The Relationship of Fluid Administration to Outcome in the Pediatric Calfactant in Acute Respiratory Distress Syndrome Trial*

Douglas F. Willson, MD[1]; Neal J. Thomas, MD, MSc[2]; Robert Tamburro, MD[2]; Edward Truemper, MD[3]; Jonathon Truwit, MD, MBA[4]; Mark Conaway, PhD[5]; Christine Traul, MD[1,6]; Edmund E. Egan, MD[7,8]; in collaboration with Pediatric Acute Lung and Sepsis Investigators Network

Objectives: Adult studies have demonstrated the relationship between fluid overload and poor outcomes in acute lung injury/acute respiratory distress syndrome. The approach of pediatric intensivists to fluid management in acute lung injury/acute respiratory distress syndrome and its *effect* on outcomes is less clear. In a post hoc analysis of our Calfactant in Acute Respiratory Distress Syndrome trial, we examined the relationship of fluid balance to in-hospital outcomes in subjects with acute lung injury/acute respiratory distress syndrome.

Design: Calfactant in Acute Respiratory Distress Syndrome was a masked randomized controlled trial of calfactant surfactant versus placebo in pediatric patients with acute lung injury/acute respiratory distress syndrome due to direct lung injury. Caregivers were encouraged to follow a conservative fluid management *guideline* based on the adult Fluid and Catheter Treatment Trial. Daily fluid balance was collected for the first 7 days after trial enrollment and correlated with clinical outcomes.

Patients and Setting: Children admitted to PICUs with acute lung injury/acute respiratory distress syndrome from 24 children's hospitals in six different countries.

Intervention: Post hoc analysis of daily fluid balance in subjects from the Pediatric Calfactant in Acute Respiratory Distress Syndrome trial.

Measurements and Main Results: Despite the conservative fluid guideline, fluid management was more consistent with a "liberal" approach. On average, study subjects accumulated 1.96 ± 4.2 L/m^2 over the first 7 days of the trial. Subjects who died accumulated on average 8.7 ± 9.5 L/m^2 versus 1.2 ± 2.4 L/m^2 in survivors. Increasing fluid accumulation was associated with fewer ventilator-free days and worsening oxygenation. Multivariable regression models that included age, gender, Pediatric Risk of Mortality score, initial oxygen saturation index and Pao_2/Fio_2 ratio, injury category, and treatment arm failed to account for the differences in fluid management.

Conclusions: Pediatric intensivists generally follow a "liberal" approach to fluid management in children with acute lung injury/acute respiratory distress syndrome. Illness severity or oxygenation disturbance did not explain differences in fluid accumulation but such accumulation was associated with worsening oxygenation, a longer ventilator course, and increased mortality. A more conservative approach to fluid management may improve outcomes in children with acute lung injury/acute respiratory distress syndrome. (*Pediatr Crit Care Med* 2013; 14:666–672)

***See also p. 716.**

[1]Department of Pediatrics, University of Virginia Health Sciences System, Charlottesville, VA.

[2]Department of Pediatrics, Penn State M.S. Hershey Medical Center, Hershey, PA.

[3]Department of Pediatrics, Children's Hospital and Medical Center of the University of Nebraska, Omaha, NE.

[4]Department of Internal Medicine, University of Virginia Health Sciences System, Charlottesville, VA.

[5]Public Health Sciences, University of Virginia Health Sciences System, Charlottesville, VA.

[6]Department of Pediatrics, Children's Hospital Cleveland Clinic, Cleveland, OH.

[7]Pneuma Pharmaceuticals, Buffalo, NY.

[8]Department of Pediatrics, State University of New York at Buffalo, Buffalo, NY.

Supported, in part, by Pneuma Pharmaceuticals, Amherst, New York.

The University of Virginia received compensation from Pneuma Pharmaceuticals to support, in part, the salaries of Drs. Willson, Truwit, Conaway, and Traul. Collaborating investigators were paid compensation for patients successfully enrolled in the study as well as support for the work of their research assistants. Dr. Willson received grant support and support for travel from Pneuma Pharmaceuticals. Dr. Thomas received grant support from Pneuma Pharmaceuticals and consulted for Discovery Laboratories. Dr. Tamburro received grant support from ONY. Dr. Tamburro's institution received funding on a per patient basis (as a participating site in the trial). Dr. Truemper received grant support and support for travel from the University of Nebraska College of Medicine, provisions of the study drug (Cattactant - supplied to Children's Hospital and Medical Center for the duration of the trial), and lectured for the Nebraska Society of Respiratory Care. Dr. Truwit received grant support from Pneuma Pharmaceuticals, NIH, and ARDSNet and support for travel from Pneuma Pharmaceuticals. Dr. Conaway received support for participation in review activities from Pneuma Pharmaceuticals. Dr. Traul received grant support and support for travel from Pneuma Pharmaceuticals. Dr. Egan served as a board member, is employed by, and is the officer and substantial owner of Pneuma Pharmaceuticals.

For information regarding this article, E-mail: dfw4m@virginia.edu

Copyright © 2013 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies

DOI: 10.1097/PCC.0b013e3182917cb5

Key Words: calfactant; direct lung injury; fluid overload; fluid restriction; hypoxemia index; oxygen saturation index; pulmonary edema; respiratory failure; surfactant

Fluid management is a routine aspect of care in the PICU, and the importance of adequate fluid resuscitation in critical illness has been highlighted by landmark studies in both adults (1) and children (2, 3). It is becoming apparent, however, that excessive fluid administration after initial resuscitation may be detrimental, particularly in the setting of acute lung injury (ALI). Pulmonary edema from increased capillary permeability worsens as intravascular hydrostatic pressure rises and oncotic pressure falls (4). Although no comparable prospective pediatric data exist, the ARDSnet Fluid and Catheter Treatment Trial (FACTT) demonstrated that a conservative approach to fluid management after stabilization was associated with improved oxygenation, shorter duration of ventilation, and decreased length of ICU stay in adult subjects with ALI (5). In view of these findings, the pediatric arm of the Calfactant in Acute Respiratory Distress Syndrome (CARDS) trial, a masked randomized study of exogenous surfactant in direct pediatric ALI (injury initiated on the alveolar side of the alveolar/capillary membrane), instituted guidelines for fluid management based on the conservative arm of the FACTT Study. Fluid balance data were prospectively collected over the first 7 days after study entry to determine any potential association of fluid balance with clinical outcomes in children with direct ALI.

MATERIALS AND METHODS

The pediatric arm of the CARDS trial was a prospective, randomized, masked, placebo-controlled trial of endotracheally instilled calfactant versus placebo in children intubated for ALI *due to direct lung injury* conducted over a 2-year period from July 2008 until July 2010. The study, registered with clinicaltrials.gov (identifier NCT00682500), was performed in accordance with the Declaration of Helsinki (1996) and the rules of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use—Good Clinical Practice Consolidated Guideline. All subjects or their legal representatives provided written informed consent, and independent ethics committees or institutional review boards at each participating center approved the study protocol. An independent Data and Safety Monitoring Board (DSMB) monitored the study throughout. The study was stopped in July 2010 at the request of the sponsor after an interim analysis suggested that further study would be futile. Twenty-four pediatric hospitals from six different countries participated (**Appendix 1**). Subject eligibility criteria for the trial consisted of the following: 1) age 37 weeks postconception to 18 years; 2) diagnosis of ALI/acute respiratory distress syndrome (ARDS) according to the American-European Consensus definition, including a Pao_2/Fio_2 ratio less than 300 (substituting $Spo_2/Fio_2 < 250$ when $Spo_2 < 97\%$ in the absence of arterial blood gases); 3) direct lung injury (injury originating on the alveolar side of the alveolar-capillary membrane, such as with pneumonia, aspiration, or near drowning); and 4) enrollment and treatment within 48 hours of endotracheal intubation. Children were excluded if they had indirect lung injury (injury initiated on the capillary side of the alveolar-capillary membrane, such as from sepsis, multiple transfusion, or pancreatitis), preexisting lung disease, their care was limited for any reason, or they had evidence of significant nonpulmonary organ dysfunction. In the event of a question regarding eligibility, participating investigators were encouraged to contact the study primary investigator or study coordinator on call for the study. All enrolled subjects were also subsequently reviewed by the study DSMB to ascertain suitability. Subjects received up to three doses of either calfactant (60 mg phospholipid/mL) or sham treatment of air placebo instilled directly into the trachea. The dose of calfactant was 30 mg per centimeter of height (100 mg/kg for subjects weighing < 10 kg) administered in two divided aliquots. Randomization was in variable blocks of four and was stratified to balance higher risk subjects between the surfactant and placebo groups. Higher risk subjects were those with immune compromise or an initial Pao_2/Fio_2 ratio less than 100 or initial oxygenation index greater than 30 (oxygenation index = $[Fio_2 \times Paw]/Pao_2 \times 100$; where Paw is the mean airway pressure). The primary outcome was 90-day all-cause mortality, but ventilator-free days (VFDs) at 28 days, PICU-free days at 28 days, short-term effects on oxygenation (as reflected in oxygen saturation index [$OSI = Fio_2 \times Paw/Spo_2 \times 100$]) (6), and adverse events were also evaluated.

As part of the trial design, investigators agreed to follow a "conservative" fluid management approach for all subjects (**Fig. 1**). Investigators and study coordinators were instructed in the fluid guidelines at the initial study visit and were given a supply of laminated cards with the guidelines to distribute to colleagues caring for CARDS subjects in their institution. Investigators were instructed to administer fluid and diuretics in accordance with the guideline (Fig. 1) if central venous pressures were available. When central venous pressure was not available, investigators were instructed to evaluate daily fluid balance and administer a diuretic if the subject was hemodynamically stable and fluid balance was positive in the previous 24 hours. Final decisions regarding fluid and diuretic administration were ultimately the purview of the attending physician. Aside from these measures, no attempt was made to direct the fluid management of specific subjects during the trial. The daily fluid balance (total fluid in minus total fluid out over 24 hr without consideration of insensible losses) was collected over the first 7 days after subject enrollment as a means of ascertaining that the fluid management of surfactant and placebo subjects was comparable.

STATISTICAL ANALYSIS

Linear regression models that included age, gender, Pediatric Risk of Mortality (PRISM) score, initial OSI and Pao_2/Fio_2 ratio, injury category, and treatment arm were used to assess the effect of these patient characteristics on fluid balances on day 1 and cumulative 7-day fluid balances. Repeated measures models were used to compare daily fluid balances by

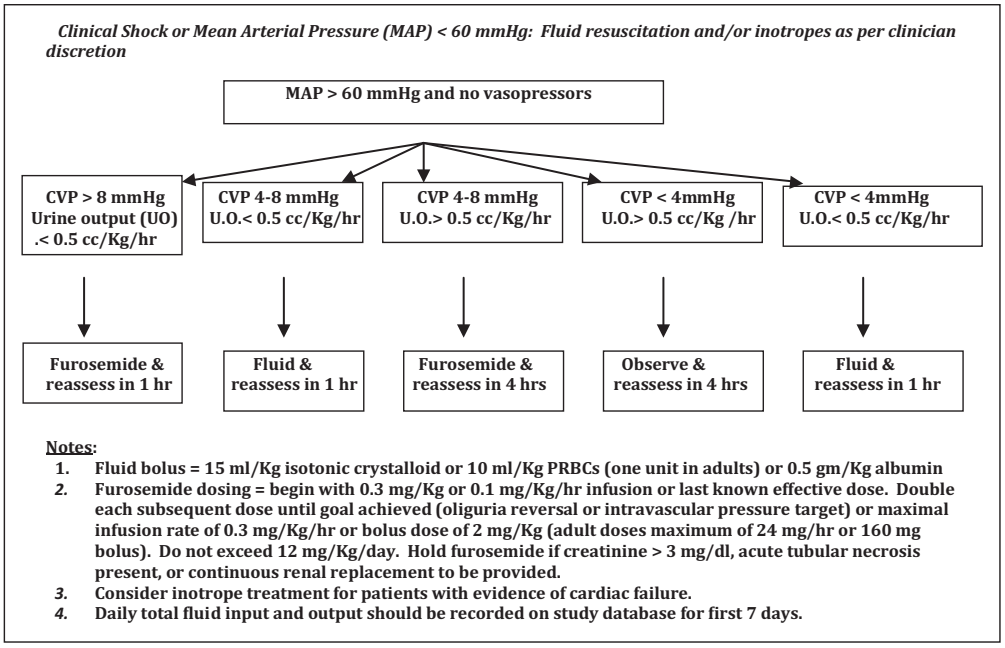

Figure 1. Simplified Fluid and Catheter Trial algorithm for fluid management. CVP = central venous pressure, PRBC = packed RBC.

in-hospital survival status and by categories of VFDs at day 28. *F* tests based on the repeated measures models were used to make specific comparisons. Similar analyses were used to assess the dependence of the OSI on daily fluid balances. All analyses were carried out in SAS 9.2 PROC MIXED (Cary, NC) and GAUSS 11.0 (Cary, NC). Means are listed as mean ± SD.

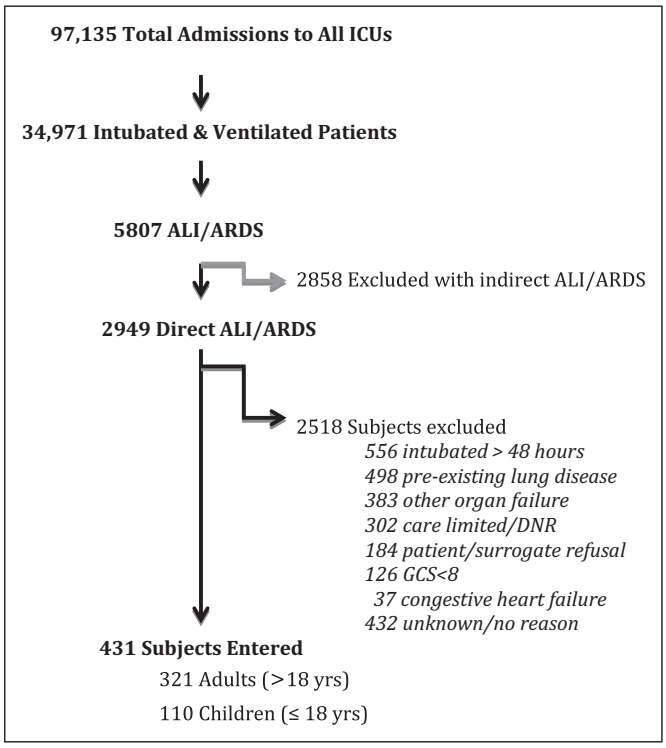

Figure 2. Flow chart for subject entry into Calfactant in Acute Respiratory Distress Syndrome trial. ALI = acute lung injury, ARDS = acute respiratory distress syndrome, DNR = do not resuscitate, GCS = Glasgow Coma Scale.

RESULTS

Thirty-four thousand nine hundred seventy one ventilated adult and pediatric subjects were screened; 2,949 of whom were identified as having direct ALI/ARDS. Of eligible subjects, 431 (15%) were entered into the trial, 110 children (≤ 18 yr old) and 321 adults (**Fig. 2**). The reasons for study exclusion are displayed in Figure 2. One pediatric subject was randomized, but not treated. These data are not available and, therefore, not included in this analysis. Of the remaining 109 pediatric subjects, 53 received placebo and 56 received calfactant surfactant. There were no statistically significant differences between groups at baseline (**Table 1**). Placebo subjects had significantly more hospital-free days at 28 days (10.4 ± 7.8 vs 6.4 ± 7.8; $p = 0.01$), but there were no other significant differences in assessed outcomes between the surfactant and the placebo groups. Ninety-nine subjects survived to hospital discharge. Of the 10 in-hospital deaths, three received placebo and seven were treated with surfactant (note that two subjects in the placebo group died after hospital discharge but before 90 days and are not included as deaths). The average duration of ventilation in survivors was 12.3 ± 12.4 days, the PICU length of stay was 16 ± 14 days, and the hospital stay was 27 ± 31 days. Demographics, diagnostic categories, and severity scores of survivors and nonsurvivors are given in Table 1.

The average daily cumulative fluid balances per meter squared (m^2) for survivors and nonsurvivors are reported in **Table 2**. The accumulated fluid balance from day 1 through day 7 was strongly associated with in-hospital mortality ($p < 0.001$). Subjects who died accumulated an average of more than 8.7 ± 1.7 L/m^2 of fluid over the first 7 days after trial entry versus 1.2 ± 0.9 L/m^2 for survivors (**Fig. 3**, ***A*** and ***B***). In order to assess whether the cumulative 7-day fluid balance was related to severity, we performed a multivariable regression of cumulative 7-day fluid balance, including age, gender, race, PRISM III, initial Pao_2/Fio_2 ratio and OSI, type of direct lung injury, risk level, and treatment. None of these factors was a significant predictor of fluid balance and the model explained only 11% of the variation in cumulative fluid balance. Similar results were found in a multivariable regression analysis of day 1 fluid balance (not presented). There was considerable variation in the cumulative fluid balances in subjects across sites. However, the number of sites (24) relative to the number of subjects (109) precluded a formal statistical analysis of the effect of site after adjusting for patient characteristics.

TABLE 1. Demographics and Diagnoses of Pediatric Calfactant in Acute Respiratory Distress Syndrome Trial Subjects

	In-Hospital Death (%) ($n = 10$)	Survived (%) ($n = 99$)	Total (%) ($n = 109$)
Average age, yr (SD)	8.9 (5.1)	5.8 (5.8)	6.1 (5.8)
Male	7 (12.5)	49 (87.5)	56 (51)
Primary diagnosis			
Viral pneumonia	3 (5.8)	49 (94.2)	52 (47.7)
Bacterial pneumonia	3 (13)	20 (87)	23 (21.1)
Aspiration pneumonia	0 (0)	17 (100)	17 (15.6)
Near drowning	1 (16)	5 (83.3)	6 (5.5)
Other	3 (27.3)	8 (72.7)	11 (10.1)
Influenza A[a]	3 (15)	17 (79)	20 (17.4)
H1N1 Strain	3 (21.4)	11 (79.6)	14 (12.8)
Immune compromised	4 (36.4)	7 (63.6)	11 (9.2)
Average Pediatric Risk of Mortality III (SD)	13.8 (6.2)	11.1 (6.9)	11.4 (6.8)

[a]Twenty of the viral pneumonia patients had influenza A; 14 had the H1N1 strain.

TABLE 2. Average Cumulative Fluid Balance mL/m² (±SD) Over First 7 Days of Calfactant in Acute Respiratory Distress Syndrome Trial[a]

Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
All ($n = 108$)	732 (1,089)	1,162 (1,913)	1,531 (2,696)	1,735 (3,157)	1,791 (3,444)	1,706 (3,652)	1,841 (4,140)
	108	108	108	108	107	106	104
Died[b] ($n = 10$)	1,784 (1,771)	3,271 (3,528)	5,600 (5,428)	6,669 (6,653)	8,163 (7,238)	8,460 (8,744)	11,745 (10,817)
	10	10	10	10	9	8	6
Survived ($n = 98$)	625 (944)	946 (1,543)	1,115 (1,845)	1,231 (2,030)	1,206 (2,178)	1,154 (2,201)	1,234 (2,393)
	98	98	98	98	98	98	98
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

[a]One subject in the survivor group, 2 months old, was missing the "height" assessment, resulting in missing values for body surface area and the cumulative fluid balances per m².

[b]Two additional subjects died after hospital discharge but before 90 d.

Increasing cumulative fluid balance was also associated with prolonged mechanical ventilation and longer duration of PICU stay and hospitalization. Fluid balance was significantly ($p < 0.001$) associated with VFDs at 28 days. Similar trends, although not statistically significant, were found for both PICU-free days ($p = 0.14$) and hospital-free days ($p = 0.06$).

The relationship between daily fluid accumulation and oxygenation was less well established. The trial did not require arterial blood gases for the assessment of oxygenation. Consequently, the OSI was used to assess changes in oxygenation (6). Adjusting for all other factors, the repeated measures models estimated that each liter per meter squared increase in fluid balance was associated with a 0.52 (SE = 0.20, $p = 0.011$) point increase in the OSI. Note that this difference included all calculated OSI values; the analysis did not change significantly when OSI values using only those where Sp_{O_2} values less than or equal to 97% were included.

DISCUSSION

Rivers et al (1), Han et al (2), and others (3, 7, 8) have reported that early aggressive fluid resuscitation improves outcome in critical illness. The ARDSnet fluid and catheter trial (FACTT), however, demonstrated that conservative fluid management after initial stabilization was associated with improved oxygenation, fewer adverse events, and a shortened duration of ventilation and ICU stay (5). Rosenberg et al (9) described similar findings in their retrospective review of the ARDSnet ARMA Trial. The importance of a negative fluid balance after the initial resuscitation and stabilization of shock has also been suggested (10–12).

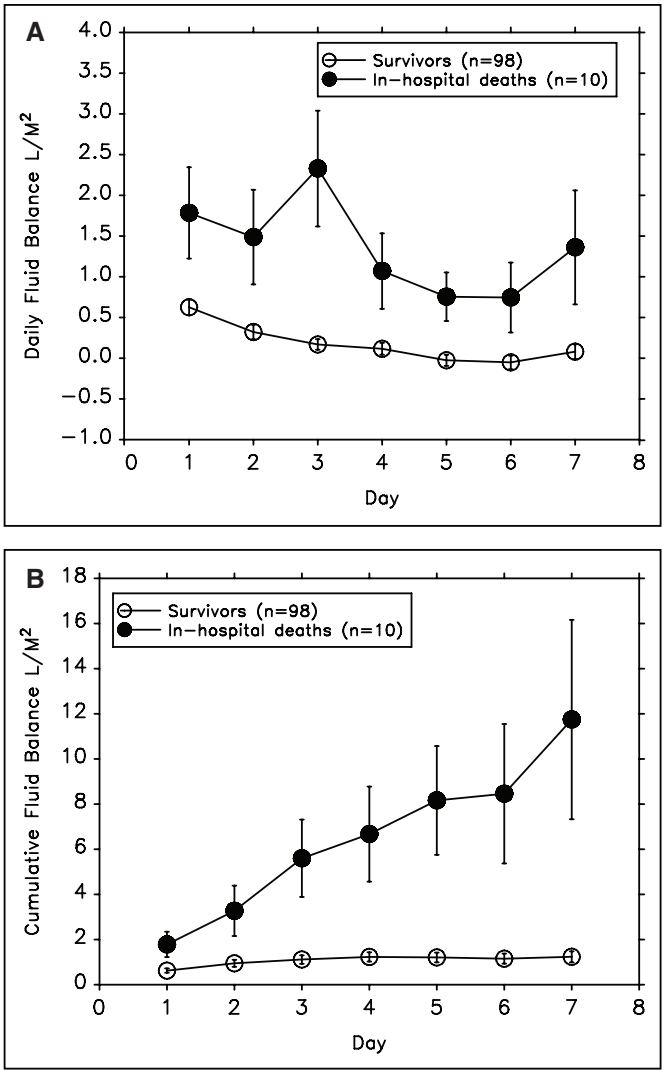

Figure 3. **A**, Daily fluid balance (±SEM) over the first 7 days of hospitalization between subjects who died in the hospital compared to survivors ($p < 0.01$ for all days). **B**, The cumulative daily balance for the two groups ($p < 0.001$ for all days).

Our trial was focused on children with direct ALI and attempted to follow the recommendations of the FACTT conservative arm with respect to total fluid administration. Since central venous catheters were not mandated for the trial (and pulmonary artery catheters are now rarely used in pediatric critical care), we advised a strategy of fluid and diuretic administration based on daily fluid balance for those subjects without a central venous catheter in place. Subjects with a central venous catheter were to be treated in accordance with the FACTT recommendations (Fig. 1). As evidenced by the reported data, the fluid balance results were more in line with the "liberal" arm of the FACTT. No subject variable or measure of severity (initial OSI, Pao_2/Fio_2 ratio, PRISM III) accounted for these differences. These results suggest that pediatric intensivists have not changed their practice in the face of the FACTT study results and did not adhere to the conservative fluid approach recommended for this clinical trial. Subjects in the conservative arm of the FACTT study on average had a negative fluid balance by day 3 after enrollment (5). On average, our subjects continued to have a daily fluid gain the first 7 days after enrollment. Survivors in the trial only began to have a slightly negative fluid balance days 5 and 6 (–25 cc/m^2 day 5, –60 cc/m^2 day 6) and had a positive fluid gain day 7 (+80 cc/m^2).

Although the present study is the first prospective investigation of this issue in children, both Valentine et al (13) and Arikan et al (14) demonstrated similar findings in retrospective reviews of fluid management in children with ALI. These studies used % fluid overload and balance/kg to express fluid balance; we chose L/m^2 because it is a more accurate reflection of body mass and allows for comparisons across different ages and weights. As an approximation and ignoring consideration of height, a child with a surface area of 1 m^2 is approximately 30 kg—thus the average of nearly 2 L/m^2 fluid gain by day 7 would be comparable to an approximate 7% fluid weight gain. Using the same approximation, nonsurvivors who gained an average of nearly 10 L/m^2 had a 33% fluid weight gain.

Increasing fluid accumulation in this trial was associated with worsening oxygenation, prolongation of mechanical ventilation, a trend toward lengthened hospital stay, and increased mortality. Although it is plausible that more critically ill subjects prone to worse outcomes needed and received greater volumes of fluid, no association between severity of illness (reflected by PRISM III scores) or initial oxygenation (reflected by Pao_2/Fio_2, Spo_2/Fio_2, or OSI) and fluid administration could be demonstrated on either the first day or over the first 7 days of the study. The association of increasing positive fluid balance and worsening outcomes has been demonstrated in other retrospective pediatric studies (9, 10, 13) (although not all) (15).

The lung inflammation in ALI is associated with capillary leak (16), and in the presence of pulmonary endothelial injury, lung water increases in direct proportion to venous pressure (4). Adequate venous pressure is necessary to support cardiac output, particularly in the early phase of resuscitation. However, increased lung water may have a deleterious effect on lung function, resulting in the need for prolonged ventilatory support with its attendant risks for morbidity and mortality. As suggested by Arikan et al (14), "the early goal of achieving adequate perfusion through liberal fluid administration might need to be shifted to the goal of attaining or maintaining euvolemia once hemodynamic stability is achieved." Our study focused only on subjects with direct lung injury, but it is reasonable to assume that lung inflammation and capillary leak in indirect lung injury (e.g., with sepsis) would be equally significant and these results would pertain to those patients as well. Indeed, previous studies that did not distinguish between "direct" and "indirect" lung injury demonstrated similar findings (9, 10, 13).

Although all data were collected prospectively, the study was not designed to evaluate the effect of fluid intake on outcomes in pediatric ALI. It is possible that illness severity not reflected in PRISM scores, initial oxygenation disturbance, or demographic factors influenced the fluid administration over the first 7 days of the trial and, consequently, was responsible for the observed differences. It is also quite possible that "severity"

changed over the course of the subjects' illness and necessitated further fluid resuscitation, accounting for the differences in fluid administration. We did not track any daily measure of severity, such as a PEdiatric Logistic Organ Dysfunction score, which might have been helpful to determine if this were the case. Nonetheless, these findings support those of other investigators who have found that pediatric intensivists generally follow an approach of fluid management comparable to the "liberal arm" of the FACTT and that this approach may have detrimental effects on outcomes (13, 14, 17). Given the routine nature of fluid administration in ALI and its possible influence on lung function, a prospective trial of conservative fluid management in pediatric ALI should be considered to definitively resolve this question.

REFERENCES

1. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
2. Han YY, Carcillo JA, Dragotta MA, et al: Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* 2003; 112:793–799
3. Carcillo JA, Davis AL, Zaritsky A: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; 266:1242–1245
4. Sibbald WJ, Shkort AK, Warshawski FJ, et al: Thermal dye measurements of extravascular water in critically ill patients: Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. *Chest* 1985; 87:585–592
5. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
6. Thomas NJ, Shaffer ML, Willson DF, et al: Defining acute lung disease in children with the oxygen saturation index. *Pediatr Crit Care Med* 2010; 11:12–17
7. Nadel S, Britto J, Booy R, et al: Avoidable deficiencies in the delivery of health care to children with meningococcal disease. *J Accid Emerg Med* 1998; 15:298–303
8. Wills BA, Nguyen MD, Ha TL, et al: Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; 353:877–889
9. Rosenberg AL, Dechert RE, Park PK, et al: Association of cumulative fluid balance on outcome in acute lung injury: A retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; 24:35–46
10. Murphy CV, Schramm GE, Doherty JA, et al: The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; 136:102–109
11. Boyd JH, Forbes J, Nakada TA, et al: Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39:259–265
12. Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators: Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 2006; 34:344–353
13. Valentine SL, Sapru A, Higgerson R, et al: Fluid balance in critically ill children with acute lung injury approximates the liberal arm of the NHLBI ARDSNet fluid and catheter treatment trial and is associated with duration of mechanical ventilation: A multi-centered retrospective cohort study. *Crit Care Med* 2012; 40:2883–2889
14. Arikan AA, Zappitelli M, Goldstein SL, et al: Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012; 13:253–258
15. Randolph AG, Forbes PW, Gedeit RG, et al; Pediatric Acute Lung Injury & Sepsis Investigators (PALISI) Network: Cumulative fluid intake minus output is not associated with ventilator weaning duration or extubation outcomes in children. *Pediatr Crit Care Med* 2005; 6:642–647
16. Ware LB, Matthay MA: The acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1334–1349
17. Flori HR, Church G, Liu KD, et al: Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. *Crit Care Res Pract* 2011; 2011:854142

APPENDIX 1: Participating Hospitals and Collaborators

Participating Hospitals	Primary Investigator	Research Assistant
Asan Medical Center, Seoul, South Korea	Lim Chae-Man, MD	
Texas Children's Hospital, Houston, Texas	Laura Loftis, MD	Ursula Kyle
British Columbia Children's Hospital, Vancouver, Canada	David Wensley, MD	Gordon Krahn
Westmead Children's Hospital, Sydney, Australia	Marino Festa, MD	Evette Gorey
Children's Hospital of Wisconsin, Milwaukee, Wisconsin	Michael Quasney, MD	Kathy Murkowski
Cincinnati Children's Hospital, Cincinnati, Ohio	Susan Poynter, MD	Marie Monaco
Morgan Stanley Children's Hospital, New York City, New York	Kathy Biagas, MD	Naresh Talathoti
Weill Cornell Children's Hospital, New York City, New York	Steven Pon, MD	Charlene Correa
Arnold Palmer Hospital for Children, Orlando, Florida	Aaron Godshall, MD	Corina Mattix
Haemek Medical Center, Afula, Israel	Amiran Lev, MD	Shibili Arshed
Inova Fairfax Hospital for Children, Fairfax, Virginia	Keith Dockery, MD	Kathy Huddleston
Jackson Memorial Hospital, Miami, Florida	Gwenn McLaughlin, MD	Andrea Castelblanco
Nationwide Children's Hospital, Columbus, Ohio	Margaret Chase, MD	Patsy Guittar

(*Continued*)

APPENDIX 1: (*Continued*) Participating Hospitals and Collaborators

Participating Hospitals	Primary Investigator	Research Assistant
Children's Hospital and Medical Center, University of Nebraska, Omaha	Ed Truemper, MD	Machelle Zink
Penn State Hershey Medical Center, Hershey, Pennsylvania	Neal Thomas, MD	Jennifer Stokes
Princess Margaret Hospital, Perth, Australia	Simon Erickson, MD	Pania Falconer
Riley Children's Hospital, Indianapolis, Indiana	Kris Bysani, MD	Terry Barclay
Royal Children's Hospital, Melbourne, Australia	Warwick Butt, MD	Carmel Delzoppo
Royal Darwin Hospital, Darwin, Australia	Dianne Stephens, MD	Jane Thomas
Starship Children's Hospital, Auckland, New Zealand	John Beca, MD	Hannah Stapelton
Ste. Justine Children's Hospital, Montreal, Canada	Philippe Jouvet, MD	Nicole Poitras
Shands Hospital for Children, Gainesville, Florida	Irina Ten, MD	Melissa Lamb
UVA Children's Hospital, Charlottesville, Virginia	Doug Willson, MD	Christine Traul, MD
Women's and Children's Hospital, Adelaide, Australia	Michael Yung, MD	Cathy Lyon