

## Acute lung injury in 2003

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During the past several decades, clinical investigators world-wide have continued to study the causes, pathophysiology, and treatment strategies for acute lung injury (ALI). This syndrome, which is characterized by nonhydrostatic pulmonary edema and hypoxemia associated with a variety of etiologies, is slowly becoming better understood as a result of these efforts.

### AMERICAN-EUROPEAN CONSENSUS COMMITTEE

Ten years ago, the American-European Consensus Committee (AECC) on the Acute Respiratory Distress Syndrome (ARDS) was formed to focus on the complex issues relating to investigations of ARDS. Until then, investigations had been hampered by lack of a uniform definition of the syndrome. The Committee recommended that ALI be defined as “a syndrome of inflammation and increased permeability associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension”<sup>[1]</sup>.

ALI may be associated with systemic injury, such as sepsis or multiple trauma, or with primary lung injury, such as aspiration or pneumonia. It is not yet entirely clear whether the pathophysiology, susceptibility to different treatments, and natural history are different between primary and secondary ALI. The operational definition for ALI and ARDS is shown in Tab 1. AECC committees also reported on potential mechanisms of ALI, risk factors, prevalence, and relevant outcomes, and on mechanisms that might promote clinical study coordination<sup>[1]</sup>.

A second report of the AECC was published in 1998<sup>[2]</sup>. This report called attention to the heterogeneous involvement of the lung parenchyma in ARDS and the possibility that ventilator induced lung injury might complicate clinical care. The subcommittee on pharmacologic treatment recognized a wide variety of interventions that might benefit patients with ARDS and recommended development of a network of committed, experienced clinical investigators to systematically evaluate new therapeutic agents in large-scale clinical trials. Although a broad international network for studying ARDS is yet to be established, an ARDS network was

**Tab 1. AECC criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)<sup>[1]</sup>.**

	Timing	Oxygenation	Chest radiograph	Pulmonary artery wedge pressure
ALI criteria	Acute onset	$p_{aO_2}/F_{iO_2} \leq 300$ mmHg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	$\leq 18$ mmHg or no clinical evidence of left atrial hypertension
ARDS criteria	Acute onset	$p_{aO_2}/F_{iO_2} \leq 200$ mmHg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	$\leq 18$ mmHg or no clinical evidence of left atrial hypertension

$p_{aO_2}$ =partial pressure of oxygen in arterial blood;  $F_{iO_2}$ =fraction of oxygen in inspired gas; PEEP=Positive end expiratory pressure.

formed in 1994 in the United States through the National Heart, Lung, and Blood Institute (NHLBI).

### **ARDS NETWORK OF NATIONAL HEART, LUNG, and BLOOD INSTITUTE, NIH**

This ARDS Network currently has 19 clinical centers (comprised of 44 hospitals) and one Clinical Coordinating Center. Each clinical center is represented on a Steering Committee that reviews and develops proposed clinical trials. Centralized data management, analysis, and other coordinating functions are provided by the Clinical Coordinating Center. Subcommittees of the Steering Committee develop and review protocols and publications and consider ethical issues. An independent Protocol Review Committee evaluates the scientific merit of proposed protocols. The final step in protocol review is provided by a Data and Safety Monitoring Board (DSMB) composed of experts in critical care and pulmonary medicine, statistics, and ethics. This DSMB advises the NHLBI on the merits of a protocol, and, once that protocol is implemented, on the conduct of the study including data quality and analysis, recruitment, and ethics.

To date, six clinical trials have been implemented. In several cases, these trials have been conducted in parallel using a matrix design so that, for example, study of a ventilation strategy and study of a pharmaceutical agent may be performed simultaneously.

The initial clinical trial completed by the Network was a randomized control trial of ketoconazole in patients with acute lung injury. This agent was studied because of its anti-inflammatory actions noted both in pre-clinical studies and in a prior phase two clinical trial that suggested potential benefit in patients with or at risk of ARDS<sup>[3]</sup>. The study of ketoconazole was completed in January 1997 and found ketoconazole to be ineffective in reducing mortality or duration of mechanical ventilation<sup>[4]</sup>.

A second trial compared lisofylline, an anti-inflammatory and anti-oxidant drug which also had shown promising results in phase two trials of immunosuppressed patients, to placebo. This agent also showed no evidence of providing beneficial effects in patients with ALI/ARDS, and the clinical trial was stopped by the DSMB at the first interim analysis after enrollment of 235 patients (116 and 119 patients into the drug and placebo groups, respectively)<sup>[5]</sup>.

A third clinical trial examined lower versus higher

tidal volume ventilation strategies in the treatment of patients with early acute lung injury<sup>[6]</sup>. Substantial pre-clinical results and conflicting results from small clinical trials provided rationale for this study. In this prospective randomized controlled trial, 861 subjects were enrolled. The mortality of 39.8 % in patients receiving high-volume ventilation contrasted with 31.0 % in patients receiving lower volume ventilation. This trial has profoundly influenced the management of patients with ALI and is predicted to result in significant improvement in survival from ALI.

A fourth clinical trial has examined the role of higher positive end-expiratory pressure (PEEP) versus lower levels of PEEP in conjunction with the low tidal volume ventilation strategy. The rationale for this study was based on a prior study of patients with ARDS in which a remarkable improvement in survival was shown when this "open lung" approach was used<sup>[7]</sup>. After enrollment of 550 patients, it was determined that there was no further improvement in survival when higher levels of PEEP were used compared to the survival seen when lower levels of PEEP were used. Although this study was terminated for futility, it should be noted that two additional trials to test this hypothesis further are in progress in Canada and Europe.

Two additional Network trials are currently in progress. The first of these is a trial examining two different strategies for managing intravenous fluids and fluid balance in patients with ALI. A liberal fluid strategy that would be predicted to improve circulation and organ perfusion is contrasted with a fluid conservative strategy that would be predicted to avoid excess accumulation of fluid in the lungs. Using a matrix design, investigators also monitor patients in this trial with either a pulmonary artery catheter or a central venous catheter to determine which monitoring mode might lead to a superior outcome. This question arose from a retrospective examination that suggested the use of a pulmonary artery catheter might be harmful<sup>[8]</sup>. This trial, which is expected to enroll 1000 patients, currently has enrolled approximately 400 patients and is ongoing.

Finally, a sixth trial that is currently in progress is a study of the effect of corticosteroids in the fibroproliferative stage of ARDS. Rationale for this study is provided by a small randomized control trial that suggested that corticosteroids may be useful in the management of late-phase ARDS<sup>[9]</sup>. To test this hypothesis, a randomized double-blind trial that compares corticosteroids to placebo in severe late-phase ARDS identified

after seven days is underway. It is the objective of this study to determine if the administration of methylprednisolone will reduce mortality and morbidity. This study will accrue a maximum of 180 patients and currently has recruited approximately 150.

During the conduct of these trials by the ARDS Network, several questions were raised by non-participating clinical investigators about the propriety of the trial<sup>[10]</sup>. Specifically, these investigators postulated that the low volume ventilation strategy, which appeared so beneficial in comparison to high volume ventilation, appeared superior because high volume ventilation was excessively harmful and was outside the standard of care. Further, it was argued that clinical trials should include a "standard care" arm, although criteria for defining that level of care were not made clear. Because of these concerns, the studies using the low volume ventilation strategy were put on hold, and investigation by the Office of Human Research Protections of the US Department of Health and Human Services was initiated. After intense examination, involving two separate panels of experts in critical care medicine, statistics, and ethics, the studies were found to be well conceived and of value. Arguments challenging the validity of the ARDS Net study have been effectively rebutted<sup>[11]</sup>, and low volume ventilation remains the strategy of choice in the care of patients with ALI/ARDS.

#### ADDITIONAL TREATMENT FOR ALI/ARDS

Several additional treatments are under investigation for the treatment of ALI/ARDS, and two will be discussed briefly.

High-frequency oscillatory ventilation, has recently been evaluated in a study of 148 adults with ARDS who required a PEEP level of  $\geq 10$  cmH<sub>2</sub>O<sup>[12]</sup>. Patients were randomized to receive either high-frequency oscillatory ventilation or conventional ventilation. The former strategy is proposed to reduce alveolar overdistension and injurious collapse and reexpansion of alveoli. The patients receiving high-frequency oscillation had more rapid early improvement in gas exchange, and a thirty day mortality of 37 %, compared to 52 % for the group receiving conventional ventilation. Further studies with this method of mechanical ventilation will hopefully, confirm the benefit associated with use of oscillatory ventilation.

Finally, the use of exogenous lung surfactant continues to be explored as a treatment for ALI/ARDS. As

reviewed recently, critical variables associated with this treatment include the choice of surfactant preparation, mode of administration, amount of surfactant to deliver, volume in which to deliver it, frequency and duration of retreatments, and, finally, the ventilation strategy during and after treatment<sup>[13]</sup>. In the first phase three trial of exogenous surfactant, aerosolized Exosurf<sup>®</sup> was administered for up to five days<sup>[14]</sup>. Results of this study were conclusively negative. Thirty day mortality in both the treated and placebo group was 41 %, and no differences were seen when groups were stratified by APACHE III score or etiology. This trial was most likely negative because of inadequate delivery of surfactant to the distal airspaces.

Following two hopeful phase two trials of Venticute<sup>®</sup><sup>[15,16]</sup>, two phase three trials of this surfactant were conducted. Parallel trials in North American and in Europe/South Africa included 221 and 227 patients, respectively, with ARDS associated with a variety of inciting events. No significant differences in survival were detected between groups treated with or without rSP-C surfactant<sup>[17]</sup>. However, a *post hoc* analysis of the subgroup ( $n=225$ ) with ARDS secondary to primary pulmonary events (pneumonia and/or aspiration) disclosed a trend toward improved survival<sup>[18]</sup>.

#### CONCLUSION

In summary, treatment of ALI/ARDS remains a challenge to the clinician and clinical investigator. Progress has been made in understanding the dangers of ventilatory-induced lung injury, and hopefully additional therapeutic strategies will emerge during the coming decade.

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