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Pharmacologic Treatments for Acute Respiratory Distress Syndrome and Acute Lung Injury

Systematic Review and Meta-Analysis

Neill Adhikari,[1] *Karen E.A. Burns*[2] and *Maureen O. Meade*[3]

1 Department of Critical Care Medicine, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada
2 Department of Critical Care Medicine, London Health Sciences Centre, London, Ontario, Canada
3 Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada

Abstract

Background: Multiple pharmacologic treatments have been studied for patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). Our objective was to systematically evaluate this literature to determine the effects of these interventions on important clinical outcomes.

Methods: We searched OVID versions of CENTRAL (The Cochrane Library Issue 3, 2003), MEDLINE (1966–week 2, January 2004), EMBASE (1980–week 4, 2004), CINAHL (1982–week 2, January 2004), and HEALTHSTAR (1995–December 2003); proceedings from four conferences (1994–2003); and bibliographies of review articles and included studies. We included randomized controlled trials (RCTs) of pharmacologic treatments compared with no therapy or placebo for established ARDS and ALI in adults admitted to an intensive care unit, with measurement of early mortality, late mortality, duration of ventilation, ventilator-free days, non-pulmonary organ dysfunction, or adverse events. We excluded trials in other populations incorporating subgroup analyses of patients with ARDS and ALI and studies of nitric oxide, partial liquid ventilation, and fluid and nutritional interventions. Two reviewers independently screened studies and abstracted data from studies included in the analysis. Data were pooled using random effects models where appropriate.

Results: We retrieved 75 potentially relevant articles and abstracts, of which 33 trials randomizing 3272 patients met our selection criteria. Meta-analysis showed no effect on early mortality for alprostadil ([prostaglandin E_1] seven studies; 693 patients; relative risk [RR] 0.95; 95% confidence interval [CI], 0.77, 1.17), acetylcysteine (five studies; 235 patients; RR 0.89; 95% CI, 0.65, 1.21), early high-dose corticosteroids (two studies; 180 patients; RR 1.12; 95% CI, 0.72, 1.74), or surfactant therapy (nine studies; 1418 patients; RR 0.93; 95% CI, 0.77, 1.12). Most trials of alprostadil, early high-dose corticosteroids, and surfactant therapy showed more adverse events in the active therapy arm. Single small RCTs demonstrated lower hospital mortality (24 patients, RR 0.20; 95% CI, 0.05, 0.81) with corticosteroids for late phase ARDS and lower 1-month mortality (30 patients, RR 0.67; 95% CI, 0.47, 0.95) with pentoxifylline for patients with metastatic cancer and ARDS. Individual trials of nine additional interventions failed to show beneficial effects on prespecified outcomes.

Conclusions: Effective pharmacotherapy for ARDS is extremely limited. Corticosteroids for late phase ARDS and pentoxifylline for patients with metastatic cancer and ARDS reduced mortality in single small studies. However, further research is required to investigate their potential benefit in the treatment of ALI/ARDS.

Background

The acute respiratory distress syndrome (ARDS), first described in 1967,[1] is characterized by diffuse inflammation of the alveolar-capillary membrane in response to various pulmonary and extrapulmonary insults.[2] These insults cause pulmonary injury by direct (e.g. gastric aspiration, pneumonia, inhalational injury, pulmonary contusion) or indirect (e.g. sepsis, trauma, pancreatitis, multiple transfusions of blood products) mechanisms. An

American-European Consensus Conference[3] formulated a widely cited definition of ARDS as follows: the acute onset of (i) hypoxemia, with a ratio of the partial pressure of arterial oxygen (P_aO_2) to the inspired fraction of oxygen (F_iO_2) of 200mm Hg or less; (ii) bilateral infiltrates on a frontal chest radiograph; and (iii) no clinical evidence of left atrial hypertension or a pulmonary artery occlusion pressure of 18mm Hg or less. Acute lung injury (ALI) includes a milder form of lung injury, with a P_aO_2/F_iO_2 ratio of ≤300mm Hg. Almost all patients with ARDS and most with ALI require mechanical ventilation to survive. The mortality of ARDS is high, estimated to be between 34% and 60%.[2] In addition, survivors have a prolonged stay in the intensive care unit (ICU) and demonstrate significant functional limitations, primarily fatigue and muscle weakness, that reduce quality of life and persist for at least 1 year after hospital discharge.[4]

Research on therapy for ARDS has focused on a variety of mechanical ventilation strategies and pharmacologic treatments. Animal and clinical studies, including randomized controlled trials, have demonstrated the role of mechanical ventilation in perpetuating lung injury,[5] leading to macroscopic damage (for example, pneumothorax), diffuse ventilator-induced lung injury, and systemic harm in the form of multiple organ system failure.[6,7] Several randomized trials have compared traditional mechanical ventilation to lung protective ventilation strategies (pressure and volume limited) strategies.[8-12] The largest and most recent study,[8] conducted by the ARDS Network, was stopped after a planned interim analysis showed a clinically and statistically significant reduction in hospital mortality from 39.8% to 31.0% ($p = 0.007$) using low tidal volume ventilation compared with traditional care. The results of this trial have convinced many clinicians and investigators that lung protective ventilation using tidal volume limitation is the most important therapeutic intervention available for patients with ARDS and ALI. More recently, a meta-analysis[13] of five randomized controlled trials (RCTs) found that lung protective ventilation decreased 28-day mortality in patients with ARDS and ALI.

The pathogenesis of ARDS (extensively reviewed elsewhere)[2,14] provides multiple potential targets for pharmacologic interventions. Regardless of the inciting cause of lung injury, the alveolar-capillary membrane is damaged with leakage of protein-rich edema fluid into alveoli. Alveolar epithelial damage involves the basement membrane and types I and II cells. Injury to type II alveolar epithelial cells leads to reduced levels and functionality of surfactant, causing increased surface tension, atelectasis, and decreased lung compliance. Endothelial damage is associated with numerous inflammatory events. These include neutrophil recruitment, sequestration and activation; formation of oxygen radicals; activation of the coagulation system, leading to microvascular thrombosis with platelet-fibrin thrombi; and recruitment of mesenchymal cells with the production of procollagen. Within the alveolar space, the balance between pro-inflammatory (e.g. tumor necrosis factor [TNF]-α and interleukins [IL]-1, -6, and -8) and anti-inflammatory mediators (e.g. IL-1 receptor antagonist and soluble TNF receptor) favors ongoing inflammation. In summary, the initial lung injury is followed by repair, remodeling, and fibrosing alveolitis.

The diversity of approaches to pharmacologic therapy for ARDS and ALI reflects the complex pathophysiology. Therapies evaluated in randomized trials in humans include corticosteroids, other anti-inflammatory agents, immunomodulating agents, pulmonary vasodilators, antioxidants, and surfactants. The evidence for inhaled nitric oxide (NO), a selective pulmonary vasodilator, was appraised in a recent systematic review,[15] which included five (RCTs) of inhaled NO for acute hypoxemic respiratory failure (including ARDS, ALI, and other diagnoses) in adults and children. The authors concluded that inhaled NO improved oxygenation for up to 72 hours without evidence of effect on the duration of mechanical ventilation or mortality (relative risk [RR] 0.98; 95% confidence interval [CI] 0.66, 1.44). A multicenter RCT published after the systematic review confirmed these clinical findings.[16]

The objective of our systematic review was to evaluate the effects of pharmacologic treatments on important clinical outcomes in patients with established ARDS and ALI. A version of this review is published and will be updated in the Cochrane Database of Systematic Reviews.[17]

Methods

Study Eligibility

We selected studies using the following inclusion criteria: RCT design; adult patients admitted to an ICU with established ARDS or ALI; any pharmacologic treatment compared with no therapy or placebo; measurement of early all-cause mortality (at or before 3 months after randomization), late all-cause mortality (beyond 3 months after randomization), duration of ventilation, number of ventilator-free days to day 28,[18] incidence of non-pulmonary organ dysfunction, or adverse events. The primary outcome was early mortality. We accepted the definitions of adult, ARDS, and ALI used by the primary study authors. Unless otherwise noted, we defined adverse events as those leading to discontinuation of the study medication. In studies without a placebo control, they were defined as 'serious adverse events' using authors' definitions.

Table I. Proposed mechanisms of action of pharmacotherapies for acute respiratory distress syndrome and acute lung injury evaluated in randomized trials

Pharmacologic therapy	Proposed mechanism of action
Alprostadil (prostaglandin E_1)	Pulmonary vasodilator Decreases neutrophil activation Decreases platelet aggregation
Acetylcysteine and oxothiazolidine carboxylate (procysteine)	Antioxidant (scavenger of free radical oxygen species)
Corticosteroids	Multiple anti-inflammatory pathways Prevents collagen deposition
Surfactant	Restores normal mechanical properties of alveoli (surface tension, alveolar opening)
Dazoxiben	Anti-inflammatory agent and pulmonary vasodilator (inhibits thromboxane synthase)
Granulocyte macrophage colony-stimulating factor	Immunomodulator (stimulates phagocytosis and functions of host defense cells)
Indomethacin	Anti-inflammatory agent (decreases thromboxane production by inhibiting cyclo-oxygenase)
Interleukin-10	Immunomodulator (anti-inflammatory cytokine)
Ketoconazole	Multiple anti-inflammatory pathways (inhibits thromboxane synthase, 5-lipoxygenase, alveolar macrophages)
Lisofylline	Multiple anti-inflammatory pathways (decreases oxidized free fatty acids and proinflammatory cytokines)
Neutrophil elastase inhibitor	Inhibits proinflammatory and tissue destroying protease
Pentoxifylline	Prevents neutrophil chemotaxis and activation (phosphodiesterase inhibitor)
Acyclovir	Treats herpes simplex virus, which can be found in the lower respiratory tract of patients with lung injury

We excluded any pharmacologic therapy administered as prophylaxis for ARDS or ALI and studies using nitric oxide, partial liquid ventilation (because this intervention uses a pharmacologic therapy as part of a strategy of mechanical ventilation), fluid management and nutritional therapies. We also excluded subgroups of patients with ARDS or ALI reported in RCTs of interventions for other populations, because of the methodologic limitations of subgroup analyses.[19]

Search Strategy

With the assistance of a professional librarian, we searched OVID versions of CENTRAL (The Cochrane Library Issue 3, 2003), MEDLINE (1966 - week 2, January 2004), EMBASE (1980 - week 4, 2004), CINAHL (1982 - week 2, January 2004), and HEALTHSTAR (1995 - December 2003). We used the MeSH term 'adult respiratory distress syndrome' and the text words 'acute lung injury, shock lung, ARDS', and ('acute' or 'adult') 'respiratory distress', without applying language restrictions. We used a highly sensitive strategy to retrieve RCTs from MEDLINE[20] and modified it for other databases. Full details of the search strategies are available from the authors. We searched conference proceedings (1994–2003) published in *American Journal of Respiratory and Critical Care Medicine*, *Chest*, *Critical Care Medicine* and *Intensive Care Medicine* and screened the bibliographies of all retrieved studies and recent review papers[21-38] for additional references.

Data Extraction

Two of the authors independently screened articles and abstracts for inclusion and retrieved all potentially relevant studies. For each study we independently extracted data on population, intervention, outcomes and study methods. We considered the following methodologic features: (i) concealment of allocation; (ii) baseline similarity of treatment and control groups (with respect to age, severity of illness, non-pulmonary organ failures, presence of sepsis, and duration of hospitalization, ICU stay, or mechanical ventilation); (iii) level of blinding (caregivers, data collectors, outcomes assessors); (iv) placebo characteristics that potentially enhanced blinding; (v) cointerventions (standardization or documentation of positive end-expiratory pressure, a lung protective ventilation strategy, weaning protocols, corticosteroids, or other cointerventions); (vi) intention-to-treat analysis (patients analyzed by assigned group and not withdrawn post randomization); and (vii) completeness of follow-up for the outcome of early mortality. We contacted trial authors when we required clarification of the primary outcomes data; four authors[39-42] provided additional information. Disagreements between reviewers were resolved by consensus and in consultation with the third author of this manuscript. We did not systematically evaluate the mechanistic quality of the pharmacologic therapies studied (e.g. whether adequate amounts of the therapeutic agent were delivered to the presumed target for sufficient time to achieve the desired biologic response).

Table II. A summary of randomized controlled trials of alprostadil for acute lung injury/acute respiratory distress syndrome (ARDS)

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Holcroft et al.[91] 1986	41 (1)	Risk factor and bilateral CXR infiltrates, compliance ≤50 mL/cm H_2O, mechanical ventilation with F_iO_2 ≥40% and PEEP ≥5cm H_2O	Risk of intracranial hemorrhage, hemodynamically unstable	Continuous IV alprostadil, maximum dose 30 ng/kg/minute (43.2 μg/kg/day) for 7 days, or placebo	30-day mortality Adverse events
Shoemaker and Appel[93] 1986	9 (1)	Risk factor: sepsis or surgery, CXR infiltrates, P_aO_2 <55mm Hg on room air or P/F <250mm Hg, mechanical ventilation, no evidence of volume overload	Not reported	Continuous IV alprostadil maximum dose 30 ng/kg/minute (43.2 μg/kg/day) for 48–72 hours, or placebo	Mortality (timepoint unclear)
Rossignon et al.[92] 1990	23 (1)	Risk factor: surgery or trauma, diffuse pulmonary infiltrates, PaO_2 ≥60mm Hg on F_iO_2 ≥50%, no left ventricular failure	Chronic obstructive pulmonary disease	Continuous IV alprostadil, maximum dose 30 ng/kg/minute (43.2 μg/kg/day) for 7 days, or placebo	Mortality (timepoint unclear) Duration of ventilation Adverse events
Slotman et al.[87] 1992[b]	147 (13)	Risk factor: trauma, surgery, sepsis, bilateral CXR infiltrates, P/F ≤150mm Hg on PEEP = 0cm H_2O or ≤200mm Hg on PEEP >0cm H_2O	Severe lung disease, liver or renal failure, severe head injury, high-dose corticosteroids	Continuous IV alprostadil, maximum dose 30 ng/kg/minute (43.2 μg/kg/day) for 7 days, or placebo	30-day mortality 6-month mortality Adverse events
Abraham et al.[94] 1996	25 (8)	Mechanical ventilation, bilateral CXR infiltrates, no LAH, P/F ≤225mm Hg, duration of ARDS <24 hours	Recent MI, liver or renal failure, neurogenic pulmonary edema	IV liposomal alprostadil, dose titrated to 3.6 μg/kg every 6 hours (14.4 μg/kg/day) for 7 days, or placebo	28-day mortality Ventilator dependence at day 8 Adverse events
Abraham et al.[95] 1999	350 (47)	AECC definition for ARDS, duration of ARDS <24 hours	Recent MI, liver or renal failure, neurogenic pulmonary edema	IV liposomal alprostadil, dose titrated to 3.6 μg/kg every 6 hours (14.4 μg/kg/day) for 7 days, or placebo	28-day mortality Duration of ventilation Adverse events
Vincent et al.[41] 2001	102 (31)	AECC definition for ARDS, duration of ARDS <24 hours	Recent MI, chronic congestive heart failure, liver or renal failure, pneumonectomy, neurogenic pulmonary edema, neutropenia	IV liposomal alprostadil, dose titrated to 1.8 μg/kg every 6 hours (7.2 μg/kg/day) for 7 days, or placebo	28-day mortality Duration of ventilation Adverse events

a Number of patients randomized (number of centers).

b This paper included 101 patients previously reported[88] and an additional 46 patients randomized in a protocol that did not include renal and liver dysfunction as exclusion criteria. Adverse events and late mortality were reported only in the initial paper.[88]

AECC = American-European Consensus Conference;[3] **CXR** = chest radiograph; **F_iO_2** = fraction of oxygen in inspired gas; **IV** = intravenous; **LAH** = left atrial hypertension; **MI** = myocardial infarction; **P_aO_2** = partial pressure of arterial oxygen; **PEEP** = positive end-expiratory pressure; **P/F** = ratio of P_aO_2 to F_iO_2.

Data Analysis

For each pharmacologic treatment, we pooled the results of studies where permitted by the available data. For studies reporting more than one treatment arm differing in medication dose, we combined data from all doses to determine an overall outcome measure for the treatment arm. We considered ICU and hospital mortality to be early mortality. We used Review Manager software, version 4.2 (Cochrane Collaboration, Oxford, UK) to aggregate data using a random-effects model, calculating an overall RR and a 95% CI for pooled categorical data. We tested the significance of the overall treatment effect using the method of DerSimonian and Laird.[43] For each pooled comparison, we used the Q statistic to test for homogeneity.[44] We considered $p = 0.05$ to be statistically significant for the test of overall treatment effect and $p = 0.10$ to be statistically significant for the test of homogeneity. No subgroup analyses or exploratory analyses to explain heterogeneity were planned. We anticipated variability in the reporting of adverse events and therefore did not pool these events across studies.

When pooled analyses included at least five studies, we constructed funnel plots of study precision versus treatment effect, in order to explore the presence of bias arising from the non-publication of small non-beneficial trials.

Results

Overall Description of Included Studies

Searches of electronic databases yielded 5705 citations. From these citations, conference abstracts, and bibliographies of retrieved studies, we identified 75 potentially relevant publications. We excluded 42 articles and abstracts for the following reasons: non-randomized;[45-51] cost-effectiveness data from a previously published RCT;[52] no placebo or standard care control group;[53] alternative diagnosis in the study population (at risk for rather than established ARDS or ALI,[54-65] sepsis,[66-70] ventilated patients in surgical ICU,[71] malaria,[72] pancreatitis,[73,74] unilateral lung injury after thoracic aneurysm surgery[75]); outcomes of interest not reported;[76,77] subgroup of patients with ARDS or ALI reported in RCT in another population;[78-83] and duplicate publication.[84-86]

Thirty-three publications describing 33 studies met our inclusion criteria. One paper[39] described two similar but separate studies of surfactant therapy. We counted this paper as two studies. One study of alprostadil (prostaglandin E_1) reported mortality data in 147 randomized patients,[87] of whom clinical outcomes in 101 patients had been previously published.[88] We counted these two publications as one study and extracted data on early mortality from the later publication[87] and data on late mortality and adverse events from the earlier publication.[88] One publication[89] reported a trial of patients randomized to receive acetylcysteine, oxothiazolidine carboxylate (procysteine), or placebo. We included the patients randomized to acetylcysteine and placebo in a pooled analysis of the effect of acetylcysteine on early mortality and described the procysteine arm separately. Another study randomized patients to acetylcysteine, acetylcysteine plus rutin (a flavanoid antioxidant), or control.[90] We combined data from both acetycysteine groups in our pooled analysis and did not analyze the effects of rutin, which we classified as a nutritional supplement.

Studies meeting our inclusion criteria randomized 3272 patients and evaluated a wide range of pharmacologic treatments with differing mechanisms of action (table I). They include seven studies of alprostadil (table II),[41,87,88,91-95] five studies of acetylcysteine (table III),[89,90,96-98] three studies of corticosteroids (table IV),[99-101] nine studies of surfactant (table V),[39,40,42,102-106] and single studies (table VI) of dazoxiben,[107] acyclovir,[108] indomethacin,[109] pentoxifylline,[110] neutrophil elastase inhibitor (ICI 200,880),[111] oxothiazolidine carboxylate,[89] interleukin-10,[112] ketoconazole,[113] lisofylline,[114] and granulocyte macrophage colony-stimulating factor (GM-CSF).[115]

Studies of the same pharmacologic therapy differed with respect to patient populations and drug administration as discussed in the following sections.

Studies of Aprostadil

All seven studies of alprostadil [41,87,88,91-95] included patients with predominantly ARDS, although three studies restricted enrollment to those with trauma, surgery, or sepsis as a risk factor.[87,88,92,93] They varied with respect to method of medication administration (continuous infusion[87,88,91-93] versus intermittent boluses[41,94,95]), formulation (liposomal in three trials[41,94,95]) and dose (ranging from 7.2 μg/kg/day[41] to 43.2 μg/kg/day[87,88,91-93] for 7 days).

Studies of Acetylcysteine

The five studies of acetylcysteine [89,90,96-98] included four enrolling primarily patients with ARDS[89,90,96,98] and one that restricted enrollment to those with mild ALI.[97] Two trials used continuous infusions[96,97] and the other three used intermittent intravenous boluses.[89,90,98] The total dose of acetyleysteine varied considerably, from 120 mg/kg[97] to 3510 mg/kg,[96] delivered over 3–10 days. The total dose delivered in one trial[90] was unclear.

Studies of Corticosteroids

The three corticosteroid studies included two trials of high dose, short course (≤48 hours) methylprednisolone early in the course of ALI[99] and ARDS.[100] The duration of ARDS prior to randomization was less than 7 days in both trials. One trial studied

Table III. A summary of randomized controlled trials of acetylcysteine and oxothiazolidine carboxylate for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Jepsen et al.[96] 1992	66 (1)	Risk factor and P_aO_2 <55mm Hg on room air or P/F <250mm Hg, duration of intubation <24 hours	Chronic lung, cardiovascular, liver or renal disease	IV acetylcysteine, bolus 150 mg/kg, then 20 mg/kg/hour continuously for 7 days (total dose 3510 mg/kg), or placebo	60-day mortality Adverse events
Suter et al.[97] 1994	61 (4)	Risk factor and mild-moderate ALI (lung injury score[116] between 0.1 and 2.5)	Cardiogenic pulmonary edema, immunocompromised	Continuous IV acetylcysteine, 40 mg/kg/day for 3 days (total dose 120 mg/kg), or placebo	1-month mortality Requirement for ventilatory support at day 3 Adverse events
Bernard et al.[89] 1997	48 (5)	Mechanical ventilation, bilateral CXR infiltrates, no LAH, P/F ≤200mm Hg or 225mm Hg if PEEP >10cm H_2O, duration of ARDS <24 hours	Severe acute or chronic liver disease, immunocompromised	IV acetylcysteine, 70 mg/kg every 8 hours for 10 days (total dose 2100 mg/kg), or IV procysteine, 63 mg/kg every 8 hours for 10 days, or placebo	30-day mortality Ventilator-free days to day 30 New organ failures[b] Adverse events
Domenighetti et al.[98] 1997	45 (4)	AECC definition for ARDS	Immunocompromised	Continuous IV acetylcysteine, 190 mg/kg/day for 3 days (total dose 570 mg/kg), or placebo	ICU mortality Duration of ventilation Adverse events
Ortolani et al.[90] 2000	36 (2)	Mechanical ventilation, bilateral CXR infiltrates, P/F ≤200mm Hg or ≤250mm Hg if PEEP ≥10cm H_2O, duration of ARDS <24 hours	Hemodynamic instability, severe heart or liver disease, "septic complications during trial"	IV acetylcysteine, 50 mg/kg every 8 hours, or IV acetylcysteine (same dose) and IV rutin, 5 mg/kg every 8 hours, all while mechanically ventilated, or control therapy (250mL of 5% dextrose in water)	30-day mortality Adverse events

a Number of patients randomized (number of centers).

b New organ failures were reported for the combined acetylcysteine and oxozothiazolidine carboxylate groups.

AECC = American-European Consensus Conference;[3] **CXR** = chest radiograph; **F_iO_2** = fraction of oxygen in inspired gas; **ICU** = intensive care unit; **IV** = intravenous; **LAH** = left atrial hypertension; **P_aO_2** = partial pressure of arterial oxygen; **PEEP** = positive end-expiratory pressure; **P/F** = ratio of P_aO_2 to F_iO_2.

Table V. A summary of randomized controlled trials of surfactant for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Reines et al.[102] 1992	49 (ND)	Sepsis induced ARDS (not described)	ND	Continuously aerosolized synthetic surfactant (colfosceril palmitate) with DPPC 40.5 mg/mL, or with DPPC 81 mg/mL, or placebo, for up to 5 days	14-day mortality Adverse events
Weg et al.[40] 1994	51 (20)	Risk factor: sepsis or sepsis syndrome present <18 hours, bilateral CXR infiltrates, P/F ≥50mm Hg and ≤299mm Hg, mechanical ventilation	Chronic lung, liver or renal disease, AIDS, pulmonary infection, cardiac ischemia or left ventricular failure	Continuously aerosolized synthetic surfactant (colfosceril palmitate) with DPPC 13.5 mg/mL: 175mL every 4 hours for 12 hours/day or 24 hours/day for 5 days (estimated aerosolized DPPC: 21.9 and 43.5 mg/kg/day, respectively), or placebo	30-day mortality Adverse events
Anzueto et al.[106] 1996	725 (63)	Risk factor: sepsis or sepsis syndrome present for <96 hours, diffuse CXR infiltrates, P/F <250mm Hg, no left ventricular failure, mechanical ventilation, duration of ARDS <48 hours	Chronic lung, liver or renal disease, acute liver failure, HIV with *Pneumocystis jiroveci* pneumonia, inhalational injury	Continuously aerosolized synthetic surfactant (colfosceril palmitate) with DPPC 13.5 mg/mL: 240mL daily for 5 days (estimated aerosolized DPPC: 112 mg/kg/day), or placebo	30-day mortality Duration of ventilation Adverse events
Gregory et al.[42] 1997[b]	43 (5)	Risk factor and mechanical ventilation, bilateral CXR infiltrates, P/F ≤200mm Hg, PEEP ≥5cm H_2O, compliance ≤50 mL/cm H_2O, PAOP ≤18mm Hg, duration of ARDS ≤48 hours	Chronic lung disease, lung cancer, AIDS, cardiogenic shock, head injury	Intratracheal bovine surfactant (beractant) 50 mg/kg for eight doses, or 100 mg/kg for four doses, or 100 mg/kg for eight doses, or standard therapy	28-day mortality Duration of ventilation Organ failures Adverse events
Walmrath et al.[104] 2000	41 (ND)	ARDS (not described)	ND	Intratracheal synthetic surfactant (lusupultide) with 1mg recombinant surfactant protein C and 50mg phospholipids per mL): 1 mL/kg up to four doses in 24 hours (medium dose), or 4 mL/kg followed by up to three doses of 2 mL/kg within 24 hours (high dose), or standard therapy	Mortality (reported only for the medium-dose and standard therapy groups; timepoint unclear) Ventilator-free days to day 28
Kesecioglu et al.[105] 2001	36 (ND)	ALI/ARDS (not described)	ND	Intratracheal porcine surfactant (HL10) with 100–200 mg/kg of phospholipids, up to four doses, or standard therapy	28-day mortality Ventilator-free days to day 28

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Table IV. A summary of randomized controlled trials of corticosteroids for acute lung injury /acute respiratory distress syndrome (ARDS)

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Weigelt et al.[99] 1985	88 (1)	Mechanical ventilation with P_aO_2 <100mm Hg on F_iO_2 = 0.4 and P_aO_2 <350mm Hg on F_iO_2 = 1	ARDS, immunocompromised, some infections, uncontrolled diabetes mellitus	IV methylprednisolone, 30 mg/kg IV every 6 hours for 48 hours, or placebo	Mortality (timepoint unclear) Duration of ventilation Adverse events
Bernard et al.[100] 1987	99 (7)	Risk factor and bilateral CXR infiltrates, P_aO_2 ≤70mm Hg on F_iO_2 ≥0.4 or P_aO_2/P_AO_2 ≤0.3, no LAH	Hypotension, burns, some infections	IV methylprednisolone, 30 mg/kg IV every 6 hours for four doses, or placebo	45-day mortality Duration of ventilation in survivors Adverse events
Meduri et al.[101] 1998	24 (4)	AECC definition for ARDS ≥7 days of mechanical ventilation Lung injury score[116] ≥2.5, with <1 point reduction from day 1 of ARDS	ARDS for ≥3 weeks, untreated infection, burns, recent gastrointestinal bleed	IV methylprednisolone, 2 mg/kg/day IV for 14 days, tapering to zero over next 18 days, or placebo	ICU and hospital mortality Duration of ventilation Organ failure-free days to day 28 Adverse events

a Number of patients randomized (number of centers).

AECC = American-European Consensus Conference;[3] **CXR** = chest radiograph; F_iO_2 = fraction of oxygen in inspired gas; **ICU** = intensive care unit; **IV** = intravenous; **LAH** = left atrial hypertension; P_aO_2 = partial pressure of arterial oxygen; P_AO_2 = partial pressure of alveolar oxygen.

a lower dose of methylprednisolone for a longer duration (1 month) in patients with non-resolving ARDS who had been mechanically ventilated for at least 7 days.[101]

Studies of Surfactant

The nine studies of surfactant[39,40,42,102-106] enrolled primarily patients with ARDS. Three restricted eligibility to patients with sepsis-induced ALI or ARDS.[40,102,106] The surfactant preparations were variable: synthetic surfactant with phospholipids,[40,102,106] synthetic surfactant with phospholipids and protein,[39,103,104] bovine surfactant,[42] and porcine surfactant.[105] The method of delivery (continuous aerosolization in early trials[40,102,106] and intratracheal instillation in later trials[39,42,103-105]) and the delivered doses (when measured) were also variable.

Methodologic Assessment of Studies

The methodologic quality of the included studies was variable (table VII). Ten studies[40,87-89,93,100,103,106,113-115] described adequate concealment of allocation. Only four studies did not report at least one prognostically important baseline characteristic,[102,104,105,107] of which three were reported in abstract form.[102,104,105] Of the remaining 29 studies, seven had at least one clinically important imbalance at baseline.[41,93-95,108,112,115] Six studies[39,89,101,106,113] conducted additional analyses adjusting for baseline imbalances. Twenty-six studies reported blinding of at least caregivers or used the term 'double-blind'. Four of the remaining studies were not placebo-controlled and did not report blinding of any study personnel.[42,103,105,110] One study used a placebo and was described as 'single-blind'.[107] Two studies explicitly reported no blinding.[90,104] Potential unblinding features associated with study medications used in trials describing caregiver blinding included hypotension with alprostadil[41,87,88,91-95] and dazoxiben,[107] hyperglycemia with corticosteroids,[99-101] and reflux of surfactant into the ventilator tubing.[39,40,102,106] Fourteen studies standardized at least one cointervention or documented its application in the treatment and control groups.[39-42,91,92,95,96,101,103,113-115] The remaining studies did not describe cointerventions. Two ARDS Network trials investigated tidal volume limitation combined with ketoconazole[113] and lisofylline[114] in a factorial design. Of the six other trials[39,41,103,105,115] published after the low tidal volume ventilation study,[8] two[39] documented encouragement of a lung protective ventilation strategy. No study reported imbalances in the application of cointerventions. All studies analyzed patients according to their assigned treatment group; however, 11 reported at least one post-randomization withdrawal[39,42,87-89,95,98,99,108] or did not clearly report this information.[40,107] Twenty-eight studies reported no losses to follow-up; the remaining studies had incomplete follow-

Table V. Contd

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Spragg et al.[103] 2003	40 (11)	Risk factor AECC definition for ARDS, duration of ARDS ≤48 hours, PEEP ≥5cm H_2O	Hemodynamic instability, severe hypoxemia, lung cancer, AIDS	Intratracheal synthetic surfactant (lusupultide) with 1mg recombinant surfactant protein C and 50mg phospholipids per mL): 1 mL/kg up to four doses in 24 hours, or 0.5 mL/kg up to four doses in 24 hours, or standard therapy	28-day mortality Ventilator-free days to day 28 Adverse events
Spragg et al.[39] 2004[c]	448 (109)	AECC definition for ARDS PEEP ≥5cm H_2O Duration of ARDS ≤48 hours (North American study) or ≤72 hours (European/South African Study)	ND	Intratracheal synthetic surfactant (lusupultide), with 1mg recombinant surfactant protein C and 50mg phospholipids per mL): 1 mL/kg up to four doses in 12–24 hours, or standard therapy	28-day mortality Ventilator-free days to day 28

a Number of patients randomized (number of centers).

b We excluded the group receiving 100 mg/kg of phospholipids for four doses because it included directly (n = 8) and randomly (n = 8) allocated patients.

c This paper described North American (221 patients, 54 centers) and European/South African (227 patients, 55 centers) studies with nearly identical methods.

AECC = American European Consensus Conference;[3] **CXR** = chest radiograph; **DPPC** = dipalmitoylphosphatidylcholine; **HIV** = human immunodeficiency virus; **ND** = not described (explicit information not provided); **PAOP** = pulmonary artery occlusion pressure; **PEEP** = positive end-expiratory pressure; **P/F** = ratio of partial pressure of arterial oxygen to fraction of oxygen in inspired gas.

up data on fewer than 1% of randomized patients[87,88,95] or did not fully describe the extent of patient follow-up.[40,102,104,114]

Effects of Pharmacotherapies on Clinical Outcomes

We conducted pooled analyses of the effect of alprostadil, acetylcysteine, early corticosteroids and surfactant therapy on early mortality (figure 1, figure 2, figure 3, and figure 4). In all analyses the test for homogeneity was not significant. We were unable to perform pooled analyses for the secondary outcomes (late mortality, duration of mechanical ventilation, ventilator-free days, incidence of non-pulmonary organ dysfunction, adverse events) because of insufficient data and variability in definitions and reporting. Individual trials of these treatments demonstrated no consistent effect on secondary outcomes (table VIII). Effects of additional therapies are summarized separately (table IX).

Alprostadil

We pooled data from seven trials (figure 1) and found no effect on early mortality (693 patients with outcomes data; RR 0.95; 95% CI, 0.77, 1.17). One study[94] showed a decreased need for ventilation at day 8 but did not use a weaning protocol. Adverse events (figure 5) led to discontinuation of study medication in five trials.[41,91,92,94,95] They occurred more frequently in the alprostadil arm and included cardiopulmonary (hypotension, dysrhythmias, hypoxia) and central nervous system (agitation) events. Data from Bone et al.[88] precluded calculating the total number of patients with adverse events; instead, all patients with hypotension are shown.

Acetylcysteine

Aggregate analysis of five studies (figure 2) showed no effect on early mortality (235 patients with outcomes data; RR 0.89; 95% CI, 0.65, 1.21). One study [97] showed a decreased need for ventilation on day 3 but did not use a weaning protocol. The five studies reported no adverse events in the placebo group and only one (rash) in the acetylcysteine group,[96] which resolved after acetylcysteine was stopped.

Early High-Dose Corticosteroids

The meta-analysis of two studies (figure 3) showed no effect on early mortality (180 patients with outcomes data; RR 1.12; 95% CI, 0.72, 1.74). The major adverse effect (figure 5) was the development of new infection during the first 7 days. The definition of new infection differed. Bernard et al.[100] excluded positive urine and sputum cultures from catheterized and intubated patients whereas Weigelt et al.[99] did not report excluding them. Both studies demonstrated a statistically significant increase in hyperglycemia with corticosteroid therapy (data not able to be pooled).

Table VI. A summary of randomized controlled trials of additional therapies for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)

Study	Patients[a] (centers)	Main inclusion criteria	Main exclusion criteria	Intervention	Clinical outcomes
Reines et al.[107] 1985	10 (1)	Risk factor: sepsis syndrome P_aO_2 <60mm Hg or intrapulmonary shunt >20% or radiologic evidence of ARDS	Major cardiac, pulmonary, renal, endocrine diseases	IV dazoxiben 100mg every 4 hours for 72 hours, or placebo	Mortality (timepoint unclear) Adverse events
Tuxen et al.[108] 1987	45 (2)	Bilateral CXR infiltrates, noncardiogenic pulmonary edema, P_aO_2 <80mm Hg with F_iO_2 ≥0.4	History of pulmonary disease or pulmonary trauma	IV acyclovir 5 mg/kg daily for 18 days or until end of mechanical ventilation, or placebo	Mortality (timepoint unclear) Duration of ventilation Adverse events
Steinberg et al.[109] 1990	10 (1)	Bilateral CXR infiltrates, P/F <200mm Hg, PEEP >5cm H20, PAOP ≤18mm Hg, duration of ventilation ≥24 hours	Chronic lung disease, pneumonia, gastrointestinal bleeding	IV indometacin, one dose of 50mg, or placebo	Mortality (timepoint unclear)
Ardizzoia et al.[110] 1993	30 (1)	Metastatic cancer, diffuse CXR infiltrates, rapid fall in P_aO_2, absence of congestive heart failure	ND	IV pentoxyfylline 100mg twice daily for 7 days, then 400mg orally three times daily, or standard therapy	1-month mortality Adverse events
Gottlieb et al.[111] 1994	25 (ND)	Risk factor for ARDS, diffuse CXR infiltrates, P/F <285mm Hg, no cardiogenic pulmonary edema	ND	IV neutrophil elastase inhibitor (ICI 200880) 350mg for up to 14 days, or placebo	Mortality (timepoint unclear)
Bernard et al.[112] 1999	60 (ND)	AECC definition of ALI	ND	IV interleukin-10 8 μg/kg or 20 μg/kg daily for 6 days, or placebo	28-day mortality Ventilator-free days to day 28 Organ failure-free days to day 28
ARDSnet[113] 2000	234 (10)	Mechanical ventilation, AECC definition for ALI and ARDS, duration of ALI or ARDS <36 hours	Neurologic disease impairing weaning, chronic lung disease, morbid obesity, liver disease, immunocompromised, burns, increased intracranial pressure	Enteral ketoconazole 400mg once daily for 21 days or until 48 hours of unassisted breathing, or placebo	Hospital mortality Ventilator-free days to day 28 Organ failure-free days to day 28 Adverse events
ARDSnet[114] 2002	235 (10)	Mechanical ventilation, AECC definition for ALI and ARDS, duration of ALI or ARDS <36 hours	Neurologic disease impairing weaning, chronic lung disease, morbid obesity, liver disease, immunocompromised, burns, increased intracranial pressure	IV lisofylline 3 mg/kg (maximum 300 mg) every 6 hours for 20 days or until 48 hours unassisted breathing, or placebo	28-day mortality Ventilator dependence at day 28 Organ failure-free days to day 28 Adverse events
Presneill et al.[115] 2002	18 (1)	Risk factor: severe sepsis, CXR infiltrate and P_aO_2 <60mm Hg on room air or P/F <287mm Hg	Malignancy, immunosuppression	IV GM-CSF, 3 μg/kg daily for 5 days, or placebo	30-day mortality SOFA score at day 5 Adverse events

a Number of patients randomized (number of centers).

AECC = American European Consensus Conference;[3] **ARDSnet** = ARDS Network; **CXR** = chest radiograph; **F_iO_2** = fraction of oxygen in inspired gas; **GM-CSF** = granulocyte macrophage colon- stimulating factor; **IV** = intravenous; **ND** = not described (explicit information not provided); **PAOP** = pulmonary artery occlusion pressure; **P_aO_2** = partial pressure of arterial oxygen; **PEEP** = positive end-expiratory pressure; **P/F** = ratio of P_aO_2 to F_iO_2; **SOFA** = sequential organ failure assessment.[117]

Table VII. Methodologic quality of studies included in the meta-analysis

Study	Baseline similarity[a]	Allocation concealment[b]	Blinding[c] and placebo features, if described[d]	Cointerventions[e]	Patients withdrawn from analysis[f]	Patients lost to follow-up[g]
Alprostadil						
Holcroft et al.[91] 1986	Age, duration of ventilation, sepsis	ND	Caregivers, investigators	Corticosteroids (one patient per group)	None	None
Shoemaker and Appel[93] 1986	Age (D)	Yes (local)	Caregivers	ND	None	None
Rossignon et al.[92] 1990	Age, duration of ventilation	ND	Caregivers	ND[h]	None	None
Slotman et al.[87] 1992	Age, sepsis[88]	Yes (central)	Caregivers	ND	None[88][i]	30-day mortality: 1 (group ND) 6-month mortality: Treatment: 3/50 Control: 2/51
Abraham[94] 1996	Age (D), APACHE II, sepsis	ND	Caregivers, opaque syringes and IV tubing	ND	None	None
Abraham et al.[95] 1999	Age (D), APACHE II, sepsis	ND	Caregivers, opaque syringes and IV tubing	Protocol for initiation of weaning, corticosteroids (treatment 25%; control 26%)	Treatment: 1/178 Control: 1/172	Treatment: 1/178 Control: 1/172
Vincent et al.[41] 2001	Age (D), SAPS II, sepsis	ND	Caregivers	Other (nitric oxide protocol)	None	None
Acetylcysteine						
Jepsen et al.[96] 1992	Age	ND	Caregivers	Corticosteroids ("no different")	None	None
Suter et al.[97] 1994	Age, SAPS II, sepsis	ND	Caregivers	ND	None	None
Bernard et al.[89] 1997	Age, APACHE II	Yes (sequentially numbered drug packs)	Caregivers, investigating team	ND	Acetylcysteine: 1/16 Oxothiazolidine carboxylate: 0/17 Control: 0/15	None
Domenighetti et al.[98] 1997	Age, SAPS II, Sepsis	ND	Caregivers	ND	Treatment: 1/23 Control: 2/22	None

Continued next page

Table VII. Contd

Study	Baseline similarity[a]	Allocation concealment[b]	Blinding[c] and placebo features, if described[d]	Cointerventions[e]	Patients withdrawn from analysis[f]	Patients lost to follow-up[g]
Ortolani et al.[90] 2000	Age, APACHE II	ND	None	"Standard care" included mechanical ventilation and corticosteroids (details not provided)	None	None
Corticosteroids						
Weigelt et al.[99] 1985	Age (D), sepsis	ND	Caregivers	PEEP applied by protocol	7/88 (group ND)	None
Bernard et al.[100] 1987	Age (A), duration of ventilation (A), organ function (A), sepsis	Yes (sequentially numbered drug packs)	Caregivers, investigating team	ND	None	None
Meduri et al.[101] 1998	Age, MODS (D), sepsis (D), other variables (A)	ND	Caregivers	Plateau pressure limited to 35cm H_2O in both groups	None	None
Surfactant						
Reines et al.[102] 1992	ND	ND	Caregivers	ND	ND	ND
Weg et al.[40] 1994	Age, APACHE II	Yes (central)	Caregivers, opaque nebulizer	Corticosteroids ("no difference")	ND	ND
Anzueto et al.[106] 1996	Age, APACHE III (A), sepsis	Yes (central)	Caregivers, opaque canister in nebulizer	ND	None	None
Gregory et al.[42] 1997	Age, sepsis, organ failures	ND	Caregivers unblinded, no placebo	Other (ventilation mode standardized)	Surfactant 100mg for eight doses: 1/19 Others: none	None
Walmrath et al.[104] 2000	ND	ND	Caregivers unblinded, no placebo	ND	None	ND
Kesecioglu et al.[105] 2001	ND	ND	Caregivers unblinded, no placebo	ND	None	None
Spragg et al.[103] 2003	Age, APACHE II, sepsis	Yes (central)	Caregivers unblinded, no placebo	Protocol for screening for ability to wean	None	None
Spragg et al.[39] 2004	Age (A), APACHE II (A in both trials), sepsis (A), organ failures, other variables (A)	ND	Caregivers; sham medication delivery in control group	LPVS recommended, weaning (screening and continuation) standardized	1/448 (group ND)	None
Miscellaneous therapies						
Reines et al.[107] 1985	ND	ND	"Single-blind"	ND	None	None

Continued next page

Table VII. Contd

Study	Baseline similarity[a]	Allocation concealment[b]	Blinding[c] and placebo features, if described[d]	Cointerventions[e]	Patients withdrawn from analysis[f]	Patients lost to follow-up[g]
Tuxen et al.[108] 1987	Age (D), sepsis	ND	Caregivers	ND	Treatment: 5/22 Control: 2/23	None
Steinberg et al.[109] 1990	Age	ND	Caregivers, investigators unblinded	ND	None	None
Ardizzoia et al.[110] 1993	Age	ND	Caregivers unblinded, no placebo	ND	None	None
Gottlieb et al.[111] 1994	Age, APACHE II	ND	Caregivers	ND	None	None
Bernard et al.[112] 1999	Shock (D), others "comparable"	ND	Caregivers	ND	None	None
ARDSnet[113] 2000	Age (A), APACHE III (A), sepsis (A)	Yes (central)	Caregivers, study coordinators, investigators	LPVS versus traditional tidal volumes studied in factorial design, weaning (screening and continuation) standardized	None	None
ARDSnet[114] 2002	Age, APACHE III, sepsis	Yes (central)	Caregivers, study coordinators, investigators	LPVS versus traditional tidal volumes studied in factorial design (194 patients) then applied (41 patients), weaning (screening and continuation) standardized	None	ND
Presneill et al.[115] 2002	Age (D), APACHE II, duration of ventilation	Yes (coded drug packs)	Caregivers, data collectors	Level of PEEP and tidal volumes similar	None	None

a See Methods for factors assessed. Those listed were clinically similar between treatment and control groups. Factors with significant clinical differences between groups and included in an adjusted analysis are noted.

b Yes denotes central randomization, local independent randomization or sequentially numbered or coded drug packs.

c See Methods for definitions. 'Double-blind' was interpreted as including caregiver blinding.

d Characteristics listed may have enhanced blinding.

e See Methods for definitions.

f The number of patients excluded from the pooled mortality analysis because of withdrawal from the study and no outcome information available.

g The number of patients with incomplete follow-up data for mortality.

h No patients received corticosteroids at time of randomization, but whether corticosteroids were given after randomization is unclear.

i Additional withdrawals and losses to follow-up are not described in the study by Slotman et al.

A = adjusted analysis; **APACHE** = Acute Physiology and Chronic Health Evaluation;[118,119] **ARDS** = acute respiratory distress syndrome; **ARDSnet** = ARDS Network; **D** = clinical differences; **IV** = intravenous; **LPVS** = lung protective ventilation strategy; **MODS** = Multiple Organ Dysfunction Score;[120] **ND** = not described (explicit information not provided); **PEEP** = positive end-expiratory pressure; **SAPS** = Simplified Acute Physiology Score.[121]

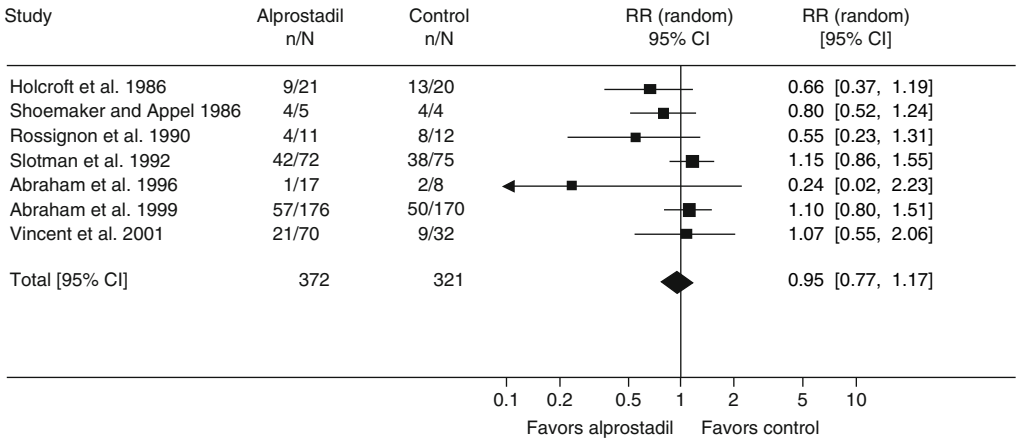

Fig. 1. Effect of alprostadil on mortality in acute respiratory distress syndrome and acute lung injury. The test for homogeneity was nonsignificant (p = 0.27). **CI** = confidence interval; **N** = number of patients randomized; **n** = number of deaths; **random** = random effects model; **RR** = relative risk. (See table II for relevant bibliographic references.)

These adverse effects did not lead to discontinuation of study medications.

Surfactant Therapy

Pooling nine studies (figure 4) demonstrated no effect on early mortality (1418 patients with outcomes data; RR 0.93; 95% CI, 0.77, 1.12). One study assessed the incidence of non-pulmonary organ dysfunction. Gregory et al.[42] followed patients for the development of organ failures (not defined) for 5 days after randomization to surfactant therapy or standard therapy and reported greater cardiovascular failure (not quantified) on day 2 in the high-dose arm compared with controls. Adverse events (figure 5) were not reported to have resulted in discontinuation of the intervention and were primarily cardiopulmonary (for example, exhalation valve occlusion, barotrauma, hypoxemia, respiratory arrest, increased peak airway pressure, hypertension, tachycardia). One trial[103] reported no adverse events leading to discontinuation of therapy.

Evaluation of Publication Bias

Funnel plots of study precision versus treatment effect (not shown) for trials of acetylcysteine, alprostadil, and surfactant therapy suggested the presence of bias arising from non-publication of small non-beneficial trials.

Additional Therapies

One study enrolling 24 patients[101] meeting consensus conference criteria for ARDS[3] showed that administration of corticosteroids for late phase non-resolving ARDS reduced mortality in the ICU (RR 0.05; 95% CI, 0.00, 0.78) and hospital (RR 0.20; 95% CI 0.05, 0.81) and reduced duration of ventilation and organ failure-free days, with no increase in infectious complications. One study of 30 patients[110] with metastatic cancer and ARDS (as defined by the authors) found that pentoxifylline reduced one month mortality (RR 0.67; 95% CI 0.47, 0.95) with no adverse events leading to discontinuation of therapy. There was no evidence of effect of any other intervention (table IX) on prespecified outcomes.

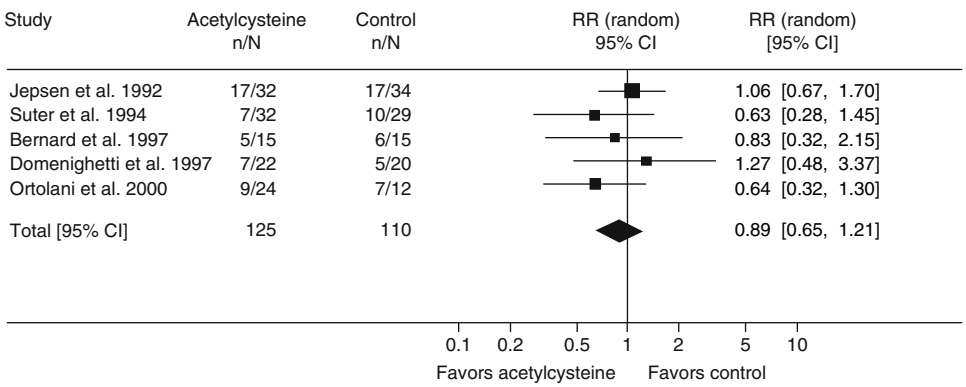

Fig. 2. Effect of acetylcysteine on mortality in acute respiratory distress syndrome and acute lung injury. The test for homogeneity was nonsignificant (p = 0.63). **CI** = confidence interval; **N** = number of patients randomized; **n** = number of deaths; **random** = random effects model; **RR** = relative risk. (See table III for relevant bibliographic references.)

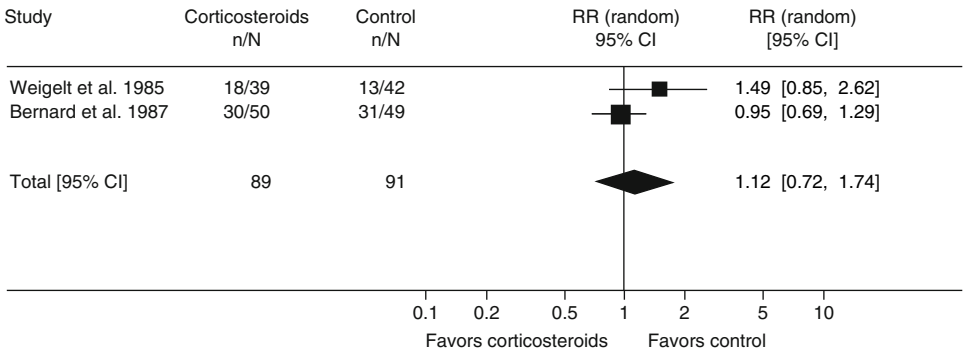

Fig. 3. Effect of early high-dose corticosteroid therapy on mortality in acute respiratory distress syndrome and acute lung injury. The test for homogeneity was nonsignificant (p = 0.16). **CI** = confidence interval; **N** = number of patients randomized; **n** = number of deaths; **random** = random effects model; **RR** = relative risk. (See table IV for relevant bibliographic references.)

Discussion

The principal finding of our systematic review is that no pharmacotherapy convincingly improves survival in patients with ARDS and ALI. We identified 33 randomized trials of pharmacologic treatments of established ARDS and ALI enrolling 3272 patients, with the first trials being published in 1985.[99,107] The median number of patients randomized per trial was low (45, range 9–725). Our pooled analyses had sample sizes of 180–1418 patients (early high-dose cotricosteroids and surfactant therapy respectively). These analyses showed that alprostadil, acetylcysteine, early administration of high-dose corticosteroids, and surfactant therapy, had no effect on early mortality. With respect to adverse effects, all trials of alprostadil and early high-dose corticosteroids and six out of seven surfactant trials with safety data showed more adverse events with active therapy. However, the potential difficulty of achieving effective blinding for alprostadil and surfactant may have biased adverse event reporting in the active treatment arms. Of the miscellaneous interventions evaluated in single small trials, corticosteroids given late in the course of ARDS decreased ICU and hospital mortality,[101] and pentoxifylline decreased mortality in patients with metastatic cancer and ARDS.[110]

Because the confidence intervals around pooled relative risks for alprostadil, acetylcysteine, early high-dose corticosteroids, and surfactant therapy are wide, we cannot exclude the possibility of a modest benefit or harm to patients. However, in each case the overall best estimate of relative risk suggested no effect. Clinical application of these therapies is therefore not currently justified. Any additional large trials should await pre-clinical and preliminary clinical studies to identify variations of dose, timing of adminis-

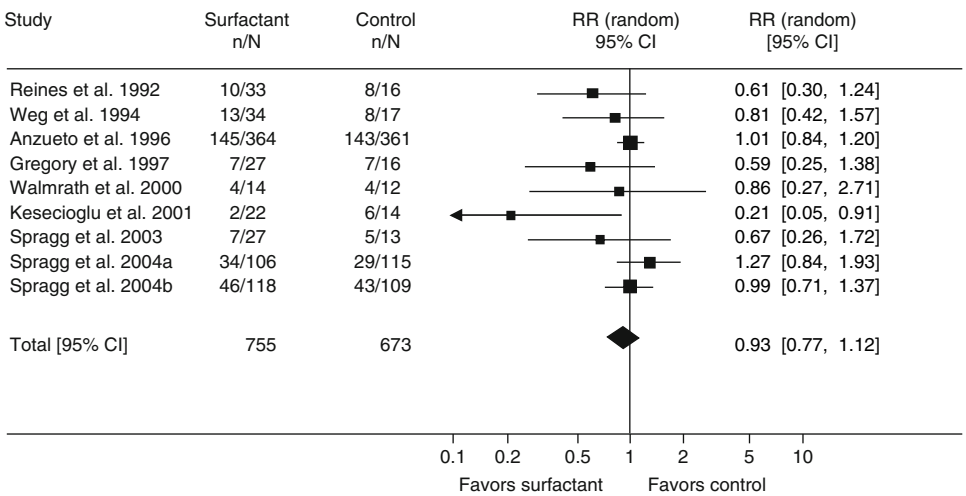

Fig. 4. Effect of surfactant on mortality in acute respiratory distress syndrome and acute lung injury. The test for homogeneity was nonsignificant (p = 0.28). Spragg 2004a (North America) and 2004b (Europe/South Africa) are reported in reference 39. **CI** = confidence interval; **N** = number of patients randomized; **n** = number of deaths; **random** = random effects model; **RR** = relative risk. (See table V for relevant bibliographic references.)

Table VIII. Effects of alprostadil, early high-dose corticosteroids, and surfactant therapy on other outcome measures in patients with acute lung injury/acute respiratory distress syndrome

Study	Intervention	Outcome measure and result[a]
Bone et al.[88] 1989	Alprostadil	Late mortality: RR 1.18 (95% CI 0.86, 1.57)
Rossignon et al.[92] 1990	Alprostadil	Duration of ventilation, mean days (SD): 24 (23) [treatment]; 20 (18) [control]
Abraham et al.[94] 1996	Alprostadil	No. patients requiring ventilation at day 8: 9/17 (treatment); 8/8 (control) [RR 0.53; 95% CI 0.34, 0.83]
Abraham et al.[95] 1999	Alprostadil	Duration of ventilation, median days: 16.9 (treatment); 19.6 (control) [p = 0.94]
Vincent et al.[41] 2001	Alprostadil	Duration of ventilation, days (not stated whether median or mean): 16 (treatment); 16.6 (control) [p = 0.94]
Suter et al.[97] 1994	Acetylcysteine	No. patients requiring ventilation at day 3: 5/32 (treatment); 14/29 (control) [RR 0.32; 95% CI 0.13, 0.79]
Bernard et al.[89] 1997	Aceytylcysteine	Ventilator-free days to day 30, median: 11 (treatment); 3 (control) [p = NS]
Domenighetti et al.[98] 1997	Acetylcysteine	Duration of ventilation, mean days (SD): 8.1 (6.5) [treatment]; 9.3 (6.6) [control] (p = NS)
Weigelt et al.[99] 1985	Methylprednisolone	Duration of ventilation, mean days (range): 20 (5–63) [treatment]; 18 (3–72) [control] (p = NS)
Bernard et al.[100] 1987	Methylprednisolone	Duration of ventilation in survivors, mean days (SD): 12.7 (14.3) [treatment]; 15.0 (13.6) [control] (p = 0.37)
Anzueto et al.[106] 1996[b]	Surfactant	Duration of ventilation, mean days (SD): 16.0 (19.1) [treatment]; 16.4 (17.1) [control] (p = NS)
Gregory et al.[42] 1997	Surfactant	Duration of ventilation (median days): 15 (50 mg/kg for eight doses group); 10 (100 mg/kg for eight doses group); 10 (control) [p = NS] Organ failures (not defined): no differences except for significantly more cardiovascular failures on day 2 in group receiving 100 mg/kg for eight doses versus control
Walmrath et al.[104] 2000	Surfactant	Ventilator-free days to day 28 (median): 14 (medium dose); not reported (high dose); 0 (control, p-value not given)
Kesecioglu et al.[105] 2001	Surfactant	Ventilator-free days to day 28, mean (SD):12.7 (9.7) [treatment]; 11.9 (11.2) [control, p = NS]
Spragg et al.[103] 2003	Surfactant	Ventilator-free days (median) to day 28 (interquartile range): 4 (0–12) [low dose]; 5 (0–18) [high dose]; 6 (0–15) [control]; differences NS
Spragg et al.[39] 2004	Surfactant	Ventilator-free days (median) to day 28 (68% range): (a) North American trial: 3.5 (0.0–21.0) [treatment]; 6.0 (0.0–21.0) [control]; (b) European/South African trial: 0.0 (0.0–0.20) [treatment]; 1.0 (0.0–20.0) [control]; differences NS

a p-Values are taken from the individual studies.

b Although the authors reported the duration of ventilation as mean (SD), the SDs were extremely small and we assumed that they were standard errors of the mean.

CI = confidence interval; **NS** = nonsignificant; **RR** = relative risk; **SD** = standard deviation.

tration, and formulation that may lead to clinical benefit. For example, a recently completed trial of HL 10[122] evaluated the only surfactant preparation shown to be potentially beneficial for ALI/ARDS,[105] a porcine surfactant with a high phospholipid concentration delivered by intratracheal installation to maximize distal airway deposition.

We found that the scientific quality[123] of included trials was variable. Methodologic strengths of a clear majority of studies included caregiver blinding or 'double-blinding',[124] analysis of early mortality by strict intention-to-treat criteria (analysis according to assigned group and zero withdrawals), and complete patient follow-up. No study documented differential application of potentially important cointerventions, although the majority provided no information about cointerventions. About one-half of the trials documented similarity between treatment groups for at least one prognostically important baseline characteristic. However, only a minority of studies described adequate allocation concealment. Our assessment of methodologic features was restricted to published descriptions, and we may therefore have underestimated the methodologic strength of some studies, especially those reported in abstract form.[102,104,105,111,112]

Strengths of this systematic review include the use of strategies to minimize bias in the selection and reporting of studies: (i) extensive literature search; (ii) duplicate independent screening of articles and data abstraction; and (iii) explicit criteria for methodologic assessment.[125] We used clinical judgment to decide *a priori* to combine studies for which a similar direction and magnitude of treatment effect could reasonably be expected. However, aggre-

Table IX. Effects of additional miscellaneous therapies on outcomes in acute respiratory distress syndrome and acute lung injury

Study	Intervention	Outcome measure and result[a]
Reines et al.[107] 1985	Dazoxiben	Mortality (timepoint unclear): RR 2.00 (95% CI 0.26, 15.62) Adverse events: none
Tuxen et al.[108] 1987	Acyclovir	Mortality (timepoint unclear): RR 1.10 (95% CI 0.54, 2.22) Duration of ventilation, mean days (SD): 21 (19) [treatment]; 15 (12) [control] (p = NS) Adverse events: none
Steinberg et al.[109] 1990	Indomethacin	Mortality (timepoint unclear): RR 0.50 (95% CI 0.06, 3.91) Adverse events: no differences in renal biochemistry
Ardizzoia et al.[110] 1993	Pentoxifylline	1-month mortality: RR 0.67 (95% CI 0.47, 0.95); 10/15 (treatment), 15/15 (control) Adverse events: none
Gottlieb et al.[111] 1994	Neutrophil elastase inhibitor (ICI 200 880)	Mortality (timepoint unclear): RR 0.27 (95% CI 10.04, 2.10)
Bernard et al.[89] 1997	Oxothiazolidine carboxylate	30-day mortality: RR 0.88 (95% CI 0.36, 2.16) Ventilator-free days to day 30, median: 20 (treatment); 3 (control) [p = NS] Adverse events: none
Meduri et al.[101] 1998	Late corticosteroids	ICU mortality: RR 0.05 (95% CI 0.00, 0.78); 0/16 (treatment), 3/8 (control) Hospital mortality: RR 0.20 (95% CI 0.05, 0.81); 2/16 (treatment), 5/8 (control) Duration of ventilation, median days: 11.5 (treatment); 23 (control) [p = 0.001] Organ failure-free days to day 28, mean (SD): 16 (8) [treatment]; 6 (5.7) [control] (p = 0.005) New VAP: 6/16 (treatment); 1/8 [control] (p = 0.70) No between group difference in infections per 100 patient days of treatment No between-group difference in new hyperglycemia
Bernard et al.[112] 1999	Interleukin-10	28-day mortality: RR 0.68 (95% CI 0.26, 1.76) Ventilator-free days to day 28, median: 15 (low-dose treatment); 6 (high-dose treatment); 9 (control) Adverse events: none
ARDSnet[113] 2000	Ketoconazole	Hospital mortality: RR 1.03 (95% CI 0.72, 1.46) Ventilator-free days to day 28, median: 10 (treatment); 9 (control) [p = 0.89] Organ failure-free days to day 28, median: cardiovascular: 22 (treatment); 23 (control) [p = NS for each] CNS: 14 (treatment); 10 (control) coagulation: 25 (treatment); 25 (contol) hepatic: 22 (treatment); 24 (control) renal: 26 (treatment); 27 (control) Adverse events: trend to more reported cardiovascular adverse events in treatment group (p = 0.07); no differences in arrhythmias or vasopressor use; no differences in incidence of elevation of liver enzymes
ARDSnet[114] 2002	Lisofylline	28-day mortality: RR 1.31 (95% CI 0.87, 1.98) Ventilator-free days to day 28, median: 9 (treatment); 11 (control) [p = 0.62] Organ failure-free days to day 28, median: cardiovascular: 23 (treatment); 23 (control) [p = NS for each] CNS: 14 (treatment); 14 (control) coagulation: 27 (treatment); 27 (control) hepatic: 25 (treatment); 25 (control) renal: 28 (treatment); 27 (control) Adverse events: no between-group difference in reported severe adverse events; increased heart rate after medication dosing in treatment group

Continued next page

Table IX. Contd

Study	Intervention	Outcome measure and result[a]
Presneill et al.[115] 2002	GM-CSF	Hospital mortality: RR 1.33 (95% CI 0.45, 3.96) SOFA score at day 5, median: 6.5 (treatment); 7 (control) [p = NS]

a p-Values are taken from the individual studies.

ARDSnet = ARDS Network; **CI** = confidence interval; **GM-CSF** = granulocyte macrophage colony-stimulating factor; **ICU** = intensive care unit; **NS** = nonsignificant; **RR** = relative risk; **SD** = standard deviation; **SOFA** = sequential organ failure assessment;[117] **VAP** = ventilator-associated pneumonia.

gated studies differed with respect to eligibility criteria, study drug formulations, methods of administration, and doses. We used random effects models to aggregate data and generate conservative confidence limits for the point estimate of the pooled treatment effect.[126]

Another limitation of this systematic review is the identification of a small number of trials of each pharmacologic therapy, most of which randomized a small number of patients. Funnel plots for trials of acetylcysteine, alprostadil and surfactant therapy suggested the existence of small, unpublished, non-beneficial trials. However, the inclusion of any such trials would not qualitatively change our findings or conclusions.[127] We did not search for RCTs of pharmacologic therapies for other related critically ill populations (such as sepsis) reporting outcomes in subgroups of patients with ALI and ARDS because of limitations in the interpretation of subgroup analyses.

Effective pharmacologic therapy for established ARDS and ALI is therefore extremely limited. We identified two potentially beneficial interventions. First, prolonged corticosteroid administration for late ARDS, which may attenuate the fibroproliferative process, was evaluated in one trial. This study[101] randomized 24 patients with late-phase ARDS and showed an impressive but clinically implausible point estimate of benefit with a wide CI (absolute risk reduction in ICU mortality 0.62; 95% CI, 0.30, 0.95; number needed to treat to prevent one ICU death, 1.6). The authors did not describe concealment of allocation; methodologic strengths include blinding of caregivers, intention-to-treat analysis, complete follow-up, and adjustment for baseline imbalances. However, the major methodologic limitation relates to the data analysis. The investigators calculated *a priori* that 99 patients would be required to detect an absolute survival improvement of 30% in corticosteroid-treated patients. Enrollment was terminated prematurely using early stopping rules based on sequential clinical trials.[128] However, this approach may inflate the treatment effect in small trials[129] by increasing the probability of confounding by imbalances in baseline prognostic characteristics. Patients in the

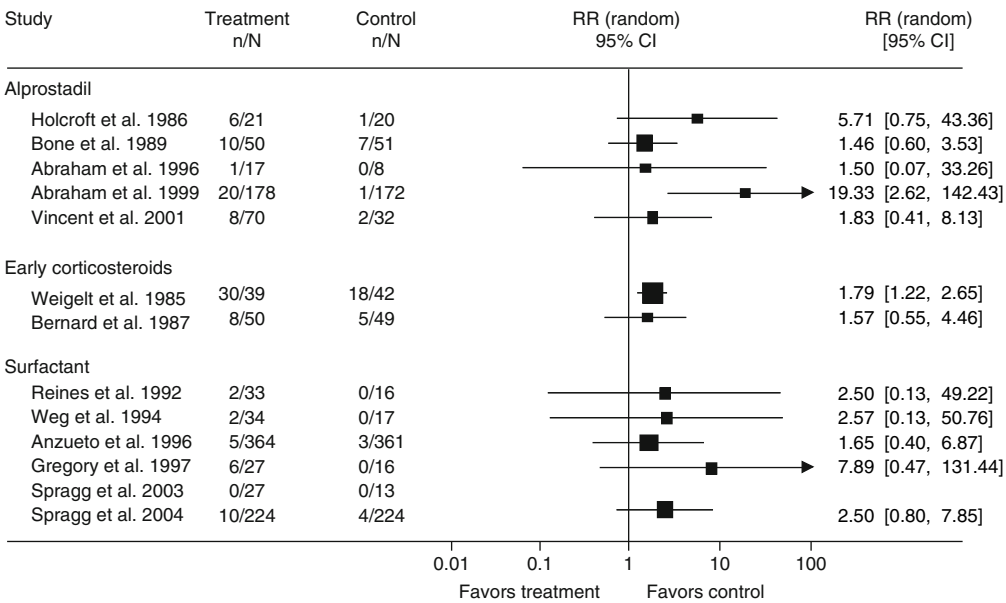

Fig. 5. Adverse events due to alprostadil, early corticosteroids, and surfactant. Adverse reactions included cardiopulmonary (hypotension, dysrhythmias, hypoxia) and neurological (agitation) events in alprostadil trials; infections in trials of early corticosteroids; and cardiopulmonary events (exhalation valve occlusion, barotrauma, hypoxemia, respiratory arrest, increased peak airway pressure, hypotension, bradycardia) in surfactant trials. **CI** = confidence interval; **N** = number of patients randomized; **n** = number of adverse events; **RR** = relative risk. (See table II, table IV, and table V for relevant bibliographic references.)

corticosteroid group had less organ dysfunction and pulmonary morbidity and thus may have had a better prognosis, a bias that may have persisted and confounded the results despite statistical adjustment. In addition, the crossover of four of the eight placebo-assigned patients to corticosteroids (as per protocol) precluded an accurate evaluation of the risk of infection associated with this treatment regimen. Therefore, this trial provides important, albeit preliminary, evidence for the efficacy of corticosteroids for late phase ARDS. The recently completed Late Steroid Rescue Study,[130] which randomized 180 patients, should provide more definitive data.

The second potentially beneficial intervention we identified was administration of pentoxifylline, a phosphodiesterase inhibitor that prevents neutrophil chemotaxis and activation. This therapy was evaluated in a randomized trial enrolling 30 patients with metastatic cancer.[110] Although unclear allocation concealment and lack of blinding threaten the internal validity of this trial, the most important limitation is lack of generalizability. Eighteen of 30 randomized patients had lymphangitic metastases that may have mimicked the characteristic radiographic changes of ARDS, resulting in diagnostic misclassification. The mortality in this trial was higher (25 of 30 patients died at 1 month) than generally observed in patients with ARDS,[2,131] which limits the applicability of the findings to lower-risk patients. Finally, the severity of patients' lung injury as defined by the widely used American-European Consensus Conference definition[3] was not clear because the authors did not describe the oxygenation criteria used for the diagnosis of ARDS, or whether ventilatory support was required. Further research is required to assess the potential role of pentoxifylline in the treatment of ALI and ARDS in patients without cancer.

There are several potential reasons to explain the large number of non-beneficial trials of pharmacologic therapies for ALI and ARDS. These explanations overlap with insights into the design of RCTs in patients with severe sepsis.[132] First, randomized trials may have been conducted before early investigations had established the optimal dose and duration of the candidate therapy that would achieve adequate tissue levels and biologic response. Second, the definition of the clinical syndrome of ALI and ARDS, although feasible to apply in clinical settings and in research, does not have optimal reliability and validity.[131,133,134] Trials may therefore have enrolled patients unlikely to respond to candidate therapies. However, an inadequate definition of ALI and ARDS cannot be the exclusive explanation for non-beneficial trials given the recent positive RCT of low total volumes in ALI patients.[8] Third, ALI and ARDS are clinically heterogeneous syndromes with various causes, genetic susceptibilities[134] and clinical courses. Trials may thus have included responsive and non-responsive subgroups. Fourth, there are many important non-pulmonary determinants of the outcome for patients with ALI and ARDS. Fifth, investigators may have overestimated the instrinsic therapeutic potential of candidate therapies. The latter three points may have contributed to the design of RCTs that were inadequately powered to reliably detect moderate clinical benefits.

Conclusion

In summary, we found that alprostadil, acetylcysteine, early administration of high-dose corticosteroids, and surfactant therapy had no beneficial effect on survival in critically ill patients with ARDS or ALI. Prolonged corticosteroid administration was effective for late phase ARDS in one small study, and a multicenter RCT[130] of this therapy was recently completed. Pentoxifylline was effective in a small study of highly selected patients with metastatic cancer and ARDS. Given the complex pathophysiology of lung injury, the lack of effective pharmacologic therapies is not surprising. Future treatment may involve a combination of lung-protective ventilation, multi-modality pharmacologic therapy, and earlier identification and better treatment of precipitating factors.

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Correspondence and offprints: Dr *Neill Adhikari*, Department of Critical Care Medicine, Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada.
E-mail: neill.adhikari@sw.ca