Published in final edited form as:

Crit Care Med. 2011 June ; 39(6): 1322–1328. doi:10.1097/CCM.0b013e3182120829.

Utilization Patterns and Patient Outcomes Associated with Use of Rescue Therapies in Acute Lung Injury

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Abstract

Objective—To investigate the practice patterns and clinical outcomes associated with use of rescue therapies in patients with acute lung injury (ALI).

Design—Secondary analysis of multi-center, randomized-controlled trial data from the National Heart, Lung and Blood Institute (NHLBI) ARDS Clinical Trials Network (ARDSNet).

Setting—Intensive care units of ARDSNet centers across the United States.

Patients—Subjects enrolled in 6 ARDSNet trials occurring between 1996–2005.

Interventions—None

Measurements and Main Results—166/2632(6.3%) of subjects received rescue therapy, defined as prone positioning [97/166 (58%)], inhaled vasodilators [47/166 (28%)], high frequency ventilation (HFV) [12/166 (7%)] or extracorporeal membrane oxygenation (ECMO) [10/166 (6%)]. Use of inhaled vasodilators increased while use of prone position decreased over time (p for trend = 0.04 and 0.0013, respectively). Multivariate predictors for use of rescue therapy included age [odds ratio (OR) per 10 years, (95% confidence intervals): 0.88, (0.78–0.99), $p=0.049$], positive end expiratory pressure (PEEP) [OR per 5 cm H₂O increase 1.33, (1.05–1.69), $p=0.019$], PaO₂/FiO₂ [OR per 5 increase: 0.98, (0.96–0.99), $p=0.017$], peak airway pressure [OR per 5cm H₂O increase: 1.11, (1.001–1.237), $p=0.047$], and study order [OR per subsequent ARDSNet study: 1.21, (1.03–1.41), $p=0.02$]. Cox proportional hazards analysis of propensity score-matched subjects showed no difference in survival for those who received rescue therapy versus those that did not [Hazard ratio (HR) for death after rescue therapy or index date 1.10, (0.67–1.78), $p=0.72$]. No differences in survival were found between those who received prone positioning versus inhaled vasodilators [propensity score-adjusted HR for prone 0.87 (0.86–2.10), $p=0.76$].

Conclusions—Rescue therapies are utilized in younger patients with more severe oxygenation deficits. Patterns of rescue therapy utilization appear to be changing over time. Within the limits of

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Dr. Walkey and Dr. Wiener report no conflicts of interest.

This work was conducted at Boston University School of Medicine.

No reprints will be ordered.

an observational study design, we did not find evidence of a survival benefit with use of rescue therapies in ALI.

MESH keywords

Respiratory Distress Syndrome; Adult; prone position; nitric oxide; extracorporeal membrane oxygenation; high frequency ventilation

INTRODUCTION

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) affect 200,000 patients yearly in the United States, with 30–40% mortality and significant long-term morbidity in survivors.(1) Although multiple clinical strategies are known to improve oxygenation in ALI/ARDS, the only strategy that has clearly been shown to reduce mortality for patients with ALI is use of low tidal volume ventilation.(2) Because adjunctive strategies such as prone positioning, inhaled vasodilators, and high frequency ventilation (HFV) have not clearly been shown to improve clinical outcomes with routine use in ALI/ARDS, many have suggested they be reserved as “rescue therapies” for patients with severe ALI/ARDS. (3, 4)

While the name “rescue therapies” suggests that these strategies are reserved until patients have failed more conventional measures, little is known about how physicians actually use these strategies in practice, or whether their use as a “rescue therapy” for patients with ARDS improves outcomes. The present study addresses these questions by investigating utilization patterns and outcomes associated with use of rescue therapies in subjects enrolled in six National Heart, Lung and Blood Institute (NHLBI) ARDS Clinical Trials Network (ARDSNet) studies.

MATERIALS AND METHODS

Patients

Deidentified data from subjects previously enrolled in NHLBI ARDSNet trials [Respiratory Management of ALI (ARMA)(2), Lisofylline and Respiratory Management of ALI (LARMA)(5), Ketoconazole and Respiratory Management of ALI (KARMA)(6), Late Steroid Rescue Study (LaSRS)(7), Assessment of Low tidal Volume and End expiratory volume to Obviate Lung Injury (ALVEOLI)(8), and Fluid and Catheter Treatment Trial (FACCT)(9, 10)] were utilized to assemble the study cohort. The ARDSNet is comprised of 42 hospitals across the United States; details regarding protocols of ARDSNet studies can be found at the ARDSNet.org website. All study procedures were approved by the Boston University School of Medicine Institutional Review Board as well as the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Study Design

Protocols for the ARDSNet trials stipulated that use of pre-specified “experimental therapies” be recorded daily for all subjects. Use of these therapies was not restricted by trial protocols. “Experimental therapies” included prone positioning, inhaled nitric oxide (iNO), inhaled prostacyclin (iPGE), extracorporeal membrane oxygenation (ECMO), high frequency ventilation (HFV), partial liquid ventilation, surfactant, and intravenous oxygen. Because these therapies were used per the discretion of the treating medical team after randomization to a trial intervention, we considered the “experimental therapy” as “rescue therapy” for the purposes of this study. Partial liquid ventilation, surfactant, or intravenous oxygen were provided to one or fewer subjects and were excluded from this analysis.

Our study had three objectives. First, we determined patient characteristics and practice patterns associated with use of rescue therapy in the cohort of ARDSNet trial subjects. Second, we performed a matched cohort study comparing survival of subjects who received rescue therapy to propensity score-matched controls who did not receive rescue therapy. Third, we compared survival between subjects who received prone positioning versus those that received inhaled vasodilator (iNO and iPGE(11)) therapy. Inhalational vasodilator therapies were combined due to the small number of subjects (n=5) receiving iPGE. Subjects receiving more than one rescue therapy were categorized by the first therapy initiated.

Subject characteristics and practice patterns

Pre-randomization (baseline) subject characteristics of those who received rescue therapy were compared to those not receiving rescue. These characteristics included demographics, comorbidities, lung injury risk factors, mechanical ventilation characteristics, study randomization groups, and duration of intensive care unit stay prior to study enrollment. Simplified Acute Physiology II Scores (SAPS II) (12) and Brussels organ dysfunction scores (13) were calculated for all subjects. In order to investigate changes in utilization of rescue therapies over time, we identified trends in use of rescue therapy across the studies, according to study start date. Studies were grouped chronologically by start date: ARMA/KARMA/LARMA (1996–1999), LaSRS (1997–2003), ALVEOLI (1999–2002) and FACCT (2000–2005).

Survival after rescue therapy versus no rescue therapy

Propensity scores for the probability of receiving rescue therapy were calculated for all subjects. Rescue therapy subjects were matched to two “controls” with the closest propensity score who did not receive rescue therapy. In order to avoid “immortal time bias” (14), survival time *from the initiation of rescue therapy* – or a matched index date for controls – was compared between subjects with rescue therapy and propensity score-matched controls. (15) Additional confounders measured at the rescue/index date were added as covariates to the survival analysis of the matched cohort in order to control for confounding due to changes in condition from baseline to rescue/index date. Thus, the potential for confounding by indication from variables present both at baseline and at the rescue/index date were addressed in the final analyses. We performed subgroup analyses of survival for prone positioning in subjects with $\text{PaO}_2/\text{FiO}_2$ less than 100 and assessed for interaction between $\text{PaO}_2/\text{FiO}_2$, rescue therapy status, and survival. (16)

Survival after prone positioning versus inhaled vasodilator therapy

We compared survival between the two most commonly utilized rescue therapies: prone positioning and inhaled vasodilators. Baseline characteristics were used to generate propensity scores for receipt of either therapy. Models were then constructed using the propensity score for rescue therapy type to control for confounding due to both baseline variables and covariates measured at the time of rescue.

Statistical analyses

The primary outcome of this study was the comparison of survival after rescue/index date between those that received rescue therapy or their propensity score-matched controls. With an alpha of 0.05 and two controls per subject with rescue therapy, 330 total subjects were needed to detect a hazard ratio for mortality of 0.67 for rescue compared with no rescue with 80% power.

Continuous data were non-Gaussian and were compared using nonparametric Wilcoxon-rank-sum or Kruskal-Wallis tests, as appropriate. Categorical data were compared with Fisher's exact test. Tests for time trends were calculated using logistic regression with study order as a continuous variable while simultaneously controlling for the individual study as a categorical variable. Details regarding construction of propensity scores and Cox proportional hazards models can be found in the Supplemental Digital Content. SAS 9.1 (Cary, NC) was used for all statistical analyses, with the exception of survival plots, which were generated with PASW statistics 18.0 (Chicago, IL).

RESULTS

Subject characteristics and practice patterns

Baseline data for the 2632 subjects included in the study cohort are shown in Table 1. 166/2632 (6.3%) of subjects received rescue therapy. As shown in Table 1, subjects who received rescue therapy were younger, with lower PaO₂/FiO₂, higher PEEP, and higher peak and plateau airway pressures. In addition, those given rescue therapy were more likely to be of non-white racial background and to have pneumonia as an ALI risk factor. Though the relationship was not linear, the proportion of subjects receiving inhaled vasodilators increased over time while use of prone positioning decreased (Table 2). At the time of rescue therapy, 25% of subjects had PaO₂/FiO₂ less than 55, while median PaO₂/FiO₂ was 80. No differences were found in use of rescue therapy according to study randomization groups (Supplementary Table 1).

Rescue therapy compared with no rescue therapy

Significant multivariate predictors for use of rescue therapy included younger age [odds ratio (OR), (95% confidence intervals (CI) per 10 years increase: 0.88, (95% CI 0.78–0.99), p=0.049], higher baseline PEEP [OR per 5 cm H₂O increase 1.33, (1.05–1.69), p=0.019], lower PaO₂/FiO₂ [OR per 5 increase: 0.98, (0.96–0.99), p=0.017], higher peak airway pressure [OR per 5cm H₂O increase: 1.11, (1.001–1.237), p=0.047], and study order [OR per subsequent ARDSNet study: 1.21, (1.03–1.41), p=0.02]. The final propensity score model for any rescue therapy (Hosmer-Lemeshow chi square = 5.89, c statistic 0.679) also included the following variables with p<0.20 : gender [OR for male sex: 1.32, (0.89–1.95), p=0.17], race [OR for non-white race 1.44, (0.97–2.14), p=0.07], and direct pulmonary injury [OR 1.31, (0.87–1.96), p=0.19].

111 subjects given rescue therapy were able to be matched to 200 controls. Supplementary Table 1 demonstrates covariates measured at baseline and at the rescue/index date for the matched cohort; matching successfully eliminated all statistically significant imbalances in measured baseline variables. However, imbalances between variables recorded at the rescue/index date for organ failure score (rescue: 1.95±1.27 vs. no rescue 1.67±1.23, p=0.04), PaO₂/FiO₂ (rescue 96.2±55.3 vs. no rescue: 135.2±61.7, p<0.001), and PEEP (rescue: 12.9±4.8 vs. no rescue: 10.5±4.5 cm H₂O, p<0.001) were present. 41/111 (36.9%) of subjects receiving rescue and 52/200 (26.0%) of matched controls died after the rescue/index date (p=0.053).

No significant differences in survival were identified comparing rescue to non-rescue subjects matched on propensity scores [hazard ratio (HR) for mortality after rescue therapy 1.36, 95% CI (0.90–2.05), p=0.14, n=311, Figure 1a]. After further adjustment for confounding variables present at the rescue/index date (non-pulmonary Brussels score, PaO₂/FiO₂, PEEP, peak airway pressure), the effect estimate for mortality associated with rescue therapy was further attenuated [HR 1.10, (0.67–1.78), n=218, p=0.72, Figure 1b]. In subgroup analysis of survival amongst subjects with PaO₂/FiO₂ less than 100, prone

position HR was 0.97 [(0.53–1.79), $p=0.94$] compared with no rescue. Overall, there was no evidence for interaction between $\text{PaO}_2/\text{FiO}_2$, rescue therapy, and survival ($p=0.72$).

Comparisons amongst rescue therapies

Of the 166 subjects receiving a rescue therapy, 97 (58%) received prone positioning, 47 (28%) inhaled vasodilator therapy, 12 (7.2%) HFV, and 10 (6.0%) ECMO. 25 (15%) of subjects received two rescue therapies. Table 3 demonstrates values for variables at baseline and rescue date stratified by type of rescue therapy.

Comparisons between prone and inhaled vasodilator therapy

Subjects who received inhaled vasodilators were younger than those treated with prone position (prone: 48.3 ± 15.0 vs. inhaled vasodilator: 40.6 ± 15.5 years, $p=0.0085$) and had higher peak airway pressures at time of rescue (prone: 37.0 ± 9.0 vs. inhaled vasodilator: 43.8 ± 13.8 cm H₂O, $p=0.005$). Significant multivariate predictors of prone positioning as compared with inhaled vasodilator therapy included presence of sepsis [OR: 0.14 (0.03–0.73), $p=0.02$], peak airway pressure [(OR per 5 cm H₂O increase 0.62 [(0.46–0.84), $p=0.002$], and study order [OR per subsequent ARDSNet study: 0.32, (0.14–0.70), $p=0.004$]. The final propensity score model for prone positioning as compared with inhaled vasodilator (Hosmer-Lemeshow chi square = 1.54, c statistic of 0.85) also included the following variables with $p<0.20$: age [OR per 10 years: 1.50, (0.95–2.36), $p=0.079$] presence of ARDS vs. ALI [OR 7.20, (0.95–54.6), $p=0.056$].

Unadjusted survival was not different between subjects who received prone positioning versus inhaled vasodilators [HR 1.23, (0.68–2.12), $p=0.48$, $n=144$, Figure 2a). After adjustment for the propensity score for use of prone position versus inhaled vasodilator, prone position was associated with HR 0.87 [(0.86–2.10), $p=0.76$, $n=86$, Figure 2b]; adjusting further for peak airway pressure and $\text{PaO}_2/\text{FiO}_2$ at time of rescue, prone positioning was associated with a HR 0.95 [(0.35–2.57), $n=65$, $p=0.92$] for survival as compared with inhaled vasodilator therapy.

DISCUSSION

This study demonstrates that adjunctive rescue therapies were used in a minority of patients (6.3%) in the ARDSNet trials. Younger patients with more severe abnormalities in oxygenation and elevated airway pressures were more likely to receive rescue therapy. Prone positioning was most common, but was less likely to be used compared with inhaled vasodilators in those with sepsis or higher airway pressures. Though changes over time were not linear, utilization of inhaled vasodilators increased and prone positioning decreased. Within the limits of observational analyses, no differences in adjusted outcomes were seen between those who received rescue therapy or did not, or between rescue modalities.

Few studies have investigated ARDS ‘rescue therapy’ practice patterns. The International Study of Mechanical Ventilation, a cross sectional study of mechanical ventilation practices, reported that use of prone positioning declined from 13% of ARDS patients in 1998 to 7% in 2004.(17) Our data also show a reduction in prone therapy over time. Observational studies of ARDS resulting from the 2009 H1N1 influenza pandemic reported widely variable utilization of prone positioning, from 3% of mechanically ventilated patients in the Canadian outbreak (18) to 33% in Spain.(19) In a survey of Canadian Critical Care Trial Group physicians, the proportion of respondents who stated they always or sometimes used inhaled vasodilator therapy (43%) or prone positioning (61.8%) in ARDS (20) appears substantially greater than that observed the ARDSNet centers. Additionally, rescue therapy utilization reported in international, multicenter randomized controlled trials of ALI

therapies also support higher rates of rescue therapy than observed in ARDSNet. For example, in trials comparing high versus lower PEEP strategies, rescue therapies (mostly iNO) were utilized in 26.6% of the French EXPRESS trial subjects (21) and 10% and of LOVS trial subjects.(22) In comparison, only 5.8% of subjects enrolled in the ARDSNet ALVEOLI trial received rescue (mostly prone position). These comparisons suggest a lower rate of use of rescue therapy in the US as compared with previously reported European and Canadian-based studies.

Overall, prone positioning, which requires no specific equipment, was most common. In multivariate analysis, subjects were more likely to receive inhaled vasodilators than prone positioning if they had higher peak airway pressures or sepsis. Reasons for an association between inhaled vasodilators and sepsis are not clear. It is possible that practitioners were more hesitant to use prone positioning during sepsis due to fear of central line disruption or abdominal sources of sepsis that would make prone positioning more difficult. Additionally, contemporaneous evidence suggested that inhaled nitric oxide responders may have lower mortality in sepsis-related ARDS. (23) On the other hand, the theoretical benefits of prone position may be more apparent in patients without direct lung injury who may have more 'recruitable' lung.(24) Subjects with higher peak airway pressures were less likely to be prone, perhaps due the possibility that prone positioning may further elevate peak pressures through loss of chest wall compliance.(25)

What conclusions might be drawn from these observations of rescue therapy practice patterns? One is that use of rescue therapy appears quite variable – comparison with other clinical trials and observational studies suggests large variations in rescue therapy utilization. Two, is that use of these therapies does not appear to be associated with clinical trial evidence for mortality outcomes - despite multiple randomized controlled trials that did not demonstrate mortality benefits to iNO,(26) prone positioning (27, 28) and HFV (29) in ARDS contemporaneous to these studies, overall use of rescue therapies did not change. Three, utilization in those subjects with poor oxygenation and high airway pressures was in line with evidence that rescue therapies do improve oxygenation (25, 29, 30). At the time of rescue therapy, however, only 25% of subjects had PaO₂/FiO₂ less than 55, while median PaO₂/FiO₂ was 80. Therefore, the majority those receiving rescue therapies appeared to have severe, but not necessarily 'refractory' oxygenation deficits below the ARDSNet trial protocol goal PaO₂ greater than 55 mm Hg.

Similar to randomized controlled trials investigating prone positioning and iNO as a primary strategy in ALI/ARDS, we did not find a survival benefit to these interventions when used as 'rescue therapies'. In addition, we did not find evidence for superiority of one rescue therapy over another (e.g., prone positioning versus inhaled vasodilator therapy; we did not have sufficient HFV or ECMO patients for meaningful outcomes comparisons). Recent meta-analyses have shown increased renal failure and no survival benefit with iNO in patients with ARDS.(30) However, there is emerging evidence for lower mortality with prone positioning in the subgroup of subjects with PaO₂/FiO₂ less than 100.(16) In addition, a recent meta-analysis has suggested a mortality benefit for HFV versus conventional ventilation, though tidal volumes of 6cc/kg were not utilized in the control groups of these trials.(31) We could not confirm these findings or show an interaction between outcomes of rescue therapy and PaO₂/FiO₂ ratio. This may be due to differences between early and protocolized use of the therapies in directed randomized controlled trials as compared with variable timing and duration when used *ad libitum* in this study.

Our study has limitations. First, it is unclear if clinical practice during ARDSNet randomized controlled trials mirrors that of routine practice, even if therapy is not limited by protocol. The lower rates of rescue therapy seen in this study compared with prior studies

may reflect lower utilization of rescue in a clinical trial setting. Additionally, attempts made to control for confounding may be limited by unmeasured confounding by indication for rescue therapy. Data provided by BIOLINCC does not identify a subject's study site; this information would have added important information regarding practice pattern variation. Finally, the sample size and power of analyses controlled for multiple potentially confounding variables was limited by missing data.

Patients with poor oxygenation or elevated airway pressures despite evidence-based lung protective ventilator strategies present considerable management difficulties. 'Rescue therapies' were utilized relatively infrequently in the ARDSNet trials and targeted to younger patients with poor oxygenation and/or elevated airway pressures. During the time frame of this study there was a trend towards decreased utilization of prone positioning and increased use of inhaled vasodilators, a trend that may not be supported by recent meta-analyses of these interventions. We did not find evidence of a survival benefit with nonprotocolized use of rescue therapy in ALI and ARDS. Further studies must be done to assess the benefits and harms of rescue therapies in patients with ARDS who have not responded to conventional measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the work of the ARDSnet Investigators, without which this work would not be possible.

Funding/Support: Dr. Wiener is supported by a career development award through the National Cancer Institute (K07 CA138772) and by the Department of Veterans Affairs.

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Figure 1.

a: Kaplan-Meier curve demonstrating unadjusted survival from time of rescue therapy (or index date) for those subjects that received rescue therapy (interrupted line) and matched controls (solid line), $p=0.14$.

b: Survival curves demonstrating survival from time of rescue therapy (or index date) adjusted for non-pulmonary Brussels score, PaO₂/FiO₂, positive end expiratory pressure level, and peak airway pressure at the index date. Subjects receiving rescue therapy are represented by the interrupted line; matched controls are represented by the solid line, $p=0.72$.

Figure 2.

a: Kaplan-Meier curve demonstrating unadjusted survival from time of rescue therapy for those subjects that received prone positioning (interrupted line) and inhaled vasodilators (solid line), $p=0.48$.

b: Propensity score-adjusted survival curves demonstrating survival from time of rescue therapy for those subjects that received prone positioning (interrupted line) and inhaled vasodilators (solid line), $p=0.76$.

Table 1

Baseline variables

Baseline Variable Mean $\pm$ SD or N (%)	Total N=2632	Rescue N=166	No Rescue N=2466	p
Age – years n=2630	50.6 $\pm$ 16.8	45.2 $\pm$ 15.8	50.9 $\pm$ 16.8	<0.001 ^a
Sex –male	1461 (55.6)	95 (57.6)	1366 (55.4)	0.63
Race				0.013 ^a
White	1845 (70.2)	100 (60.6)	1745 (70.8)	
Black	477 (18.1)	36 (21.8)	441 (17.9)	
Other	308 (11.7)	29 (17.6)	279 (11.3)	
BMI – kg/m ² n=2439	27.9 $\pm$ 7.2	28.1 $\pm$ 7.4	27.9 $\pm$ 7.2	0.77
Primary ALI Risk factor				
Pneumonia	1044 (41.1)	81 (48.8)	963 (39.1)	0.014 ^a
Sepsis	625 (23.8)	30 (18.1)	595 (24.1)	0.089
Aspiration	397 (15.1)	21 (12.7)	376 (15.3)	0.43
Trauma	237 (9.0)	15 (9.0)	222 (9.0)	1.0
Multiple transfusions	64 (2.4)	1 (0.6)	63 (2.6)	0.18
Other	260 (9.9)	16 (9.6)	244 (9.9)	1.0
Pulmonary cause of ALI	1141 (54.8)	102 (61.5)	1339 (54.3)	0.077
ARDS	2231 (84.7)	152 (92.7)	2079 (86.2)	0.017 ^a
SAPS II score n=2632	47.3 $\pm$ 14.2	48.4 $\pm$ 13.7	47.3 $\pm$ 14.1	0.26
Brussels organ failure score	1.87 $\pm$ 0.90	1.89 $\pm$ 0.97	1.87 $\pm$ 0.99	0.76
Co-morbidities				
Diabetes	408 (15.8)	26 (15.9)	382 (15.8)	1.0
AIDS	155 (6.0)	10 (6.1)	145 (6.0)	0.86
Metastatic or hematologic malignancy	120 (4.6)	3 (1.8)	113 (4.5)	0.11
End stage renal failure/dialysis	40 (1.55)	1 (0.61)	39 (1.61)	0.51
End stage liver disease	23 (0.89)	2 (1.2)	21 (0.87)	0.65
Tidal volume - cc/kg of IBW n=2151	8.4 $\pm$ 2.2	8.0 $\pm$ 2.0	8.4 $\pm$ 2.2	0.054
PaO ₂ /FiO ₂ n=2576	127 $\pm$ 59.8	105 $\pm$ 60	129 $\pm$ 60	<0.001 ^a
PEEP – cm/H ₂ O n=2632	9.3 $\pm$ 4.2	11.6 $\pm$ 5	9.2 $\pm$ 4.1	<0.001 ^a
Pplat – cm/H ₂ O n=1958	28.2 $\pm$ 7.9	32.7 $\pm$ 10.4	28.0 $\pm$ 7.6	<0.001 ^a
Peak Pressure – cm/H ₂ O n=2235	34.2 $\pm$ 9.5	37.5 $\pm$ 11.7	34.0 $\pm$ 9.3	0.0003 ^a
PaCO ₂ mmHg n=2495	39.6 $\pm$ 10.8	41.9 $\pm$ 11.1	39.5 $\pm$ 10.8	0.0057 ^a
Arterial pH n=2321	7.38 $\pm$ 0.09	7.36 $\pm$ 0.95	7.38 $\pm$ 0.09	0.057
Minute ventilation L/min n=2586	12.5 $\pm$ 4.07	13.2 $\pm$ 4.10	12.5 $\pm$ 4.1	0.013 ^a
Mean Pulmonary artery pressure – mmHg N=465	28.9 $\pm$ 7.9	30.8 $\pm$ 7.3	28.8 $\pm$ 7.9	0.38
Duration of intubation prior to enrollment (days) - median (IQR) n=2437	1.0 (1, 1)	1.0 (1, 1)	1.0 (1,1)	0.46
Duration of ICU stay	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 2)	0.28

Baseline Variable Mean $\pm$ SD or N (%)	Total N=2632	Rescue N=166	No Rescue N=2466	p
prior to enrollment (days) - median (IQR) n=2628				

^a denotes p<0.05

Abbreviations: sd: standard deviation, BMI: body mass index, ALI: acute lung injury, ARDS: acute respiratory distress syndrome, SAPS: simplified acute physiology score, AIDS: acquired immunodeficiency syndrome, IBW: ideal body weight, PEEP: positive end expiratory pressure, Pplat: plateau pressure, IQR: interquartile range.

Use of rescue therapy in each National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network study.

Table 2

Rescue Therapy	ARMA/KARMA/LARMA 3/1996-3/1999 N=902	LaSRS 8/1997-11/2003 N=180	ALVEOLI 10/1999-2/2002 N=550	FACCT 6/2000-10/2005 N=1000	P
Any rescue	41 (4.6)	24 (13.3)	32 (5.8)	69 (6.9)	0.83
Prone	31 (3.4)	17 (9.4)	24 (4.4)	25 (2.5)	0.002 ^a
iNO/iPGE	9 (1.0)	5 (2.8)	6 (1.1)	27 (2.7)	0.036 ^a
ECMO	1 (0.11)	1 (0.56)	0	8 (0.8)	nd
HFV	0	1 (0.56)	2 (0.36)	9 (0.9)	nd
Combination	12(1.3)	2 (1.1)	0	11 (1.1)	0.38

^a denotes p<0.05

Abbreviations: ARMA: Respiratory Management of Acute Lung Injury, LARMA: Lisofylline and Respiratory Management of Acute Lung Injury, KARMA: Ketoconazole and Respiratory Management of Acute Lung Injury, LaSRS: Late Steroid Rescue Study, ALVEOLI: Assessment of Low tidal Volume and End expiratory volume to Obviate Lung Injury, FACCT: Fluid and Catheter Treatment Trial, iNO: inhaled nitric oxide, iPGE: inhaled prostacyclin, ECMO: extracorporeal membrane oxygenation, HFV: high frequency ventilation, Combination: use of two or more rescue therapies, nd: analysis not done, too few subjects for stable statistical model.

Table 3

Clinical variables for each rescue therapy

Baseline Variable Mean $\pm$ SD or N (%)	Primary Rescue Therapy				
	Prone N=97	INO/PGE n=47	P (prone vs. INO/PGE)	ECMO N=10	HFV N=12
Age - years	48.3 $\pm$ 15.0	40.6 $\pm$ 15.5	0.0085 ^a	36.6 $\pm$ 14.4	45.3 $\pm$ 19.4
Sex - male	59 (60.8)	25 (54.4)	0.47	4 (40.0)	7 (58.3)
Race			0.16		
White	61 (62.9)	25 (54.3)		7 (70.0)	7 (58.3)
Black	22 (22.7)	8 (17.4)		2 (20.0)	4 (33.3)
Other	14 (14.4)	13 (28.3)		1 (10.0)	1 (8.3)
BMI - kg/m ²	28.0 $\pm$ 7.7	28.9 $\pm$ 7.8	0.52	28.5 $\pm$ 4.9	25.1 $\pm$ 4.8
Primary ALI Risk factor					
Pneumonia	47 (48.5)	23 (48.9)	1.0	6 (60.0)	5 (41.7)
Sepsis	14 (14.4)	12 (25.5)	0.11	3 (30.0)	1 (8.3)
Aspiration	14 (14.4)	4 (8.5)	0.43	0	3 (25.0)
Trauma	11 (11.3)	2 (4.3)	0.22	1 (10.0)	1 (8.3)
Multiple transfusions	1 (1.0)	0	1.0	0	0
Other	9 (9.2)	5 (10.6)	0.77	0	2 (16.7)
Pulmonary cause of ALI	61 (62.9)	27 (57.5)	0.59	6 (60.0)	8 (67.7)
ARDS	91 (93.8)	41 (87.2)	0.15	9 (90.0)	11 (91.7)
SAPS II score	46.9 $\pm$ 13.3	50.0 $\pm$ 15.4	0.42	51.9 $\pm$ 12.0	51.8 $\pm$ 10.7
Brussels organ failure score at enrollment	1.81 $\pm$ 0.98	2.0 $\pm$ 0.93	0.23	2.4 $\pm$ 0.97	1.6 $\pm$ 0.9
Brussels organ failure score at rescue	1.99 $\pm$ 1.28	1.87 $\pm$ 1.11	0.85	2.5 $\pm$ 1.4	1.67 $\pm$ 1.37
Co-morbidities					
Diabetes	17 (17.5)	6 (13.3)	0.63	1 (10.0)	2 (16.7)
AIDS	7 (7.2)	2 (4.4)	0.72	0	1 (8.3)
Metastatic or hematologic malignancy	2 (2.1)	1 (2.1)	1.0	0	0
End stage renal failure	1 (1.0)	0	1.0	0	0
Combination					N=25
					40.5 $\pm$ 16.5
					15 (62.5)
					16 (66.7)
					2 (8.3)
					6 (25.0)
					26.7 $\pm$ 5.9
					11 (44.0)
					7 (28.0)
					3 (12.0)
					1 (4.0)
					0
					2 (8.0)
					11 (44.0)
					23 (92.0)
					50.6 $\pm$ 16.3
					2.3 $\pm$ 0.8
					2.2 $\pm$ 1.0 ^b
					5 (20.8)
					0
					0
					0

Baseline Variable Mean $\pm$ SD or N (%)	Primary Rescue Therapy				
	Prone N=97	INO/PGE n=47	P (prone vs. INO/PGE)	ECMO N=10	HFV N=12
End stage liver disease	1 (1.0)	1 (2.1)	0.53	0	0
Tidal volume - cc/kg of IBW	8.2 $\pm$ 2.1	7.4 $\pm$ 1.39	0.13	7.5 $\pm$ 2.36	7.9 $\pm$ 2.0
PaO ₂ /FIO ₂ at enrollment	103.5 $\pm$ 61.4	105.4 $\pm$ 59	0.90	116 $\pm$ 58.6	111 $\pm$ 55
PaO ₂ /FIO ₂ at rescue	93.5 $\pm$ 46.9	85.7 $\pm$ 48.5	0.14	82.7 $\pm$ 65.6	94.9 $\pm$ 45.6
PEEP - cm/H ₂ O	11.1 $\pm$ 4.9	12.6 $\pm$ 5.7	0.14	11.8 $\pm$ 2.85	11.8 $\pm$ 4.8
Pplat - cm/H ₂ O	32.2 $\pm$ 9.24	34.5 $\pm$ 11	0.40	31.0 $\pm$ 6.2	32.4 $\pm$ 16.5
Peak pressure at baseline - cmH ₂ O	36.1 $\pm$ 9.4	42.0 $\pm$ 14.2	0.05	33.6 $\pm$ 9.7	36.1 $\pm$ 16.5
Peak at rescue date	37.0 $\pm$ 9.0	43.8 $\pm$ 13.8	0.005 ^a	37.5 $\pm$ 6.5	36.4 $\pm$ 2.1
Mean Pulmonary artery pressure - mmHg	31.4 $\pm$ 7.4	30.7 $\pm$ 6.9	0.51	34.8 $\pm$ 7.7	26.5 $\pm$ 8.7
Duration of intubation prior to enrollment (days) - median (IQR)	1 (1, 1)	1 (0, 1)	0.92	1 (1, 1)	1.0 (0, 1)
Duration of ICU stay prior to enrollment (days) - median (IQR)	1 (1, 4)	2 (1, 3)	0.87	2 (1, 1)	1.0 (0, 2.5)
Time from enrollment to rescue (days) - median (IQR)	3 (1, 6)	1.0 (1, 5)	0.52	2 (1, 5)	6.5 (2, 10)
Duration of rescue Rx (days) - median (IQR)	2 (1, 4)	2 (1, 4)	0.79	4.5 (3, 8)	3 (1, 4)

^a Denotes p<0.05^b Denotes p<0.05 combination compared with single rescue therapy

Abbreviations: sd: standard deviation, BMI: body mass index, ALL: acute lung injury, ARDS: acute respiratory distress syndrome, SAPS: simplified acute physiology score, AIDS: acquired immunodeficiency syndrome, IBW: ideal body weight, PEEP: positive end expiratory pressure, Pplat: plateau pressure, IQR: interquartile range, Combination: use of two or more rescue therapies.