2 <150 mmHg	16% reduction in mortality
PEEP optimization	Typically,10-20 cmH2O, personalized using advanced techniques	Improves oxygenation, prevents atelectrauma
Driving pressure minimization	Target <14 cmH2O	Stronger correlation with survival than tidal volume alone
ECMO	Rescue therapy for severe refractory ARDS	Outcomes depend on center expertise; 39% vs 62.5% mortality in high vs low-volume centers

Pharmacological Interventions

Regarding, anti-inflammatory approaches, corticosteroids remain pivotal in ARDS management, with timing and dosing critically influencing outcomes. Early dexamethasone (6 mg/day for 10 days) initiated within 48 hours of ARDS onset reduces 60-day mortality by 15% (Number Needed to Treat = 7), particularly in hyperinflammatory phenotypes characterized by elevated IL-6 (>200 pg/mL) and C-Reactive Protein (CRP) (>15 mg/dL) [20, 21]. The CoDEX

trial demonstrated that high-dose dexamethasone (20 mg/day tapered over 10 days) increases ventilator-free days (6.6 vs. 4.0 days) in moderate-to-severe COVID-19 ARDS, though 28-day mortality did not significantly differ (56% vs. 62%). However, conflicting evidence exists, the ARDSNet LaSRS trial found no mortality benefit with moderate-dose methylprednisolone (2 mg/kg/day) initiated ≥7 days after diagnosis, highlighting the importance of early administration [22]. Novel agents like IL-1β antagonists (anakinra) show promise in hyperinflammatory subgroups, reducing mechanical ventilation duration by 2.8 days compared to placebo, while imatinib, a tyrosine kinase inhibitor, decreases pulmonary edema (EVLW reduction from 12.3 ± 3.1 to 9.8 ± 2.6 mL/kg) by stabilizing endothelial junctions [20, 23, 24].

Neuromuscular Blocking Agents (NMBAs) such as Cisatracurium, a benzylisoquinoline NMBA, improves oxygenation and reduces ventilator days in early severe ARDS (PaO_2/FiO_2 <150 mmHg) via dual mechanisms: mitigating ventilator-induced lung injury (VILI) through patient-ventilator synchrony and directly suppressing cytokine release (IL-6, IL-8) [20, 22]. The ACURASYS trial demonstrated a 9.8% mortality reduction with 48-hour continuous cisatracurium infusion (15 mg bolus followed by 37.5 mg/hour), though subsequent studies like the ROSE trial showed no benefit in milder cases [20, 22]. Notably, cisatracurium's Hoffman degradation pathway minimizes metabolite accumulation in renal/hepatic dysfunction, reducing ICU-acquired weakness risk compared to vecuronium (12% vs. 27%). Current guidelines reserve NMBAs for severe early ARDS with persistent desynchrony despite sedation optimization [22, 23].

Sedation strategies employing light sedation protocols (RASS - Richmond Agitation-Sedation Scale: -1 to 0) using dexmedetomidine or propofol reduce mechanical ventilation duration by 2.1 days and delirium incidence by 33% compared to benzodiazepines [20, 23]. Daily sedation interruptions paired with spontaneous breathing trials enhance ventilator liberation, shortening ICU stays by 4.3 days. Dexmedetomidine's α_2-agonist properties enable rapid awakening (1.3 vs. 4.7 hours post-midazolam) while maintaining hemodynamic stability, though it requires careful titration in shock states [23, 24]. Emerging strategies integrate closed-loop sedation systems using bispectral index (BIS) monitoring to maintain optimal sedation depth while minimizing drug accumulation [24].

Conservative fluid strategies targeting central venous pressure (CVP <4 mmHg) or extravascular lung water (EVLW <10 mL/kg) increase ventilator-free days by 2.5 days versus liberal approaches, as demonstrated in the FACTT trial [22, 23]. Albumin supplementation (25 g every 6 hours) in hypoalbuminemic ARDS (serum <2 g/dL) reduces pulmonary edema by 32% through oncotic pressure restoration, though it requires co-administration with diuretics to

avoid volume overload. Novel approaches include angiopoietin-2 inhibitors (trevogrumab) to reduce vascular leakage and ultrafiltration devices for precise fluid removal in oliguric patients [23, 24].

Investigational Therapies - Phase III trials are evaluating mesenchymal stem cells (MSCs) for their immunomodulatory and alveolar repair effects, with early data showing 18% improvement in oxygenation indices [23, 24]. Aspirin, despite observational data suggesting ARDS prevention benefits, failed to reduce inflammation in the LIPS-A trial, though sub analyses showed promise in septic ARDS subgroups [22, 23]. Inhaled anticoagulants (nebulized heparin) and statins (rosuvastatin) are under investigation for mitigating fibrin deposition and endothelial dysfunction, respectively [23, 24].

Table 2: Pharmacological Interventions in ARDS

Intervention	Dosage/Timing	Effect
Corticosteroids (Dexamethasone)	6 mg/day for 10 days, within 48 hours of onset	15% reduction in 60-day mortality
Neuromuscular blocking agents (Cisatracurium)	48-hour continuous infusion in early severe ARDS	9.8% reduction in mortality
Light sedation protocols	Target RASS -1 to 0	Reduces mechanical ventilation duration by 2.1 days
Conservative fluid management	Target CVP <4 mmHg or EVLW <10 mL/kg	Increases ventilator-free days by 2.5 days
Albumin supplementation	25 g every 6 hours in hypoalbuminemic ARDS	Reduces pulmonary edema by 32%

Integrated Approach to ARDS Management

ARDS management increasingly emphasizes phenotype-specific strategies, distinguishing between hyperinflammatory (elevated IL-6, IL-8, PAI-1) and hypoinflammatory subtypes. Hyperinflammatory phenotypes exhibit greater mortality (33–50%) but show improved responses to corticosteroids (15% mortality reduction) and conservative fluid strategies, whereas hypoinflammatory subtypes benefit from higher PEEP and liberal fluid approaches [25, 26, 27]. Biomarker-driven protocols, such as targeting IL-1β inhibition (anakinra) in hyperinflammatory patients or adjusting PEEP based on alveolar recruitability, optimize outcomes by aligning therapies with underlying pathophysiology [25, 26, 28]. Machine learning models now aid phenotype identification (89% accuracy) using clinical variables like heart rate, minute ventilation, and CRP, enabling dynamic treatment adjustments [25, 26, 27].

Effective ARDS care bundles integrate lung-protective ventilation (4–8 mL/kg PBW, PEEP titration), early prone positioning (≥16 hours/day for PaO_2/FiO_2 <150 mmHg), conservative fluid management (targeting CVP <4 mmHg), and protocolized sedation [27, 29]. Implementation challenges include staff training gaps, workflow disruptions, and resource limitations, particularly in non-tertiary centers. However, bundled strategies improve adherence to evidence-based practices, reducing mortality by 16% and increasing ventilator-free days by 2.5 days compared to isolated interventions [27, 30]. The ROSE framework (Resuscitation, Optimization, Stabilization, Evacuation) standardizes phased fluid management, while multidisciplinary teams enhance protocol compliance [29].

COVID-19 ARDS diverges from classical ARDS through preserved lung compliance early in disease, higher thrombotic risk (18% vs. 3%), and variable responsiveness to prone positioning [6, 28]. While lung-protective ventilation remains central, anticoagulation and delayed intubation strategies are more prominent in COVID-19. In resource-limited settings, ARDS management adapts using the Kigali criteria (clinical hypoxemia without advanced imaging) and prioritizes cost-effective interventions like conservative fluids and manual prone positioning [31, 32]. Outcomes hinge on healthcare environment capabilities: high-volume ECMO centers report 39% mortality vs. 62.5% in low-resource settings, underscoring the need for context-specific protocols [27, 31, 32].

Conclusion and Future Directions

ARDS management has advanced through evidence-based ventilatory strategies, with lung-protective ventilation (tidal volumes 4–8 mL/kg PBW, plateau pressure <30 cmH2O) and prone positioning (>12 hours/day for severe ARDS) remaining cornerstones, reducing mortality by 22% and 16%, respectively [27, 33]. Pharmacologically, corticosteroids (e.g., early dexamethasone) and neuromuscular blockers (cisatracurium in early severe ARDS) demonstrate conditional benefits, though their efficacy depends on phenotype and timing [27, 34, 35]. Integrated approaches combining these strategies with conservative fluid management and personalized PEEP titration show promise, particularly when guided by biomarkers (e.g., IL-6, CRP) and respiratory mechanics [33].

Critical gaps persist, including uncertainty in optimal corticosteroid dosing, NMBA timing, and PEEP individualization [27, 34]. Heterogeneity in ARDS phenotypes—hyperinflammatory (elevated cytokines, responsive to immunosuppression) versus hypoinflammatory (lower mortality, better PEEP response) remains underexplored in clinical protocols [35, 36]. Additionally, 30% of ARDS cases in resource-limited settings lack access to advanced therapies like ECMO, underscoring disparities in care.

Emerging therapies aim to address these gaps in ARDS management. Cell-based therapies, particularly mesenchymal stem cells (MSCs), show promise with an 18% improvement in oxygenation indices through immunomodulatory effects [36]. Targeted biologics are also being explored, with IL-1β antagonists like anakinra and tyrosine kinase inhibitors such as imatinib demonstrating potential in reducing pulmonary edema and inflammation, especially in hyperinflammatory subgroups of ARDS patients [34]. Additionally, artificial intelligence is making its way into ARDS management, with AI-driven decision support systems capable of adjusting ventilation parameters in real-time. These systems have shown to improve driving pressure and oxygenation in 60% of cases [33].

Future priorities in ARDS management include several key areas. Researchers are focusing on validating biomarkers such as Angiopoietin-2 (Ang-2) and soluble Receptor for Advanced Glycation End-products (sRAGE) to stratify patients for tailored therapies in phenotype-driven trials [35, 37]. There is also a push for global inclusivity by adapting protocols for resource-limited settings using the Kigali criteria and implementing cost-effective interventions [38]. Precision ventilation is another area of focus, with multicenter trials testing PEEP titration via electrical impedance tomography and driving pressure algorithms [36].

Lastly, researchers are exploring combination therapies that investigate potential synergies between immunomodulators (such as anti-IFN-γ) and ultra-protective ventilation strategies.

The 2035 research agenda emphasize personalized medicine, leveraging molecular subphenotypes and machine learning to transform ARDS from a syndromic diagnosis to a treatable trait [37].

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