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ARDS Network (NHLBI) Studies – Successes and Challenges in ARDS Clinical Research

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History and Goal of ARDS Network

In order to hasten the development of effective therapy for Acute Respiratory Distress Syndrome (ARDS), the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, initiated a clinical network to carry out multi center clinical trials of ARDS treatments. The ARDS Network was established as a contract program in 1994 following a national competition.

The ARDS Network is a clinical research network of approximately 42 hospitals, organized into 12 clinical sites, and a Clinical Coordinating Center (Massachusetts General Hospital; David Schoenfeld Ph.D. and B. Taylor Thompson MD) (Box 1). The Principal Investigators from each site together with the NHLBI Project Scientist (Andrea Harabin Ph.D.) form the Network Steering Committee, the main governing body of the Network. The Steering Committee (Gordon Bernard MD, Steering Committee Chair) is responsible for identification of promising new agents for the treatment of ARDS, setting Network priorities, developing protocols, facilitating the conduct and monitoring of the trials, and reporting study results. A Protocol Review Committee provides an independent scientific evaluation for the NHLBI on each new protocol. The Data and Safety Monitoring Board (DSMB) monitors the conduct of the trial and advises the NHLBI on the quality of the trial and may suggest early termination of the study for either unanticipated large beneficial effects or for safety concerns.

The goal of the Network is to efficiently test promising agents, devices, or management strategies to improve the care of patients with ARDS. The ARDS Network has been a pivotal significant advance in the conduct of groundbreaking clinical research in ALI and ARDS, and a number of important questions regarding optimal clinical care of these patients have been answered, and we are awaiting results of the ongoing trials.

The significant success of this multicenter clinical trial network for ARDS is documented by the significant number of patients enrolled in the first ARDSNet clinical trials (Figure 7). Comprehensive information, including the clinical study protocols, regarding all of the completed and ongoing clinical trials is available on the website at www.ardsnet.org, but a brief summary of the ARDSNet clinical trials is provided below.

Ketoconazole for ALI/ARDS

Study status: Completed

Study dates: Mar 1996 — Feb 1998

The first clinical trial completed by the Network was a randomized, controlled trial of Ketoconazole versus placebo in patients with acute lung injury and ARDS. Ketoconazole was chosen because of its anti-inflammatory actions noted in the laboratory and because previous Phase II clinical trials suggested benefit in patients with or at risk for ARDS. This trial was stopped early by the DSMB in January 1997 after finding Ketoconazole to be ineffective.¹

Lower Tidal Volume Trial

Study status: Completed

Study dates: Mar 1996 — Jul 1999

This landmark third trial examined lower tidal volume ventilation versus a traditionally recommended larger tidal volume approach in patients with acute lung injury. This trial was undertaken because extensive animal studies and two small clinical trials suggested lung stretch with larger tidal volumes may injure the lung or prevent recovery. However, two other clinical trials raised questions about this hypothesis and the use of smaller tidal volumes is not always easy to do. The ARMA study was a randomized, controlled multi-center 2×2 factorial study consisting of a drug treatment (Ketoconazole vs. placebo) and a ventilation strategy (6ml/kg tidal volume vs. 12ml/kg tidal volume). The ventilator arm of the protocol was designed to compare different ventilator strategies (Box 1) and their effect on mortality and morbidity. The lower tidal volume strategy (6 ml/kg) improved survival and the study was stopped early after enrollment of 861 subjects.²

Late Steroid Rescue Study (LaSRS)

Study status: Completed

Study dates: Aug 1997 — Nov 2003

The late phase of ARDS is often characterized by excessive fibroproliferation leading to gas exchange and compliance abnormalities. While corticosteroids are not effective in early ARDS, several case reports and uncontrolled case series and one small randomized, controlled trial suggest that corticosteroids may be useful in the management of late-phase ARDS. To test this hypothesis, a randomized, double-blinded trial comparing corticosteroids to placebo in severe, late-phase ARDS after seven days was conducted. The objective of the LaSRS study was to determine if the administration of corticosteroids, in the form of methylprednisolone sodium succinate, in severe late-phase ARDS, would have a positive effect on this fibroproliferation, thereby reducing mortality and morbidity. In addition, bronchoalveolar lavage and serum were collected during the first week of the study to search for inflammatory markers of fibroproliferation. The study enrolled 180 subjects. The study was completed in November of 2003.³ While an increase in ventilator free days was noted during the first 28 days of study, safety concerns around neuromuscular and hyperglycemia side effects blunted enthusiasm for recommending steroids for the routine treatment of persistent ARDS.

Lysophylline for ALI/ARDS

Study status: Completed

Study dates: Feb 1998 — Jun 1999

The LARMA study was a randomized, double-blind, placebo- controlled multi-center 2×2 factorial study where each patient was randomized between Lisofylline and Placebo. It was designed to test whether the administration of lisofylline early after the onset of ALI or ARDS would reduce mortality and morbidity. The study was stopped by the Data and Safety Monitoring Board (DSMB) for futility at the first scheduled interim analysis. The decision was based on predetermined criteria, which required a positive trend toward improvement in day 28 survival among the LSF recipients for the trial to continue as a phase III trial. The results of this study were published in January 2001.⁴

ALVEOLI Study

Study status: Completed

Study dates: Nov 1999 — Mar 2002

Prospective, Randomized, Multi-Center Trial of Higher End-expiratory Lung Volume/Lower FiO₂ versus Lower End-expiratory Lung Volume/Higher FiO₂ Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome.

This study was a prospective, randomized, controlled multi-center trial. The objective was to compare clinical outcomes of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) treated with a higher end-expiratory lung volume/lower FiO₂ versus a lower end-expiratory lung volume/higher FiO₂ ventilation strategy. The study was named ALVEOLI and was based on a Phase II study of patients with ARDS showing a remarkable improvement in survival in patients managed with this open lung approach.⁵ This approach involved both low tidal volumes and higher PEEP, among other interventions, to keep the lung open and it was not clear if the lower tidal volumes or the higher PEEP levels, or both contributed to the marked improvement. The ALVEOLI study tested lower tidal volumes with higher PEEP (Figure 1) and, after enrolling 549 patients, found no further improvement in survival with higher PEEP.⁶

In the absence of data proving superiority of lower or higher PEEP for survival, clinicians may elect to use lower PEEP levels to avoid ventilator-induced lung injury from over distension in patients whose airway pressures are high. Lower levels may also be preferable when there is overt barotrauma or when higher PEEP levels cause hypotension. Higher PEEP levels may be preferable in patients who do not have these limiting factors, especially if there is a clear indication of improved oxygenation, reduced dead space, or improved lung compliance when higher PEEP levels are applied.

Fluid and Catheter Treatment Trial - FACTT

Study status: Completed

Study dates: Jun 2000 — Oct 2005

Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter(PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome ARDS and Prospective, Randomized, Multi-Center Trial of “Fluid Conservative” vs. “Fluid Liberal” Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

This study examined two different strategies for managing intravenous fluids and fluid balance in patients with acute lung injury. During ARDS, the lung is vulnerable to the

accumulation of fluid in the airspaces. There is considerable variation in current recommendations about how to best use and adjust intravenous fluids and there were no large randomized clinical trials available to guide clinicians. This trial tested a fluid liberal strategy (that would be expected to improve the overall state of the circulation) versus a fluid conservative strategy (that would potentially avoid excess lung fluid accumulation). A second goal of this trial was to determine if a Pulmonary Artery Catheter (PAC) is superior to a smaller, and less invasive central venous catheter in the management of patients with ARDS. This important question arose from a retrospective examination of practice at six hospitals that suggested the pulmonary artery catheter, which has been widely used to guide management of patients with ARDS for many years, may actually be harmful.⁷ A subsequent consensus conference reviewed this and numerous other studies of PAC effectiveness and concluded that randomized controlled trials in patients with ARDS and sepsis were urgently needed.⁸

This trial attempted to answer two important questions in a single trial using a 2×2 factorial design. The goals of the studies were to 1) assess the safety and the efficacy of PAC vs. CVC guided management in reducing mortality, need for mechanical ventilation, and morbidity in patients with ALI and ARDS; and 2) assess the safety and efficacy of “fluid conservative” vs. “fluid liberal” management strategies on lung function, non-pulmonary organ function, as well as mortality and the need for mechanical ventilation. Patients were treated with the specific fluid management strategy (to which they were randomized) for 7 days or until unassisted ventilation, whichever occurs first. The study enrolled 1000 patients and showed no benefit with PAC-guided fluid therapy over the less invasive CVC guided therapy. The study also showed that the liberal approach, which resulted in fluid balance that mirrored traditional ICU practices (Figure 7), was inferior to the new conservative approach. The conservative approach improved the number of days free from mechanical ventilation and the intensive care unit without harming other organ function including kidney function or the need for dialysis. The survival was similar with both approaches, but survivors managed with the conservative approach were liberated from the mechanical ventilator 3.2 days faster (Figure 7). In addition, the need for transfusions was reduced by using the conservative approach whether guided by a CVC or a PAC (Figure 7). The conservative approach to fluid management did not increase the incidence of hypotension (Figure 7) or need for vasopressors (Figure 7). To realize the benefits from this approach, most clinicians will need to substantially change their fluid management practices.^{9,10}

Albuterol for the Treatment of ALI (ALTA)

Study status: Closed

Study dates: Aug 2007 — Sep 2008

A prospective, randomized trial of Aerosolized Albuterol vs. Placebo to test the safety and efficacy of aerosolized beta-2 adrenergic agonist therapy for improving clinical outcomes in patients with acute lung injury. Aerosolized beta-2 agonist therapy was anticipated to diminish the formation of lung edema, enhance clearance of lung edema and decrease pulmonary inflammation in patients with acute lung injury. Because beta-2 agonists have been shown to reduce permeability induced lung injury, it was anticipated that the severity of lung injury would be reduced by aerosolized beta-2 agonist therapy. The therapy may work by enhancing resolution of pulmonary edema by upregulating alveolar epithelial fluid transport mechanisms that will in turn enhance the clearance of alveolar edema. A reduction in the severity of lung injury and the quantity of alveolar edema should result in earlier extubation and more ventilator free days, improved pulmonary oxygen uptake, and improved lung compliance.

The study design was a phase II/III prospective, randomized double-blind, placebo controlled trial (<http://clinicaltrials.gov/ct2/show/NCT00434993>):

- In Phase II, patients will be treated with aerosolized albuterol 5.0 mg vs. normal saline (n=40-50) administered every 4 hours for 10 days following randomization or until 24 hours following extubation, whichever occurs first. The protocol stipulates that the 5.0 mg dose will be reduced to 2.5 mg if patients exceed defined heart rate limits.
- In Phase III, the 5.0 mg dose will be used unless there is evidence that this dose has an unacceptable safety profile or dose reductions for tachycardia occur in a large fraction of patients. In that case, a lower dose of 2.5 mg will be used.
- Patients will be followed for 90 days or until discharge from the hospital to home with unassisted breathing whichever occurs first.

This study was stopped for futility by the Data Safety and Monitoring Board and the study results have been submitted for publication.

EDEN – Omega Study

Study status: Open

Study dates: Nov 2006 —

Prospective, Randomized Trial of initial trophic enteral feeding followed by advancement to full-calorie enteral feeding vs. early advancement to full-calorie enteral feeding (<http://clinicaltrials.gov/ct2/show/NCT00609180>).

This trial will be run simultaneously with a trial of omega-3 fatty acid, gamma-linolenic acid, and anti-oxidant supplementation vs. a comparator. The ARDSNet trial used an omega 3 and antioxidant supplement added to “usual” feeding (not any specifically commercially available product). The study stopped for futility. “Futility” means there was no realistic chance that the intervention could be proven to be beneficial with the size trial we had planned. It would not be appropriate to make any conclusions about any other feeding product based upon our study, as it would also be inappropriate to conclude that our treatment was “harmful”. The database for this study has been analyzed and the report has been submitted for publication. (*See also section on Nutrition in ALI/ARDS*)

The EDEN portion of the 2×2 factorial design continues as it has not been terminated by the DSMB. This portion of the trial is designed to determine if early aggressive full feeding of patients with ALI will result in improved outcome vs. a more conservative feeding strategy that provides only “token” calories for the first 6 days followed by full feeding in both arms thereafter. This trial is anticipated to complete its enrollment in the Spring of 2011 with a study report available by the Fall of 2011.

SAILS Study

Study status: Open

Study dates: Mar 2010 —

Statins for Acutely Injured Lungs from Sepsis (SAILS) is a trial of rosuvastatin versus placebo comparator for the treatment of patients with ALI or ARDS. The objective is to assess the efficacy and safety of oral rosuvastatin in patients with sepsis-induced ALI. The hypothesis of this study is that pleiotropic anti-inflammatory effects of rosuvastatin therapy will improve mortality in patients with sepsis-induced ALI.

This study is a prospective, randomized, controlled multi-center trial. Upon admission to the ICU, rosuvastatin or placebo will be administered through an enteral feeding tube or administered orally following extubation when patients are able to safely take oral medications. The type and placement of the enteral feeding tube (nasogastric, nasoenteric, PEG, orogastric, oroenteric, etc.) and the ability to safely take oral medications will be determined by the patient's primary team. Study drug will be blinded with an identical appearing placebo. The first study drug dose (rosuvastatin or placebo) will be administered within 4 hours of randomization as a loading dose of 40 mg followed by maintenance doses of 20 mg per day. The primary efficacy measure is hospital mortality to day 60. (<http://clinicaltrials.gov/ct2/show/NCT00979121>) The estimated study completion date is September 2012 with an estimated patient enrollment of 1000 patients.

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Box 1**National Heart Lung and Blood Institute ARDS Clinical Trials Network principal investigators and their associated network centers**

Jay Steingrub, MD	Baystate Medical Center, Massachusetts
Herb Wiedemann, MD	Cleveland Clinic
Neil McIntyre, MD	Duke University
Ben Deboisblanc, MD	Louisiana State University
Michael Matthay, MD	University of California San Francisco
Marc Moss, MD	University of Colorado
Roy Brower, MD	Johns Hopkins, University of Maryland
Alan Morris, MD	University of Utah
Jon Truwit, MD	University of Virginia
Len Hudson, MD	University of Washington
Art Wheeler, MD	Vanderbilt University
Duncan Hite, MD	Wake Forest University

Coordinating Center: David Schoenfeld, Ph.D., Massachusetts General Hospital

INCLUSION CRITERIA: Acute onset of

1. $\text{PaO}_2/\text{FiO}_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
Males = $50 + 2.3 [\text{height (inches)} - 60]$
Females = $45.5 + 2.3 [\text{height (inches)} - 60]$
2. Select any ventilator mode
3. Set ventilator settings to achieve initial $\text{V}_T = 8 \text{ ml/kg PBW}$
4. Reduce V_T by 1 ml/kg at intervals ≤ 2 hours until $\text{V}_T = 6 \text{ ml/kg PBW}$.
5. Set initial rate to approximate baseline minute ventilation (not $> 35 \text{ bpm}$).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

pH GOAL: 7.30-7.45**Acidosis Management: (pH < 7.30)**

If pH 7.15-7.30: Increase RR until pH > 7.30 or $\text{PaCO}_2 < 25$
(Maximum set RR = 35).

If pH < 7.15 : Increase RR to 35.

If pH remains < 7.15 , V_T may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).

May give NaHCO_3

Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

I: E RATIO GOAL: Recommend that duration of inspiration be $\leq$ duration of expiration.

PART II: WEANING

- Conduct a SPONTANEOUS BREATHING TRIAL daily when:**
 1. $\text{FiO}_2 \leq 0.40$ and $\text{PEEP} \leq 8$.
 2. PEEP and $\text{FiO}_2 \leq$ values of previous day.
 3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
 4. Systolic BP $\geq 90 \text{ mmHg}$ without vasopressor support.
 5. No neuromuscular blocking agents or blockade.

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%

Use a minimum PEEP of $5 \text{ cm H}_2\text{O}$. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO_2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

PLATEAU PRESSURE GOAL: $\leq 30 \text{ cm H}_2\text{O}$

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T .

If Pplat $> 30 \text{ cm H}_2\text{O}$: decrease V_T by 1 ml/kg steps (minimum = 4 ml/kg).

If Pplat $< 25 \text{ cm H}_2\text{O}$ and $\text{V}_T < 6 \text{ ml/kg}$, increase V_T by 1 ml/kg until Pplat $> 25 \text{ cm H}_2\text{O}$ or $\text{V}_T = 6 \text{ ml/kg}$.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1 ml/kg increments to 7 or 8 ml/kg if Pplat remains $\leq 30 \text{ cm H}_2\text{O}$.

B. SPONTANEOUS BREATHING TRIAL (SBT):

If all above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of UP TO 120 minutes of spontaneous breathing with $\text{FiO}_2 \leq 0.5$ and $\text{PEEP} \leq 5$:

1. Place on T-piece, trach collar, or CPAP $\leq 5 \text{ cm H}_2\text{O}$ with $\text{PS} \leq 5$
2. Assess for tolerance as below for up to two hours.
 - a. $\text{SpO}_2 \geq 90$: and/or $\text{PaO}_2 \geq 60 \text{ mmHg}$
 - b. Spontaneous $\text{V}_T \geq 4 \text{ ml/kg PBW}$
 - c. $\text{RR} \leq 35/\text{min}$
 - d. $\text{pH} \geq 7.3$
 - e. No respiratory distress (distress = 2 or more)
 - > HR $> 120\%$ of baseline
 - > Marked accessory muscle use
 - > Abdominal paradox
 - > Diaphoresis
 - > Marked dyspnea
3. If tolerated for at least 30 minutes, consider extubation.
4. If not tolerated resume pre-weaning settings.

Definition of UNASSISTED BREATHING
(Different from the spontaneous breathing criteria as PS is not allowed)

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to $5 \text{ cm H}_2\text{O}$ without pressure support or IMV assistance.

Figure 1.

Lower Tidal Volume / Higher PEEP Reference Card for ARMA and ALVEOLI Studies.

(From: <http://www.ardsnet.org>)

Figure 2.
Patient enrollment in the ARDS Network multicenter clinical trials from 1996 through 2005.

Figure 3. Change in body weight over the first seven days of conservative vs. liberal fluid management in ALI patients in FACTT. Differences were statistically different from day 1 through day 7. After seven days, patients in the liberal arm had gained approximately 7 kg while those in the conservative arm were near their baseline weight.

Figure 4. Patients in FACTT who received conservative fluid management had approximately 3 more days alive and free of mechanical ventilation requirement (ventilator free days) during the first 28 days of study.

Figure 5.

Whether managed with a central venous catheter or a pulmonary artery catheter, patients receiving conservative fluid management required significantly fewer red cell transfusions. The bars illustrate the percentage of patients who did not require any red cell transfusions during the first seven days of study.

Figure 6.

Bars show percentage of patients who never developed hypotension vs. those who developed hypotension during the first 7 days of study in FACTT. There was no difference in the incidence of hypotension whether management was with a PAC or a CVC, nor was there a difference whether managed in the fluid conservative arm vs. the fluid liberal arm.

Figure 7. Vasopressor use in liberal and conservative arms of FACTT. There were no significant differences in vasopressor requirements during the first week of study.