Respiratory Failure and ARDS

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PLAN

1- Respiratory Failure definition
2- Mechanical Ventilation
3- ARDS (Acute respiratory distress syndrome): definition and Pathophysiology
4- ARDS: updates in Management.
5- ARDS: Prognosis, severity scores; long-term sequelae in survivors.
1-Respiratory Failure definition
Respiratory Failure

the inability of the cardiac and pulmonary systems to maintain an adequate exchange of oxygen and CO2 in the lungs
Classification of Respiratory Failure

Inhaling Affects PaO2

Exhaling Affects PCO2

**Respiratory failure**

**Hypoxemic (Oxygenation failure)**
PaO₂ ≤ 60 mm Hg on 60% oxygen

- Acute (minutes to hours)
- Chronic (several days or longer)

**Hypercapnic (Ventilatory failure)**
PaCO₂ > 45 mm Hg and pH < 7.35

- Acute (minutes to hours)
- Chronic (several days or longer)

Fig. 68-2
1-Respiratory Failure definition:

1-Type I or Hypoxemic (PaO2 <60 at sea level) (no hypercapnia)

2-Type II or Hypercapnic (PaCO2 >45) often type II is a combination of hypoxemic and hypercapnic.
1-Respiratory Failure definition

2-Type III Respiratory Failure: Perioperative respiratory failure.
• Increased atelectasis due to low functional residual capacity (FRC) in the setting of abnormal abdominal wall mechanics.
• Often results in type I or type II respiratory failure.
• Can be ameliorated by anesthetic or operative technique, posture, , incentive spirometry , post-operative analgesia, attempts to lower operative analgesia, attempts to lower intra-abdominal pressure.

3-Type IV Respiratory Failure: Due to Shock
• Type IV describes patients who are intubated and ventilated in the process of resuscitation for shock and the Goal of ventilation is to stabilize gas exchange
1-Respiratory Failure definition

Hypoxemic respiratory failure causes:

• Low FiO2
• Impaired diffusion
• Impaired O2 delivery ex: severe anemia, or cardiac dysfunction
• V/Q mismatch
• Shunt
• hypoventilation
Range of V/Q Relationships
Shunt

• 2 Types
  – 1. Anatomic- passes through an anatomic channel of the heart and does not pass through the lungs ex: ventricular septal defect
  – 2. Intrapulmonary shunt- blood flows through pulmonary capillaries without participating in gas exchange ex: alveoli filled with fluid
  – Patients with shunts are more hypoxemic than those with VQ mismatch and usually do not respond even to high FiO2 supplementation.
Diffusion Limitations

- Gas exchange is compromised by a process that thickens or destroys the membrane
  - 1. Pulmonary fibrosis
  - 2. All Interstitial lung diseases
  - 3. ARDS
Diffusion Limitation

Fig. 68-5
Alveolar Hypoventilation

Mainly causes hypercapnic respiratory failure but can cause hypoxemia
Increased pCO2 with decreased PO2
1-Restrictive lung disease ex: abnormalities of the chest wall: Flail chest, morbid obesity, kyphoscoliosis.
2-CNS diseases: suppressed drive to breathe drug OD, narcotics, head injury, spinal cord injury
3- Abnormalities of the airways and alveoli- air flow obstruction and air trapping: Asthma, COPD, and cystic fibrosis.
4-Neuromuscular diseases: respiratory muscles are weakened: ex: Guillain-Barre, muscular dystrophy, myasthenia gravis and multiple sclerosis.
1-Respiratory Failure definition

Causes of Hypercapnia:

• Decrease in minute ventilation due to either decrease in TV or RR or to an increase in dead space.

• Or increase CO2 production.
Failure to Ventilate

Neurological
- Respiratory Center
  - Opioids, Anesthetics, Brain Injuries
- Cervical Nerves C3, 4, 5
  - Spinal Injuries
- Phrenic Nerves
  - Chest trauma, Surgery
- Neuromuscular Junction
  - Neuromuscular Blockers
  - Myasthenia Gravis

Muscular
- Myopathy
  - Steroids
  - Myasthenia Gravis
  - Polyneuropathy/Polymyopathy of Critical Illness
  - Diaphragm
  - Intercostals

Failure to Protect Airway

Anatomical
- Airway Obstruction
  - Upper: teeth, tongue
  - Glottic: laryngeal edema, laryngospasm
  - Lower: bronchospasm, inhaled objects
- Chest Wall
  - Flail Chest
- Pleural Cavity
  - Pneumothorax
  - Hemothorax
  - Pleural Effusion
- Abdominal Compression
  - Ascites/Hemoperitoneum
  - Surgical Packs etc
1-Respiratory Failure definition

• Correct hypoxemia by
  Increase FiO2 and/or increase PEEP
• Correct hypercapnia by
  Increase Minute ventilation through increasing RR and/or TV.
1-Respiratory Failure definition: Risks of Oxygen Therapy

- **O₂ toxicity:**
  - Very high levels (>1000 mmHg) CNS toxicity and seizures
  - Lower levels (FiO₂ > 60%) and longer exposure:
    - Capillary damage, leak and pulmonary fibrosis
  - PaO₂ >150 can cause retrolental fibroplasia
  - FiO₂ 35 to 40% can be safely tolerated indefinitely

- **CO₂ narcosis:**
  - PaCO₂ may increase severely to cause respiratory acidosis, somnolence and coma
  - PaCO₂ increase secondary to combination of:
    - a) abolition of hypoxic drive to breathe
    - b) increase in dead space
    - c) Haldane effect.
2-Mechanical Ventilation
Consider non-invasive ventilation particularly in the following settings

- COPD exacerbation (BIPAP)
- Cardiogenic pulmonary edema=CHF (BIPAP or CPAP) (it helps decreased preload and afterload)
- Obesity hypoventilation syndrome (BIPAP)
- Sleep Apnea (CPAP)
- Pneumonia (BIPAP)
- Noninvasive ventilation may be tried in selected patients with asthma or non-cardiogenic Pulmonary edema.
2-Mechanical Ventilation

Indications for Mechanical Ventilation

• Cardiac or respiratory arrest
• Tachypnea or bradypnea with respiratory fatigue or impending arrest.
• Acute respiratory acidosis (=acute hypercapnic respiratory failure)
• Refractory hypoxemia Refractory hypoxemia (when the P a O 2 could not be maintained above 60 mm Hg with inspired O 2 fraction (F I O 2 )>1.0)
• Inability to protect the airway associated with depressed levels of consciousness
• Shock associated with excessive respiratory work
• Inability to clear secretions with impaired gas exchange or excessive respiratory work.
• Newly diagnosed neuromuscular disease with a vital capacity <10-15 mL/kg.
• Short term adjunct in management of acutely increased intracranial pressure (ICP)
Mechanical Ventilator

Mechanical Ventilation

Settings
- Tidal Volume
- FiO2
- Rate
- Mode

Complications
- Cardiac Output
- Barotrauma
- O2 Toxicity
- Infection
- ICP
- Nasal/Oral Injury
- Cuff Trauma

Assist Control
- IMV
- SIMV
- Pressure Support
- PEEP
- CPAP
Control Mode or CMV

1. TV and RR are fixed.
2. Used for patients who are unable to initiate a breath (anesthetized or paralyzed). CMV delivers the preset volume or pressure at pre-set rate regardless of the patient’s own inspiratory effort.
3. Spontaneously breathing patients must be sedated and/or pharmacologically paralyzed so they don’t breathe out of synchrony with the ventilator.
4. Ventilator does all the work.
Assist Control

1. A/C delivers the preset volume or pressure in response to the patient’s own inspiratory effort, but will initiate the breath if the patient does not do so within the set amount of time.

2. Patient Assists or triggers the vent – can breathe faster but not slower

3. Vent has back-up rate

4. May need to be sedated to limit the number of spontaneous breaths since hyperventilation can occur.

5. This mode is used for patients who can initiate a breath but who have weakened respiratory muscles.
Synchronous Intermittent Mandatory Ventilation-SIMV

1. SIMV delivers the preset volume or pressure and rate while allowing the patient to breathe spontaneously in between ventilator breaths.

2. Each ventilator breath is delivered in synchrony with the patient’s breaths, yet the patient is allowed to completely control the spontaneous breaths at own TV.

3. SIMV is used as a primary mode of ventilation, as well as a weaning mode.

4. During weaning, the preset rate is gradually reduced, allowing the patient to slowly regain breathing on their own.

5. The disadvantage of this mode is that it may increase the work of breathing and respiratory muscle fatigue.
Pressure Support Ventilation

1. PSV is preset pressure that augments the patient’s spontaneous inspiratory effort and decreases the work of breathing.

2. The patient completely controls the respiratory rate and tidal volume.

3. PSV is used for patients with a stable respiratory status and is often used with SIMV to overcome the resistance of breathing through ventilator circuits and tubing as a weaning mode as well.
Pressure support

Pressure Support reduces the workload of inspiration

Fig 3

Pressure

Volume

500ml Tidal Volume

FRC CPAP RESTORES FRC

With Pressure Support

Without Pressure Support

P4 P3
2-Mechanical Ventilation

- CPAP=EPAP=PEEP
- PS=IPAP-EPAP or IPAP=PS+EPAP
High Frequency Ventilation

1. HFV delivers a small amount of gas at a rapid rate (as much as 60-100 breaths per minute.)

2. This is used when conventional mechanical ventilation would compromise hemodynamic stability, during short-term procedures, or for patients who are at high risk for pneumothorax.

3. Sedation and pharmacological paralysis are required.
Inverse Ratio Ventilation

1. The normal inspiratory:expiratory ratio is 1:2 but this is reversed during IRV to 2:1 or greater (the maximum is 4:1).

2. This mode is used for patients who are still hypoxic even with the use of PEEP. The longer inspiratory time increases the amount of air in the lungs at the end of expiration (the functional residual capacity) and improves oxygenation by re-expanding collapsed alveoli - acts like PEEP.

3. The shorter expiratory time prevents the alveoli from collapsing again.

4. Sedation and pharmacological paralysis are required since it’s very uncomfortable for the patient.

5. For patients with ARDS continuing refractory hypoxemia despite high levels of PEEP.
• 3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

- Alveolar epithelial injury of type I cells contributes to the pulmonary oedema and the breakdown of this epithelial barrier exposes the underlying basement membrane, predisposing to bacteraemia and sepsis.
- Injury to type II alveolar cells leads to impaired surfactant synthesis and metabolism resulting in increased alveolar surface tension and alveolar collapse.
- Histopathologically there is diffuse alveolar damage with neutrophil infiltration, alveolar haemorrhage, and hyaline membrane formation.
- The acute phase is followed by a fibroproliferative phase in some with various degrees of fibrosis, neovascularisation and later resolution.
- Vascular injury and remodelling may lead to pulmonary arterial hypertension which may compromise right ventricular function, exacerbating hypoxaemia and leading to poor clinical outcome.
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

- **Injury or Exudative- 1-7 days**
  - Interstitial and alveolar edema and atelectasis
  - Refractory hypoxemia and stiff lungs

- **Reparative or Proliferative-1-2 weeks after**
  - Dense fibrous tissue, increased PVR and pulmonary hypertension occurs

- **Fibrotic-2-3 week after**
  - Diffuse scarring and fibrosis, decreased surface area, decreased compliance and pulmonary hypertension
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology
ARDS (Acute respiratory distress syndrome): definition and Pathophysiology


• Noteworthy for establishing the standard for the clinical diagnosis of ARDS for subsequent clinical trials.
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

• What was wrong with the old definition of ARDS: **1) acute onset of hypoxemia with PaO2 / FiO2 ratio <= 200 mm Hg, 2) bilateral infiltrates on chest X-ray, with 3) no evidence of left atrial hypertension?**

• No explicit criteria for defining “acute” — leading to ambiguity regarding cases of acute-on-chronic hypoxemia.

• High interobserver variability in interpreting chest X-rays.

• Difficulties identifying / ruling out cardiogenic or hydrostatic pulmonary edema, especially in an era of plummeting pulmonary artery catheter use.

• PaO2 / FiO2 ratio is sensitive to changes in ventilator settings.
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

- **Meet the New ARDS: Expert panel announces new definition, severity classes (JAMA):**
- The panel’s findings, endorsed by the European Society of Intensive Care Medicine, the American Thoracic Society (ATS) and the Society of Critical Care Medicine (SCCM), emerged from meetings in Berlin to try to address the limitations of the earlier AECC definition. Authors published their results in the May 21 2012 online edition of JAMA.
- The proposed “Berlin definition” predicted mortality ever-so-slightly better than the existing definition (created at the 1994 American-European Consensus Conference/AECC), when applied to a cohort of 4,400 patients from past randomized trials. The Berlin definition would include the following:
  - “Acute lung injury” no longer exists. Under the Berlin definition, patients with PaO2/FiO2 200-300 would now have “mild ARDS.”
  - Onset of ARDS (diagnosis) must be acute, as defined as within 7 days of some defined event, which may be sepsis, pneumonia, or simply a patient’s recognition of worsening respiratory symptoms. (Most cases of ARDS occur within 72 hours of recognition of the presumed trigger.)
  - Bilateral opacities consistent with pulmonary edema must be present but may be detected on CT or chest X-ray.
  - There is no need to exclude heart failure in the new ARDS definition; patients with high pulmonary capillary wedge pressures, or known congestive heart failure with left atrial hypertension can still have ARDS. The new criterion is that respiratory failure simply be “not fully explained by cardiac failure or fluid overload,” in the physician’s best estimation using available information. An “objective assessment”— meaning an echocardiogram in most cases — should be performed if there is no clear risk factor present like trauma or sepsis.
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

• The new Berlin definition for ARDS would also categorize ARDS as being mild, moderate, or severe:

• **ARDS Severity** PaO2/FiO2 (on PEEP of 5)
  **Mortality** (observed in cohorts)

  • Mild 200 – 300 (27%)
  • Moderate 100 – 200 (32%)
  • Severe < 100 (45%)
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

### Clinical Disorders Associated with the Development of ALI/ARDS

#### Direct insult

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
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</thead>
<tbody>
<tr>
<td>Aspiration pneumonia</td>
<td>Inhalation injury</td>
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<tr>
<td>Pneumonia</td>
<td>Pulmonary contusions</td>
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<tr>
<td></td>
<td>Fat emboli</td>
</tr>
<tr>
<td></td>
<td>Near drowning</td>
</tr>
<tr>
<td></td>
<td>Reperfusion injury</td>
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</table>

#### Indirect insult

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Acute pancreatitis</td>
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<tr>
<td>Severe trauma</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Shock</td>
<td>Transfusion-related TRALI</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td></td>
<td>Burns</td>
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<tr>
<td></td>
<td>Head injury</td>
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<td></td>
<td>Drug overdose</td>
</tr>
</tbody>
</table>
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

NIH-NHLBI ARDS Network
Cause of Lung Injury

- Pneumonia: 40%
- Sepsis: 22%
- Aspiration: 15%
- Transfusion: 5%
- Other: 10%
- Trauma: 8%
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

<table>
<thead>
<tr>
<th>Letter</th>
<th>Meaning</th>
<th>Scale</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>G</td>
<td>Gas exchange</td>
<td>0</td>
<td>Pao2/Fio2 ≥ 301</td>
</tr>
<tr>
<td></td>
<td>(to be combined with the numeric</td>
<td>1</td>
<td>Pao2/Fio2  200 -300</td>
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<tr>
<td></td>
<td>descriptor)</td>
<td>2</td>
<td>Pao2/Fio2  101 – 200</td>
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<tr>
<td></td>
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<td>3</td>
<td>Pao2/Fio2  ≤ 100</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td></td>
<td>Spontaneous breathing, no PEEP</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>Assisted breathing, PEEP 0-5 cmH2O</td>
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<tr>
<td></td>
<td>C</td>
<td></td>
<td>Assisted breathing, PEEP 6-10 cmH2O</td>
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<tr>
<td></td>
<td>D</td>
<td></td>
<td>Assisted breathing, PEEP  ≥ 10 cmH2O</td>
</tr>
<tr>
<td>O</td>
<td>Organ failure</td>
<td>A</td>
<td>Lung only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>Lung + 1 organ</td>
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<td></td>
<td></td>
<td>C</td>
<td>Lung + 2 organs</td>
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<td></td>
<td></td>
<td>D</td>
<td>Lung + ≥ 3 organs</td>
</tr>
<tr>
<td>C</td>
<td>Cause</td>
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<td>Unknown</td>
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<td></td>
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<td>Associated diseases</td>
<td>0</td>
<td>No coexisting disease that will cause death</td>
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<tr>
<td></td>
<td></td>
<td>1</td>
<td>within 5 yr</td>
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<td></td>
<td></td>
<td>2</td>
<td>Coexisting disease that will cause death within</td>
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<td></td>
<td>5 yr but not within 6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coexisting disease that will cause death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>within 6 mo</td>
</tr>
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</table>
Acute lung injury & multisystem organ failure (MSOF): definitions, causes and risk factors, epidemiology.

- Acute respiratory distress syndrome (ARDS) affects some 10% to 15% of ICU patients and is associated with mortality rates of 40% to 50%.
- Although ARDS is the most severe form of acute respiratory failure, refractory hypoxia is an uncommon cause of death in these patients.
- The majority of patients who have ARDS die from multiple-organ dysfunction syndrome (MODS), and ARDS should, therefore, be seen as a systemic disease.
3-ARDS (Acute respiratory distress syndrome): definition and Pathophysiology

- Recently completed studies suggest that patients with the adult respiratory distress syndrome (ARDS) manifest early evidence of multiple-site endothelial injury.
- Extra-pulmonary disease is usually the cause of death in these patients.
- Furthermore, prognosis in individual cases of ARDS is strongly influenced by specific organ failures (e.g., hepatic and renal failure).
- The mechanisms by which ARDS and extrapulmonary organ system failure interact, however, are poorly delineated.
- Was addressed in this article the unifying hypothesis that uncontrolled ongoing inflammation, which is often but not always caused by infection, is the essential link between ARDS and its progression to multiple system organ failure.

Extrapulmonary manifestations: renal, GI, CVS, CNS, neuromuscular, metabolic, immunologic, etc.

**Figure 1**. The incidence of nonpulmonary organ failure in patients with ARDS. Abnormalities are most consistently observed in the kidneys. However, hepatic dysfunction has also been reported in as many as 95 percent of patients with ARDS.
Figure 3. The mechanisms of nonpulmonary organ failure and oxygen uptake-oxygen delivery abnormalities in ARDS may be divided into two broad categories: (1) altered blood flow distribution, and (2) direct endothelial or parenchymal injury. The mechanism whereby alterations in blood flow distribution or direct organ damage produce organ failure and altered systemic gas exchange is discussed in the text.
Figure 4. Gas exchange abnormalities in the lungs and systemic organs in ARDS. Left, damage to the alveolar-capillary membrane in ARDS and the ensuing alveolar edema impair the transfer of oxygen from the alveolus to the alveolar capillaries (eg, V/Q abnormality). The hypothesis that ARDS is a syndrome of widespread endothelial and parenchymal damage predicts that gas exchange in peripheral organs will be altered in a manner analogous to the pulmonary gas exchange alterations that occur in ARDS; ie (right) direct damage to nonpulmonary organs may result in increases in interstitial edema or decreases in recruitable capillary reserves, leading to increased diffusion distances for oxygen. This, in effect, represents an impairment to the transfer of oxygen from capillary to cell, as manifested by the systemic (eg, VO₂/QO₂) gas exchange abnormalities.
4-ARDS: updates in Management.
Approaches to therapy and prevention.

• Neuromuscular paralysis improves ventilator-patient synchrony and often improves oxygenation. (ACURASYS STUDY)

• This multicenter RCT of 340 patients with severe ARDS (PaO2/FiO2 ratio <150), found early use of 48 hours of neuromuscular blockade reduced mortality and improved oxygenation compared to placebo (NNT of 11 to prevent one death at 90 days in all patients, and a NNT of 7 in a prespecified analysis of patients with a PaO2:FiO2 less than 120). Of note, patients randomized to paralytic did not have an increased incidence of ICU-acquired weakness at 28 days.

• Neuromuscular paralysis should be instituted when adequate oxygenation (oxygen saturation >88%) cannot be achieved despite low tidal volume ventilation and adequate sedation, particularly if there is still evidence of ventilator-patient dyssynchrony.

• Intermittent doses of paralytics can be used as effectively as a continuous IV infusion.

• If a patient is on a continuous IV infusion of a paralytic, a train of 4 monitoring device should be used to monitor the muscle fibre twitch response to the drug.

Approaches to therapy and prevention.

- **Conservative IV fluid management: (FACTT trial)**
  - A randomized study, comparing conservative vs. liberal fluid management (via explicit protocols) applied over seven days to 1000 patients with acute lung injury.
  - Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management shortened the duration of mechanical ventilation and ICU stay without increasing nonpulmonary-organ failure.
- Patient's fluid balance should be maintained as slightly negative or neutral (providing the patient is not in shock).
- The goal is to keep the central venous pressure (CVP) <4 or pulmonary artery occlusion pressure (PAOP) <8.
- Fluid restriction in ARDS is thought to reduce pulmonary microvascular pressure, thereby reducing the driving force for development of pulmonary oedema and allowing net re-absorption of pulmonary oedema.

Approaches to therapy and prevention.

- Restricting IV fluids for ARDS patients helps them get off the ventilator faster, in general. But a small follow-up study to the FACTT trial suggests that for some ARDS survivors, that approach may come at a cost of increased cognitive dysfunction for more than a year after hospital discharge.

Approaches to therapy and prevention.

• PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy.

• These results, along with previous studies of PACs in the MICU population, suggest that the PAC should not be routinely used for the management of acute lung injury.

• The use of a central line is recommended to monitor the CVP and to evaluate fluid status in patients with ARDS.

Approaches to therapy and prevention.

• **Antibiotics**
  
  • In patients who have an infectious cause for ARDS (pneumonia or sepsis), the prompt initiation of antibiotics is important.
  
  • Empirical antibiotics targeted at the suspected underlying infection should be used initially after obtaining appropriate cultures including blood, sputum, and urine cultures.
  
  • There are no data to support the use of antibiotics in patients who have ARDS without infection.
4-Supportive management (*excluding mech. vent.*). Approaches to therapy and prevention.

- **Supportive care**
- Standard supportive care of critically ill patients includes
  - prevention of DVT.
  - blood glucose control (140 to 180 target).
  - prophylaxis against stress-induced GI bleeding when indicated.
  - haemodynamic support to maintain a mean arterial pressure >60 mmHg,
  - and transfusion of packed RBCs in patients with Hb <70 g/L (<7 g/dL).
Approaches to therapy and prevention.

- **ECMO (CESAR TRIAL)**
  - Highlighting both regionalization of care and use of ECMO, this trial showed that transfer to an ECMO-ready facility (75% of those transferred actually received ECMO) led to an NNT of 6 to prevent one death or severe disability at six months compared to standard care.
  - The study was limited by the lack of a mandated lung-protective strategy in the control group; 93% of those transferred for possible ECMO received a lung-protective strategy, compared to 70% in the control group, making this a possible confounder in the observed outcome difference.

Approaches to therapy and prevention.

Inhaled Nitric Oxide

Physiology of inhaled nitric oxide therapy
- Selective pulmonary vasodilatation (decreases arterial and venous resistances)
- Decreases pulmonary capillary pressure
- Selective vasodilatation of ventilated lung areas
- Bronchodilator action
- Inhibition of neutrophil adhesion
- Protects against tissue injury by neutrophil oxidants

Approaches to therapy and prevention.

Low-dose Inhaled Nitric Oxide in Patients with Acute Lung Injury: A Randomized Controlled Trial

- In patients with documented ARDS and severe acute lung injury (PaO₂/FiO₂ ≤ 250) but without sepsis or other organ system failure, iNO at 5 ppm:
  - Induces short-term improvements in oxygenation with a 20% increase in PaO₂ that were maintained only during 24 - 48 hours.
  - Does not improve clinical outcomes or mortality

These data do not support the routine use of inhaled nitric oxide in the treatment of acute lung injury or ARDS.

Inhaled nitric oxide may be considered (Grade C recommendation) as a salvage therapy in acute lung injury or ARDS patients who continue to have life threatening hypoxemia despite optimization of conventional mechanical ventilator support.

Approaches to therapy and prevention.

- **Rescue Therapies**
- Following on the heels of a systematic review out of Toronto in 2007, this analysis of the evidence again demonstrates the lack of clinical benefit with inhaled nitric oxide in ARDS and acute lung injury, with an increased risk of acute kidney injury.

4-Supportive management (*excluding mech. vent.*) Approaches to therapy and prevention.

**Prone Positioning**

- Improves arterial oxygenation in more than 70% of patients in early stage of ARDS (a decrease in $\text{FiO}_2 \geq 20\%$ is expected).
- No baseline features that differentiate between responders and non-responders are known.
- After the patient back to the supine position, the oxygenation might return to the basal supine value, or remain elevated.
- Does not increase survival at the end of the 10-day study period, at the time of discharge from the ICU, or at six months.
- However in the most severely ill and hypoxemic patients with a $\text{Pao}_2/\text{FiO}_2 \leq 88 \text{ mmHg}$, a, SAPS II $> 49$, a high tidal volume $> 12 \text{ ml/kg}$ of PBW, or all three, it may reduce mortality and limit VILI.
- The optimum daily duration is not known. In clinical practice, the duration ranges between six and 12 hours/day.
- The optimum total duration and number of pronations depends on the effects on arterial oxygenation of supine repositioning.
Approaches to therapy and prevention.

- Prior studies on prone positioning were limited by short duration of pronation.
- The Prone-Supine II Study randomized 342 adults at 25 centers to prone position 20 hours per day for the duration of ARDS, or 24 hour supine position.
- No significant change in ICU or 28 day mortality was identified.
- However, the prone position group experienced a statistically significant increased incidence of adverse events including need for additional sedation, airway obstruction, transient hypoxia, hypotension/arrhythmia, and loss of venous access.

Approaches to therapy and prevention.

- **Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA).**
  - In this multicenter, prospective, randomized, controlled trial, they randomly assigned 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position.
  - Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Fio2) of less than 150 mm Hg, with an Fio2 of at least 0.6, a positive end-expiratory pressure of at least 5 cm of water, and a tidal volume close to 6 ml per kilogram of predicted body weight.
  - The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001). The hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI], 0.25 to 0.63).
  - Unadjusted 90-day mortality was 23.6% in the prone group versus 41.0% in the supine group (P<0.001), with a hazard ratio of 0.44 (95% CI, 0.29 to 0.67).
  - The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group.
  - Conclusions In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality.
Approaches to therapy and prevention.

**Effect of Prolonged Methylprednisolone in Unresolving ARDS**

- **Rationale:** Within seven days of the onset of ARDS, many patients exhibit a new phase of their disease marked by fibrotic lung disease or fibrosing alveolitis with alveolar collagen and fibronectin accumulation.

- **Patient selection:** Severe ARDS/ ≥ 7 days of mechanical ventilation with an LIS ≥ 2.5/No evidence of untreated infection

- **Treatment protocol:** Methylprednisolone
  - Loading dose 2 mg/kg
  - 2 mg/kg/24 hours from day 1 to day 14
  - 1 mg/kg/24 hours from day 15 to day 21
  - 0.5 mg/kg/24 hours from day 22 to day 28
  - 0.25 mg/kg/24 hours on days 29 and 30
  - 0.125 mg/kg/24 hours on day 31 and 32

- In patients with unresolving ARDS, prolonged administration of methylprednisolone was associated with improvement in lung injury and MODS scores and reduced mortality.

Meduri GU et al., *JAMA* 1998
Approaches to therapy and prevention.

• Treatment: Corticosteroids
• This study randomized 180 patients with persistent ARDS (7 to 28 days after onset) to methylprednisolone (daily dose 2 mg/kg x 14 days then 1 mg/kg x 7 days) vs. placebo.
• Hospital mortality and 180-day survival were comparable, but patients enrolled 14 or more days after ARDS onset had increased 60-day mortality (35% vs. 8% placebo, p = .02).

Approaches to therapy and prevention.

- This study of 91 patients with severe ARDS has added fuel to the debate over systemic corticosteroid use in acute lung injury.
- The intervention group received steroids within 72 hours of ARDS diagnosis and a slow taper.
- Steroid recipients had decreased duration of mechanical ventilation and ICU stay.
- The higher proportion of patients with catecholamine-dependent shock among controls, cross over from control to steroids in “nonresponders” at day 7, and 2:1 randomization of treatment to control are among the concerns raised since its publication.

Approaches to therapy and prevention.

- **Corticosteroids for ARDS from H1N1 influenza**
  - Databases suggest that 60-70% of patients with severe respiratory failure due to H1N1 received steroids. Brun-Buisson *et al.* looked back at a French registry including 208 patients with H1N1 and ARDS, 83 of whom received steroids. They found a hazard ratio of 2.4 for death associated with steroid administration, rising to 2.8 after applying their propensity scoring model. Receipt of steroids <3 days after intubation increased the association. *AJRCCM* 2011;183:1200-1206.

- Meanwhile, in South Korea, Kim *et al.* retrospectively observed 245 consecutive patients admitted to ICUs with H1N1 in 2009-2010 (162 of whom were intubated). They constructed a case-control analysis (steroids-no steroids, respectively). The steroid group was far sicker, with more ARDS, mechanical ventilation, secondary pneumonias, and also had a high prevalence of receipt of prior corticosteroids. After applying their propensity-matching analysis, the authors conclude that steroids were independently associated with mortality and superinfections (odds ratio 2.2 for death in 90 days). *AJRCCM* 2011;183:1207-1214.
Approaches to therapy and prevention.

- Interestingly, patients with ARDS with higher levels of GM-CSF in their BAL fluid are more likely to survive.
- GM-CSF maintains homeostasis in the lung and is required for proper maturation of alveolar macrophages, which are themselves responsible for surfactant clearance/balance and pulmonary innate immunity.
- GM-CSF also promotes survival and growth of alveolar epithelial cells — the very cells injured in ARDS.

Approaches to therapy and prevention.

- I.V. beta-agonists for ARDS harmed people; BALTI-2 stopped early (RCT, Lancet)
- Injecting beta-agonists continuously into the veins of people with acute respiratory distress syndrome (ARDS) for a week.
- If you spray some albuterol on alveolar epithelial cells in a dish, it upregulates their cAMP production and doubles the rate at which they clear fluid across their basement membranes.
- And in the single-center 2006 BALTI trial, intravenous albuterol given to people with ARDS reduced their plateau pressures by 6 cm H2O and seemed to substantially reduce their “lung water” (measured by thermodilution). Although those getting IV beta-agonists also had a much higher rate of supraventricular arrhythmias.
- What They Did: Fang Gao Smith et al randomized 326 adolescent & adult patients with ARDS to receive a continuous infusion of either salbutamol (albuterol), a short-acting beta agonist, or placebo intravenously for up to 7 days. The trial was funded by the U.K.’s Department of Health.
- Results: When given to people with ARDS, intravenous salbutamol/albuterol hurt people: 55 of 161 patients receiving IV salbutamol died (34%) vs. 38 of 163 receiving placebo (23%), a statistically significant difference. This was at an early interim analysis — the trial was stopped at this point.
- The causes of death were not identifiable with precision, because recording cause of death was not part of the study protocol, and the information had to be sought post-hoc. But among patients receiving albuterol, ten times as many patients had tachycardias or arrhythmias necessitating study drug stoppage, and 10 had lactic acidosis requiring study drug stoppage (vs. 1 in the placebo group).
Approaches to therapy and prevention.

- **Beta-agonist therapy unhelpful for ALI / ARDS (RCT, AJRCCM)**
- Led by Matthay, the ARDSNet folks randomized 282 patients with ALI or ARDS to receive either 5 mg of nebulized albuterol or placebo every 4 hours for 10 days (or until 24 hours after being extubated).
- The trial was stopped early for futility (n=1,000 original enrollment target). There was no difference in the number of ventilator-free days (1’ endpoint), nor in survival to hospital discharge (2’ endpoint). The albuterol patients’ heart rates were 4 beats faster but there were no dysrhythmias or other adverse events to speak of.
Approaches to therapy and prevention.

- Omega-3 fatty acids for acute lung injury/ARDS are useless-to-harmful (OMEGA RCT, JAMA)
- Numerous small (n~100), single-center randomized trials have shown a benefit of omega-3 fatty acids in acute lung injury and ARDS (reduced mortality, length of stay, and organ failure; improved oxygenation and respiratory mechanics).
- A meta-analysis combining these studies suggested a stat. significant benefit in mortality (risk ratio 0.67), ventilator requirement (-5 days), and ICU stay (-4 days).
- In the NHLBI-funded OMEGA study, they randomized 272 adults with ALI/ARDS to receive either twice daily omega-3 fatty acids plus antioxidants, or placebo.
- OMEGA was stopped early for futility, which may have been an understatement: the intervention patients had 3 fewer ventilator-free days (p=0.02), 3 more days in the ICU (p=0.04), and an absolute 10% increase in mortality (26.6% vs. 16.3%, p=0.054, just barely not stat. significant).
Approaches to therapy and prevention.

- Stapleton et al report results of a phase II trial of 14 days of omega-3 fish oil vs. placebo in 90 people with acute lung injury or ARDS.
- There was no difference in the primary endpoint (inflammatory marker IL-8 in BAL fluid), nor in any clinical outcome.
Approaches to therapy and prevention.

  - Statins reduce healthy volunteers’ inflammatory response to inhaled or injected lipopolysaccharide.
  - Craig et al report the results of HARP, in which the UK investigators gave 80 mg of simvastatin or placebo to 60 patients with **acute lung injury and ARDS**, for up to 14 days.
  - There were no differences in mortality (30%), ventilator-free days or ICU/hospital stay.
  - However, the one-third of the treated group who were left to analyze after 14 days had significantly lower SOFA organ dysfunction scores.
  - They also had a non-statistically significant improvement in hemodynamics at day 14 (0 of 9 [simvastatin] vs. 3-4 of 10 [placebo] requiring vasopressors or inotropes, p=0.05-0.09), and significantly lower IL-8 in BAL fluid.
  - No adverse events were noted.
  - Larger trials are underway to explore this further. \( n=60 \).
Approaches to therapy and prevention.

- Several trials have shown that treatment with exogenous surfactant can result in improvement in oxygenation and synthetic surfactant containing recombinant surfactant protein C has excellent activity in animal models.
- A prospective randomized blinded study was performed at 161 centers using this surfactant: recombinant surfactant protein C.
- Surprisingly, surfactant administration had no clinical benefit to patients with severe direct ALI.
- The unexpected lack of improvement in oxygenation, coupled with the results of in vitro tests, suggested that the administered suspension may have had insufficient surface activity.
- This trial is the most recent of a relatively long list of studies failing to show benefits of surfactant administration in adult ARDS.

Approaches to therapy and prevention.

- **FACTT post-hoc**: Transfusion might cure, kill or both during shock & acute lung injury...who knows? (Crit Care)
- FACTT showed less fluids (which could include blood) are better for ALI/ARDS, but transfusion wasn’t controlled and its contribution to the outcomes is unknown.
- So ARDSNet crunched some numbers. Parsons et al parsed the original FACTT data and found all the patients who had septic shock in the first 24 hours (n=285). They further identified those who “should have” gotten blood early after randomization as part of early goal-directed therapy, using all the available hemodynamic data (Scvo2, blood pressure, central venous pressure, and hemoglobin). (n=85). All, of course, also had acute lung injury or ARDS.
- After multivariate analysis, there was no detectable association between transfusion and mortality or ventilator free days.
Approaches to therapy and prevention.

Other Drug Therapy

- Prostaglandin E1 (PGE1) (pulmonary vasodilatation and anti-inflammatory effects on neutrophils/macrophages)
- Aerosolized prostacyclin (PGI2) (selective pulmonary vasodilatation of ventilated lung areas)
- Almitrine (selective pulmonary vasoconstrictor of nonventilated lung areas)
- Surfactant (prevents alveolar collapse and protects against intrapulmonary injury and infection)
- Antioxidants (protect the lung from free oxygen radical production)
- Partial liquid ventilation (recruitment of collapsed areas and anti-inflammatory effect)
- Anti-inflammatory drugs (Ibuprofen - ketoconazole)

No recommendation can be made for their use - Rescue modality in the patient with refractory hypoxia?
Approaches to therapy and prevention.

Combination of different therapeutic approaches?

- Combination of iNO and prone position (Papazian L, et al. Crit Care Med. 1998.)
- Combination of iNO and almitrine (Gallart L, et al. Am J Respir Crit Care Med. 1998.)
- Combination of iNO and iv prostacycline (Kuhlen R, et al. Intensive Care Med. 1999.)
Mechanical Ventilation Treatment

- ARDS Network. **Ventilation with lower tidal volumes as compared with traditional tidal volumes for ALI and ARDS.** N Engl J Med. 2000;342:1301-8. Results of the ARMA study found the use of low (6 ml/kg predicted weight) rather than “standard” (12 ml/kg predicted weight) tidal volumes reduced mortality from 40 to 30%. These results form much of the basis for use of low-stretch/low tidal volume ventilation strategy in acute lung injury.

Amato MBP, Barbas CSV, Medeiros DM, et al. **Effect of a protective-ventilation strategy on mortality in ARDS.** N Engl J Med. 1998;338:347-54. Small, randomized, study famous for using a combination of the lower inflection point of the pressure-volume curve to set PEEP, recruitment maneuvers (CPAP 35-40 cm x 40 sec.), and low-tidal volumes (< 6cc/kg). **28-day mortality was lower in the intervention group,** but the conventional group had an unusually high mortality (71%). Patients overall received higher PEEP than in the ARMA study.
Mechanical Ventilation Treatment

- **Comparisons of High vs. Low PEEP**
  Brower RG, Lanken PN, MacIntyre N, et al. *Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.* N Engl J Med 2004;351:327-36. A NHLBI ARDS net randomized trial comparing high and low PEEP strategies in 549 patients with ALI or ARDS found no significant difference in mortality, ventilator-free days, ICU-free days, or organ failure-free days in the two groups.

- **Meade MO, Cook DJ, Guyatt GH, et al.** *Lung open ventilation study investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.* JAMA 2008; 299:637-45. This study also found no significant difference in 28-day mortality with higher PEEP (28.4 vs 32.3%, p = 0.2) despite lower rates of refractive hypoxemia (4.6 vs. 10.2%, p = 0.01) and reduced pre-defined need for rescue therapies (5.1 vs. 9.3%, p = 0.045). Of note, the target plateau pressure was higher than in other high vs. low PEEP studies (\(\leq 40\) cm H2O).

- **Mercat A, Richard JC, Vielle B, et al.** *Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.* JAMA 2008;299:646-55. The ExPress study compared low vs. high PEEP in 767 patients with ARDS receiving low tidal volume ventilation. In the high-PEEP group, PEEP was adjusted to a target plateau pressure of 28 to 30 cm H2O regardless of oxygenation while target PEEP in the minimal distension group was 5 to 9 cm H2O. Mortality at 28 days did not differ, but the high-PEEP group had a higher median number of ventilator-free days and required fewer “rescue” interventions such as proning. It appears the greatest benefit to a high-PEEP strategy is in patients with more severe lung edema, but whether there is a survival benefit in this subpopulation is still unclear.
Mechanical Ventilation Treatment

Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis.

• Trials comparing higher vs lower levels of positive end-expiratory pressure (PEEP) in adults with acute lung injury or acute respiratory distress syndrome (ARDS) have been underpowered to detect small but potentially important effects on mortality or to explore subgroup differences.

DATA EXTRACTION:
• Data from 2299 individual patients in 3 trials were analyzed using uniform outcome definitions. Prespecified effect modifiers were tested using multivariable hierarchical regression, adjusting for important prognostic factors and clustering effects.

RESULTS:
• There were 374 hospital deaths in 1136 patients (32.9%) assigned to treatment with higher PEEP and 409 hospital deaths in 1163 patients (35.2%) assigned to lower PEEP (adjusted relative risk [RR], 0.94; 95% confidence interval [CI], 0.86-1.04; P = .25). Treatment effects varied with the presence or absence of ARDS, defined by a value of 200 mm Hg or less for the ratio of partial pressure of oxygen to fraction of inspired oxygen concentration (P = .02 for interaction). In patients with ARDS (n = 1892), there were 324 hospital deaths (34.1%) in the higher PEEP group and 368 (39.1%) in the lower PEEP group (adjusted RR, 0.90; 95% CI, 0.81-1.00; P = .049); in patients without ARDS (n = 404), there were 50 hospital deaths (27.2%) in the higher PEEP group and 44 (19.4%) in the lower PEEP group (adjusted RR, 1.37; 95% CI, 0.98-1.92; P = .07). Rates of pneumothorax and vasopressor use were similar.

CONCLUSIONS:
• Treatment with higher vs lower levels of PEEP was not associated with improved hospital survival. However, higher levels were associated with improved survival among the subgroup of patients with ARDS (severe cases).

JAMA 2010 Mar 3;303(9):865-73.
Mechanical Ventilation Treatment

- In a multicenter, randomized, controlled trial conducted at 39 intensive care units in five countries, were randomly assigned adults with new-onset, moderate-to-severe ARDS to HFOV targeting lung recruitment or to a control ventilation strategy targeting lung recruitment with the use of low tidal volumes and high positive end-expiratory pressure.

- The primary outcome was the rate of in-hospital death from any cause. Results On the recommendation of the data monitoring committee, the trial was stopped after 548 of a planned 1200 patients had undergone randomization. The two study groups were well matched at baseline. The HFOV group underwent HFOV for a median of 3 days (interquartile range, 2 to 8); in addition, 34 of 273 patients (12%) in the control group received HFOV for refractory hypoxemia.

- In-hospital mortality was 47% in the HFOV group, as compared with 35% in the control group (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; P = 0.005). This finding was independent of baseline abnormalities in oxygenation or respiratory compliance.

- Patients in the HFOV group received higher doses of midazolam than did patients in the control group (199 mg per day [interquartile range, 100 to 382] vs. 141 mg per day [interquartile range, 68 to 240], P<0.001), and more patients in the HFOV group than in the control group received neuromuscular blockers (83% vs. 68%, P<0.001). In addition, more patients in the HFOV group received vasoactive drugs (91% vs. 84%, P = 0.01) and received them for a longer period than did patients in the control group (5 days vs. 3 days, P = 0.01).

- Conclusions In adults with moderate-to-severe ARDS, early application of HFOV, as compared with a ventilation strategy of low tidal volume and high positive end-expiratory pressure, does not reduce, and may increase, in-hospital mortality.

<table>
<thead>
<tr>
<th>Alternative therapies for ARDS</th>
<th>Study design</th>
<th>Intervention</th>
<th>Results</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical studies</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids 75-78</td>
<td>Randomized clinical trial</td>
<td>Different regimen of methylprednisolone i.v.</td>
<td>No difference in mortality</td>
<td>Should not used in late ARDS (evidence level 1, grade B)</td>
</tr>
<tr>
<td>Statins 79</td>
<td>Retrospective cohort study</td>
<td>Presence and timing of statin administration</td>
<td>Statin use was not associated with improved outcome</td>
<td>Needed more studies</td>
</tr>
<tr>
<td>Surfactant 80, 81</td>
<td>Multiple-center, prospective, randomized, double-blind, placebo-controlled trial, phase III study</td>
<td>Exosurf with DPPC of 13.5 mg/ml, or placebo Continuously aerosolized for 240 mL daily for up to 5 d</td>
<td>No difference in length of mechanical ventilation</td>
<td>Should not used, evidence level 1, grade A</td>
</tr>
<tr>
<td>Nitric oxide (NO) 82-84</td>
<td>Randomized, multicenter studies</td>
<td>5-40 ppm Inhaled NO</td>
<td>No benefits in mortality rate</td>
<td>Should not used, evidence level 1, grade A</td>
</tr>
<tr>
<td>Liposomal prostaglandin E1 85</td>
<td>Randomized clinical trial</td>
<td>Liposomal prostaglandin E1 or placebo infused intravenously for 60 min every 6 hrs for 7 days</td>
<td>No changes in the duration of mechanical ventilation and did not improve day 28 survival</td>
<td>Should not used, evidence level 1, grade C</td>
</tr>
<tr>
<td>Ketoconazole 86</td>
<td>Randomized multicenter trial</td>
<td>Ketoconazole 400 µg enterally up to 21 days or placebo</td>
<td>No mortality benefits and no difference in mortality rate or duration of mechanical ventilation</td>
<td>Should not used, evidence level 1, grade B</td>
</tr>
<tr>
<td>Lisofylline 87</td>
<td>Phase III randomized, double-blind controlled trial</td>
<td>Lisofylline 3 µg/kg/hr every 6 hours for 20 days</td>
<td>No difference in mortality rate or duration of mechanical ventilation</td>
<td>Should not used, evidence level 1, grade C</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitor 88</td>
<td>Multiple-center, double-blind, placebo-controlled trial</td>
<td>Continuous infusion of sivelestat at a dose of 0.16 mg/kg for the duration of mechanical ventilation plus 24 hrs for a maximum of 14 days</td>
<td>Negative trend in long-term mortality rate</td>
<td>Should not used</td>
</tr>
<tr>
<td>Activated protein C 89, 90</td>
<td>Observational and experimental studies</td>
<td>APC (24 µg/kg/h for 96 h) or placebo in a double-blind fashion within 72 hours of the onset of ALI</td>
<td>No difference in 60-day mortality or number of ventilator-free days</td>
<td>Should not used, evidence level 1, grade A</td>
</tr>
<tr>
<td>Beta-adrenergic agonist 91-92</td>
<td>Randomized, controlled trials</td>
<td>Aerosolized albuterol or saline placebo every 4 hours for up to 10 days</td>
<td>Ventilator free days were not significantly different. No differences in hospital mortality</td>
<td>Should not used, needed more studies</td>
</tr>
<tr>
<td>Omega-3 fatty acids 93</td>
<td>Phase II randomized controlled trial</td>
<td>Administration of enteral fish oil or saline placebo for up to 14 days</td>
<td>No differences in organ failure score, ventilator-free days, 60-day mortality or 60-day mortality between groups</td>
<td>Should not used, needed more studies</td>
</tr>
<tr>
<td><strong>Preclinical studies</strong></td>
<td></td>
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<tr>
<td>Cell-based therapies 94-97</td>
<td>Animal studies (mice)</td>
<td>Intrapulmonary administration of MSC or intravenous</td>
<td>Decrease in inflammatory response, improvement of lung injury</td>
<td>Under research</td>
</tr>
<tr>
<td>Keratinocyte growth factor (KGF) 98</td>
<td>Animal studies (rats)</td>
<td>Recombinant human KGF intravenously immediately after irradiation</td>
<td>Severity of lung fibrosis decreased in KGF group</td>
<td>Under research</td>
</tr>
</tbody>
</table>

*The study was stopped prematurely at the recommendation of an external Data and Safety Monitoring Board.*
4-Supportive management (*excluding mech. vent.*). Approaches to therapy and prevention.

Table 3 Current therapeutic strategies available for the management of patients with ARDS/ALI (general supportive measures are not included)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Indication</th>
<th>Benefit</th>
<th>Caution</th>
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</thead>
<tbody>
<tr>
<td>Lung protective ventilation with:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1) Low tidal volume (6 ml/kg)</td>
<td>All ARDS/ALI patients</td>
<td>Improves mortality</td>
<td>Potential for de-recruitment</td>
</tr>
<tr>
<td>2) Moderate PEEP as per ARDS Network guidance(^a)</td>
<td></td>
<td>Reduces circulating inflammatory cytokines</td>
<td>May need increased sedation</td>
</tr>
<tr>
<td>3) Plateau pressure of (&lt;30\ cm H(_2)O)</td>
<td></td>
<td></td>
<td>Haemodynamic deterioration</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>Severe hypoxaemia</td>
<td>Improves oxygenation</td>
<td>Pressure sores</td>
</tr>
<tr>
<td>High frequency oscillatory ventilation</td>
<td>Severe hypoxaemia</td>
<td>Improves oxygenation</td>
<td>Endotracheal tube displacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nursing issues</td>
</tr>
<tr>
<td>Conservative fluid strategies</td>
<td>All ARDS/ALI patients</td>
<td>Improves lung function</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces the duration of mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Low dose early corticosteroids</td>
<td>Early ARDS</td>
<td>Improves oxygenation</td>
<td>ICU myopathy and neuropathy</td>
</tr>
<tr>
<td></td>
<td>Severe hypoxaemia</td>
<td>May provide survival benefit</td>
<td>Do not give after 14 days of onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of infection</td>
</tr>
<tr>
<td>ECMO</td>
<td>Severe ARDS Relatively contraindicated in patients with high pressure ventilatory support for (&gt;7) days</td>
<td>May improve survival when patients transferred to a dedicated centre</td>
<td>Risks of haemorrhage (in particular ICH), risk of large invasive lines</td>
</tr>
</tbody>
</table>

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICH, intracranial haemorrhage; ICU, intensive care unit; PEEP, positive end expiratory pressure.
4-ARDS: updates in Management.

Improves mortality:
• Low Tidal volume strategy.
• Cisatracurium only in very severe ARDS
• Prone Position only in very severe ARDS
• High PEEP only in very severe ARDS
• Transfer to ECMO facility????
• Steroids before day 14????
4-Supportive management (*excluding mech. vent.*). Approaches to therapy and prevention.

- **Clinical Takeaway:** For those keeping score at home, it’s now ARDS 12 (or so), Feeble Humans 4 (for low tidal volume ventilation, high PEEP only in severe ARDS, prone positioning only in severe ARDS, and cisatracurium only in severe ARDS).
5-Prognosis, severity scores; long-term sequelae in survivors.

**Mortality from ARDS**

- ARDS mortality rates - 31% to 74%
- The variability in the rates quoted is related to differences in the populations studied and in the precise definitions used.
- The main causes of death are nonrespiratory causes (i.e., die with, rather than of, ARDS).
- Respiratory failure has been reported as the cause of death in 9% to 16% of patients with ARDS.
- Early deaths (within 72 hours) are caused by the underlying illness or injury, whereas late deaths are caused by sepsis or multiorgan dysfunction.
- There is a controversy about the role of hypoxemia as a prognostic factor in adults. Nevertheless, in some studies, both Pao₂/Fio₂ ratio and Fio₂ were variables independently associated to mortality.

Ware LB. Crit Care Med. 2005.
5-Prognosis, severity scores; long-term sequelae in survivors.

- This study provides the longest and most comprehensive follow-up of ARDS survivors to date, emphasizing the importance of long-term neuromuscular and psychiatric dysfunction despite nearly complete recovery of lung function.
- Non-pulmonary problems are usually dominant in impairment of ARDS survivors.
- Low exercise tolerance, fatigue, and weakness are common a year after discharge.
- Pulmonary function tests usually normalized, other than a diffusion impairment.
- At 12 months, only 6% of subjects had exertional hypoxia, and none of the 109 patients required supplemental oxygen at rest.
5-Prognosis, severity scores; long-term sequelae in survivors.

One-year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

- Persistent functional limitation
  - Extrapulmonary diseases (primarily): Muscle wasting and weakness (corticosteroid-induced and critical-illness-associated myopathy)
  - Entrapment neuropathy
  - Heterotopic ossification
  - Intrinsic pulmonary morbidity (5%): Bronchiolitis obliterans organizing pneumonia
  - Bronchiolitis obliterans

5-Prognosis, severity scores; long-term sequelae in survivors.

• Mortality: Reported mortality rates vary widely. A pooled mortality estimate from a recent systematic review suggests that the mortality for ARDS is between 36 and 44%, with little change over the two decades up to 2006.

• In contrast to this, the ARDS Network clinical trials conducted over the last two decades show a clear decline in mortality among their study populations between 1997 and 2009 (figure 1).

• Several factors may have contributed to the decline in mortality rates, including the introduction of permissive hypercapnia and protective lung ventilation as well as improved supportive measures such as early antibiotics, ulcer and thrombosis prophylaxis, better fluid management, and improved nutritional and other organ support.
5-Prognosis, severity scores; long-term sequelae in survivors.

**Figure 1** Observed 60 day mortality from ARDS Network clinical Trials from 1997 to 2009. ARMA, Acute Respiratory Distress Syndrome Management with Lower versus Higher Tidal Volume (ARMA-6 patients received Vt of 6 ml/kg) (ARMA-12 patients received Vt of 12 ml/kg); ALVEOLI, Assessment of Low tidal Volume and Elevated End-expiratory Volume to Obviate Lung Injury; FACTT, Fluid and Catheter Treatment Trial; ALTA, Albuterol for the Treatment of ALI; OMEGA, Omega-3 Fatty acid, Gamma-Linolenic Acid, and Antioxidant Supplementation in the Management of ALI or ARDS. Adapted with permission from Spragg et al.
Web sites of interest

• ARDS Support Center: www.ards.org
• ARDS Foundation: www.ardsil.com
• National Heart, Lung, and Blood Institute ARDS Network (ARDSNet) www.ardsnet.org
THANK YOU.