Take an evidence-based approach to treating acute lung injury

Recognize and promptly address ALI and ARDS to reduce substantial patient harm.

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During the Vietnam War, wounded soldiers received treatment for their injuries at temporary field hospitals. Survival rates after battle trauma increased because of rapid medical response and the development of new techniques procedures, medicines, and technologies, including mechanical ventilation. A soldiers’ condition described as “shock lung” increased in prevalence and later came to be called acute respiratory distress syndrome (ARDS). Since then, acute lung injury (ALI) has become a common term, and ARDS refers to the more severe form of ALI.

ALI and ARDS are life-threatening conditions that researchers often pair together because of their close relationship. They’re thought to occur at a rate of about 75 cases per 100,000, with a mortality rate between 30% and 50%. Researchers have continued to examine the best way to diagnose ALI and ARDS, study the mechanisms that cause harm, develop the best plan of care and therapeutic interventions, and adopt methods to prevent the problem.

**ALI’s two phases**

Experts at 1994’s North American-European Consensus Conference established four key criteria for ALI and ARDS. ALI criteria are:

- an acute onset of lung injury
- chest X-ray showing diffuse bilateral infiltrates
- a PaO₂/FiO₂ ratio less than 300 mm Hg (normal PaO₂/FiO₂ is 500 mm Hg)
- pulmonary artery occlusion pressure less than 19 mm Hg with no evidence of heart failure.

The same criteria apply to ARDS, except in ARDS, the PaO₂/FiO₂ ratio is less than 200 mm Hg.

Various conditions increase the risk of ALI/ARDS, including pneumonia, aspiration of gastric contents, inhalation injury, near-drowning, reperfusion pulmonary edema, pulmonary contusion, sepsis, severe trauma, extensive burns, multiple blood transfusions, drug overdose, acute pancreatitis, and bone marrow transplantation. Following the initial injury or condition, patients rapidly decline to respiratory failure, with subsequent intubation and mechanical ventilation required in almost all cases.

ALI/ARDS is a two-phase condition: the acute exudative phase and the late or fibroproliferation phase. In the acute phase, soon after the initial injury, neutrophils are called into action by a release of local and systemic cytokines, chemokines, and endotoxins. Part of the inflammatory process, these mediators include a host of agents, such as tumor necrosis factor alfa, various interleukins (such as IL-1, IL-6, and IL-8), platelet-activating factor, nitric oxide, prostacyclin, reactive oxygen species, histamine, and bradykinin. The neutrophils respond to the trigger and move into the pulmonary circulation,
where they adhere to the endothelial walls. They then prompt the release of various inflammatory and vasoactive agents (and release several of their own), before migrating through the endothelial walls of the pulmonary capillaries into the lung parenchyma. The neutrophil activity, along with contributions from eosinophils and macrophages, causes rapid deterioration. The lungs then develop inflammation, increased pulmonary vascular permeability resulting in edema and flooded alveoli, inactivated surfactant, atelectasis, and reduced compliance. Along with the increased work of breathing, the patient develops refractory hypoxemia (marked by a poor response to oxygen therapy) and respiratory failure. Normally, hypoxemia in the pulmonary circulation causes local pulmonary vasoconstriction, which reduces perfusion and helps balance the ventilation/perfusion (V/Q) match. This protective mechanism helps maximize oxygen uptake in the lungs and maintain tissue oxygenation.

But with the development of ALI/ARDS, the pulmonary capillary endothelium loses its capability to act as a barrier (becoming “leaky”), and also becomes faulty in providing the defense mechanism for hypoxic pulmonary vasoconstriction. The resulting V/Q abnormalities contribute to refractory hypoxemia.

During the development of ALI/ARDS, fibroblasts also become activated. Collagen and fibrin deposits begin to collect as coagulation occurs in the flooded alveoli. Some patients "turn the corner" at this point and the repair process begins with a reversal of inflammation and edema, rebuilding of the endothelium and alveolar epithelium, dissolution of the fibrin (fibrinolysis), and replenishing of the surfactant. These patients survive; over time, normal lung function and normal lung architecture return.

If the second phase develops and fibroproliferation occurs, patients move into severe illness, prolonged mechanical ventilation, and often death. A fibrin matrix develops in the alveoli (sometimes called a hyaline membrane). The lungs become more fibrotic and difficult to ventilate as compliance greatly decreases. The inflammation and edema cause airways to narrow, resistance to airflow increases, and areas of consolidation or atelectasis increase.

The cascade of cytokines, chemokines, and endotoxins not only affects the pulmonary system, but also causes harm and reduces normal function in many other organs. Studies have found that mortality isn’t related to respiratory failure, but instead to sepsis syndrome and multiple organ failure.

On a related note, the Food and Drug Administration recognized transfusion-related acute lung injury (TRALI) as the most common cause of mortality associated with transfusion, occurring at a rate of around one case per 5,000 transfusions containing plasma, with mortality in the range of 6% to 23%. In 2004, a consensus panel defined TRALI with criteria similar to that of ALI. The seven TRALI criteria are:

- an acute onset of lung injury
- chest X-ray showing diffuse bilateral infiltrates
- a PaO₂/FiO₂ ratio less than 300 mm Hg (or SpO₂ less than 90% on room air)
- no evidence of left atrial hypertension
- no preexisting ALI before transfusion
- presentation during or within 6 hours of the transfusion
- no timely relationship to an alternative risk factor for ALI (such as aspiration, pneumonia, shock, or sepsis).

Recognizing ALI
Initially, patients developing ALI/ARDS will often be on low levels of oxygen support, but as the disease progresses, the level of support provided by oxygen therapy rapidly increases to a maximum level, with little success of reversing the downward slide in oxygenation. Despite an FiO₂ of 1.0, the patient’s SpO₂ values and blood gas results (SaO₂ and PaO₂) drop as moderate to severe hypoxemia develops. Cyanosis may become apparent in the nail beds and around the lips. Breath sounds will decrease and you may hear crackles, particularly in the gravity-dependent zones of the lungs, as fluid moves into airways and alveoli. Tachypnea and tachycardia appear and the patient shows signs of increased work of breathing, as reflected in increased use of accessory muscles, nasal flaring, and intercostal retractions. Expiratory grunting may be present, which increases intrathoracic pressure and causes a self-generated temporary spike in positive expiratory pressure.

Quick diagnosis
Certain diagnostic studies can help assess the cause of respiratory distress, rule out other possible diagnoses, and confirm the diagnosis of ALI/ARDS.

- A complete blood cell count with differential, blood cultures, urinalysis, and sputum culture with sensitivity help pinpoint infectious causes for the distress.
- Arterial blood gas analysis can reveal hypoxemia and acid-base imbalances.
- Clinicians may use bronchoscopy to assess the condition of the lower airways and obtain samples or washings for pathological studies.
- A chest X-ray evaluates the lungs for consolidation,
pleural effusions, pneumothorax, and other possible causes or contributing factors to the respiratory problem.

- Hemodynamic monitoring assesses the cardiovascular system and verifies the criterion of a relatively low wedge pressure in the pulmonary arterial/left atrial system. This assessment helps distinguish ALI/ARDS (which results in noncardiogenic pulmonary edema) from cardiogenic pulmonary edema, which is reflected by elevated pulmonary capillary wedge pressures.

**Treating the patient**

Research in the treatment for ALI/ARDS is ongoing, and various strategies have met with some success. Because preventing acute respiratory failure is the foremost priority, providing ventilatory support through mechanical ventilation is the primary treatment. Lung-protective ventilation using low tidal volumes, pressure-limited ventilation, and low to moderately high positive end-expiratory pressure (PEEP) to reduce the barotrauma and volutrauma that can occur with mechanical ventilation are preferred.⁶

As the abnormal areas of the lung open and collapse, repetitive shear forces and stresses affect tissues. To help avoid this recruitment and de-recruitment of the collapsed alveoli and airways, an alternative way to achieve lung-protective ventilation is via an open-lung strategy to recruit and stabilize collapsed tissues. (This approach works better in diffuse disease, but may cause harm with more localized, lobar involvement.) Clinicians can choose from many approaches and techniques in open-lung strategy, including sustained high-level continuous positive airway pressure, sighs, intermittent high-level PEEP, and short 2-minute periods of super-PEEP (set at 20 to 40 cm H₂O). None of these approaches, however, stands out as the best choices based on current evidence.⁶

To evaluate the advantages, disadvantages, and risks of different treatment strategies, evidence-based nursing provides a rating scale from Level I to Level V. Level I indicates the most reliable evidence available and Level V indicates a higher risk of bias that overestimates therapy efficacy. The following treatment options stem from an evidence-based study on ALI/ARDS management, which reviewed and evaluated the evidence supporting certain treatments based on their impact on the duration of mechanical ventilation and hospital mortality:⁶

- **Tidal volume** should be set or targeted at 6 mL/kg of a patient's predicted body weight (PBW). Plateau pressure (measured during a brief pause at end inspiration) should be maintained at 30 cm H₂O or less (Level I evidence). This "low tidal volume, low plateau pressures" approach has been the most successful in reducing ventilator days and hospital mortality. Note that this approach doesn't use ideal body weight, which overestimates PBW, and if used would result in a higher tidal volume target than that established by using PBW.⁷ The calculation for PBW uses the following formulas:
  - PBW (in kilograms) for males = 50 + 0.91(height in centimeters - 152.4)
  - PBW (in kilograms) for females = 45.5 + 0.91(height in centimeters - 152.4).

With use of low tidal volume, increased PaCO₂ (hypercapnia) and respiratory acidosis will often occur. Letting PaCO₂ increase and tolerating the acidosis is a strategy called permissive hypercapnia, which is another piece of the lung-protection strategy collection.⁸ PaCO₂ can be permitted to rise gradually; guidelines suggest an increase at the rate of 10 mm Hg/hour up to a maximum of 80 mm Hg/hour. The strategy of allowing the pH to decrease instead of using buffering agents is still controversial, and more research is needed in this area.⁹

- **PEEP** should be used with the low tidal volume strategy previously described. High-level evidence doesn't support setting the PEEP level by using the low inflection point on the pressure-volume curve. PEEP use helps restore functional residual capacity, recruit collapsed alveoli and prevent collapse in unstable alveoli, and improve oxygenation. Prolonged high-level PEEP, however, may cause overdistension and damage to normal alveoli, while the positive pressure may affect venous blood return to the heart with a resultant drop in cardiac output.⁵

The National Institutes of Health (NIH) ARDS Network trial has provided some consensus among investigators and clinicians regarding a workable strategy to balance PEEP and F>O₂ settings.⁷(See NIH ARDS Network protocol.) Using these settings provides a standard and furthers research by reducing variability in practice.

- **High frequency oscillatory ventilation (HFOV)** so far has shown only temporary improvement in oxygenation and no high-level support for reducing mortality, but researchers are calling for larger, high-quality and better-powered studies to examine HFOV. Respiratory rates in HFOV range from 60 to over 900 breaths/minute with low tidal volume.

- **Prone positioning** has high-level evidence that shows it improves oxygenation and may reduce mortality, but again, larger, high-quality studies are needed to establish this treatment as a standard of care. (Problems in published research include use of insufficient time in the
prone position, use of nonstandardized mechanical ventilation strategy, and noncompliance with the study protocol for prone positioning. Prone positioning restores functional residual capacity and alters the V/Q ratio by shifting blood from the posterior bases of the lungs to the anterior plane of both lungs. Patients placed in a prone position shouldn't be turned prematurely, as this interrupts the positive changes associated with prone positioning. Patients have tolerated prone positioning for up to 20 hours at a time, but there's no consensus as to how long a patient should remain prone.

- Continuous lateral rotational therapy and kinetic bed therapy are also considerations in positioning patients with ALI/ARDS. Rotational and kinetic therapies have some evidence of reducing ventilator-associated pneumonia, reducing ventilator and ICU days, and improving oxygenation. These studies weren't restricted to the ALI/ARDS population, so additional studies are required. Cost-benefit analysis may also influence the use of rotational therapy and kinetic therapy because of the high rental costs for the equipment.

- Partial liquid ventilation uses perfluorocarbon in conjunction with mechanical ventilation to fill the lungs to functional residual capacity. This liquid works as an agent in which oxygen and carbon dioxide can diffuse. This method is also involved with recruiting and stabilizing alveoli whose surfactant layer isn't functioning well, and cleansing the alveoli of the cells and mediators of inflammation. Partial liquid ventilation reduces the inflammatory response and prevents increase in lung injury, but it doesn't appear to reduce mechanical ventilation days or mortality.

- Inhaled nitric oxide (INO) provides direct drug delivery to the pulmonary system and brings about smooth muscle relaxation and vasodilation. INO provides a short-term improvement in pulmonary artery pressure and in oxygenation. At this time, INO appears to have a role in short-term rescue therapy.

- Extracorporeal membrane oxygenation (ECMO) and surfactant replacement therapy (SRT) are under investigation by researchers for ALI/ARDS treatments. The conclusion in the evidence-based evaluation of ECMO shows no benefit to the patient with a severe case of ARDS (Level II evidence). SRT shows no improvement in oxygenation, no decrease in ventilator days, and no decrease in mortality for the patient with ALI/ARDS, according to Level II evidence.

- Pharmacologic therapy is aimed at reducing the inflammatory response. Researchers have studied various agents, including ibuprofen, ketoconazole (which has anti-inflammatory properties), pentoxifylline (which blocks neutrophil activation), and lisophylline (a derivative of pentoxifylline). None of these agents have strong evidence of benefiting patients in the early stage of ALI/ARDS.

N-acetylcysteine and procysteine (antioxidants) are supported by Level II evidence that they'll reduce the duration of ALI days or improve the lung injury score. High-dose methylprednisolone has the same level of evidence supporting its use in patients with unresolved ARDS (7 days or more duration) but isn't supported for use in cases of early ARDS. In two specific cases, experts recommended high-dose steroids. For patients with Pneumocystis carinii pneumonia and ARDS, high-dose corticosteroids have Level I support. For patients who have ARDS as a result of fat embolization, there's mid-level support for administration of high-dose steroids.

- Fluid management is a problem in ALI/ARDS because of the change in the capillary endothelium, where permeability is increased and edema occurs due to the leakage of protein-rich plasma. Level II evidence supports a strategy of reducing extravascular lung water, which can improve oxygenation and decrease ventilator days and mortality. An ongoing ARDS Network study of fluid management should shed new light on the process, once it's completed.

- Nutritional support always needs special considera-

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**NIH ARDS Network protocol**

Below are the recommended $F_{O_2}$/PEEP combinations from the NIH ARDS Network protocol. At the given $F_{O_2}$, use the lowest PEEP that offers acceptable oxygenation.  

<table>
<thead>
<tr>
<th>$F_{O_2}$</th>
<th>PEEP (cm H$_2$O)</th>
</tr>
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<tbody>
<tr>
<td>0.30</td>
<td>5</td>
</tr>
<tr>
<td>0.40</td>
<td>5 or 8</td>
</tr>
<tr>
<td>0.50</td>
<td>8 or 10</td>
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<tr>
<td>0.60</td>
<td>10</td>
</tr>
<tr>
<td>0.70</td>
<td>10, 12, or 14</td>
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<tr>
<td>0.80</td>
<td>14</td>
</tr>
<tr>
<td>0.90</td>
<td>14, 16, or 18</td>
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<tr>
<td>1.0</td>
<td>18, 22, or 24</td>
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tion for patients on mechanical ventilation. Because ALI/ARDS carries a high metabolic demand, strong nutritional support must meet the demand from the increased metabolism and provide the substrates needed for new tissue development. Recent studies have shown that polyunsaturated fatty acids and gamma-linolenic acid work toward reducing vascular permeability, platelet aggregation, and some of the proinflammatory agents; they also may increase oxygenation. Based on the evidence, there’s Level I support for using polyunsaturated fatty acids such as eicosapentaenoic acid and gamma-linolenic acid.  

**Early detection**

Earlier detection of high-risk patients can help to prevent ALI/ARDS. Be sure to use aspiration precautions, especially with patients who may have swallowing difficulty, those receiving feeding tubes, and patients with diminished or loss of gag reflex. Clinicians must follow infection control measures with all patients, including hand hygiene measures, proper wound care, and invasive-catheter maintenance. Sedation and pain management make patients more comfortable and can reduce the risk of self-extubation. The latest evidence-based guidelines from the Institute for Healthcare Improvement recommend giving ventilator patients a “sedation vacation” once a day to help reduce the risk of ventilator-associated pneumonia. Some patients may need pharmacologic paralysis to reduce oxygen requirements and decrease metabolic demands. Mechanical ventilation and PEEP increase the possibility of pneumothorax, so perform careful assessment for tension pneumothorax. The three mainstays for care are:  
* preventing complications  
* providing adequate support  
* giving the disease time to resolve.

**Educate patients**

Many patients with ALI/ARDS are fully aware of their surroundings despite being in critical condition. Provide education regarding mechanical ventilation (including machinery, ventilator monitors and alarms, the endotracheal tube, and suctioning) to both the patient and family. Some patients may benefit from using communication tools, such as letter boards or symbol charts. With the high rate of mortality, extend special related consideration and education to both the patient and family. If the disease resolves, it may take months for the patient to recover and some residual effects may never clear completely. If the disease worsens, you may need to discuss terminal withdrawal of life support and end-of-life issues. Encourage patients to be hopeful, but temper your message with reality. You can find well-written education materials and suggestions for support resources on the Internet at the ARDS Support Center, [http://www.ards.org](http://www.ards.org).  

**First, do no harm**

ALI and ARDS are complex and serious conditions that require many resources and multidisciplinary teamwork. As research continues to focus on the most effective treatment measures, stay abreast of the findings and use wisdom when putting together different strategies. “First, do no harm” should top your list when caring for patients with ALI/ARDS. Evidence-based practice guidelines provide a way to rank care options. Nevertheless, sometimes the art and science of medicine don’t walk the same path at the same time, so instinct plays an important role as you knit together a care plan. ALI/ARDS treatment may become more cause-specific (such as TRALI), and several approaches may help to handle the entire spectrum of the disease. 

**REFERENCES**


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