ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)
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Definition
ARDS is a clinical syndrome of lung injury with hypoxic respiratory failure caused by intense pulmonary inflammation that develops after a severe physiologic insult. The disease process may either be:
- A primary insult – disease process begins in the lungs: pneumonia, aspiration, near drowning, smoke inhalation, hydrocarbon ingestion, oxygen toxicity
- A secondary insult – lungs may be affected due to a systemic disease process: sepsis/SIRS, shock, trauma, cardiac arrest, burns. The lung then suffers from an indirect injury due to a systemic inflammatory response syndrome (SIRS). Pulmonary edema develops from increased permeability of the alveolar-capillary membrane.

The American-European Consensus Conference defines ARDS and ALI as:
- Acute onset of respiratory symptoms
- Chest radiograph with bilateral infiltrates
- Pulmonary artery wedge pressure (PAWP) of less than 18 mmHg (indicating no evidence of left heart failure)
- ALI: PaO$_2$/FIO$_2$ ratio < 300 mmHg
- ARDS: PaO$_2$/FIO$_2$ ratio < 200 mmHg

Epidemiology
- ARDS accounts for approximately 1-3% of admissions to the PICU.
- Shock, sepsis, and drowning are the most common causes of ARDS in pediatrics.
- Mortality rates in children and adults with ARDS are similar. The average mortality rate is 52% (range 28.5%-90%). Improved management of children with ARDS has decreased mortality rates (currently described as 30-50%). In patients with ARDS, death is primarily due to sepsis or multiple organ dysfunction. Death secondary to refractory respiratory failure is relatively rare.
- Poor prognostic factors include: failure of oxygenation improvement after 6 days, high oxygenation index, liver dysfunction/cirrhosis, sepsis, non-pulmonary organ dysfunction, organ transplantation, HIV infection, active malignancy, PaO2/FiO2<100, right ventricular dysfunction

Pathophysiology
ALI/ARDS are the end result of an aggressive inflammatory process. Present scientific thinking suggests that the balance between pro-inflammatory mediators (TNF alpha, IL-1 beta, IFN gamma, LT alpha, IL-2, IL-8, IL-12, IL-18, PAF, LTB, Kinins, NO, GM-CSF, Chemokines, MIF, etc.) and anti-inflammatory mediators (sTNFR, sIL-1R, TGF beta, IL-4, IL-6, IL-10, IL-11, IL-13, PGE$_2$, G-CSF,
antioxidants, etc.) is deranged. The inflammation results in increased permeability of pulmonary capillaries and alveoli, a protein-rich pulmonary edema, surfactant depletion/inactivation, and ultimately (after 5-7 days) development of pulmonary fibrosis. Loss of pulmonary vasomotor tone occurs due to refractory hypoxemia resulting in mild pulmonary hypertension. Also, ARDS is a heterogeneous process, i.e. different portions of the lung have varying degrees of disease.

The pathological features of ARDS involve 3 overlapping phases:
1. Inflammatory or exudative phase (0-7 days)
2. Proliferative phase (7-21 days)
3. Fibrotic phase (after 7-10 days)

**Management**
Treatment of ARDS is supportive with:
- Maintenance of adequate oxygenation, cardiac output, and nutritional support
- Prevention of secondary pneumonia, other infections, and ventilator induced lung injury.

The therapeutic strategies are discussed below.

**1. Causative factors:** Treat the initiating insult, especially if infectious. Treat shock with volume, vasopressors, etc. as necessary.

**2. Ventilatory strategies:** Over the last 20 yrs, a growing body of experimental and clinical evidence highlights potentially harmful consequences of endotracheal intubation and mechanical ventilation including infections, such as ventilator-associated pneumonia. In addition, clinical and experimental studies implicate the delivery of excessive mechanical stress through mechanical ventilation in the generation and / or perpetuation of lung injury. In response to these concerns, lung protective strategies that limit tidal volumes, plateau pressures, or both have been developed. The goal of ventilating a patient with ARDS, then, is to maintain adequate gas exchange while minimizing ventilator induced lung injury. Factors implicated in ventilator induced lung injury include:
- High FiO₂ > 60%: leading to oxygen toxicity
- Barotrauma: alveolar injury from exposure to excessive pressures
- Volutrauma: Repetitive opening and closing of alveoli causing shear stress and triggering further inflammation

**Indications for Intubation and application of PEEP:**
1. Worsening lung disease clinically and on radiographs
2. Hypoxemia despite facemask (provides 50% - 90% FiO₂)
3. Increased work of breathing secondary to inadequate minute ventilation, increased dead space, decreased functional residual capacity (FRC), decreased lung compliance

*Patients at risk for ARDS do not benefit from prophylactic application of PEEP. Although PEEP is a valuable part of supportive therapy, it does not alter the disease process that leads to the development of ARDS.

To minimize lung injury (NEJM 2000 ARDS Network study):

- Increase PEEP to recruit alveoli, increase mean airway pressure, improve oxygenation, increase functional residual capacity, and decrease alveolar edema. Use enough PEEP (range from 8 to 20) to allow for FiO₂ ≤0.6. A higher FiO₂ exposes the lung to oxygen toxicity; therefore all efforts should be made to decrease the FiO₂ ≤0.6. The PEEP should be 2-3 cmH₂O greater than the lower inflection point of a static Pressure-Volume curve and should be associated with the best compliance. Lower oxygen saturations of 88%-95% or paO₂ 55-80mmHg can be accepted in order to minimize oxygen toxicity. If permissive hypoxia is being accepted, assure adequate end organ oxygen delivery.

- Low tidal volume with a goal of 6 ml/kg should be used. This goal tidal volume can be decreased if plateau airway pressures are > 30cm H₂O. Therefore goal plateau pressure is <30. The preferred mode of ventilation is time cycled, pressure regulated, and volume controlled.

- Set a ventilatory rate to achieve pH 7.3-7.45. Often, permissive hypercapnia with a pH down to 7.2 is allowed to minimize ventilator induced lung injury. Be vigilant of I-time, inspiratory time, while setting the rate. A longer I-time optimizes pulmonary recruitment.

- Avoid paralysis if possible.

- I:E ratio can be decreased to 1:1 if required for poor oxygenation and to improve recruitment. A longer I-time usually of 0.8 or longer is preferred to optimize re-recruitment.

The ARDS Network study demonstrated that the above strategy compared to traditional ventilatory methods (Tidal volumes 12 ml/kg, etc.) decreased mortality (31% vs. 39.8%), increased ventilator free days, and decreased plasma interleukin concentrations in adult patients with ARDS. A pediatric study has not been performed to date.

3. Non-Conventional Ventilation

A. High frequency ventilation (HFV)- Some pediatric studies have shown early use of HFV results in improved oxygenation and outcomes. The
• Advantages of HFV
  o Use of low VT
  o Avoidance of barotrauma
  o Maintenance of near normal PaCO₂

• Disadvantage of HFV
  o Patient must remain paralyzed

B. Liquid Ventilation – It is presently being evaluated in the laboratory setting and is not clinically available. In this type of ventilation perfluorocarbons partially or fully fill the lungs to remove the air-liquid interface and support alveoli, thus preventing their collapse.

4. Fluid Administration – The patient should be aggressively fluid resuscitated for any signs / symptoms of shock in order to optimize end organ perfusion. Once hemodynamic stability is achieved, fluid administration should be minimized to decrease the alveolar-capillary leak and pulmonary edema. Aggressive diuresis should also be considered once hemodynamic stability is achieved. Nutritional support should be initiated as early as possible (TPN or enterally).

5. Prone Positioning – Has been used since mid 1970’s in an effort to improve regional lung perfusion and oxygenation. Although there is no evidence on beneficial effects on outcomes, this strategy has a low risk/benefit and therefore is employed in select patients. Risks are mainly logistical, i.e. dislodgement of endotracheal tube or vascular lines, increased intra-abdominal pressure, feeding intolerance, and edema (facial). The greatest effects are achieved when patients are maintained prone for 12 hours or longer and oxygenation improves in 60-70% of patients.

6. Nitric Oxide – iNO is a selective pulmonary vasodilator with a short half-life and no systemic hemodynamic effects. iNO improves oxygenation and V/Q matching by increasing blood flow to well ventilated lung and shunting blood away from poorly ventilated lung. Also, pulmonary pressures are decreased in turn reducing right ventricular afterload. Studies using iNO in ARDS have shown initial improvements of oxygenation (~60% of patients) however no sustained improvement after 1-2 days. In addition, no reduction in morbidity/mortality has been shown with iNO treatment in ARDS. iNO may be used as a temporary rescue when there is refractory hypoxemia with conventional treatment.

7. Corticosteroids – The anti-inflammatory actions of steroids have not been shown to be beneficial in the early course of ARDS. However a prospective adult study with prolonged administration of methyl-prednisone in patients with ARDS>7 days showed reduced lung injury and reduced mortality. Therefore, steroids may be used in later stages (during the fibrotic phase) to help wean patients from the ventilator.
**8. Surfactant** – ARDS does cause derangements in surfactant composition. However, studies demonstrating any benefit to surfactant replacement in pediatric populations are lacking. Again, surfactant use can be considered when oxygenation cannot be achieved with conventional methods.

**9. ECMO** – Although shown to be beneficial in neonates with RDS, ECMO is not recommended routinely in pediatric patients with ARDS. In pediatric ARDS, ECMO is reserved for the patients that do not respond to conventional management.

**Conclusions:**
1. ARDS is a process of diffuse pulmonary inflammation with increased vascular and alveolar permeability.
2. The physiologic process is restrictive lung disease and hypoxemia occurs due to edema and V/Q mismatch.
3. The ventilatory treatment involves increasing mean airway pressure to improve oxygenation.
4. Ventilator induced lung injury can be minimized by maintaining high PEEP, low tidal volume, peak pressures < 35 cm H₂O, and FiO₂ < 60%.
5. Death is primarily due to multi-organ dysfunction (usually cardiovascular collapse), and not ARDS primarily. Therefore, all other supportive measures should be optimized.