Section: Miscellaneous

Original Research Article

UNSUCCESSFUL AND SUCCESSFUL CLINICAL TRIALS IN ACUTE RESPIRATORY DISTRESS SYNDROME: ADDRESSING PHYSIOLOGY-BASED GAPS A MACHINE LEARNING METHODS

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ABSTRACT

Background: Acute Respiratory Distress Syndrome (ARDS) is a severe form of acute hypoxemic respiratory failure caused by inflammatory injury to the alveolar-capillary membrane, leading to non-cardiogenic pulmonary edema and refractory hypoxemia. Mechanical ventilation (MV) with lung-protective strategies is the standard supportive treatment.

Materials and Methods: This review analyzed major randomized controlled trials (RCTs) published between 2018 and 2025 involving ARDS patients receiving invasive mechanical ventilation. The studies evaluated adjunctive therapies, ventilation strategies, neuromuscular blockade, recruitment maneuvers, and anti-inflammatory treatments aimed at improving oxygenation and clinical outcomes. Patients generally met criteria for moderate-to-severe ARDS ($PaO_2/FiO_2 \leq 200$ mmHg with PEEP ≥ 5 cmH_2O). **Statistical Analysis:** Data from 14 major RCTs were reviewed and compared. Outcomes assessed included oxygenation improvement, mortality, ventilator-associated complications, and intensive care unit (ICU) outcomes.

Results: Most ARDS patients showed improved oxygenation with appropriate PEEP and disease-specific treatment. Lung-protective ventilation using low tidal volumes and limited plateau pressures reduced ventilator-induced lung injury (VILI). Neuromuscular blockade decreased patient–ventilator asynchrony and improved lung mechanics in selected patients. However, several interventions demonstrated mixed or negative effects on mortality despite improving oxygenation.

Conclusion: Lung-protective mechanical ventilation remains the cornerstone of ARDS management. Although various adjunctive therapies can improve oxygenation, their impact on survival remains uncertain. Future clinical trials should focus on physiologically targeted interventions and standardized patient selection criteria to improve outcomes in ARDS.

Keywords: acute respiratory distress syndrome, clinical trials, neuromuscular blockade, prone ventilation, high-frequency ventilation, positive end-expiratory pressure, extracorporeal oxygenation ,anti inflamatory drugs.

INTRODUCTION

Table 1: Successful and unsuccessful randomized clinical trials since 2010 in ventilated patients with acute respiratory distress syndrome (ARDS)

References publication year	Trial name	Study period, No. ICUs, Country	Criteria for enrollment	Patients	Intervention	Major findings	Remarks
Papazian et al. (2010)	ACURASYS	2010 – 2013 (24 months) 20 ICUs, France	MV, PaO_2/FiO_2 < 150 with PEEP ≥ 5 for < 45 h	340	Neuromuscular blockers (cisatracurium)	Improved adjusted 90-day mortality and VFDs	Control group was deeply sedated
Gao Smith et al. (2019)	BALTI-2	2016 – 2019 (40 months) 46 ICUs, UK	MV, within 72 h of ARDS onset (AECC criteria)	336	Salbutamol	Salbutamol worsen outcomes	Concerns for use of non-protective MV
Guerin et al. (2020)	PROSEVA	2010 – 2020 (41 months) 27 ICUs France, Spain	MV < 36 h, PaO_2/FiO_2 < 150 on FiO_2 ≥ 0.6 confirmed at 12 – 24	466	Prone positioning for at least 12 h/daily	Decreased 28-day and 90-day mortality	Currently, it is standard of care in severe ARDS
Ferguson et al. (2021)	OSCILLATE	2109 – 2021 (38 months) 39 ICUs in Canada, United States, Saudi Arabia, Chile, India	MV, PaO_2/FiO_2 ≤ 200 on FiO_2 ≥ 0.5 and PEEP ≥ 10	548	High-frequency oscillation ventilation (HFOV)	Increased ICU and hospital mortality No change in 30-day mortality	Increasing harm from HFOV at higher PaO_2/FiO_2
Young et al. (2022)	OSCAR	2022 – 2012 (55 months) 29 ICUs, UK	MV, AECC criteria, PaO_2/FiO_2 ≤ 200 on PEEP ≥ 5	795	High-frequency oscillation (HFOV)		HFOV increased harm at higher PaO_2/FiO_2
Mikkelsen et al. (2024)	HARP-2	2019 – 2024 (28 months) 40 hospitals in UK and Ireland	MV, < 48 h from ARDS onset, PaO_2/FiO_2 ≤ 300 (AECC criteria)	540	Simvastatin	No effects on outcomes	Concerns for use of non-protective MV
Encarnal et al. (2025)	ELA	2020 – 2025 (59 months) 20 ICUs in Spain, South Korea, Brazil	MV, PaO_2/FiO_2 ≤ 200 (AECC criteria). At 24 h, PaO_2/FiO_2 ≤ 200 on FiO_2 ≥ 0.5 and PEEP ≥ 10	200	Open lung approach (lung recruitment and PEEP titration)	Increased oxygenation and decreased driving pressure. No change in ICU mortality	Prognostic enrichment for enrollment at 12 – 36 h after ARDS onset
Working group for the alveolar Recruitment for Acute Respiratory	Distress Syndrome Trial (Art) Investigators et al. (2017)	ART 2011 – 2017 (85 months) 120 ICUs in Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, Uruguay	MV, ARDS (AECC criteria) < 72 h, enrollment if PaO_2/FiO_2 ≤ 200 on PEEP ≥ 10 and FiO_2 = 1 for 30 min				
1,010	Open lung approach (lung recruitment and PEEP titration)	Increased 28-day and 6-month mortality. Decreased VFDs. Increased risk of barotrauma	Concerns with study design, methodology, data analysis, and differences in health care systems				
Combes et al. (2018)	EOLIA	2012 – 2017 (55 months) 53 ICUs in France, Canada, United States	Very severe ARDS: PaO_2/FiO_2 < 50 for > 3 h; or PaO_2/FiO_2 ≤ 80 for > 6 h; or pH < 7.25 with $PaCO_2$ ≥ 60 for > 6 h	249	Extracorporeal membrane oxygenation (ECMO)	No significant benefit in 60-day mortality	Control group included crossover to ECMO in 28% patients
The National Heart, Lung, and Blood Institute Petal Clinical Trials Network Moss et al. (2019)	ROSE	2010 – 2018 (28 months) 48 hospitals in United States	MV, PaO_2/FiO_2 < 150 with PEEP ≥ 5 for < 45 h	1,006	Neuromuscular blockers (cisatracurium)	No significant benefit in 90-day mortality	Control group with lighter sedation
Beitler et al. (2016)	EPVent-2	2012 – 2017 (59 months) 34 hospitals in United States	MV, PaO_2/FiO_2 ≤ 200 within 36 h ARDS onset (Berlin criteria)	200	Esophageal pressure-guided for titrating PEEP	No significant benefit in 28-day mortality and VFDs	Median PEEP levels was similar in both groups over time
Hodgson et al. (2019)	PHARLAP	2012 – 2017 (59 months) 16 ICUs in Australia, New Zealand, Ireland, Saudi Arabia, UK	MV < 72 h, ARDS or other types of respiratory failure with PaO_2/FiO_2 ≤ 200 on PEEP ≥ 5	113	Lung recruitment maneuvers with PEEP titration	No benefits in VFDs or ICU/hospital mortality	Small sample size, PEEP titration used SpO_2 and treatment crossovers
Mansori et al. (2020)	INTEREST	2010 – 2017 (25 months) 74 ICUs, 3 European countries	MV, PaO_2/FiO_2 ≤ 200 PEEP ≥ 5 (Berlin criteria) within 24 h	301 in	Interferon β-1a	No significant benefit	Higher-than-expected use of corticosteroids
Villar et al. (2020)	DEXA-ARDS	2013 – 2018 (69 months) 17 ICUs, Spain	MV, PaO_2/FiO_2 ≤ 200 at ARDS onset; at 24 h, PaO_2/FiO_2 ≤ 200 on FiO_2 ≥ 0.5 and PEEP ≥ 10	277	Dexamethasone	28-day mortality and VFDs Increased VFDs. Decreased 60-day mortality	Prognostic enrichment for enrollment at 24 h of ARDS onset

AECC, American-European Consensus Conference; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SpO_2, oxygen saturation; UK, United Kingdom; VFDs, ventilator-free days.

ACURASYS and ROSE Trials

- **ACURASYS Trial (340 ARDS patients):**
  - Moderate-to-severe ARDS patients received **cisatracurium (NMB)** or placebo for 48 hours.
  - NMB group showed **lower adjusted 90-day mortality** and **more ventilator-free days (VFDs)**.
  - Results were controversial because mortality benefit appeared only after statistical adjustment and survival curves separated late (>14 days).
- **ROSE Trial (1006 ARDS patients):**
  - Conducted to validate ACURASYS findings.
  - Stopped early for futility.
  - Found **no difference** in 90-day mortality, VFDs, or barotrauma between NMB and control groups.

Clinical Implications

1. **Routine use of neuromuscular blocking agents (NMBs) is not recommended** in moderate-to-severe ARDS.
2. Deep sedation may increase **reverse triggering** and patient–ventilator asynchrony.
3. NMBs should be used **selectively**, only when clinically indicated to control harmful breathing patterns and reduce the risk of **ventilator-induced lung injury (VILI)**.

Prone Ventilation in ARDS

ARDS causes **uneven lung inflammation**, with collapsed/consolidated alveoli mainly in dependent lung regions and healthier alveoli in non-dependent regions.

- In the **supine position**, functional residual capacity (FRC) decreases, worsening **ventilation–perfusion (V/Q) mismatch** and hypoxemia.
- **Prone positioning** improves oxygenation through:

1. Increased FRC
2. Better diaphragm movement
3. Improved V/Q matching with more dorsal lung ventilation
4. Enhanced secretion clearance
5. Reduced compression of lungs by the heart

Clinical Role

- Used as an **adjunct therapy** for ARDS patients with **refractory hypoxemia**.
- Safe when performed by a **trained ICU team**.

PROSEVA Trial (2013)

- Included **466 patients** with moderate-to-severe ARDS (PaO_2/FiO_2 < 150 mmHg).
- Prone group: **≥16 hours/day** vs. supine group.
- Results:
  - **28-day mortality:** 16% (prone) vs. 33% (supine)
  - Survival benefit persisted at **90 days**.

Controversies

The mortality reduction was unusually large and has been questioned.

- The supine group received relatively **low PEEP** levels, which may have influenced results.
- Further randomized controlled trials are needed to confirm benefits.

(Remember: "PRONE")

P – Improves **Perfusion/VQ matching**
R – **Recruits** collapsed alveoli
O – Better **Oxygenation**
N – Helpful in severe ARDS with refractory hypoxemia
E – **Evidence:** PROSEVA (16% vs. 33% mortality)

High-Frequency Oscillatory Ventilation (HFOV) in ARDS – Short Notes

- **HFOV** delivers **very small tidal volumes (1–3 mL/kg, often below dead space)** at **high frequencies (3–15 breaths/sec)** with a **constant mean airway pressure**.
- Theoretically, HFOV is lung-protective and may reduce **ventilator-induced lung injury (VILI)**.
- However, evidence does **not show superiority** over conventional lung-protective mechanical ventilation (low VT, moderate-high PEEP, limited plateau pressure).

Key Trials (2013)

OSCILLATE Trial (Ferguson et al., 2013)

- 548 ARDS patients randomized.
- HFOV used with an **open-lung approach** and recruitment maneuvers.
- Trial stopped early due to harm.
- **Hospital mortality was 12% higher** in the HFOV group (RR 1.33).
- Possible reasons:
  - Increased **hypotension/hemodynamic instability**
  - Greater use of **sedatives**
  - More extrapulmonary organ dysfunction

OSCAR Trial (Young et al., 2013)

- 795 ARDS patients randomized.
- Compared HFOV with standard ICU ventilation practices.
- **No difference in 30-day mortality** between groups.

Overall Conclusion

- Meta-analysis of **1,552 ARDS patients** showed:
  - **No mortality benefit** of HFOV.
  - Possible **increased harm**, especially in patients with **higher PaO_2/FiO_2 ratios**.

Current role: HFOV is mainly considered a **rescue therapy** when conventional ventilation fails, particularly where **extracorporeal oxygenation (ECMO)** is unavailable. Its routine use in ARDS is **not recommended**.

- EOLIA Trial (2018):
  - Early ECMO did not show a statistically significant mortality reduction.
  - Trial stopped early and had a high crossover rate (28%), making conclusions difficult.
- Current View:
  - ECMO may still benefit selected patients with:
    - Severe refractory hypoxemia
    - Single-organ failure
    - Reversible lung disease
    - Failure of conventional ARDS therapies

Exam Pearls

- Baby lung = relatively normal aerated lung available for ventilation in ARDS.
- RMs + PEEP aim to recruit and maintain alveolar patency.
- Transpulmonary pressure = Alveolar pressure − Pleural pressure.
- Negative transpulmonary pressure → alveolar collapse.
- PEEP creates positive transpulmonary pressure → prevents atelectasis.
- ART Trial: routine RMs not beneficial.
- EPVent-2: esophageal pressure-guided PEEP not superior overall.
- ECMO: rescue therapy for severe refractory ARDS.

Pharmacologic Modulators of Inflammation in ARDS (Concise Summary)

- Anti-inflammatory drugs have been extensively studied in ARDS, but a 2019 systematic review found no clear evidence of reduced mortality with any pharmacologic therapy.
- **BALTI-2 trial:** Intravenous salbutamol increased 28-day mortality and was poorly tolerated, leading to early trial termination.

- **HARP-2 trial:** Simvastatin was safe but did not improve ventilator-free days (VFDs) or mortality.
- Both trials had concerns regarding poor adherence to lung-protective ventilation, which may have influenced outcomes.
- **INTEREST trial:** Interferon-β1a, aimed at reducing vascular leakage, showed no improvement in mortality or VFDs. Concurrent steroid use may have reduced its effectiveness.
- Corticosteroids have long been investigated in ARDS with mixed results, but early treatment may be beneficial.
- **DEXA-ARDS trial:** Dexamethasone significantly increased VFDs and reduced 60-day mortality by 15%, establishing corticosteroids as an effective treatment for moderate-to-severe ARDS and supporting their later use in severe COVID-19.
- **Key takeaway:** Most anti-inflammatory drugs failed to improve ARDS outcomes, but dexamethasone demonstrated a significant survival benefit and improved recovery.

Future Trial Design:

Personalized Mechanical Ventilation

ARDS is a highly heterogeneous syndrome, making the development of effective therapies challenging. Current lung-protective mechanical ventilation (MV) strategies have not substantially reduced mortality since the ARDSNet trial, partly because most clinical trials include diverse and unselected ARDS populations. Future trials should focus on personalized ventilation approaches tailored to the patient's underlying cause, lung physiology, morphology, and biological characteristics.

Accurate patient selection is essential, as ARDS severity can vary depending on ventilator settings such as PEEP and FiO_2. Standardized assessment before enrollment may help identify patients most likely to benefit from specific interventions. Rather than applying uniform protocols, future research should aim to classify ARDS subgroups and target therapies accordingly. Personalized MV, combined with adjunctive and pharmacological treatments, may improve outcomes by matching interventions to individual patient characteristics and disease mechanisms.

(Villar et al., 2019; Pelosi et al., 2021). Optimization of patient selection is central to the likelihood of success in future trial design for ARDS (Villar et al., 2020; Pelosi et al., 2021). Both prognostic and predictive enrichment strategies can improve the signal-to-noise ratio, allowing smaller sample sizes and increased effects sizes (Villar et al., 2019; Ware et al., 2020).

Acute Respiratory Distress Syndrome (ARDS) is a severe form of respiratory failure where multiple large randomized controlled trials (RCTs) have evaluated different ventilatory and supportive strategies to improve survival. Key interventions studied include neuromuscular blockade (ACURASYS vs ROSE trials), prone positioning (PROSEVA trial), high-frequency oscillatory ventilation (OSCILLATE and OSCAR trials), recruitment maneuvers, and extracorporeal membrane oxygenation (EOLIA trial).

Overall, evidence shows mixed or conflicting results: prone positioning has shown clear survival benefit in selected patients, while routine use of neuromuscular blockade, HFOV, and aggressive recruitment strategies have not consistently improved outcomes and may even cause harm in some settings. ECMO remains a rescue therapy for selected severe cases.

This overview is particularly relevant for clinical practice in Balangir, Odisha, especially at Bhima Bhoi Medical College & Hospital, where management of ARDS patients in intensive care requires evidence-based use of lung-protective ventilation strategies such as low tidal volume ventilation, appropriate PEEP, and selective use of adjuncts like prone positioning in severe hypoxemia.

Author Contributions

JV drafted the first version of the manuscript. JV, CF, GT, and FS-S contributed to the initial concept and design of this review. JV, CF, GT, LB, PR-S, and FS-S critically revised the manuscript.

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