API DK LAHARI

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ACUTE RESPIRATORY DISTRESS SYNDROME

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CONTENTS

1.	ARDS THROUGH THE EYES OF A PHYSICIAN - DR. MEGHANA DEEPAK MADI	2
2.	VOICE OF EDITORS - DR. ARCHITH BOLOOR DR. ARCHANA BHAT	4
3.	PRESIDENT DESK - DR. MURALIDHARA YADIYAL B	5
3.	API DK CHAPTER SECRETARY'S REPORT - DR. PAVAN M. R	6
4.	LUNG ULTRASOUND IN ARDS - DR. SUNIL KARANTH , DR. MAHESH PADYANA	8
5.	PHARMACOTHERAPHY IN ACUTE RESPIRATORY DISTRESS SYNDROME - DR. AJITH KUMAR A.K, DR. KOUSHIK S R	15
6.	MASTERING THE ART OF PRONE VENTILATION - DR. MAHESH PADYANA, DR. SUNIL KARANTH	23
7.	TELE ICU – AN INVENTION AND A NECESSITY TO STAY ON - DR. SHARATH BABU S	31
8.	THE HEART OF THE PANDEMIC - DR. SEETHA LAKSHMI	34
9.	UNDERSTANDING THE LUNG PHENOTYPES OF ARDS - DR. RADHA M G	37

ARDS THROUGH THE EYES OF A PHYSICIAN

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Ashbaug DG, coined the term acute respiratory distress (ARDS) in a landmark article published in The Lancet on August 12, 1967. Although first published in 1967, the history of ARDS dates back to the early 20th century. The 1918-19 Influenza pandemic was a key event followed by the Polio epidemic of 1952 which led to the invention of Iron lung ventilators. Over the last six decades, the management of ARDS has seen a sea of changes. The ventilators have evolved, the modes have improved and so is our understanding of the etiopathogenesis of ARDS. ARDS continues to be the cause of approximately 10% of ICU admissions worldwide and accounts for approximately 40% of ICU mortality.

While I was getting trained in Manipal Hospital, Bangalore, Dengue and H1N1 outbreaks happened. It is then I got interested in the nuances of ARDS management. I still recall a Software Engineer who was transported to MHB with severe H1N1 pneumonia. He arrested midway during transport due to hypoxemia and was revived within the ambulance by the accompanying critical care team. Overnight he was prone positioned and continued on lung protective ventilation. One fine morning I was pleasantly surprised to see him reading a newspaper, already tobe extubated. Tears of happiness and words of gratitude from the patient, the patient attenders make these events all the more special.

The COVID -19 pandemic tested the limits of critical care to its zenith. The burgeoning number of positive cases across the world, ever increasing need for ICU facilities catapulted the expectations on critical care practitioners. The pandemic also tested our resilience and resolve. Suddenly ventilators, ECMO, awake proning became topics

of prime- time debates across all the news channels. The COVID 19 pandemic made ARDS a household name. On the flip side, COVID 19 pandemic paved way for a deeper understanding of various phenotypes, utility of ECMO, awake proning, newer monoclonal antibodies and the resurgence of steroids in the management of severe ARDS. More importantly, a gradual shift towards targeted therapy in ARDS started gaining grounds.

When Dr. Archith Boloor asked me to be the Guest Editor for the present edition of API- DK Lahari, without batting an eyelid I knew I would focus on ARDS. I felt this would go a long way in acclimatizing the physician community with the intricacies of ARDS management. In the present edition I have tried to focus on core topics of ARDS management like prone ventilation, bedside Lung ultrasound, steroids in ARDS, and lung phenotypes. Along with that we have two frontline warriors of COVID 19 sharing their experiences of managing the crisis at grass root level. All the guest authors have specialized in critical care post their training in Medicine or Pulmonary medicine. This was a deliberate attempt on my part to increase the awareness among medicine post graduates to take critical care as their career.

ARDS definition has undergone three revisions in the last two decades. ARDSnet, PROSEVA, CAESAR are the landmark trials which have brought about tectonic shifts in ARDS management. Despite this, ARDS with its varied etiologies and patho- physiology continues to be an “Enigma” in the medical field.

I am very happy that APIDK chapter is bringing out edition as a fitting tribute to Ashbaug.

Happy reading.

EDITORIAL MESSAGE

Dear readers,

As we turn the pages of this month's edition, we invite our readers to delve into a world where creativity meets inspiration, and every story about ARDS sparks a thought. At API DK LAHARI we believe in celebrating the various voices and experiences of the doctors involved in patient care and commitment.

In our future issues we hope to get thought provoking insights that challenge the medical profession .In this issue there are curated narratives from well experienced doctors on ARDS and beyond. Thank you for reading our API DK e magazine and we hope it inspires the thirst for knowledge and transformation .We invite you to share your thoughts , suggestions and stories as we strive to create a platform that reflects our shared experiences in this vast medical field

Happy reading

Warm regards,

Dr. Archith Boloor
Editor in Chief

Dr. Archana Bhat
Executive Editor

PRESIDENT MESSAGE

Warmest greetings of the season to all of you. Hope this newsletter of API finds you in the best of your health and spirits. I consider it both my privilege and honour to be president of the API for this year and it is only with the support and warmth of all the members and office bearers that I will be able to do justice to my role during my tenure. So, while being grateful to each one of you for being there for API, I specifically thank Dr. Archith Boloor and Dr. Archana Bhat for taking stewardship towards the release of our own API Lahari, thus helping in carrying on the legacy of API. Wish you all a good read and a great life ahead. Long live API!

Yours sincerely,

Dr. Muralidhara Yadiyal B
President, API, Mangalore (DK) chapter

SECRETARY REPORT

Dr. Pavan M R
Secretary

Monthly API meeting was conducted on 19th April, 2025 in Hotel Avatar, Attavar. The guest lecture on the day titled 'Two 1st in the category for better management of diabetes & CKM risk' was delivered by Dr. Sudeep K, Professor of Endocrinology, Father Muller's medical college, Mangalore. The session was chaired by Dr. Chakrapani M, Medical superintendent and Professor of medicine, Kasturba medical college, Mangalore.

Founder president of API D.K chapter Dr. B.H Krishnamurthy was honored on the coral jubilee celebration. Other founding members present on the occasion were Dr. Mohan Pai, Dr. Sundar Bhat, Dr. Narasimha Hegde, Dr. R L Kamath, Dr. M V Prabhu, Dr. P S Bhat & Dr. Mohammed Ismail.

Dr. B. H Krishnamurthy spoke on the occasion.
Dr. Muralidhar Yadiyal spoke about environmental hazards of using plastic bottled water.

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LUNG ULTRASOUND IN ARDS

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In the last two decades, Lung ultrasound (LUS) has occupied the centre stage and has become the fifth pillar of medical examination after inspection, palpation, percussion and auscultation for an Intensive care physician. LUS has become a very important tool for diagnosis, management and monitoring of patients with Acute Respiratory Distress Syndrome (ARDS). Besides its clinical utility, its low cost, short learning curve and portability make it an instant hit in the complex environment of the intensive care unit (ICU). LUS provides a "functional approach" that might impact the intensivist's decision-making ability after a patient's clinical evaluation and help in real-time management changes, such as, fluid therapy, adjustment of ventilatory setting, patient's position (supine vs prone), antibiotic management, chest drainage etc.

Historically, Daniel Lichenstein who is considered the "Father of Modern LUS", spear-headed the dawn of a new era in 1995 with the description of "**lung sliding**" for ruling out pneumothorax, "**comet-artefact**" for alveolarinterstitial syndrome, "**lung point**" an ultrasound sign specific for the diagnosis of pneumothorax, "**lung pulse**" as an early sign of complete atelectasis and dynamic air bronchogram as a sign of alveolar consolidation.

Examination in ARDS using LUS

Ultrasound examination of lungs involves the use of a phased array probe or curvilinear probe (Fig-1). A linear probe (Fig 2) is used for studying the pleural line morphology.

Fig 1: Curvilinear probe Fig 2: Linear probe

The lung fields are divided from 4 to 12 zones depending on which method of LUS is used. Most authors recommend the use of 12 zones model (Fig 3), which we will discuss in this article.

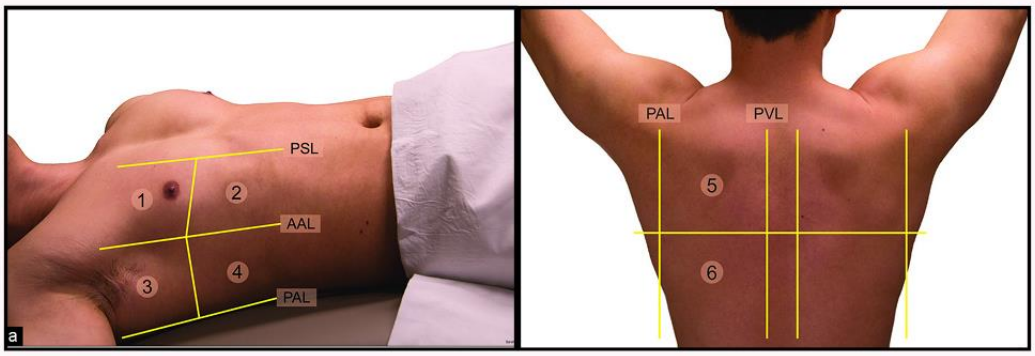

Fig 3: Zones in LUS. PSL- parasternal line; AAL- Anterior Axillary Line; PAL- Posterior axillary line; PVL- paravertebral line

The lung ultrasound is performed first in the longitudinal plane (cranio-caudal direction with probe marker pointing towards the head of the patient) which helps in visualizing a single intercostal space with ribs shadows on two sides of the acoustic window and the pleural line in between (bat sign) (Fig-4).

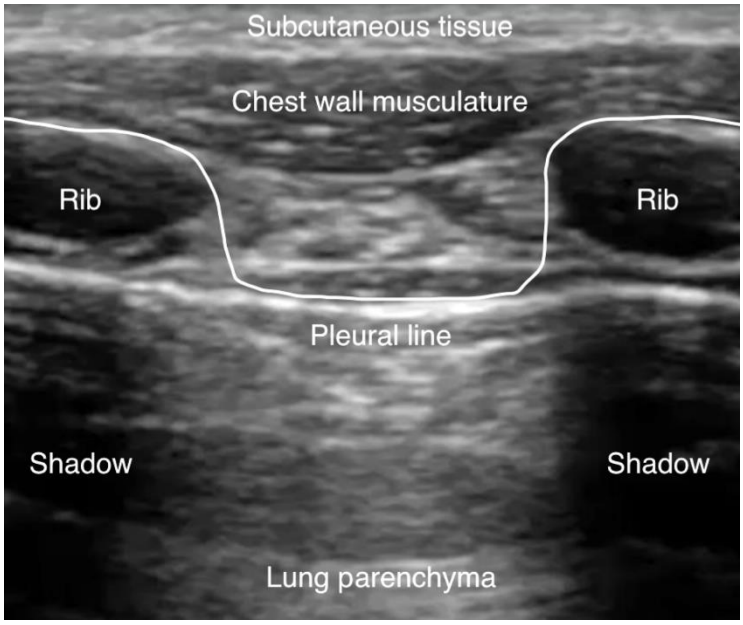

Figure 4: Normal lung parenchyma in longitudinal plane – "Bat sign".

Alternatively, a transverse plane view can be performed along the length of the ribs where in the rib shadows don't interfere with the images. However, a higher B line count may be seen in this view. The patterns seen on LUS is scored as below (Fig-5):

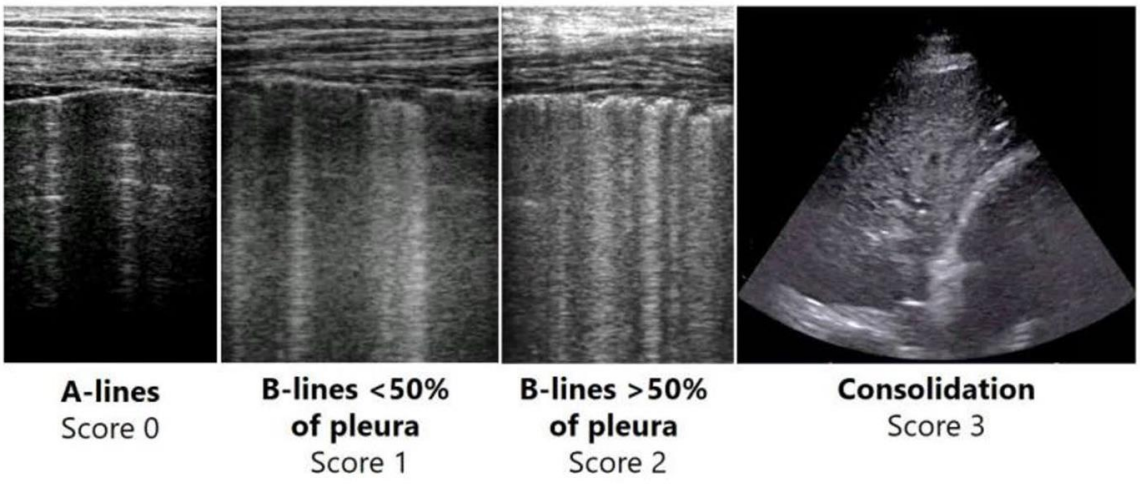

Figure 5: B line scoring in LUS

Diagnosis of ARDS

Diagnosis of ARDS with the help of LUS is not described in the Berlin's definition. However, the Kigali modification of the Berlin definition (Table 1) designed specifically for the diagnosis of ARDS in resource limited settings uses LUS as a diagnostic tool. With the Kigali modification, bilateral B-lines or consolidations on LUS were allowed to fulfil the imaging criteria for ARDS.

	Berlin Criteria	Challenges in Resource Poor Settings	Kigali Modification of the Berlin Criteria
Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms	None	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	$Pa_{O_2}/F_{I_{O_2}} \leq 300$	Scarcity of arterial blood gas diagnostics	$Sp_{O_2}/F_{I_{O_2}} \leq 315$
PEEP requirement	Minimum 5 cm H_2O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)	Scarcity of mechanical ventilators	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT	Scarcity of chest radiography resources	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic edema if no risk factor present)	None	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic edema if no risk factor present)

Table 1: Kigali Modification of Berlin definition for ARDS.

Differentiation between cardiogenic pulmonary oedema and ARDS can become challenging in the clinical context. LUS can provide a fairly sensitive diagnostic method to help in the differentiation. Pulmonary oedema of cardiogenic origin manifests as fairly symmetrical antero-lateral B-profile from apex to base and a thin pleural line with good pleural slide. However, ARDS presents with an interstitial syndrome and antero-lateral B profile from apex to base having asymmetric distribution with thickened pleural lines and **subpleural shredding** or reduced gliding in the context of spared A lines. LUS has a sensitivity of 97% and specificity of 95% in diagnosing cardiogenic pulmonary oedema with interstitial syndrome pattern.

Furthermore, transthoracic echocardiography as a part of Point of care ultra sound (POCUS) assessment can help in differentiating cardiogenic pulmonary edema from ARDS. There is good correlation between B-lines and Extravascular lung water (EVLW). The venous excess with ultrasound score (VExUS) evaluating lung, liver and kidney can also be added as an adjunct to determine if fluids can be administered to a patient or not.

LUS is also useful in ruling out pleural effusions, lung collapse and other pathologies for the hypoxia.

LUS for guiding management of ARDS:

Besides diagnosis, LUS can be used for monitoring and assessing response to treatment and ventilatory strategies in patients with ARDS. This is all the more relevant in very sick patients needing very high levels of ventilatory support, needing proning or ECMO where use of imaging modalities like CT scans may not be feasible. On serial LUS, changes in the images could suggest improvement or worsening of the lung as a response to therapy or progression of the disease respectively. A decrease in LUS-score may suggest lung recovery, while an unexpected increase in the same, may suggest progression of ARDS or super imposed infection.

The visualization of a linear-arborescent dynamic air bronchogram within a consolidation is highly specific for ventilator-associated pneumonia. After making a diagnosis, LUS or LUS-score variations can be used to follow up response to antibiotic therapy, response to Positive end expiratory pressure (PEEP), response to recruitment measures. The score is also useful to detect both global and regional variations in aeration for various facets of care including diagnosis, response to ventilatory modifications and response to treatment.

LUS can also help to predict success of extubation after a spontaneous breathing trial (SBT) where a worsening score before and after SBT with deaeration of lung predicts extubation failure.

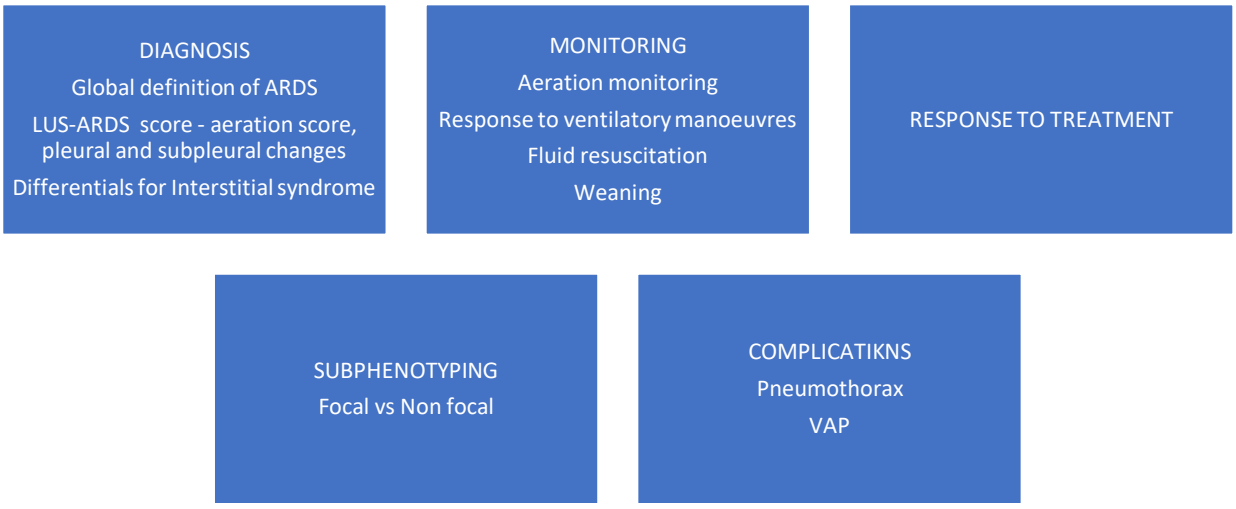

Figure 6: Summary of utility of LUS in ARDS

Conclusion:

LUS has made a drastic change in our approach to diagnose, monitor and assess response to therapy for patients with ARDS. Its short learning cover, portability, availability in resource limited settings and many more makes this the fifth step of clinical examination complementing our existing skill.

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PHARMACOTHERAPY IN ACUTE RESPIRATORY DISTRESS SYNDROME

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Acute Respiratory Distress Syndrome (ARDS) is characterized by dysregulated inflammation, accumulation and activation of leukocytes, platelets, uncontrolled activation of coagulation, and altered alveolar endothelial, epithelial barriers, leading to pulmonary edema.(1) Given its high incidence and devastating outcomes, decades of research have tried to establish methods to improve care for the patients with ARDS. Despite years of research and experience, care for ARDS remains supportive in nature and mortality remains high at 34-45%.(2)

As our understanding of the disease has evolved, several non-pharmacologic and pharmacologic interventions have been studied and tested. Non- pharmacologic measures mainly include lung protective ventilation strategies, and methods to improve fluid distribution in lungs. Pharmacologic strategies have targeted Ventilator- Associated Lung Injury (VALI)/ Self- Inflicted Lung Injury (SILI), dead space ventilation, inflammation, alveolar epithelial and capillary endothelial injury and dysfunctional fluid clearance.(3)

Neuromuscular blockade (NMB), corticosteroids, inhaled pulmonary vasodilators, vitamin C, β- agonists, statins, mesenchymal stromal cells, granulocyte- macrophage colony stimulating factors (GM-CSF), surfactant, interferon β- 1a, N- acetyl cysteine, inhaled heparin, are few among many other interventions that have been tested as pharmacological treatment options in ARDS. Among them, neuromuscular blockade, corticosteroids, and inhaled pulmonary vasodilators are widely available and used. This review focusses on evidence and utility for usage of these agents, with special emphasis on corticosteroids in ARDS.

Commonly Used Therapies	*Other Investigational Agents*
Neuromuscular Blockade	**Vitamin C**
Inhaled Pulmonary Vasodilators	**β- agonists**
Corticosteroids	**Statins**
	Mesenchymal Stromal Cells
	GM-CSF
	Surfactant
	Interferon β- 1a
	N- acetyl cysteine
	Inhaled Heparin
	Aspirin
	Neutrophil- Elastase inhibitors

Neuromuscular Blockade

Pathophysiologic Target/s:

1. Prevention of VALI/ SILI, Patient- Ventilator Asynchrony
2. Reduction in the release of inflammatory mediators

Beneficial Effects:

Vigorous spontaneous respiratory efforts in patients with severe ARDS may lead to worsening of lung injury through several mechanisms. Changes in pleural pressure with respiration are transmitted uniformly in normal lungs. However, in the injured lung, transmission of pleural pressure is non-uniform. Dependent areas of the lung are in close physical contact with the diaphragm. As the diaphragm contracts forcefully during vigorous spontaneous efforts, the dependent areas of the lung experience a more pronounced negative pleural pressure. The non-uniform distribution of pleural pressure results in air movement from the non-dependent to the dependent lung by the “pendelluft” phenomenon.(4) This intra-pulmonary movement of air leads to injury to the Dependent lung, one of the hallmarks of ARDS. A spontaneous respiratory effort may be triggered at the end of the inspiratory phase of a mechanical breath in some patients, through a phenomenon called “reverse triggering”, leading to patient-ventilator asynchrony. These harmful effects of spontaneous respiratory efforts in the injured lung are overcome with the use of NMB. Abolition of vigorous spontaneous efforts may thus prevent damage to

the injured lung. Abolition of spontaneous respiratory efforts may also reduce the oxygen consumption by decreasing the work of breathing and elimination of the resting muscle tone. Besides, improved patient-ventilator synchrony may allow safer, and more precise titration of tidal volumes and ventilation pressures.(5)

Possible Harmful Effects:

1. Critical Illness Polymyoneuropathy(6)
2. Deep Vein Thrombosis
3. Increased cardiovascular events
4. Exposure Keratitis
5. Awareness

Agents and Mode of Usage:

Cisatracurium: 15 mg of cisatracurium besylate rapid infusionàcontinuous infusion of 37.5 mg/ hour for 48 hours(7,8)

Evidence:

- ARDS et Curarisation Systematique (ACURASYS) trial(7) showed that in patients with moderate-to-severe ARDS, a strategy of 48 hours of deep sedation with muscle paralysis induced by an intravenous infusion of cisatracurium resulted in a lower incidence of barotrauma and higher adjusted overall survival at 90 days than deep sedation alone.
- Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial(8) was performed to reexamine the benefits of cisatracurium-induced paralysis in patients early after the onset of ARDS. The trial was stopped early for futility. The results were markedly different from those of the ACURASYS trial. In the ROSE trial, there was no between-group difference in the number of patients with barotrauma, and mortality at 90 days was virtually identical in the two groups (42.5% of patients in the intervention group and 42.8% in the control group died).
- The difference in findings between the trials have been attributed to depth of sedation achieved in the trials, likely inclusion of a more hypoxic patient in ROSE trial (P/F of <150 on PEEP ≥5 cm H_2O vs P/F of <150 on PEEP ≥8 cm H_2O in ROSE trial), shorter enrollment time in ROSE trial (Median Time of 16 hours [IQR 6-29 hours] vs 8 hours [IQR 4-16 hours] in ROSE trial).(3)
- Impact on mortality outcomes- inconclusive.

Bottom Line:

Routine use of neuromuscular blockade is not recommended. Neuromuscular Blockade is a reasonable approach in preventing VALI/ SILI and ventilator- patient dyssynchrony, from a physiologic perspective only after conventional strategies of sedation and analgesia. Given that both ACURASYS and ROSE trials have not reported long term neuromuscular complications, easier application of prone ventilation strategies with use of cisatracurium, a tailored approach of using neuromuscular blockade in patients with severe ARDS, and vigorous spontaneous efforts, is acceptable.

Inhaled Pulmonary Vasodilators

Pathophysiologic Target/s:

1. Reduction of ventilation- perfusion mismatch
2. Reduction of dead space ventilation

Beneficial Effects:

In patients with ARDS, at microscopic level, both thromboembolic and endothelial injury resulting in decreased pulmonary blood flow and hypoxic vasoconstriction is described.(9) This results in ventilation- perfusion mismatch and increased dead space ventilation. Inhaled Nitric Oxide (iNO) and Prostacyclins have been used as therapeutic agents with goals of improving oxygenation and reducing dead space ventilation in patients with ARDS.

iNO, after diffusion through the alveoli into the pulmonary vasculature, and vasodilation through cGMP mediated smooth muscle relaxation, results in improved perfusion to ventilated areas of the lung. This results in improved ventilation- perfusion matching. Prostacyclins act on G- protein coupled receptors in the pulmonary vasculature, increase cAMP and result in vascular smooth muscle relaxation, thereby improving oxygenation.(10,11)

Possible Harmful Effects:

1. Formation of reactive nitrogen and oxygen species, especially when used with higher oxygen concentrations
2. Methemoglobinemia
3. Hypotension
4. Renal Failure

Agents and Mode of Usage:

5 ppm of Nitric Oxide, preferably administered into the inspiratory limb of ventilator tubing, as near to the patient as possible.(12) PGE1 (alprostadil) 20 µg with normal saline nebulized over 30 minutes.(13) PGI_2 (epoprostenol) as a 20,000 ng/mL solution and nebulize at a rate of 8 mL/hour; titrate down based on clinical response by reducing

the concentration to 10,000 ng/mL while continuing to nebulize at a rate of 8 mL/hour.(14) Continuation of these agents are based on clinical response (10-20% increase in P/F ratio),

Evidence:

- iNO- Meta-analysis reported that there no beneficial effects: despite signs of oxygenation and initial improvement, and iNO did not appear to improve survival and might be hazardous, as it may cause kidney function impairment.(15)
- Prostacyclins- Meta- analysis included 1 randomised controlled trial in adults that reported a trend towards improved blood oxygen levels, for participants who were treated with alprostadil (prostaglandin E1). But a clear advantage of the use of aerosolized prostacyclin in critically ill adults with low blood oxygen levels could not be identified as mortality data was not provided.(13)

Bottom Line:

Inhaled Pulmonary Vasodilators, though result in improved oxygenation, have failed to demonstrate tangible improvements in mortality and other outcome measures. They may have some usefulness in patients with concurrent right ventricular failure, or as a temporizing measure for patients requiring transportation, or as a short-term rescue therapy for patients with refractory hypoxia before initiation of extracorporeal support. Their routine use is not recommended.(3)

Corticosteroids

Pathophysiologic Target/s:

1. Inflammation

Beneficial Effects:

ARDS is characterized by an early, exudative phase with increased capillary permeability, plasma extravasation, and leukocyte infiltration. This early phase is often followed by the proliferative and fibrotic phases, with continued

inflammatory reaction.(16) Given the potent anti- inflammatory action of corticosteroids, they have been studied with a substantial heterogeneity of timing, dosing and duration. Appropriate timing, dosing and duration results in improved respiratory physiology, including better oxygenation, higher respiratory system compliance, and lower requirement for vasopressor support. Also, higher ventilator-free days. There have been no reports of increased incidence of super- infections.

Possible Harmful Effects:

1. Dysglycemia
2. Increase in neuromuscular weakness
3. Requirement of re- initiation of ventilatory support
4. Increased mortality when used in patients with >14 days after ARDS onset

Agents and Mode of Usage:

Methylprednisolone:

Study	Timing	Dosing	Duration
Meduri 2007(17)	<72 hours of ARDS onset	1 mg/kg loading dose; 240 mL normal saline at 10 mL/h of 1 mg/kg/day daily infusion	14 days; followed by halving of doses on day 15, 22 and 26, up to day 28
Steinberg 2006(18)	7-28 days of ARDS onset	2 mg/kg loading dose; 50 mL of 5% dextrose in water of 0.5 mg/kg; daily infusion every 6 hours	14 days; followed by 0.5 mg/kg every 12 h for 7 days, then tapering of dose over 4 days

Dexamethasone: 20 mg IV once daily for 5 days, then 10 mg IV once daily for 5 days(19)

Evidence:

- Early/ High Dose/ No taper (Methylprednisolone- 30mg/kg diluted in 50 mL of 5% dextrose administered over 30 minutes, 4 such doses, in 24 hours): No difference in mortality or reversal of ARDS.(20)

- Early Low Dose/ Long Duration/ Gradual Taper (Within 72 hours of ARDS onset, Methylprednisolone- 1 mg/kg loading dose; 240 mL normal saline at 10 mL/h of 1 mg/kg/day daily infusion, 14 days): Decreased duration of mechanical ventilatory support, ICU length of stay, and mortality.(17,19)

- Late/ Low Dose/ Long Duration/ Gradual Taper (7- 28 days after ARDS onset, 2 mg/kg loading dose; 50 mL of 5% dextrose in water of 0.5 mg/kg; daily infusion every 6 hours, 14 days): improved respiratory physiology, including better oxygenation, higher respiratory system compliance, and lower requirement for vasopressor support, more ventilator-free days. No difference in mortality at 60 and 180 days. Higher mortality in patients enrolled after 14 days of ARDS onset. Higher incidence of neuromuscular weakness.(18)

Bottom Line:

Early initiation of low dose corticosteroids in patients with ARDS is beneficial. Late initiation (>14 days) is harmful. The incidence of neuromuscular weakness is higher, especially if used in conjunction with neuromuscular blockade.

***Take home points*:**

1. Routine use of neuromuscular blockade is not recommended. Their use is reserved for patients with severe ARDS and ventilator dyssynchrony, only after sedation and analgesia are optimized.
2. Inhaled Pulmonary Vasodilators as of now lack evidence for mortality benefit but can serve as rescue agents for severe hypoxemia, especially with concurrent pulmonary arterial hypertension.

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MASTERING THE ART OF PRONE VENTILATION

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Background:

Charles Brayn in 1974 proposed prone ventilation as a manoeuvre to improve ventilation of the dorsal part of lung in patients with acute respiratory distress syndrome (ARDS). Two years later case series showed improvement in oxygenation after prone ventilation. The trials conducted in 2001 and 2004 have shown improvement of oxygenation with prone ventilation. PROSEVA (Prone Positioning in Severe Acute Respiratory Distress Syndrome), a landmark study in 2013 showed mortality benefit among moderate to severe ARDS patients who were prone ventilated for at least 16 hours. Study showed improvement in not only oxygenation but also lung mechanics after prone ventilation. Over the last decade, prone ventilation has solidified its role in the management of ARDS patients. Recent pandemic of COVID-19 also taught us the benefits of awake proning among non-intubated ARDS patients. This article summarizes the physiological rationale behind prone ventilation, the indications, contraindications, and future directions.

Physiology of prone ventilation:

In supine position dorsal pleural pressure is increased by the weight of the ventral lung, heart and abdominal viscera. This compression results in reduced transpulmonary pressure in dorsal lung region. ARDS leading to interstitial oedema also increases weight of the lung, thereby increasing pleural pressure gradient between dorsal

and ventral lung regions. This results in poor ventilation of dorsal lung region. Following physiological benefits are seen with prone ventilation

1. **Improved Oxygenation**: Prone ventilation facilitates better distribution of ventilation to the dorsal lung regions, which are typically more affected in ARDS. By reducing the compression of these regions and promoting recruitment of collapsed alveoli, prone positioning enhances oxygenation, leading to improved arterial oxygen levels and oxygen delivery to tissues.

2. **Enhanced Ventilation-Perfusion Matching**: ARDS often results in areas of the lungs with reduced ventilation but maintained perfusion, leading to ventilation-perfusion mismatch and hypoxemia. Prone positioning helps to optimize this matching by redistributing blood flow to better-ventilated lung regions, thereby improving overall lung function and gas exchange efficiency.

3. **Reduction in Ventilator-Induced Lung Injury:** Traditional supine ventilation can exacerbate lung injury in ARDS patients due to increased pressure on dependent lung regions. Prone ventilation redistributes this pressure, reducing the risk of ventilator-induced lung injury, including volutrauma, barotrauma, and atelectrauma. This can ultimately mitigate further damage to the lungs and contribute to lung-protective ventilation strategies.

4. **Prevention of Ventilator-Associated Pneumonia (VAP):** Prone positioning facilitates drainage of respiratory secretions, reducing the risk of retained mucus and bacterial colonization in dependent lung regions. This can help prevent ventilator-associated pneumonia, a common complication in mechanically ventilated patients with ARDS, thus potentially reducing the duration of mechanical ventilation and ICU stay.

5. **Improved Homogeneity of Lung Ventilation:** Prone ventilation promotes more uniform aeration of the lungs by reducing the gravitational gradient of lung density. This helps to homogenize ventilation across different lung regions, mitigating areas of atelectasis or consolidation and improving overall lung compliance and respiratory mechanics.

6. **Potential Mortality Reduction:** Clinical trials, including the landmark PROSEVA trial, have demonstrated a significant reduction in mortality rates among ARDS patients treated with prone ventilation compared to those receiving supine ventilation. This suggests that prone positioning may confer a survival benefit in severe ARDS, making it a crucial intervention in the management of critically ill patients.

Indication for prone ventilation:

1. Severe Hypoxemia: Mild ARDS with Pao2/FiO2 ratio >200 mm hg has not shown mortality benefit by prone ventilation.

In moderate ARDS, especially when PF ratio is <150 mm Hg prone ventilation is encouraged as an elective strategy rather than only using it as rescue strategy.

2. Hypercarbia: Prone ventilation has shown benefit in subset of patients with moderate to severe ARDS and hypercarbia.

3. Acute Cor- pulmonale: ARDS can lead to acute cor pulmonale resulting in hemodynamic compromise and organ dysfunctions. Hypoxemia, hypercapnia, high driving pressure and plateau pressure ≥27 cmH2O in severe ARDS are the risk factors for acute cor pulmonale. Prone ventilation helps in unloading right ventricle by improving cardiac index and heart rate.

Method

1. Preparation:

a. Ensure that patient is relatively stable hemodynamically.
b. Deep sedation, preferably paralysis with a muscle relaxant is preferable to avoid discomfort and risk of self- extubation.
c. Minimum of five members, one exclusive to ensure airway is safeguarded are required while turning the patient.
d. Necessary pillows/support to maintain cushioning to chest and pelvis region to be arranged in advance.
e. Lines and tubes to be secured and ventilator settings to be adjusted to maintain best possible oxygenation.

2. Positioning:

a. Carefully turn the patient onto their stomach while maintaining cervical spine alignment and ensuring safety.
b. Position the patient with their arms extended forward or alongside their body, depending on comfort and accessibility for medical interventions.
c. Utilize supportive devices such as pillows, foam wedges, or specialized prone positioning beds to maintain proper alignment and reduce pressure points.
d. Face and eyes to be safeguarded with head- rings to avoid pressure effects.

e. Second hourly change in position of head is necessary to prevent pressure on one side.

3. Securing Lines and Tubes:

a. Secure invasive lines (e.g., central venous catheter, arterial line) and tubes (e.g., endotracheal tube, nasogastric tube, urinary catheter) to prevent displacement or obstruction during prone positioning.

b. Ensure the patency of airway by suctioning post prone position.

c. Monitoring to be continued with pulse oximeter, arterial blood pressure.

d. ECG leads to be connected over back and monitoring to continue.

4. Ventilator Adjustment:

a. Lung protective strategy with adequate PEEP and low tidal volume as per ARDS protocol to maintain Plateau pressure (Pplat) below 30 cm of H_2O.

5. Monitoring during the prone ventilation:

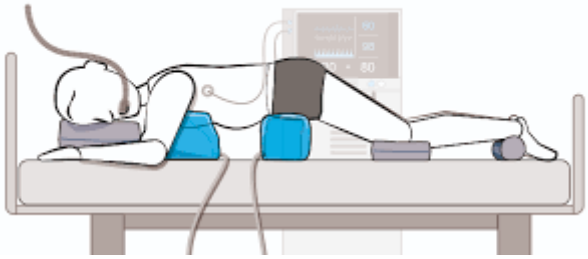
a. Arterial blood gas and SpO_2 monitoring to assess clinical response to prone ventilation at regular intervals.

6. Duration and Rotation:

a. Prone ventilation sessions typically last for several hours to maximize the physiological benefits while minimizing the risk of complications.

b. Rotate the patient back to the supine position at regular intervals (e.g., every 16 to 24 hours) to allow for repositioning, skin assessment, and nursing care.

The following link published by NEJM group describes the method of prone ventilation in detail- https://youtu.be/E_6jT9R7WJs?si=Egrz8Z51M8ztDXbk .



Picture 1: positioning a patient in prone ventilation.

Contraindications

Absolute contraindication for prone ventilation is unstable spinal fracture.

Relative contraindications include unstable hemodynamics (if patient on multiple vasopressor support, arrhythmias), facial trauma or open eye injuries, increased Intracranial pressure. However, in patients with severe ARDS hypotension could be secondary to hypoxia itself which may improve after prone ventilation. After ensuring adequate flow of vasopressors through central venous access, prone ventilation can be attempted in hypotensive patients. Intra cranial pressure (ICP) monitoring can be offered for patients who are at risk of increased ICP and require proning. Full term pregnancy might pose significant challenge for prone ventilation. This will need modification during positioning to avoid compression of gravid uterus and will need continuous foetal monitoring. Open abdomen/abdominal compartment syndrome also relative contraindication for prone ventilation. Decision of proning should be taken on case-to-case basis whenever there are relative contraindications.

Complications:

1. Hemodynamic instability: Hypotension, arrhythmia management becomes difficult during prone ventilation. Kinking of venous access, compression of lines could lead to worsening of hemodynamics. Improper positioning could also impair venous return and impact hemodynamics.
2. Endotracheal Tube Displacement: Prone positioning may increase the risk of endotracheal tube displacement or obstruction due to changes in neck position and pressure on the airway. Regular assessment of tube position, securement, and patency is necessary to ensure adequate ventilation and prevent accidental extubation.
3. Pressure Injuries: Prolonged pressure on bony prominences and soft tissues during prone positioning can lead to the development of pressure injuries, particularly over the face, chest, pelvis, and extremities. Proper padding, positioning devices, and frequent repositioning are essential to prevent pressure-related skin damage and maintain skin integrity. Brachial plexus injury could result in if proper position is not maintained.
4. Facial Edema and Eye Complications: Patients in the prone position may experience facial edema, particularly around the eyes and dependent areas of the face. This can lead to discomfort, impaired vision, and corneal abrasions. Eye protection, lubrication, and regular assessment of ocular integrity are important to prevent eye complications during prone ventilation.
5. Improper positioning also can lead to barotrauma, volutrauma and thereby can increase risk of ventilator associated lung injury.

6. Gastrointestinal Disturbances: Prone positioning may exacerbate gastric distension, gastroesophageal reflux, and aspiration risk, particularly in patients with impaired gastric motility or elevated intra-abdominal pressure. Adequate gastric decompression, prokinetic agents, and elevation of the head of the bed can help mitigate gastrointestinal complications during prone ventilation.

Responders and Non- responders- how to identify?

Not all patients respond to prone ventilation. Immediate improvement in plateau pressure (in volume control ventilation) or tidal volume (in Pressure control ventilation) post proning could indicate that patient may likely respond to prone ventilation. Delayed responders are those who show response for proning at the end of 16- 20 hours.

Future considerations in Prone ventilation:

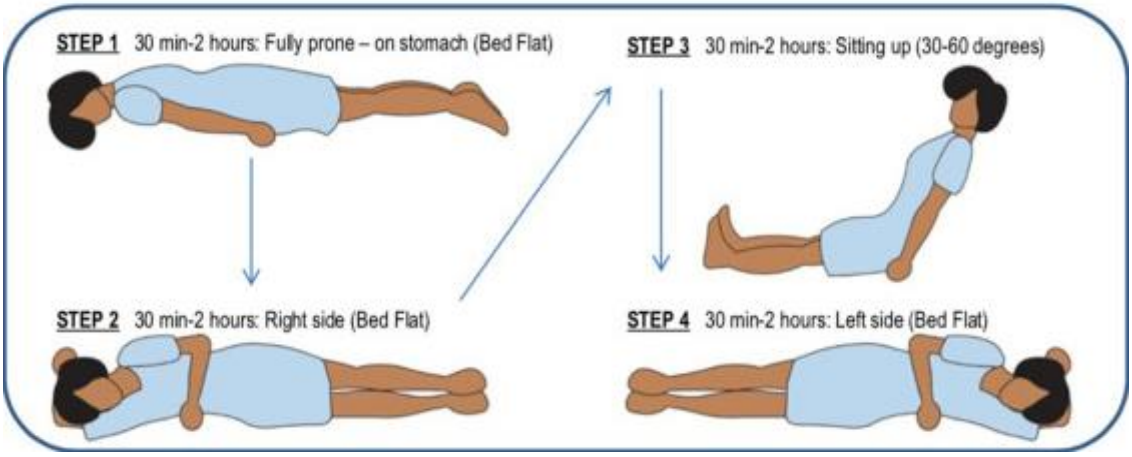
1. Proning on ECMO

PRONECMO Randomized Clinical Trial published in 2023 concluded that prone ventilation showed no significant benefit among patients who are undergoing VV ECMO for severe ARDS. There was no reduction in ECMO days between patients who were prone ventilated compared to who were not proned. Study had included predominantly COVID ARDS patients, hence generalising this for all ARDS may not be appropriate. Timing and duration of proning during VV ECMO is still not clear and needs studies in the future to determine the same. Oxygenation improvement has been demonstrated in prior studies. Although prone ventilation is technically difficult, it's not impossible and deemed to be safe.

2. Awake proning:

Mild to moderate ARDS where patient is managed with high flow nasal cannula oxygen could be right candidates for awake proning. COVID ARDS showed definite improvement in oxygenation with the above manoeuvre among non-intubated patients preventing ICU transfer.

To conclude, prone ventilation is safe and rewarding in moderate to severe ARDS. Early initiation before the onset organ dysfunction can help in early recovery. Prone ventilation, when used wisely and correctly can be a game changer in the treatment of ARDS.



Picture 2: Steps of awake Prone ventilation.

Conclusion:

To conclude with, prone ventilation when initiated early in patient with Moderate to severe ARDS does have mortality benefit. Decision regarding the initiation of the same has to be case driven.

Take home message:

1. Prone ventilation facilitates better distribution of ventilation to the dorsal lung regions, which are typically more affected in ARDS.
2. In moderate ARDS, especially when PF ratio is <150 mm Hg prone ventilation is encouraged as an elective strategy rather than only using it as rescue strategy.
3. Unstable spinal fracture is absolute contra- indication for prone ventilation.
4. Future RCTs are necessary to prove the mortality benefit of awake proning in non- intubated patients.

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TELE ICU – AN INVENTION AND A NECESSITY TO STAY ON

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The great Sir Albert Einstein has said "*Necessity is the mother of all inventions*." The inventions borne out of such necessities may not necessarily be useful once such necessity cease to exist. The COVID 19 pandemic is one such necessity which had brought about sea of changes in many walks of human lives. The very magnitude of the problem and the nature of spread made the medical fraternity to invent and adopt things that were necessary to cope with the needs and demands of humanity. The COVID pandemic had put public health infrastructure under a lot of stress. The material resources such as oxygen delivery systems, High Flow nasal Oxygen (HFNO), Ventilators, ICUs were made available to meet the needs of increasing demand. However, making available the trained human resource, such as intensivists, anaesthetists, pulmonologists, ICU trained nurses, to use these physical resources, posed a significant challenge. This necessity made public health administrators to seek the help of TELE ICU.

This flagship programme was started during the first wave of COVID pandemic in April 2020 by Ministry of Health and Family welfare, Govt of Karnataka, of which, I was a part of. The District Hospitals were converted into COVID hospitals to manage the Cat C / Severe COVID patients. These patients were sick and required at least oxygen as a part of management along with other medications and close monitoring in ICUs/HDUs. The programme was conceptualised on "**THE HUB & SPOKES"** model. The hub being state head quarter at Bangalore and spokes being the District COVID hospitals.

TELE ICU ROUNDS

The Intensivist/anaesthetist/pulmonologists of the hub collected the necessary data of all the COVID patients in ICU the previous night and would take the rounds with the physician/nodal officer in charge of the ICU through zoom meetings. The rounds were reciprocal in nature. The video calls enabled the hub specialists to even see the patients, monitor the vitals, and view ventilator graphics in real time thus, aiding to make necessary decisions in consensus with the specialists. Of course, video calls made in the handheld devices had their limitation such as poor visibility and poor connectivity. These Tele ICU rounds enabled the state administrators to realise real time infrastructural shortcomings in these COVID hospitals as they were also part of supervisory team of the hub and take necessary actions to fulfil those shortcomings with quick actions instead of waiting for the issue to reach them through proper channels. The average duration of the Tele ICU rounds was 1 hour – 1.5 hour long during peak of COVID waves. The discussions included intubating the COVID patients from NIV, prone ventilations of intubated patients, requirement of dialysis and the plan of dialysis by nephrologists, use of newer drugs like mono- cloncal antibodies.

The Tele ICU rounds slowly became platforms of sharing experiences of various spoke hospitals and learning platform for other spoke hospitals and even for the specialists of the Hub facility too!!! The discussions held in Tele ICU rounds were promptly conveyed to the patient bystanders as a part of counselling, which helped in instilling a feel of confidence and trust in those anxious and worried souls. The Hub facility even took efforts to train the staff nurses in ICU monitoring and nursing procedures to update and hon their skill sets. As it was carried out for almost 1.5 years, it helped a sense of camaraderie and fellowship among all the hub and spoke specialists. During the fag end of the COVID pandemic i.e. the so called 3 wave it became a platform of peer learning.

The way forward

The public health facility in Karnataka has 150 SDH/taluka hospitals, 180 CHCs (Community Health Centres) which post COVID have enormously upgraded their physical infrastructure. Thus, these institutions have large untapped potential which can cater to the community especially in a future pandemic scenario. However, due to various reasons the human resource upgradation in these institutions may take time. The state government is already on its way to tap this potential by continuing the Tele ICU HUB & Spoke model of connectivity. The District Hospitals which were spoke hospitals are now being made the hub hospitals, with all their previous experience and continue the Tele ICU rounds with spoke hospitals which are as of now only SDH/TH. The technology used for tele ICU rounds are being upgraded with use of 360^0 camera with audio outputs and software to collect and maintain data of spoke hospital including radiological and laboratory data.

As with any invention borne out of necessity, the TELE ICU is being pursued further with refinements and advancements. As the private health players are venturing into AI in health care delivery, it is only prudent for the public health system to upgrade and use the technology for the betterment of the people.

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1. 17^{th} issue, National Health Profile 2022, GOI

THE HEART OF THE PANDEMIC

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I heard the phone ring again for the 10th time in the last hour. It was Monday morning on December 28th, 2019. I was driving from our University hospital to the Cancer centre to see patients. I had just arrived in Tampa, Florida from the Society of Hospital Epidemiology meeting in Washington the night before. I recall reading on the flight, the article on a novel coronavirus that was causing respiratory illnesses in parts of China. Little did I know that by the time I landed, we would be heading into a hurricane of panic and chaos! I slid the button on my phone and placed it on my ear while the charging cord of the phone tugged back on it. I said “Hello” while disconnecting the charger, half tired and half impatient.

I heard back “Dr. Lakshmi, this is the Emergency Room. We have a patient who just returned from China and is feeling fatigued with shortness of breath. We will wait for you to go in and let us know what the next steps should be. We have informed the infection control department and they are here getting the isolation cart ready. Nobody will be going in the room until you come and see the patient”. I could sense the uncertainty and overwhelm in her voice. I said “Ok, I will be there in 15 minutes” as I pressed the turn signal to make the U turn and drive back to the main University hospital.

As I walked into the ER, the nurse walked with me towards the corner room the patient was located in. I saw my infection control nurse standing next to the isolation cart. He watched me as I put on my isolation gown, shoe

covers, hair cover, mask, face- shield and gloves, giving me directions and corrections. He gave me the thumbs up after I had finished wearing my gear. I took a deep breath as I entered the ante room. An anteroom is a small room or an entryway that leads into a larger space. These rooms are often used in hospitals/clinics to protect patients and staff from contaminants. I knocked on the door and saw a small woman in her early 40s sitting up anxiously. She had just arrived from China.

At that time the official guidance from CDC was to categorize patients into high risk/low risk cases depending on their travel history / whether they had been in Hubei province/ whether they had been in touch with anyone who had symptoms of the novel coronavirus. Her travel bus was diverted on the outskirts of Hubei province and rest of the screening questionnaire was negative, so she didn't meet criteria for further testing. As I walked out into the ante room, I saw my infection control nurse patiently waiting outside the door watching as I carefully doffed my gear. As I walked out into the ER hallway, the patient's medical team debriefed on the case, infection control procedures, nursing procedures and next steps. I remember the faces of the medical team like it was yesterday, the courage, the humanity and the camaraderie of these brave people inspires me every day.

In the early days of COVID, trying to get a test that would actually detect COVID was next to impossible! Fortunately, we had one of the best labs and leaders in the lab who were able to validate the test in house. Thus, we were able to offer testing to suspected cases early on before the COVID testing was widely available. We were even able to offer testing to local hospitals in times of dire need. The ability to test early helped us adjudicate cases early and prevent clogging up rest of the hospital flow, especially for non-COVID related care.

We registered for multiple clinical trials assessing the efficacy of monoclonal antibodies and antiviral. Soon there would be release of I V Bamlanivimab and oral Remdesvir both of which formed the major part our therapeutic arsenal for prevention and treatment. The COVID management guidelines changed every few days which was challenging for the physicians, nursing staff, hospital administration and patients alike. We started our day with multidisciplinary rounds in the COVID units to provide a team approach and facilitate conversations/ disposition planning among multiple teams. In the early days when no visitation was allowed the healthcare teams provided additional phone calls to family members of each patient to provide updates. Our multidisciplinary team approach results in us having one of the lowest lengths of hospital stay (2nd percentile) and mortality (16th percentile) for the COVID patients in the country.

Fortunately, in December 2020 COVID-19 vaccines became available to healthcare workers which was a welcome relief. However, with it came the mistrust, the misdirected anger towards health care workers and tribal polarized

grouping between people who supported universal vaccination and those who didn't. It was perhaps one of the hardest times to be in the healthcare field. Within a few weeks we had gone from being called heroes to being called anarchists.

I saw first-hand people die for their beliefs. I held hands and spent many last hours with dying patients who had refused to get vaccinated and anguished health care team that was exhausted and felt injured. This conflict probably highlights at its core an individual's autonomy over their body and their ability to choose for themselves, which, rightfully so, rubs up against the communal conscience. Where does individual autonomy to choose for their body end and the good of the collective social conscience begin?

This pandemic has exposed our strengths and our vulnerabilities, but most of all it left a state of disconnect in its wake that is yet to heal. The world's largest and longest study on human happiness found that being in connected relationships is the biggest predictor of human wellbeing. The COVID- 19 pandemic tested every aspect of human existence, none more importantly than our ability to stay connected to one another in times of duress. My hope is that, in some ways, this destructive force of the pandemic makes us take a deeper look at our collective human conscience and ask some fundamental questions that will lead to creation of more cohesive, accepting community of our powers and perils.

UNDERSTANDING THE LUNG PHENOTYPES OF ARDS

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Importance of phenotypes:

ARDS is a clinical syndrome characterised by acute hypoxemic respiratory failure with Pa02:FIO2 <300 and bilateral pulmonary opacities not fully explained by cardiac failure or volume overload (1). ARDS is syndrome with a wide variety of aetiology and pathologies, leading to complex biological and clinical heterogeneity. For these reasons, there are limited therapies for ARDS, which has a high mortality rate. Under recognition is predominantly due to clinical heterogeneity with diverse triggers and durations of respiratory failure. This has contributed to the failure of experimental therapies in randomised controlled trials for the successful discovery of new treatments (2). Even with decades of research on ARDS since its first definition in 1967, therapeutic interventions reducing mortality are limited. There is a paucity of practice-changing discoveries.

Phenotype is a clinical entity determined by genotype and influenced by environment. Phenotypes encompass subsets or subtypes characterised by their natural history, clinical and biochemical features and response to treatment.

Novel approaches to combat heterogeneity by targeting homogenous subgroups or phenotyping are sought for ARDS. patients. Phenotyping into homogenous subgroups would likely promote the identification of effective therapies. Molecular phenotyping of melanoma has led to prolonged survival (3). Gene mutation typing in breast

cancer patients, and biomarker-based phenotyping of eosinophilic asthma patients has led to effective targeted therapies (4). Research on this approach to treating ARDS could shift protocolised care to precision medicine.

Compared with decades of research in "classical ARDS", clinical trials in COVID19 acute respiratory distress syndrome (ARDS)-CARD syndrome (CARDS), used a uniform trigger and achieved greater success with effective therapies within short span of time. Most importantly, steroids were used for moderate to severe CARDS (5). This finding provides important insights for further research on subgroups of patients with classical ARDS. Even within CARDSs, the biological response is heterogeneous.

The sub phenotypes of ARDS can be broadly classified into three phenotypes viz.

1. Physiologic phenotypes
2. Biologic phenotypes
3. Clinically derived phenotypes

The FDA recommends prognostic and predictive enrichment strategies in clinical trials to enhance treatment efficacy (6). Selecting sub- phenotypes of patients at higher risk for poor outcomes for enrolment in clinical trials is called **prognostic enrichment.** The selection of patients who are more likely to respond to a given therapy due to the mechanism of benefit is called **predictive enrichment.**

Understanding the various phenotypes would aid in moving from one size fits all to more tailored therapies.

PHYSIOLOGIC PHENOTYPES

Many physiological phenotypes have been identified and targeted for managing ARDS. The **PaO2:FiO2** ratio a common and age-related physiological strategy, stratifies ARDS into mild, moderate and severe ARDS. This is one of the prognostic enrichments strategies. Mortality increases as the PaO2:FiO2 ratio decreases.This does not need expert interpretation.

The ACCURACYS trial of early continuous neuromuscular blockade and the PROSEVA trial of prone ventilation targeted patients with moderate to severe ARDS (PaO2:FiO2 ratio<150 mm Hg).

Dead space ventilation and driving pressure are other physiological phenotypes (7).

Physiological phenotypes are limited in that they are dynamic. For example, the application of high PEEP could shift a patient from one subgroup of severe ARDS to another.

BIOLOGIC PHENOTYPES IN ARDS

There is growing interest in the identification of biologic sub- phenotypes**. Genomic transcriptomic and metabolomic factors** have been studied. Plasma protein biomarkers are well studied and include markers of systemic inflammation, epithelial injury and endothelial injury.

The baseline level of soluble receptor for advanced glycation end products (sRAGE), a marker of endothelial injury, is an independent predictor of mortality at 90 days (8).

Both baseline and rising IL-18 are associated with increased mortality in patients with sepsis-induced ARDS (9).

Hyper-inflammatory and hypo- inflammatory phenotypes are described in ARDS, and the hyperinflammatory phenotype is characterised by exaggerated inflammation and is associated with an increased incidence of shock, multiorgan failure and increased mortality.

Biologically driven ARDS phenotypes are limited by the inability to be quantified at the bedside, and these phenotypes are dependent on research methods.

CLINICALLY DERIVED PHENOTYPES IN ARDS

The risk factors leading to ARDS, type of injury (direct/indirect), and time course of ARDS radiographic patterns of pulmonary infiltrates are all clinical sub- phenotypes with distinct characteristics.

Trauma-related ARDS patients have better outcomes than non-trauma ARDS patients (10).

Pulmonary and extrapulmonary ARDS have distinct physiological and radiological patterns.

Table1: Differences between pulmonary and extra pulmonary ARDS.

	DIRECT INJURY/ PULMONARY ARDS	INDIRECT INJURY EXTRAPULMONARY
Ground glass opacification/ Consolidation	Evenly distributed	Uneven; GGO> Consolidation
Stiffness	Lungs	Chest wall
Recruitability	??Less	Better
Biological patterns	Markers of epithelial injury >markers of endothelial injury	Markers of endothelial injury>epithelial injury

Radiographic patterns of pulmonary infiltrates can be focal or no- focal. Along with physiological and biochemical subtypes, these subtypes have been classified into homogenous patterns and prognoses. The MURRAY lung score and RALE score include radiographic patterns to stratify the severity of lung injury. The RALE has a predictive ability with an AUC of 0.82 (11).

Misclassification is one of the inherent challenges with clinical phenotyping.

CONCLUSION

Very few strategies have improved the survival of patients with ARDS (e.g., low tidal volume-ARMA (NEJM 2000) and prone ventilation in severe ARDS-PROSEVA (2013 NEJM)). Mortality remains very high. In the last decade, the scientific community has realised that ARDS is heterogeneous and that the concept of one size fits all does not hold good. Several novel methods have emerged to identify meaningful subgroups. Overcoming this complexity involves identifying homogenous phenotypes and tailoring targeted therapies. Precision medicine with awareness of phenotypes and research comprising combinations of physiologically, clinically, and biologically derived phenotypes may impact future clinical trials and can enhance our understanding of the disorder, with potential future clinical implications.

Take Home Message

1. Identifying the sub- phenotypes in ARDS will help in tailoring the treatment and make it more individualized.
2. As in other disease processes, precision medicine is the way forward even in ARDS management.
3. Phenotyping helps in prognostic and predictive enrichment of therapies offered in ARDS.

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3. Phenotypes in ARDS: Moving towards Precision Medicine: Pratik Sinha, Current opinion inthe CCM: 2019

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GUIDANCE FOR AUTHORS AND CONTRIBUTORS

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