CUTIC RESPIRATORY DISTRESS syndrome (ARDS) was originally termed the adult respiratory distress syndrome because it resembled the clinical picture of infant respiratory distress syndrome (IRDS), and both exhibited hyaline membranes at autopsy. Avery and Mead first reported that lung surfactant quantity and activity were abnormal in infants with IRDS and surfactant replacement has subsequently become standard therapy for premature infants at risk for or having IRDS. Petty and Ashbaugh described qualitative and quantitative surfactant deficiencies in their initial description of ARDS and the subsequent scientific literature (recently reviewed by Notter) has supported the role of surfactant dysfunction in both ARDS and less severe acute lung injury (ALI). Surfactant replacement in ARDS and ALI has been

**Context** Despite evidence that patients with acute lung injury (ALI) have pulmonary surfactant dysfunction, trials of several surfactant preparations to treat adults with ALI have not been successful. Preliminary studies in children with ALI have shown that instillation of a natural lung surfactant (calfactant) containing high levels of surfactant-specific protein B may be beneficial.

**Objective** To determine if endotracheal instillation of calfactant in infants, children, and adolescents with ALI would shorten the course of respiratory failure.

**Design, Setting, and Patients** A multicenter, randomized, blinded trial of calfactant compared with placebo in 153 infants, children, and adolescents with respiratory failure from ALI conducted from July 2000 to July 2003. Twenty-one tertiary care pediatric intensive care units participated. Entry criteria included age 1 week to 21 years, enrollment within 48 hours of endotracheal intubation, radiological evidence of bilateral lung disease, and an oxygenation index higher than 7. Premature infants and children with preexisting lung, cardiac, or central nervous system disease were excluded.

**Intervention** Treatment with intratracheal instillation of 2 doses of 80 mL/m² calfactant or an equal volume of air placebo administered 12 hours apart.

**Main Outcome Measures** Ventilator-free days and mortality; secondary outcome measures were hospital course, adverse events, and failure of conventional mechanical ventilation.

**Results** The calfactant group experienced an acute mean (SD) decrease in oxygenation index from 20 (12.9) to 13.9 (9.6) after 12 hours compared with the placebo group’s decrease from 20.5 (14.7) to 15.1 (9.0) (P = .01). Mortality was significantly greater in the placebo group compared with the calfactant group (27/75 vs 15/77; odds ratio, 2.32; 95% confidence interval, 1.15-4.85), although ventilator-free days were not different. More patients in the placebo group did not respond to conventional mechanical ventilation. There were no differences in long-term complications.

**Conclusions** Calfactant acutely improved oxygenation and significantly decreased mortality in infants, children, and adolescents with ALI although no significant decrease in the course of respiratory failure measured by duration of ventilator therapy, intensive care unit, or hospital stay was observed.
largely unsuccessful. Three prospective, randomized controlled clinical trials of surfactant replacement demonstrated little or no benefit in adults with ARDS or ALI who were treated with aerosolized synthetic Exosurf (Burroughs Wellcome, Kirkland, Quebec), and instilled semisynthetic Survaanta (Abbott Laboratories, Abbott Park, Ill), and instilled recombinant surfactant-specific protein C–based Venticute (ALTANA Pharma, Konstanz, Germany).

Surfactant preparations differ in both phospholipid and protein composition and the failure of previous trials may relate to these differences. The importance of the hydrophobic surfactant apoprotein surfactant-specific protein B (SP-B) has only recently been recognized. Calfactant is a modified natural surfactant with a ratio of phospholipids to apoprotein SP-B similar to that found in natural bovine surfactant. Biophysical and biological testing demonstrates activity equal to natural surfactant and resistance to inhibition by either proteins associated with lung injury or by lysosphospholipids.

We hypothesized that a natural surfactant containing high levels of SP-B, such as calfactant, might prove effective in ARDS or ALI. A positive acute response to calfactant administration in an open-label trial in 29 children ventilated for ALI was reported in 1996 and a subsequent controlled but unblinded study of 42 patients replicated this acute improvement and demonstrated a shortened ventilator and intensive care unit course. The positive results in those preliminary studies led to the current multicenter, blinded, controlled trial of calfactant compared with placebo in infants, children, and adolescents with respiratory failure from ARDS or ALI.

METHODS

Patients
Twenty-one pediatric intensive care units (PICUs) across the Pediatric Acute Lung Injury and Sepsis Investigator network enrolled patients over a 3-year period from July 2000 to July 2003. Institutional review boards at each institution approved the study protocol. Informed consent was obtained from a parent or guardian prior to enrollment. Demographic information obtained included age, sex, and race/ethnicity (white, black, Hispanic, or other). Race/ethnicity was determined from the medical record.

Entry criteria included age 1 week to 21 years; respiratory failure due to radiographically evident bilateral parenchymal lung disease; enrollment within 24 hours of initiation of mechanical ventilation (extended to 48 hours after the initial 50 patients); and an oxygenation index higher than 7 (oxygenation index = (fraction of inspired oxygen) × (mean airway pressure) × 100/PaO2).

Exclusion criteria included prematurity (corrected gestational age <37 weeks); status asthmaticus; head injury with Glasgow Coma Scale of less than 8; chronic lung disease defined by home oxygen or diuretic use; brain death, do not resuscitate orders, ongoing cardiopulmonary resuscitation, or limitation of life support; significant airway disease that might delay extubation; uncorrected congenital heart disease, preexisting myocardial dysfunction, or cardiogenic pulmonary edema.

Randomization was stratified to balance the severity of lung injury between groups at study entry. Stratification was based on evidence of increased mortality in patients with an oxygenation index of 13 or higher (fast entry) compared with an oxygenation index higher than 7 but less than 13 (slow entry) within 6 hours of the initiation of mechanical ventilation (Jim Fackler, MD, written communication, May 2000).

Study Protocol
Patients were randomized to receive intratracheal instillation of 2 doses of 80 mL/m² calfactant (35 mg/mL of phospholipid suspension in saline) or an equal volume of air placebo. For infants weighing less than 10 kg, the equivalent newborn dose of calfactant was 3 mL/kg. Treatment was administered in 4 equal aliquots instilled intratracheally via a small catheter. Patient positions were changed between aliquots (left decubitus, head up then down; right decubitus, head up then down) and sedation and neuromuscular blockade were given for the procedure. Gas exchange was maintained by manual ventilation with 100% oxygen using pressures comparable with those previously used on mechanical ventilation. By protocol, a second intervention was performed a mean (SD) of 12 (2) hours later if the oxygenation index remained higher than 7.

To maintain blinding, a pharmacist drew the next (opaque) envelope from the appropriate fast entry or slow entry file previously randomized centrally in blocks of 2 and 4 and sent the syringes of calfactant or placebo to the PICU in an opaque container. A respiratory therapist not otherwise involved with the care of the patient placed opaque tape on the endotracheal tube and performed the intervention. Physicians, investigators, and nurses caring for the patient remained blinded to treatment assignment throughout the study.

Participating investigators agreed to follow ventilator guidelines limiting tidal volume of less than 8 mL/kg; fraction of inspired oxygen of less than 0.6; peak inspiratory pressure of less than 40 mm Hg; and PaCO₂ of less than 40 and less than 60 mm Hg. Blood gases and ventilator settings were evaluated through study day 14.

Treatment with other surfactants was prohibited and the clinical care team determined all other aspects of the patient’s care. All data were collected prospectively.

Study Drug
Calfactant (Infasurf produced by ONY Inc, Amherst, NY) is a modified natural lung surfactant approved by the Food and Drug Administration for IRDS and produced by expressing the phospholipids, neutral lipids, and hydrophobic apoproteins SP-B and surfactant-
oximetry were monitored continuously and recorded at 5-minute intervals for 30 minutes after the intervention. Complications at the time of study intervention included any significant change in vital signs (eg, bradycardia, hypotension) or sustained (>30 seconds) oxygen saturation of less than 80%. Safety outcomes included mortality, pulmonary complications (air leaks, pulmonary hemorrhage, and nosocomial pneumonia), and any unexpected adverse events.

Management of the Study

The original study design called for enrollment of 300 patients and completion in 2 years. Sample size calculation based on pilot study data suggested a 25% reduction in the 13-day average ventilator course for pediatric respiratory failure would require 274 patients with an α level of .05 and a β level of .10. After the first year, it became apparent that participating centers were enrolling fewer patients than expected. The data and safety monitoring board endorsed a 1-year study extension and closure of the study at the end of that year regardless of enrollment. The data and safety monitoring board conducted an interim safety analysis when 100 patients had been enrolled. No significant differences in adverse events or deaths were found. However, mortality was higher than in the previous 2 studies, prompting a blinded review of all deaths by the board. The board concluded that the increase in deaths was due to the inclusion of immunocompromised children in the current study. At the direction of the Food and Drug Administration, the board continued to review the findings with each additional 10 deaths. The study was stopped at the predetermined 3-year limit and was not stopped because of mortality differences. The mortality difference we found was not discovered until after the study was closed.

Statistical Analysis

Tests were used to compare groups with respect to categorical outcomes. The Wilcoxon rank sum test was used to compare groups with quantitative outcomes. Cure-rate models were used to compare time with successful extubation. Repeated measures models were used to compare the oxygenation index within subjects over time. In post hoc analyses, logistic regression models were used to assess treatment effects on mortality, which were adjusted for fast or slow entry stratification factor; study site (sites with ≤10 patients enrolled were treated as 1 site); age category (<1 year, 1-5 years, 6-13 years, >13 years); and immune status (immunocompromised vs uncompromised). All variables and the subset of variables found to be significant were then tested in multivariate models that included the treatment group. We used statistical software to fit the cure rate models (GAUSS, Aptech Systems, Kent, Wash) and for other analyses (SAS Version 8.2, SAS Institute, Cary, NC). Statistical significance was considered to be P < .05.

RESULTS

A total of 153 patients provided consent, but 1 parent withdrew consent prior to treatment. Seventy-seven patients were randomized to the calfactant group and 75 patients were randomized to the placebo group (Figure 1). All data were included in an intention-to-treat analysis.

At study entry, 91% of patients met ARDS criteria and all patients met ALI criteria. There were no significant differences between groups in demographic profile, severity of illness at randomization, or coexisting diagnoses or comorbidities (Table 1). Although not statistically significant, there were 5 additional bone marrow transplant patients in the placebo group and 3 additional near-drowning patients in the surfactant arm; both groups had high baseline mortality. Eight protocol violations were identified: 6 patients (3 placebo and 3 calfactant) had an initial oxygenation index of less than 7 but met all other entry criteria and 2 patients (1 placebo and 1 calfactant) received nonprotocol surfactant admin-
istration after the study intervention. Adherence to the ventilator guidelines was comparable between groups. Fraction of inspired oxygen and peak pressures were within guidelines more than 90% of the time and PaCO₂ was higher than 40 mm Hg more than 80% of the time.

Mortality was significantly greater in the placebo group compared with the calfactant group (27/75 vs 15/77; odds ratio [OR], 2.32 [95% confidence interval {CI}, 1.15-4.85]) when all deaths were considered and was still significant when death without recovery from respiratory failure was considered (TABLE 2). Respiratory failure was given as the primary cause of death in 40% of patients and as a major contributor of death in 43% of patients. Calfactant patients averaged a mean (SD) of 13.2 (10) ventilator-free days at 28 days while placebo patients averaged 11.5 (10.5) ventilator-free days (P =.21). The cumulative percentages of extubated patients in each group over the first 28 days appear in FIGURE 2.

Oxygenation as measured by oxygenation index significantly improved with both doses of calfactant (FIGURE 3). Improvement after the first intervention was not adequate to preclude retreatment in most patients, however, as most calfactant (70%) and placebo patients (79%) received a second intervention per the study protocol because their oxygenation index remained greater than 7.

Infants younger than 12 months constituted 26% of the population. Mortality in this subgroup of placebo patients was more than 3 times that of calfactant-treated patients (9/19 vs 3/21; P = .02). Ventilator-free days were also statistically fewer in placebo patients (mean [SD], 7.0 [9.9] vs 15.2 [10.3]; P = .01).

Table 2 reports other clinical outcomes. More placebo patients did not respond to conventional mechanical ventilation after the study intervention. Comparison of duration of oxygen therapy, hospital and PICU lengths of stay, and hospital charges revealed no statistical differences between groups. Immediate complications associated with instillation were more frequent in calfactant patients and were similar to the acute responses of newborns to surfactant instillation. Hypotension was seen in 9% of calfactant instillations compared with 1% of placebo instillations (P = .005). All patients with hypotension responded to volume infusion. Transient hypoxia occurred in 12% of calfactant instillations compared with 3% of placebo instillations (P = .008), but resolved when the calfactant instillation was slowed and/or the positive-pressure ventilation was transiently increased. No patient was removed from the study because of treatment complications. The incidence of air leaks was 13% in the calfactant group and 16% in placebo group (P = .65). Nosocomial pneumonia was seen in 6% of calfactant patients and 11% of placebo patients (P = .40). No systemic complications were ascribed to the intervention in either group.

The ORs and associated 95% CIs of the treatment effect on mortality adjusted for factors identified a priori (fast vs slow entry, center) or a posteriori

| Table 1. Demographics, Severity, and Diagnoses  
<table>
<thead>
<tr>
<th>Calfactant (n = 77)</th>
<th>Placebo (n = 75)</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>7.2 (6.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (65)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>43 (56)</td>
</tr>
<tr>
<td>Black</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (10)</td>
</tr>
<tr>
<td><strong>Severity of Illness</strong></td>
<td></td>
</tr>
<tr>
<td>Pediatric Risk of Mortality Score</td>
<td>15 (9.4)</td>
</tr>
<tr>
<td>Entry</td>
<td></td>
</tr>
<tr>
<td>Fast</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Slow</td>
<td>43 (53)</td>
</tr>
<tr>
<td>Initial oxygenation index, mean (SD)</td>
<td>20.0 (12.9)</td>
</tr>
<tr>
<td>Initial ratio of PaO₂/FIO₂, mean (SD)</td>
<td>128 (54)</td>
</tr>
<tr>
<td><strong>Etiologic or Coexisting Diagnoses</strong></td>
<td></td>
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<tr>
<td>ARDS or sepsis</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
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<tr>
<td>Viral, non-RSV</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>8 (10)</td>
</tr>
<tr>
<td>RSV</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Near drowning</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (8)</td>
</tr>
<tr>
<td><strong>Comorbidity Due to Immunocompromised Status</strong></td>
<td></td>
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<tr>
<td>Bone marrow transplant</td>
<td>10 (13)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cancer only</td>
<td>9 (12)</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; FIO₂, fraction of inspired oxygen; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus.
*Values are number (percentage) unless otherwise indicated. P > .05 for all comparisons.
Table 2. Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Calfactant (n = 77)</th>
<th>Placebo (n = 75)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>In hospital</td>
<td>15 (19)</td>
<td>27 (36)</td>
<td>.03</td>
</tr>
<tr>
<td>Without extubation</td>
<td>12 (16)</td>
<td>24 (32)</td>
<td>.02</td>
</tr>
<tr>
<td>Immunocompromised, No./total (%)</td>
<td>11/22 (50)</td>
<td>18/30 (60)</td>
<td>.58</td>
</tr>
<tr>
<td>Immune-competent, No./total (%)</td>
<td>4/55 (7)</td>
<td>9/45 (20)</td>
<td>.08</td>
</tr>
<tr>
<td>Conventional mechanical ventilation failure†</td>
<td>13 (21)</td>
<td>26 (42)</td>
<td>.02</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>3 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Use of nitric oxide</td>
<td>9 (12)</td>
<td>10 (13)</td>
<td>.80</td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation after entry</td>
<td>7 (9)</td>
<td>15 (20)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Secondary outcomes, mean (SD)

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<tr>
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<tbody>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric intensive care unit</td>
<td>15.2 (13.3)</td>
<td>13.4 (11.6)</td>
<td>.71</td>
</tr>
<tr>
<td>Hospital</td>
<td>25.0 (22.5)</td>
<td>24.8 (32.3)</td>
<td>.78</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>17.3 (16)</td>
<td>18.3 (31)</td>
<td>.97</td>
</tr>
<tr>
<td>Hospital charges, $‡</td>
<td>205 (220)</td>
<td>299 (640)</td>
<td>.68</td>
</tr>
</tbody>
</table>

*Values are number (percentage) unless otherwise indicated.
†Some patients had more than 1 alternative treatment.
‡In thousands.

There were 77 patients in the calfactant group and 75 in the placebo group. The patients who died or went on to extracorporeal membrane oxygenation were by definition never extubated. Estimation was based on the cure rate models in Betensky and Schoenfeld.15

Comment

Infants, children, and adolescents with ALI who received calfactant in this multicenter study had decreased mortality, more rapid improvement in oxygenation index, and were less likely to respond to conventional mechanical ventilation. The primary outcome variable, ventilator-free days, was not significantly different between groups. Transient hypoxia and hypotension were more common with calfactant treatment but these effects were mild and did not necessitate withdrawal from the study. The positive effect of calfactant in this trial is consistent with our preliminary studies of calfactant in children.13,14

Infant respiratory distress syndrome results from quantitative deficiency of surfactant leading to respiratory failure from progressive atelectasis. Surfactant is also deficient in ARDS and ALI, but is further inhibited by inflammatory mediators, plasma proteins, and cellular debris from seeping into the airspace.13,16 Consequently, the challenges for successful surfactant replacement therapy in ARDS and ALI are more complex than for IRDS. Two surfactants effective in IRDS had disappointing results when tested in large clinical trials in ARDS and ALI.6,7

The previously observed acute benefits of calfactant on lung function were replicated herein.13,14 Both doses of calfactant improved oxygenation, demonstrating that it can form a functioning film in the injured lung. Calfactant did not, however, restore lung function to normal nor did all of the patients respond positively. Only 55% of calfactant patients (vs 33% of placebo patients) had a 25% or greater improvement in oxygenation index by 12 hours after the first intervention. Unfortunately, the study was not large enough to conclusively identify factors that might separate responders from non-responders.

Unlike our previous trial,14 the duration of respiratory failure was not improved with calfactant. The average duration of ventilation in calfactant compared with placebo patients was similar (11.3 vs 10.8 days), as were lengths of stay and hospital charges. The absence of benefit in these parameters may be a consequence of the disproportionate survival of marginal calfactant-treated patients. As was observed with the introduction of surfactant therapy in premature infants, increased survival may actually increase the need for prolonged supportive care.17

Severity of initial lung injury was expected to influence survival. Mortality rate was indeed higher in fast (37%) compared with slow entry (20%) subgroups. Mortality was lower in both strata for calfactant patients (26% calfactant vs 46% placebo for fast entry and 14% vs 26% for slow entry, respectively). Unresolved respiratory failure was given as the primary cause or a major contributor in 83% of deaths and lack of improvement in oxygenation after the intervention was strongly associated with mortality. Improvement in lung function offers a plausible mechanism whereby calfactant treatment might increase survival because, unlike studies of ARDS in adults,18,20 respiratory failure was a significant cause of death in this pediatric trial.

Overall mortality in this study was higher than in the pilot study14 (14% in pilot study vs 28% herein), attributable to the inclusion of the previously excluded immunocompromised patients whose mortality rate (56%) was 4 times that of immunocompetent patients (13%). Mortality rates were lower...
for calfactant patients in both the immunocompromised (50% vs 60%) and immunocompetent (7% vs 20%) subgroups. We were concerned, however, that the numerically greater number of immunocompromised patients in the placebo group (30 in the placebo group vs 22 in the calfactant group; \(P = .17\)) may have influenced the observed overall mortality difference between the groups. The ORs for mortality with placebo treatment approached but did not reach statistical significance \((P = .08)\) after post hoc adjustment for immune status (Table 3). This study was not powered sufficiently to detect effects in specific patient subgroups.

The reasons for the failure of surfactant in the 3 large adult ARDS trials are unclear, but the content of the hydrophobic surfactant apoprotein SP-B in the exogenous surfactant may be a critical factor. Congenital absence of SP-B in humans causes lethal neonatal respiratory distress syndrome and mice who are bred deficient of SP-B die at birth of respiratory failure. The SP-B protein by itself confers full biophysical and biological activity on surfactant phospholipids. The surfactant used in the study has the highest level of resistance to inactivation as determined by in vitro and in vivo experimental testing due to its high ratio of protein SP-B to phospholipids. It has greater surface activity and physiological activity in animal lungs than Exosurf or Survanta, which are 2 surfactants previously used to treat ARDS in adults. Additionally, the amount of calfactant administered in this trial was more than 3 times the estimated normal lung surfactant content of 20 mg/kg.

Differences in the predominant mechanism of lung injury may be an additional explanatory factor for the positive results of this study compared with the adult studies. Post hoc analysis of data from the protein-C surfactant (Venticute) study suggested patients with ARDS or ALI due to direct lung injury (eg, pneumonia, aspiration) responded positively to surfactant whereas patients with ARDS or ALI due to indirect lung injury (eg, sepsis) had little response or possibly a negative response. Our findings were similar. Calfactant significantly improved oxygenation and reduced mortality relative to placebo (8% vs 37%; \(P = .007\)) in the subgroup with direct ARDS or ALI while having little effect in patients with indirect ARDS or ALI. The majority of patients in the adult studies had indirect ARDS or ALI, but this mechanism affected only a minority of our patients (35%).

The strengths of the study were that it was multicentered, controlled, and blinded. Treatment groups were also well-matched demographically, by diagnoses, and by objective measures of severity of illness (Pediatic Risk of Mortality Score) and lung injury (oxygenation index), but was less well-matched on immune status. The study was underpowered, however, and failed to demonstrate a significant difference between groups in its primary outcome of ventilator-free days. Interpretation of the observed mortality differences must also be tempered by the post hoc recognition that there was an insufficient number of patients in immunocompromised compared with nonimmunocompromised subgroups to determine subgroup treatment effects. While we acknowledge the limitations of post hoc analysis, future clinical trials of ARDS or ALI should prospectively...
stratify for immune status as well as the mechanism of lung injury.

In this multicenter, randomized, blinded trial, calfactant administration early in the course of pediatric acute respiratory failure resulted in acute improvement in oxygenation and was associated with lower mortality. Adverse effects of the therapy were minimal.

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Author Contributions: Dr Willson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Willson, Markovitz, Bauman, Jacobs, Jefferson, Conaway, Egan. Acquisition of data: Willson, Thomas, Markovitz, DiCarlo, Pon, Jacobs, Jefferson. Analysis and interpretation of data: Willson, Thomas, Markovitz, Bauman, DiCarlo, Pon, Jacobs, Jefferson, Conaway, Egan. Drafting of the manuscript: Willson, Thomas, Jacobs, Conaway. Critical revision of the manuscript for important intellectual content: Willson, Thomas, Markovitz, Bauman, DiCarlo, Pon, Jacobs, Jefferson, Conaway, Egan. Administrative, technical, or material support: Willson, Thomas, Bauman, DiCarlo, Pon, Jacobs, Jefferson. Study supervision: Willson, Thomas, Bauman, Jacobs, Jefferson.

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REFERENCES
Clinical trials are increasingly focusing on outcomes not traditionally studied in alcohol clinical trials. As reported by O’Malley et al. in the January 2005 issue of JAMA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has identified craving as an eligibility criterion for inclusion in several clinical trials, a change driven by the recognition of craving as a central mechanism of relapse. This has led to a reconsideration of the efficacy of naltrexone, a medication that requires a high degree of self-management and has not been consistently shown to reduce craving for alcohol and that this may contribute to the lack of a progressive decline in heavy drinking. However, craving for alcohol and that this may contribute to the lack of a progressive decline in heavy drinking. In a secondary analysis of individuals with at least 4 days of abstinence prior to starting medication showed that the naltrexone 380 mg dosage significantly increased the likelihood of abstinence compared with placebo, which does represent additional benefit. Further studies are needed to examine treatment outcomes over longer periods and across different subgroups of alcoholics.

Ameisen suggests that naltrexone does not eliminate craving for alcohol and that this may contribute to the lack of a progressive decrease in heavy drinking. However, craving is an elusive concept and has not been consistently shown to be a good predictor of relapse. In addition, several clinical studies have reported that naltrexone does reduce craving. Clinical trials are increasingly focusing on outcomes such as heavy-drinking events rather than craving because these outcomes directly predict the negative consequences of alcoholism.

Baclofen is a promising medication and offers another potential pharmacological approach to treatment of alcoholism. We agree that it should be studied further.

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Letter by Dr Ameisen notes that the number of heavy drinking days did not progressively decrease in our trial, suggesting that longer treatment would be of no additional benefit. We believe that maintenance of a reduction in heavy drinking is itself of benefit to patients. What might constitute additional benefit is a complex matter and may include progressive reduction of heavy drinking, establishment of abstinence, or improved quality of life. In our trial, participants who had 7 days or more of lead-in abstinence dramatically reduced their heavy drinking with naltrexone. Furthermore, a secondary analysis of individuals with at least 4 days of abstinence prior to starting medication showed that the naltrexone 380 mg dosage significantly increased the likelihood of abstinence compared with placebo, which does represent additional benefit. Further studies are needed to examine treatment outcomes over longer periods and across different subgroups of alcoholics.

Baclofen is a promising medication and offers another potential pharmacological approach to treatment of alcoholism. We agree that it should be studied further.

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Incorrect Wording: In the Caring for the Critically Ill Patient entitled “Effect of Exogenous Surfactant (Calfactant) in Pediatric Acute Lung Injury: A Randomized Controlled Trial” published in the January 26, 2005, issue of JAMA (2005;293:470-476), the word “less” incorrectly was used instead of “more.” On page 474, the first sentence in the “Comment” section should be “Infants, children, and adolescents with ALI who received calfactant in this multicenter study had decreased mortality, more rapid improvement in oxygenation index, and were more likely to respond to conventional mechanical ventilation.”

Incorrect Wording: In the Original Contribution entitled “Staphylococcus aureus Endocarditis: A Consequence of Medical Progress” published in the June 22/29, 2005, issue of JAMA (2005;293:3012-3021), the word “outside” incorrectly was used instead of “inside.” On page 3012, the third sentence of the “Results” section of the abstract should have read “Most patients with health care–associated S aureus IE (131 patients, 60.1%) acquired the infection inside of the hospital.”