**Objectives**

- Describe the clinical features and diagnosis of ALI / ARDS
- Review the epidemiology, pathophysiology and etiology of ALI / ARDS
- Review supportive care and oxygenation in ALI / ARDS
- Mechanical ventilation strategies for ALI / ARDS patients
- Novel therapies for the treatment of ALI / ARDS

**What is ARDS?**

- Asbaugh, Bigelow & Petty described ARDS as: "A syndrome of acute respiratory failure in adults characterized by non-cardiogenic pulmonary edema manifested by severe hypoxemia caused by right to left shunting through collapsed or fluid-filled alveoli."

- The Berlin Definition: "An acute, diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight, and a loss of aerated tissue."

**ALI vs ARDS**

- Acute Lung Injury (ALI) is a term used for patients with significant hypoxemia (PaO2 / FiO2 < 300)

- Acute Respiratory Distress Syndrome (ARDS) is a subset of ALI patients with severe hypoxemia (PaO2 / FiO2 < 300)
What is ARDS?

- Cytokines recruit neutrophils to the lungs, where they become activated and release toxic mediators (e.g., reactive oxygen species and proteases) that damage the capillary endothelium and alveolar epithelium.

- Damage to the capillary endothelium and alveolar epithelium allows protein to escape from the vascular space.

What is ARDS?

- In normal, healthy lungs there is a small amount of fluid that leaks into the interstitium. The lymphatic system removes this fluid and returns it into the circulation keeping the alveoli dry.

What is ARDS?

- ARDS is a consequence of an alveolar injury which produces diffuse alveolar damage. The injury causes the release of pro-inflammatory “cytokines”.

- Cytokines are substances that are secreted by the immune system which carry signals locally between cells, and thus have an effect on other cells. They are a category of signaling molecules that are used extensively in cellular communication.

What is ARDS?

- The oncotic gradient that favors resorption of fluid is lost and fluid pours into the interstitium, overwhelming the lymphatic system.

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What is ARDS?

- Breakdown of the alveolar epithelial barrier allows the air spaces to fill with bloody, proteinaceous edema fluid and debris from degenerating cells. In addition, functional surfactant is lost, resulting in alveolar collapse.
What is ARDS?

Healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli.

Lung injury interrupts this balance causing excess fluid in both the interstitium and alveoli.

Results of the excess fluid include impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure.

Exudative Stage (0-6 Days)

Characterized by:

- Accumulation of excessive fluid in the lungs due to exudation (leaking of fluids) and acute injury.
- Hypoxemia is usually most severe during this phase of acute injury, as is injury to the endothelium (lining membrane) and epithelium (surface layer of cells).
- Some individuals quickly recover from this first stage; many others progress after about a week into the second stage.

Proliferative Stage (7-10 Days)

Characterized by:

- Connective tissue and other structural elements in the lungs proliferate in response to the initial injury, including development of fibroblasts (cells giving rise to connective tissue).
- The terms "stiff lung" and "shock lung" frequently used to characterize this stage.
- Abnormally enlarged air spaces and fibrotic tissue (scarring) are increasingly apparent.

Fibrotic Stage (>10-14 Days)

Characterized by:

- Inflammation resolves.
- Oxygenation improves and extubation becomes possible.
- Lung function may continue to improve for as long as 6 to 12 months after onset of respiratory failure, depending on the precipitating condition and severity of the initial injury.
- Varying levels of pulmonary fibrotic changes are possible.

What is ARDS?

ARDS is a multisystem syndrome – not a “disease”

Three distinct stages (or phases) of the syndrome including:

1. Exudative stage
2. Proliferative (or fibroproliferative) stage
3. Fibrotic stage
Causes of ARDS

- No “single” causative factor - can be triggered by traumatic or non-traumatic events.
- Over 60 possible causes have been identified but the four most frequent causes include:
  1. Sepsis
  2. Aspiration
  3. Pneumonia
  4. Severe Trauma

Sepsis

- Most common cause of ARDS. ¹
- Higher risk in septic patients with a history of alcoholism (70% incidence in pts with chronic alcohol use vs 31% in patients w/o chronic use)²


Aspiration

- Precise reason for this is unknown but may be a result of an exaggerated response when the immune system encounters a new and highly pathogenic organism (i.e. H1N1)
- Animal studies have shown that aspiration of non-acidic gastric contents can also cause widespread damage to the lungs suggesting that gastric enzymes and small food particles also contribute to the lung injury. ²

Severe Trauma

ARDS is a complication of severe trauma and is most common following:

A) Bilateral lung contusion following blunt trauma.

B) Fat embolism after long bone fractures – ARDS typically appears 12 to 48 hours after the trauma (occurs less frequently since immobilization protocol).


C) Sepsis that develops several days or more after severe trauma or burns.

D) Massive traumatic tissue injury may directly precipitate or predispose a patient to ARDS.


Ventilator Associated Lung Injury

Acute lung injury caused by mechanical ventilation. Can be caused by:

1. High inflation pressure – Barotrauma

2. Over distension – Volutrauma

3. Repetitive opening & closing of alveoli – Atelectrauma
Berlin Definition of ARDS

2. Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or CT scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.

3. The patient’s respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (eg, echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present.

4. A moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO₂/FiO₂). The severity of the hypoxemia defines the severity of the ARDS:

   - **Mild ARDS**: The PaO₂/FiO₂ is >200 mmHg, but ≤300 mmHg, on ventilator with PEEP ≥5 cm H₂O.

   - **Moderate ARDS**: The PaO₂/FiO₂ is >100 mmHg, but ≤200 mmHg, on ventilator with PEEP ≥5 cm H₂O.

   - **Severe ARDS**: The PaO₂/FiO₂ is <100 mmHg on on ventilator with PEEP ≥5 cm H₂O.

Clinical Presentation of ARDS

- Tachypnea
- Increasing dyspnea, hyperventilation
- Respiratory distress
- Labored respiration’s, retractions
- Cyanosis
- Tachycardia, hypertension, restlessness, anxiety

General Treatment & Support of ARDS

Key components of supportive care include:

1. Intelligent use of sedatives and neuromuscular blockade
2. Hemodynamic management
3. Nutritional support
4. Control of blood glucose
5. Evaluation and treatment of nosocomial pneumonia
6. Prophylaxis against deep vein thrombosis (DVT) and gastrointestinal (GI) bleeding.

Acute Respiratory Distress Syndrome

Characterized by:

- Acute onset
- Bilateral infiltrates on CXR sparing the costophrenic angles
- PaO₂ / FiO₂ < 300 (< 200 is severe)
- Increased edema and decreased surfactant production
- Ground glass appearance on CXR
**Mechanical Ventilation & ARDS**

- ARDS frequently requires mechanical ventilation
- Majority of patients require MV due to Type 1 – Hypoxic Respiratory Failure
- Preponderance of evidence suggests that a “Low Tidal Volume Ventilation” strategy improves mortality. ¹⁻⁴


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**Low Tidal Volume Ventilation (LTVV)**

- A 2004 meta-analysis of six randomized trials (1297 patients) found that LTVV significantly improved 28 day mortality (27.4 vs 37 %) and hospital mortality (34.5 vs 43.2 %), when compared to conventional mechanical ventilation.¹

- A 2012 meta-analysis of four randomized trials (1149 patients) also found that LTVV reduced hospital mortality (34.2 vs 41 %), when compared to conventional mechanical ventilation.²


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**Low Tidal Volume Ventilation (LTVV)**

**Problems / Questions**

1. Hypercapnic respiratory acidosis in some patients.
   - Expected and generally well tolerated by patients.

2. Auto-PEEP
   - In theory, the higher respiratory rates used to maintain minute ventilation during LTVV may create auto-PEEP by decreasing the time available for complete expiration. A subgroup analysis from the ARDSnet trial detected negligible quantities of auto-PEEP in both the LTVV and conventional mechanical ventilation groups.¹


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**Low Tidal Volume Ventilation (LTVV)**

**Initial Settings¹**

1. Calculate Ideal Body Weight (IBW)
   - Males = 106 + [6 x (height in inches – 60 in)]
   - Females = 105 + [5 x (height in inches – 60 in)]

2. Set initial tidal volume to 8 ml/kg IBW
3. Reduce tidal volume to 7 ml/kg IBW then 6 ml/kg IBW over the next 1-3 hours.
4. Set respiratory rate to ≤ 35 bpm to match baseline minute ventilation

**Low Tidal Volume Ventilation (LTVV)**

**Adjusting Settings**
1. Adjustments to tidal volume are based on the Plateau pressure reading.
2. Goal is to maintain Plateau pressure ≤ 30 cmH2O.
3. If Plateau pressure rises above 30 cmH2O, the tidal volume setting is decreased by 1 ml/kg IBW increments to a minimum of 4 ml/kg IBW.
4. Using LTVV when Plateau pressures are not high has also shown benefit.

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**Open Lung Ventilation**

- Ventilation strategy that combines low tidal volume ventilation (LTVV) and enough applied PEEP to maximize alveolar recruitment.
- Goal is to prevent overdistension and minimize cyclic atelectasis.
- Some studies report decrease in mortality and hospital stay but studies are flawed.
- No universally accepted protocol is yet available.

Typically, LTVV is utilized with various methods (lower inflection point, using highest PEEP while maintaining Plateau pressure ≤ 30 cmH2O, etc.)

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**What Mode Is Best in ARDS??**

- Volume Control (VC)
- Pressure Control (PC)
- Airway Pressure Release Ventilation (APRV)
- Oscillator / Jet Ventilation

- No mode or type of ventilation has been “proven” to work best in terms of
**BiLevel vs APRV**

In BiLevel normal ratio there IS time for spontaneous breathing from the lower PEEP level.

In APRV there IS NOT time for spontaneous breathing from the lower PEEP level.

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**Airway Pressure Release Ventilation (APRV)**

- CPAP is then reinstated and the previous volume is restored in the lungs.
- High CPAP level increases MAP.
- Timed intervals when pressure drops allows for ventilation.
- Patient can be apnic and mode will still work.
- Newer ventilators have added the ability to add pressure support to spontaneous breaths.

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**APRV – Initial Settings**

- **P-Low** = 0-8 cmH2O
- **P-High** = set to deliver 4-8 ml/kg IBW but keep < 35 cmH2O
- **T-Low** = 0.5-1.0 sec
- **T-High** = set to ensure effective MV
- **Release Rate** = 10 per minute

(Note: Two of the above – T-Low, T-High, and Release Rate – are set depending on type of vent. Third value is determined by those settings.)

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**Settings Adjustment in APRV**

- Nearly every setting change results in a positive...and negative effect on oxygenation and/or ventilation.

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**Airway Pressure Release Ventilation (APRV)**

- APRV was originally intended for patients with stiff lungs.
- Recent research has proven the mode to be as effective as conventional ventilation in both ventilating and oxygenating patients with only mild pulmonary problems or with normal lung compliance.
- Clinical use is still mainly for patients with very low compliance and poor oxygenation.
Managing Oxygenation in APRV

- Increase PEEP HI and/or decrease rate by small amounts. While either change may improve SpO2's, either change may reduce MV.
- Reduce TLow which may also reduce MV.
- Increase FiO2 as needed but the target level should be 0.60.

Managing pH, PCO2, VE in APRV

- Decrease PEEP HI to allow the pt. to increase their spontaneous Tv.
- Increase frequency. This will increase the number of “Releases” per minute.

Weaning From APRV

- When oxygenation improves, initiate “Drop & Stretch” protocol.
- D&S protocol attempts to avoid de-recruitment by lowering P high by 2 to 3 cm H2O at a time and lengthening T high by increments of 0.5 to 2.0 seconds.
- When P-High is < 16 cmH2O and T-High is 12-15 seconds, switch pt over to CPAP/PSV at standard settings.
Novel Therapies for ARDS

- Prone Positioning
- Nitric Oxide
- Inhaled Prostacycline
- Recruitment Maneuvers
- ECMO

Supportive Therapies to Improve Oxygenation

- Prone Positioning

Most mechanically ventilated patients are cared for in the supine position.

Studies have shown by flipping the patient over into the prone position may improve oxygenation.

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Nitric Oxide

- Nitric oxide is a selective pulmonary vasodilator
- Redistributes pulmonary blood flow from unventilated lung units to ventilated lung units resulting in decrease V/Q mismatch
- Because it is selective it does not produce systemic side effects

![Nitric Oxide Diagram](image)

Aerosolized Prostacyclin

- Aerosolized prostacyclin (Flolan) has been shown to be as effective as Inhaled Nitric Oxide (NO) as a selective pulmonary vasodilator.
- Flolan is FDA approved for the treatment of primary pulmonary hypertension by intravenous (IV) infusion.
- Prostacyclin, administered by inhaled aerosol, selectively dilates the pulmonary vascular bed.

![Aerosolized Prostacyclin](image)

Recruitment Maneuvers

- A recruitment maneuver is a sustained increase in airway pressure with the goal to open collapsed lung tissue.

**EXAMPLE**

1. Sedation (?) & Pre-oxygenate with 100% FiO2
2. Change mode to CPAP and add 30 cm H₂O for 30 - 40 seconds.
3. Monitor Vt and oxygenation for 15 - 30 min. If unresponsive, repeat at CPAP of 35 to 40 cm H₂O.

![Recruitment Maneuvers](image)
Effects of Lung Recruitment

Before Lung Recruitment

After Lung Recruitment

Other Novel Therapies

- Surfactant Therapy – inconsistent results
- Antioxidant Therapy – inconsistent results
- Glucocorticoid Therapy – inconsistent results (keep < 14 days)

In Summary….

- ARDS is a multisystem syndrome – not a “disease”
- Characterized by accumulation of excessive fluid in the lungs with resulting hypoxemia and ultimately some degree of fibrotic changes.
- The most frequent causes of ARDS include sepsis, aspiration, pneumonia and severe trauma
- Treatment is primarily supportive and can non-traditional types of ventilation and oxygenation strategies.