High-dose Oral Ambroxol for Early Treatment of Pulmonary Acute Respiratory Distress Syndrome: an Exploratory, Randomized, Controlled Pilot Trial

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ABSTRACT

Objective: To evaluate efficacy of high-dose oral ambroxol in acute respiratory distress syndrome (ARDS) with respect to ventilator-free days (VFD).

Design: Prospective, randomized, placebo-controlled, blinded pilot trial.

Patients: Sixty-six mechanically ventilated patients (1 month to 12 years) with ARDS who were hand-ventilated for <24 hr before pediatric intensive care unit admission.

Interventions: Patients randomized to oral ambroxol (40 mg/kg/day, in four divided doses) (n = 32) or placebo (n = 34) until 10 days, extubation or death whichever is earlier.

Measurements and Main Results: Majority (91%) had pneumonia and bronchiolitis. Two study groups were similar in baseline characteristics. Mean partial pressure of arterial oxygen/fraction of inspired oxygen and oxygenation index were >175 and <10, respectively, with no difference in the two study groups. VFD were similar in the two study groups. Overall mortality was 26%. No adverse events were noted with ambroxol.

Conclusions: Among ventilated pulmonary ARDS patients with oxygenation index of <10, mortality was 26%. Ambroxol did not improve VFD. Study with higher and more frequently administered doses of ambroxol in larger sample is suggested after having generated relevant pharmacokinetic data among critically ill children.

KEYWORDS: ambroxol, acute respiratory distress syndrome, children, ventilator-free days in 14 days.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) in children is usually caused by “direct” pulmonary causes [1], more so in resource-poor economies [2, 3]. Release of cytokines and oxidants, protease-antiprotease imbalance, surfactant deficiency and alveolar biofluid overproduction are final common pathways, irrespective of cause. Despite pathologic understanding of ARDS, its management continues to be challenging. Though lung-protective ventilatory strategy improved outcome [4], search for an effective drug continues [5]. Majority of pharmacotherapeutic interventions, e.g., steroid [6], anti-oxidants [7, 8], surfactant replacement [9] and β-agonists [10, 11],
have targeted a single pathway of otherwise complex process, and failed. Drug acting on multiple pathogenetic pathways may succeed clinically [8].

Ambroxol has mucoactive [12], anti-inflammatory, anti-oxidant and surfactant-promoting properties [13]. Moreover, it gets concentrated selectively in lungs [14]. Though clinical data are scanty [14–18], ambroxol—a safe and economical drug—may be considered for treatment of ARDS for its potential to improve gas exchange [19–21]. If clinical efficacy could be established, ambroxol would be an attractive therapeutic option for its low cost and toxicity. Current exploratory randomized blinded controlled pilot trial was designed to evaluate efficacy of high-dose oral ambroxol in children (age, 1 month to 12 years) requiring ventilation for pulmonary ARDS (pARDS), with specific reference to ventilator-free days in 14 days (VFD14) in resource-constraint setting. Improvement in ventilatory and oxygenation parameters were secondary objectives.

MATERIALS AND METHODS

Patients
All intubated, ventilated patients in 12-bed pediatric intensive care unit (PICU) were screened for study eligibility each day over 14-month period (August 2007–September 2008). Entry criteria included all consecutive children (age, 1 month to 12 years) with respiratory failure owing to diffuse bilateral pulmonary infiltrates, partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300, positive end expiratory pressure (PEEP) ≥5 cm H2O and ventilated for ≥12 hr [22]. Patients with persistent hypotension (defined as systolic blood pressure <5th centile [70 mmHg +2 * age in years]) despite resuscitation for initial 12 hr were excluded to avoid indirect lung injury and to concentrate on pARDS only, considering higher biological plausibility of ambroxol in the later. Patients hand-ventilated for >24 hr before mechanical ventilation was excluded to limit risk of significant barotrauma. Patients with active bleeding requiring blood/fluid volume replacement, chronic/restrictive lung disease, reactive/upper airway disease, neuromuscular respiratory failure, raised intracranial pressure, congenital, valvular or myocardial heart disease, cardiogenic pulmonary edema and/or post-operative patients were excluded to limit confounders. Patients with acute renal failure were excluded as ambroxol is excreted mainly from kidneys.

Study drug
Oral ambroxol is used for treatment of pulmonary diseases and reported to be safe [23]. Higher intravenous doses in adults (1000 mg/day) [14, 16] and preterm newborns (30 mg/kg/day, 7 days) [15, 24] were also safe. Orally administered ambroxol gets absorbed rapidly with 73% bioavailability with time to peak plasma concentration being ~2 hr in an adult study [25]. Elimination t1/2 is biphasic—with an α t1/2 of 1.3 hr and β t1/2 of 8.8 hr [25]. Thus, 40 mg/kg/day (in four divided doses) may be considered to be an acceptable maximal safe oral dose for children. Though intestinal absorption in critically ill patients is different from healthy person, this dose was considered as starting point for the pilot study.

Study protocol
Trial was designed and analyzed according to Consolidated Standards of Reporting Trials recommendations and checklist (Fig. 1) [26]. After informed consent from father/legal guardian, eligible patients were randomized to intervention or placebo using computer-generated random number table within 24 hr of PICU admission. Study assignments were serially numbered in opaque and sealed envelopes. Intervention group received oral ambroxol (40 mg/kg/day) in four divided doses for 10 days or until extubation, whichever was earlier. Identical-looking tablets of ambroxol (of 50 mg) and placebo were prepared, and packs containing dosage for 20 kg body-weight patient were dispensed. Tablets were crushed, suspended in water and administered through nasogastric tube. Investigators, doctors, nurses and data manger were blinded to treatment assignment. Institutional ethics committee approved the study protocol.

At enrollment, patients’ demographics, baseline assessment and Pediatric Risk of Mortality III (PRISM-III) were recorded. Vitals, oxygen saturation on pulse oximeter (SpO2) and central venous
pressure (if required) were monitored continuously and recorded 2 hourly. Ventilator settings, blood gases, end-tidal CO2 and chest radiograph data were collected for initial 28 days or until extubation, whichever was earlier. In addition, pulmonary status and respiratory support, extubation readiness, fluid balance, caloric and protein intake and pediatric logistic organ dysfunction (PeLOD) score [27] recorded. Investigations were recorded if available, and reflected the values obtained closest to 0800 am.

Patients in both groups were managed according to prevalent unit protocol for ventilation, sedation, hemodynamics, nutrition, extubation readiness and general nursing care. Lung-protective ventilation was
employed, and included pressure-control ventilation with peak inflating pressure <30 cm H2O, PEEP 5–10 cm H2O, tidal volume 5–6 ml/kg, FiO2 <0.6 and permissive hypercapnea (PaCO2 >80torr while pH >7.25) if required. Aim was to achieve optimal oxygenation (PaO2 60–80 mmHg, SpO2 88–92%), while limiting barotrauma. Sedation protocol involved continuous diazepam (midazolam in some) and morphine infusions to achieve and maintain Ramsay Score of 3–4 [28], with morning sedation interruption. Intravenous fluid was initiated as 2/3 maintenance, and feed was introduced at the earliest. Once patients were on full feed, volume was relaxed to full maintenance. After achievement of spontaneous breathing, oxygenation index (OI) <6, decrease and/or plateau in ventilator support over 12 hours, patients were tested for extubation readiness. Patient status was verified at discharge from PICU. If died, primary and secondary causes of death were recorded. Adverse events were monitored and reported to Institutional Ethics Committee.

Study outcomes

Considering difficulty in achieving mortality benefit in current critical care scenario [29] and unclear contribution of ARDS to mortality [30], composite outcome measure like ventilator-free days (VFD) incorporating both mortality and ventilation duration are being considered [31]. Primary outcome was VFD14, which is defined as number of days from point of successful weaning to day 14 (D14) of enrollment. Death during first 14 days is considered to be equivalent to unresolved respiratory failure, and thus is equated to zero VFD14. Secondary outcome measures included all-cause mortality, ventilator days among survivors, number of patients alive and ventilator-free on D14, time-to-recovery from ARDS (i.e., when patients met extubation readiness criteria after randomization), changes in ventilation and oxygenation parameters.

Statistical analysis

Simple unrestricted randomization was used to allocate patients in two groups. Nonparametric Mann–Whitney U test and X2 test (or Fisher’s exact test, if required) were used to compare groups with quantitative outcomes. Survival analysis using Kaplan Meier curves was performed for time-to-event data, e.g., ventilation duration, time-to-recovery and PICU stay. Repeated measures analysis of variance was planned to assess trend in ventilation and oxygenation parameters. SPSS version 16 was used for statistical analysis. A p < 0.05 was considered significant.

RESULTS

Out of 67 eligible patients, 33 were randomized to ambroxol, while 34 to placebo (Fig. 1). Per-protocol analysis was performed after excluding one patient in ambroxol group who developed acute renal failure on day 2, leading to discontinuation of drug. Management included unmonitored hand-ventilation with self-inflating bag for initial few hours (usually upto 24 h) in emergency room (ER) or pediatric wards (PWs) before PICU admission as, more often than not, ventilator was not available for immediate application. Of 66 patients, 42(64%) had moderate to severe ARDS (PaO2/FiO2; >200) [22] at randomization. Thirteen of the remaining 24 patients, who had mild ARDS (PaO2/FiO2; 201–300) at enrollment, progressed in severity subsequently. Two groups were comparable for demographic profile, nutritional status, severity of illness at randomization, diagnoses, metabolic profile, cause of lung injury as well as in baseline respiratory characteristics (Tables 1 and 2). Bronchopneumonia and bronchiolitis were the commonest (91%) causes of pARDS. Three patients (4.5%) had chemotherapy-induced febrile neutropenia. Eight (12%) (four in each group) patients had positive blood culture at PICU admission—Staphylococcus aureus (3), Burkholderia cepacia (2), Acinetobacter (1), E. coli (1) and Candida (1).

VFD14 was similar in two groups (p = 0.56), so was time-to-recovery from ARDS and other clinical outcomes (Table 3 and Fig. 2). PaO2/FiO2, OI, need for PEEP, tidal volume and PaCO2 were also similar during first 14 days (Figs 3 and 4). Health care associated infections (HCAIs) were seen in 25(38%) patients, more in placebo group (16/34 vs. 9/32; p = 0.11). Out of these, 19(76%) were culture positive, gram-negative bacilli (14) being the commonest (Candida, 4; Staphylococcus, 3). Bloodstream infections (14) were commonest followed by urinary tract infections (11). All-cause mortality was 25.8% (17/66), with similar distribution of early
of deaths were ascribed to HCAIs, while one succumbed to hyperkalemia-induced arrhythmia. Among survivors, median (interquartile range) ventilation duration was 7 (6) and 8 (4.5) days in ambroxol and placebo groups, respectively. Diarrhea was noted in 6 (19%) patients receiving ambroxol. One patient developed renal failure on D2 of ambroxol. Serial blood pressure and cardiac component of PeLOD score were comparable in the two groups during first 14 days, contrasting the experimental data [33].

- ARDS was considered as primary cause of death in 53% (9/17) patients, three of them were immunocompromised. Forty-one percent (7/17) of deaths were ascribed to HCAIs, while one succumbed to hyperkalemia-induced arrhythmia. Among survivors, median (interquartile range) ventilation duration was 7 (6) and 8 (4.5) days in ambroxol and placebo groups, respectively. Diarrhea was noted in 6 (19%) patients receiving ambroxol. One patient developed renal failure on D2 of ambroxol. Serial blood pressure and cardiac component of PeLOD score were comparable in the two groups during first 14 days, contrasting the experimental data [33].

### Table 1. Baseline patients' characteristics at enrollment

| Characteristics                        | Placebo (n = 34) | Ambroxol (n = 32) |
|----------------------------------------|------------------|-------------------|
| Age (year), median (IQR)               | 1.15 (3.22)      | 1.37 (3.42)       |
| Age, Number (%)                        |                  |                   |
| < 1 year                               | 16 (47%)         | 13 (40%)          |
| 1–5 years                              | 11 (32%)         | 14 (44%)          |
| >5 years                               | 7 (21%)          | 5 (16%)           |
| Sex ratio (M:F)                        | 23:11            | 22:10             |
| Nutritional status (reference, NCHS median)a |                  |                   |
| Normal (>80%)                          | 18 (56%)         | 17 (50%)          |
| PEM grade 1 (71–80%)                   | 5 (16%)          | 4 (12%)           |
| PEM grade 2 (61–70%)                   | 5 (16%)          | 8 (24%)           |
| PEM grade 3 (51–60%)                   | 3 (9%)           | 5 (15%)           |
| PEM grade 4 (≤50%)                     | 1 (3%)           | 0 (0%)            |
| Serum albumin at admission, median (IQR), gm/dl | 2.29 (0.88)      | 2.60 (1.00)       |
| Number of patients with hypoalbuminemia (%)b | 24 (70.6%)       | 23 (71.9%)        |
| PRISM III score, median (IQR)          | 5.00 (7.00)      | 6.00 (7.75)       |
| PeLOD score, median (IQR)c             | 5.50 (10.00)     | 10.00 (10.00)     |
| Cause of pARDS                        |                  |                   |
| Pneumonia                              | 29 (85%)         | 27 (84%)          |
| Bronchiolitis                          | 5 (15%)          | 1 (3%)            |
| Kerosene poisoning                     | 0 (0%)           | 2 (6%)            |
| Aspiration pneumonia                   | 0 (0%)           | 1 (3%)            |
| Pulmonary hemorrhage                   | 0 (0%)           | 1 (3%)            |
| Blood culture positive                 | 4 (12%)          | 4 (13%)           |
| Febrile Neutropenia                    | 2 (6%)           | 1 (3%)            |

IQR = interquartile range; PEM = protein energy malnutrition; pARDS = Pulmonary Acute Respiratory Distress.

*Malnutrition was graded based on the criteria defined by Indian Academy of Pediatrics.

bHypoalbuminemia was defined as an albumin level of <3.4 g/dl for patients >7 months and <2.5 g/dl for patients <7 months [32].

cPeLOD: Pediatric Logistic Organ Dysfunction (non-pulmonary) Score.

### Table 2. Baseline respiratory characteristics at enrollment

| Respiratory characteristics | Placebo (n = 34) | Ambroxol (n = 32) |
|-----------------------------|------------------|-------------------|
| PaO2:FiO2 ratio,a           | 177.1 (70.7)     | 190.6 (81.6)      |
| Mean (SD)                   |                  |                   |
| Severity of ARDS, number (%)|                  |                   |
| Mild ARDS                   | 10 (29%)         | 14 (44%)          |
| (P/F ratio; 201–300)        |                  |                   |
| Moderate ARDS               | 20 (59%)         | 14 (44%)          |
| (P/F ratio; 101–200)        |                  |                   |
| Severe ARDS                 | 4 (12%)          | 4 (12%)           |
| (P/F ratio ≤100)            |                  |                   |
| PEEP, mean (SD)             | 6.5 (2.5)        | 6.2 (1.6)         |
| Quantitative pulmonary involvement (as per chest radiograph) | | |
| 1 quadrant                  | 0 (0%)           | 0 (0%)            |
| 2 quadrant                  | 2 (6%)           | 2 (6%)            |
| 3 quadrant                  | 7 (21%)          | 6 (19%)           |
| 4 quadrant                  | 25 (73%)         | 24 (75%)          |
| MAP, mean (SD)              | 12.3 (5.1)       | 11.7 (4.2)        |
| OI, mean (SD)               | 9.5 (10.8)       | 7.6 (4.6)         |
| VT (ml/kg), mean (SD)       | 5.7 (1.7)        | 5.4 (1.3)         |
| PIP, mean (SD)              | 19.4 (6.9)       | 18.6 (4.2)        |
| Murray’s lung injury score  |                  |                   |
| Mild to moderate (0.1–2.5)  | 26 (76%)         | 22 (69%)          |
| Severe (>2.5)               | 8 (24%)          | 10 (31%)          |

IQR = interquartile range; SD = standard deviation; PaO2 = partial pressure of arterial oxygen; FiO2 = fraction of inspired oxygen; PEEP = positive end expiratory pressure; PIP = peak inflating pressure; MAP = mean airway pressure; OI = oxygenation Index; VT = tidal volume.

*aArterial blood gases in both groups were assessed at 0800 hours daily.
DISCUSSION

Current study add to scarcely available data on clinical characteristics and outcomes of ventilated pediatric ARDS patients from developing economies [2, 3, 34]. Ours being a tertiary care hospital without referral and transport system, we usually receive patients very late. Thus, patients are likely to be the severest of lot. Pneumonia and bronchiolitis were commonest (90%) causes of ARDS, making it a syndrome of relatively homogeneous etiology in our setting as against 40–65% reported from industrialized economies (Table 4). PRISM-III score calculated from data collected during first 24 h of PICU admission were comparable with that in other pediatric ARDS studies [35, 37]. However, as all of our patients were resuscitated and received post-resuscitation supportive care (including hand-ventilation) for significant period in ER/PWs before being shifted to PICU, many vital signs might have improved by the time they reached PICU. Thus, actual PRISM-III scores at beginning of hand-ventilation in ER/PWs is likely to be higher than ones calculated at PICU admission, making them sicker than what got reflected in PRISM-III scores. All-cause mortality (of 26%) is significantly higher compared with industrialized economies (Table 4) after factoring in higher mean PaO2/FiO2 (>175), lower mean OI (<10) and lesser number of patients with immunocompromised status. Poor referral, advanced stage of illness at admission and suboptimal post-resuscitation care in ER/PWs may be one set of possible causative factors. While in PICU, suboptimal patients–nurse ratio, poorly trained critical care nurses and poor infection control practices may be another. These are the issues of concern and indicate potentials of improvement in critical care in the study settings.

Early treatment was planned to have potential beneficial effects of ambroxol early during acute phase

Table 3. Primary and secondary outcome variables

| Outcome | Placebo (n = 34) | Ambroxol (n = 32) | p* |
|---------|-----------------|------------------|----|
| **Primary outcome variable** | | | |
| Ventilator-free days at D14 (VFD14)b | 5.0 (7.0) | 5.0 (9.7) | 0.56 |
| Ventilator-free days at D14 (VFD14) (mean ± SD) | 4.4 (3.6) | 5.0 (4.5) | – |
| **Secondary outcome variables** | | | |
| Alive and ventilator-free at D14c | 24 (71%) | 21 (66%) | 0.45 |
| Ventilator days among survivorsb | 8.0 (4.5)(n = 25) | 7.0 (6.0) (n = 24) | 0.55 |
| Number of days to recover from ARSD among survivorsb | 10.0 (5.0)(n = 25) | 8.5 (7.0)(n = 24) | 0.54 |
| PICU stay among survivors (day)b | 12.00 (5.00) | 11.50 (7.75) | 0.42 |
| All-cause mortalityc | 9 (26%) | 8 (25%) | 0.89 |
| Early deaths (≤3 days)c | 3 (38%) | 4 (44%) | 0.77 |
| Late deaths (>3 days)c | 5 (62%) | 5 (56%) | – |

*p-values are based on Mann–Whitney U test for number of VFD14, ventilator days among survivors, time-to-recovery from ARDS, duration of PICU stay; χ2 test (or Fisher Exact Test) for number of patients alive and ventilator-free at day 14, all-cause mortality.

bData expressed as median (interquartile range).

cData expressed as number (percentage).

dAmong survivors, number of days from randomization to meeting extubation readiness criteria for 24 consecutive hours through day 14.

Fig. 2. Kaplan–Meier curves comparing time-to-recovery from ARDS in the two groups (censored for in-PICU mortality; Log-Rank test, p = 0.94).
Fig. 3. Dot plot showing trend of mean $\text{PaO}_2$:FiO$_2$ ratio, oxygenation Index and PEEP during first 14 days.
of illness. We demonstrated safety, tolerance and role of high-dose oral ambroxol (40 mg/kg/day, in four divided doses) in ventilated pARDS patients for the first time. Ambroxol failed to improve oxygenation, ventilation, VFD, time-to-recovery, mortality and thus to suggest therapeutic potential in pARDS in the study setting owing to small sample size. Two-thirds of patients had hypoalbuminemia and thus gut edema, possibly affecting ambroxol’s bioavailability. Dosage chosen was maximal safe dose based on available clinical data. Therapeutic efficacy and safety of further higher dose may be subject of future scrutiny. Higher doses may also be helpful in eradicating pathogens adhered to bronchiolar/alveolar epithelium [39]. Ambroxol selectively gets concentrated in lungs within 3 min of intravenous administration, but it falls

Fig. 4. Dot plot showing trend of mean tidal volume and PaCO₂ during first 14 days.
| Clinical Profile | Dahlem et al. [35] | Curley et al. [36] | Flori et al. [37] | Wilson et al. [9] | ANZICS [38] | Hu et al. [3] | Zhu et al. [2] | Chetan et al. [34] | Index study |
|------------------|---------------------|------------------|------------------|------------------|--------------|--------------|--------------|------------------|------------|
| Study period     | 1998–2000           | 2001–2004        | 1996–2000        | 2000–2003        | 2004–2005    | 2006–2007    | 2009          | 2003–2006        | 2007–2008  |
| Country of study | Netherlands         | USA              | USA              | USA              | Australia and New Zealand | China        | China         | India            | India      |
| Pneumonia        | 11.4%               | 56%              | 35%              | 34%              | 46%          | 75%          | 63%           | 18%              | 82%        |
| Bronchiolitis    | 15.9%               | 14%              | –                | 7%               | 12%          | –            | –             | –                | 9%         |
| Aspiration       | –                   | 11%              | 15%              | 8%               | 8%           | –            | –             | –                | 6%         |
| Sepsis           | 34.1%               | 15%              | 13%              | 36%              | 17%          | 15%          | 34%           | 30%              | 3%         |
| Near drowning    | –                   | –                | 9%               | 5%               | 3%           | –            | 2%            | 6%               | –          |
| Cardiac disease  | –                   | –                | 7%               | –                | –            | 9%           | –             | –                | –          |
| PaO₂/FiO₂ ratio  | 211.5<sup>a</sup>   | 147 and 153<sup>a,b</sup> | ? | 128 and 126<sup>a,b</sup> | ? | ? | ? | ? | 177.1 and 190.6<sup>a,b</sup> |
| Oxygenation Index| NA                  | 15.0 and 18.0<sup>a,b</sup> | ? | 20.0 and 20.5<sup>a,b</sup> | ? | ? | ? | ? | 9.5 and 7.6<sup>a,b</sup> |
| Immuno-compromised Status | 9.1% | NA | ? | 34% | ? | ? | ? | ? | 4.5% |
| Others           | 9.1%                | 4%               | 21%              | 11%              | 9%           | –            | 1.5%          | 40%              | 2%         |
| Mortality        | 27%                 | 8%               | 22%              | 28%              | 35%          | 45%          | 30%           | 70%              | 26%        |

NA = Information not available; ? = information could not be retrieved due to non-accessibility of full manuscripts.

<sup>a</sup>Mean.

<sup>b</sup>In the two arms of the study cohort.
dramatically at 2 h [33]. Thus, for sustained clinical effect, more frequent administration (4 hourly or even 2 hourly) may be required. As pARDS was mostly caused by pneumonia and bronchiolitis and majority (92%) of survivors required ventilation for ≤14 days, D14 may be an optimal reference for measure of VFD in the study setting. This pilot trial is relied on a convenience sample, results (Table 3) from which indicates need of sample size of 388 patients in each arm with one-sided significance level (z error) of 0.05 and 80% power to detect 20% improvement in the observed median VFD14 of 5 days (i.e., reduction of 1 day in VFD14) [40].

Strengths include randomized design and carefully planned protocols to define ventilator management, sedation and extubation readiness to minimize variations in daily management of patients. There are many limitations as well, major one being the unregulated unmonitored hand-ventilation before PICU admission, which may have caused barotrauma. Lack of specific information on its duration may be a potential confounder. Study cohort was restricted to pARDS only. These issues are unavoidable and need to be tolerated to develop clinically efficacious interventions in the prevalent settings. However, these would affect generalizability of results. Study was underpowered to demonstrate difference in VFD14. There is lack of data on pharmacokinetics of enterally administered ambroxol in critically ill children. It needs to be addressed before conducting similar study in future. Further, inflammatory, oxidative and anti-protease markers should also be evaluated to assess its pharmacologic efficacy. Stratification according to severity of ARDS may identify a subgroup of responders.

CONCLUSIONS
Study provides useful information on prevalent situation in the resource-constraint economies, informs about limitations in conducting trials in these settings and questionable generalizability of their results. Pediatric pARDS is mostly caused by pneumonia and bronchiolitis. After factoring in higher PaO2/FiO2, lower OI and lesser patients with immunocompromised states, mortality is high compared with industrialized peers. High-dose oral ambroxol failed to improve VFD14. In the current cost-conscious health care environment, its potential as adjuvant therapy should be explored after having addressed the aforementioned issues. Large, prospective study of appropriate power with higher doses of oral ambroxol administered more frequently is desirable. VFD14 as composite outcome measures is suggested for ventilated pediatric pARDS patients; however, it needs further validation.

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