The term acute respiratory distress syndrome (ARDS) was first coined in 1967 to define a clinical syndrome categorized by progressive hypoxemia, dysnea, and increased work of breathing that is unresponsive to standard respiratory therapy. Acute respiratory distress syndrome presents as acute respiratory failure with noncardiogenic pulmonary edema and severe hypoxemia. Historically, this syndrome of potentially fatal pulmonary complications described in critically ill patients was further divided into acute lung injury (ALI) and ARDS, with ALI representing a more mild presentation of ARDS. More recently, the concept of ALI has been replaced with mild, moderate, and severe classifications for ARDS.

Despite the substantial progress made in understanding the mechanism of this disease process, ARDS continues to be a major clinical concern. The estimated prevalence in the intensive care unit (ICU) ranges from 4% to 9%, with up to 50% of patients with mild ARDS progressing to moderate or severe forms of the disease. Acute respiratory distress syndrome is associated with substantial mortality rates as high as 46%. In addition, ARDS is a major contributor to health care costs, with approximately $25,000 to $75,000 spent treating each episode. Prompt recognition of the clinical syndrome and initiation of management strategies are required to minimize mortality and improve outcomes in affected individuals. This article provides an overview of ARDS with a specific focus on current and evolving pharmacological treatment strategies for this potentially devastating disease state.

**Diagnosis and Causes**

The most recent representation of the ARDS diagnostic criteria is reflected in the Berlin definition, which was updated in 2011 from the original definition developed in 1994 by the American European Consensus Conference on ARDS. According to the Berlin definition, for a diagnosis of ARDS to be confirmed, the disease state must be characterized by acute onset of bilateral infiltrates evident on chest radiograph and a pulmonary artery wedge pressure of 18 mm Hg or less with no clinical evidence of left atrial hypertension. The degree of severity...
Pathophysiology and Clinical Course

Acute respiratory distress syndrome can be characterized by 3 progressive clinical stages, the exudative, proliferative, and fibrotic phases (Table 1). The lungs move through this series of phases, regardless of the initial cause of the lung injury. The specific time frames associated with each phase vary considerably in the existing literature. In the initial exudative phase, also called the acute phase, widespread damage to the alveolar epithelium is present. The compromised epithelium increases the permeability of the alveolar-capillary barrier allowing fluid, rich in protein, to accumulate in the alveoli. Continued damage to the epithelium occurs secondary to release of proinflammatory mediators. Cytokines recruit neutrophils to the lungs, causing production of reactive oxygen species and proteases. Alveolar damage and impairment of surfactant production ultimately causes alveolar collapse and impaired gas exchange.

During the proliferative stage, also known as the subacute phase, the pulmonary edema seen in the exudative phase begins to resolve. During this time, the membranes within the alveoli have become overwhelmed by plasma proteins, fibrin, and cellular debris. Multiple detrimental pathways are activated causing impaired surfactant production, enhanced neutrophil activation, and stimulation of the complement and coagulation cascades. Type II alveolar cells proliferate during this phase, which is the body’s initial attempt to repair the lung injury. Unfortunately, the inflammatory mediators produced within the lungs commonly migrate into the bloodstream causing cellular apoptosis in other organs. Mortality is often not associated with hypoxemia or hypercapnia but rather from multisystem organ dysfunction.

The fibrotic, or chronic, phase is the final stage of ARDS. Not all patients progress to the later stages of the disease process, as some experience an uncomplicated course and recover quickly. Collagen deposition leads to pulmonary fibrosis, which is the hallmark feature of late-stage ARDS. Fibrosis can compromise the pulmonary vascular area by destroying alveoli and commonly leads to chronic inflammation. Recovery from ARDS begins to occur as a result of a rise in alveolar type II cells, which promote fluid removal. Type II cells begin to differentiate into type I cells returning the epithelial layer to normal and ultimately providing disease resolution.

Pharmacological Treatment Strategies

Treatment of ARDS occurs through a combination of strategies that attempt to reduce pulmonary edema while reversing oxygen-exchange issues. The only treatment option that has shown to reduce mortality rates is lung-protective mechanical ventilation. A multitude of different pharmacological agents have been investigated for the treatment of ARDS with most failing to show consistent clinical benefit. Deciding on a management strategy for these patients can be challenging, because of the complexity of the disease and conflicting existing evidence. Although the most important aspect in the treatment of ARDS is lung-protective mechanical ventilation, this column focuses on the pharmacological options that can assist in the supportive management of this disease process (Table 2).

Corticosteroids

Corticosteroids have been studied for years in the prevention and treatment of ARDS because of the anti-inflammatory and immunomodulatory characteristics they exhibit. Beneficial effects are due to inhibition of the inflammatory cascade at different stages of immune-mediated injury to the lung. Glucocorticoids inhibit the NF-κB signaling pathway, which in turn inhibits interleukin 1, interleukin 6, and tumor necrosis factor α, which are all inflammatory mediators in the process of ARDS. In addition, steroids inhibit interleukin

Copyright © 2015 American Association of Critical-Care Nurses. Unauthorized reproduction of this article is prohibited.
3, interleukin 5, and interleukin 8 while amplifying the antifibrotic properties of cortisol, promoting T-cell stimulation, impairing fibroblast proliferation, and minimizing collagen deposition. Potential benefit must be weighed against possible risks, including hyperglycemia, impaired wound healing, enhanced susceptibility to future infections, and extended muscle weakness.

Corticosteroids have been studied in the different phases of ARDS and are most efficacious in the early and late phases. Many randomized clinical trials have shown a decrease in ICU mortality rate, ventilation days, and inflammatory markers. In the latest study by Meduri et al, low-dose methylprednisolone administered in the first 72 hours after ARDS diagnosis resulted in reduced days on mechanical ventilation and in the ICU. In an earlier study, Steinberg et al used a moderate dose of methylprednisolone started 7 to 28 days after the diagnosis of ARDS. This study showed that although methylprednisolone increased the number of ventilator-free days, the mortality rates were comparable between groups. As clinical trials evolve, the trend continues to show beneficial results in ARDS with treatment of corticosteroids. In 2008, the Society of Critical Care Medicine published the latest recommendations for the use of corticosteroids in the treatment of ARDS. Moderate-dose glucocorticoid, defined as methylprednisolone 1 mg/kg as a load over 30 minutes followed by 1 mg/kg over 24 hours per day via continuous infusion for 14 days with slow-dose tapering, is recommended.

Neuromuscular Blocking Agents
Neuromuscular blocking agents are commonly used in patients with severe gas-exchange deficiencies to facilitate mechanical ventilation when sedation is insufficient. Skeletal muscle inhibition produced through the use of neuromuscular blocking agents eliminates patient effort in the breathing process. Facilitation of paralysis helps reduce the risk of ventilator-induced injury by improving chest wall compliance, preventing patient-ventilator dyssynchrony, minimizing inflammatory mediator release, reducing overinflation of the lungs, and decreasing oxygen demand. However, older studies have reported conflicting evidence describing that the use of neuromuscular blocking agents may potentially be associated with prolonged neuromuscular weakness that may make weaning ventilation more challenging.

Inhaled Vasodilators
Inhaled vasodilators, including nitric oxide and prostacyclins, selectively lead to vasodilation within the pulmonary vasculature that assists in improving oxygenation status without substantial adverse effects on systemic hemodynamics. Nitric oxide dilates the vasculature by increasing conversion to cyclic guanosine monophosphate resulting in smooth muscle relaxation. Prostacyclins, such as epoprostenol and alprostadil, act on the prostaglandin receptors to increase levels of cyclic adenosine monophosphate to cause relaxation of the vasculature. The vasodilation produced by these agents also may lead to other beneficial pulmonary and cardiovascular effects, including reduced pulmonary vascular resistance, minimized right ventricular afterload, and increased right ventricular stroke volume. In addition, nitric oxide may impede

---

### Table 1: Clinical Phases of Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>Approximate Time Frame</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exudative</td>
<td>Days 1-6</td>
<td>• Injury to the endothelium and epithelium with increased permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Accumulation of fluid in alveoli</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Accumulation of inflammatory markers in lungs</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Days 7-14</td>
<td>• Reabsorption of pulmonary fluid overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Proliferation of type II alveolar cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intensification of inflammatory and coagulation pathways</td>
</tr>
<tr>
<td>Fibrotic</td>
<td>After day 14</td>
<td>• Repair of alveolar epithelium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary fibrosis caused by collagen deposition</td>
</tr>
</tbody>
</table>

*Developed from the studies by Shafeeq and Lat and Matthay and Zemans.*

---

Copyright © 2015 American Association of Critical-Care Nurses. Unauthorized reproduction of this article is prohibited.
**Table 2: Summary of Pharmacological Treatment Options for Acute Respiratory Distress Syndrome**

<table>
<thead>
<tr>
<th>Class</th>
<th>Commonly Studied Agents</th>
<th>Dosing</th>
<th>Potential Beneficial Outcome</th>
<th>Significant Adverse Effects</th>
<th>Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Methylprednisolone</td>
<td>1 mg/kg per day</td>
<td>Decreased ICU mortality rate, ventilation days, and inflammatory markers</td>
<td>Hyperglycemia, impaired wound healing, enhanced susceptibility to infections, muscle weakness</td>
<td>Blood pressure, blood glucose, electrolytes</td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td>Cisatracurium Bolus: 0.1-0.2 mg/kg Continuous: 0.5-10 μg/kg per minute</td>
<td>Reduced mortality rates, ventilation days, and days with organ failure</td>
<td>Prolonged neuromuscular weakness</td>
<td>Twitch response measured by peripheral nerve stimulation, level of sedation</td>
<td></td>
</tr>
<tr>
<td>Inhaled vasodilators</td>
<td>Nitric oxide b</td>
<td>5-20 ppm</td>
<td>Improved oxygenation status</td>
<td>Inhaled formulation generally safe, rare methemoglobinemia, bleeding events, kidney injury</td>
<td>Arterial blood gas, oxygen saturation, methemoglobin</td>
</tr>
<tr>
<td>Exogenous surfactant replacement</td>
<td>Beractant b</td>
<td>~100 mg lipids/kg</td>
<td>Improved oxygenation status</td>
<td>Bradycardia</td>
<td>Heart rate</td>
</tr>
<tr>
<td>β₂-Adrenergic agonists</td>
<td>Salbutamol b (albuterol)</td>
<td>15 μg/kg per hour</td>
<td>Lower lung water content and plateau pressure</td>
<td>Vasodilatory effects, tachycardia, cardiac ischemia</td>
<td>Heart rate, blood pressure</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Ketoconazole b</td>
<td>200-400 mg daily</td>
<td>May help prevent development of ARDS</td>
<td>Drug interactions, hepatic injury</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>N-acetylcysteine b</td>
<td>1-10 mL of 20% or 2-20 mL of 10% every 2-6 h</td>
<td>Improvement in lung injury scores</td>
<td>Generally well-tolerated</td>
<td>Allergic reaction</td>
</tr>
</tbody>
</table>

*Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ppm, parts per million.

*a Developed from references 2, 4, and 9 to 20.

*b Off-label use.*
neutrophil and platelet activation seen in acute inflammation. Prostacyclins are increasingly becoming the vasodilator of choice due to lower cost compared with nitric oxide. Existing evidence demonstrates that inhaled vasodilators have not been associated with reduced ventilator days or mortality rates. However, this inhaled therapy may be beneficial in improving oxygenation, so it should be considered in patients with refractory hypoxemia.

Exogenous Surfactant Replacement

The body’s natural surfactant supply is composed of 90% lipids and 10% protein and is responsible for preventing alveolar collapse by reducing surface tension within the lung. In addition, surfactant possesses anti-inflammatory properties, enhances phagocytic cell activity, and scavenges free oxygen radical species. Because of the disruption in the endogenous surfactant system in ARDS, the administration of exogenous surfactant appears to be a reasonable treatment strategy. Surfactant was originally administered as an aerosolized product, but tracheal instillation is now preferred because of concerns over low levels of alveolar deposition with the aerosolized formulation. Use of surfactant has not been shown to have beneficial effects on mortality rates or ventilator-free days, but oxygenation status was improved. Efficacy of exogenous surfactant may be questionable because synthetic products may be easily inactivated in the lungs and large volumes are needed to cover the lung surface area. Because of the widespread benefit seen in pediatric lung injury trials, further investigation of the use of exogenous surfactant in adult ARDS is warranted.

β2-Adrenergic Agonists

β2-Adrenergic agonists can enhance fluid clearance from the alveolar space. These agents increase sodium and chloride transport across the epithelial membrane via the Na+/K+ ATPase pump, which subsequently causes water to move in the direction of the electrolyte shift. Two potential mechanisms have been proposed to explain β2-agonist effect on fluid clearance, including augmentation of intracellular cyclic adenosine monophosphate upregulating the Na+/K+ ATPase pump and minimizing permeability between the alveolar-capillary barriers. Beneficial effects may also be seen due to cytoprotection and reduced endothelial permeability. β2-Agonists have been evaluated through both the intravenous and inhaled routes in clinical trials with inhaled formulations demonstrating a superior adverse effect profile. The place in therapy of these agents may be limited because of the risk of detrimental cardiac side effects, including tachyarrhythmias and cardiac ischemia.

Ketoconazole

In addition to antifungal properties, ketoconazole also may play a role in the treatment of ARDS because of its anti-inflammatory properties. Ketoconazole inhibits formation of thromboxane A2, which is responsible for strong vasoconstriction. In addition, ketoconazole impairs production of leukotrienes, which, when they accumulate, attracts other proinflammatory mediators to the site of injury. Release of cytokines from macrophages located within the alveoli also is hindered with the use of ketoconazole. Studies have shown that the use of ketoconazole may help prevent the development of ARDS, but it has no impact on the mortality rate in patients with established disease. Significant barriers impede routine use of ketoconazole in critically ill patients, including a multitude of drug interactions and the need for an acidic environment for absorption through the enteral route.

Antioxidants

Antioxidant therapies have been proposed as a potential treatment strategy because reactive oxygen species, produced by neutrophils and macrophages, contribute to tissue damage in ARDS. N-acetylcysteine, which is traditionally used for acetaminophen overdoses, serves as a glutathione precursor. Glutathione is a natural antioxidant found in healthy lung tissue, but concentrations are depleted in patients with ARDS. The use of enteral nutrition high in omega-3 fatty acids may provide an additional source of antioxidant supplementation. Vitamins E and C also can be provided to minimize oxidative stress caused by ARDS. Overall, evidence suggests that antioxidant therapy likely offers no mortality benefit but may reduce the extent of lung injury.

Statins

HMG (3-hydroxy-3-methyl-glutaryl) CoA-reductase inhibitors, which are more commonly known as statins, possess multiple physiological benefits in addition to their ability to lower cholesterol level. Statins are thought to attenuate many underlying mechanisms that cause...
ARDS. In animal and human models, statin use has reduced local and systemic inflammatory processes as well as histological evidence of lung injury.\textsuperscript{21} Recent large-scale, randomized clinical trials have not found any clinical benefit to the use of statins in ARDS. Lack of improvement in outcomes combined with a questionable safety profile has led to statins no longer being recommended for the treatment of ARDS.\textsuperscript{21,22}

Emerging Treatment

The emerging concept of regenerative medicine, including stem cell therapy and growth factors, can assist in the healing of damaged lung tissue. Contact between stem cells and the alveoli facilitates advantageous effects including anti-inflammatory and immunomodulatory properties and may improve integrity of the endothelial barriers.\textsuperscript{19,23} Mesenchymal stem cells are considered low in their immunogenicity, which opens up the option for use in different disease states. Both animal and human models have shown potential benefit of mesenchymal stem cell therapy for ARDS.\textsuperscript{23} The optimal route of delivery is still under investigation, with stem cells being administered directly into the lung in recent human models.\textsuperscript{19}

Keratinocyte growth factor (KGF) plays a pivotal role in repair of lung injury. Endogenous KGF assists in the proliferation of type II alveolar cells in ARDS, which are responsible for improving tissue repair. In addition, KGF may play a helpful role during the injury process of the disease by enhancing fluid clearance from the alveoli and minimizing endothelial permeability and edema.\textsuperscript{12} Palifermin, an intravenous formulation of KGF, is being investigated in a phase II clinical trial.\textsuperscript{24} Conversely, levels of vascular endothelial growth factor have been found to be higher than normal in patients with ARDS. This growth factor is associated with control of vascular permeability. Vascular endothelial growth factor inhibitors could be a potential future therapeutic option.\textsuperscript{19}

Conclusion

Since the initial recognition of ARDS in 1967, substantial advancement has occurred in understanding the pathophysiology and treatment strategies for this disease process. Declining mortality rates in the past decades can be attributed to lung-protective ventilation combined with enhanced supportive measures, particularly corticosteroids and neuromuscular blocking agents. Because of the persistence of relatively high mortality rates and serious complications associated with ARDS, there continues to be significant effort in discovering pharmacological agents that improve clinical outcomes. In the coming years, we can expect that new treatment strategies will be investigated and available for use in the management of ARDS.

REFERENCES


