

There is no alternative to the use of knowledge as a core resource to improve health care and to minimise the consequences of natural and human-made disasters. We need to balance the drive for innovation and new interventions in health care with the best use of resources that already exist from past research. The huge task of evidence generation and implementation requires global sharing of the workload, fair contributions to the global knowledge pool, and even distribution of this knowledge for local implementation. Current disparities between high-income and low-income countries, and between and within wealthy countries, are a substantial barrier. When knowledge begins to flow freely in all directions, it will quickly become apparent just how valuable, indispensable, and renewable this resource is. The Evidence Aid survey is an important step in both redressing the imbalances that have built up and providing a model for how health care more generally can build stronger connections between needs and knowledge.

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As we finalised this Comment, we were sadly reminded of the limits on one of the resources for improving health: individuals who provide the insight, enthusiasm, and integrity needed to generate, disseminate, and implement knowledge. One of these bright lights went out on Jan 1, 2012, with the death of our friend and colleague Alessandro Liberati. We dedicate this Comment to him.

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## $\beta$ -agonists for ARDS: the dark side of adrenergic stimulation?

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See [Articles](#) page 229

In *The Lancet*, Fang Gao Smith and the [BALTI-2](#) study investigators<sup>1</sup> report the findings of their [phase-3](#) randomised trial of intravenous salbutamol for acute respiratory distress syndrome (ARDS). The trial, based on reliable preclinical evidence and an encouraging phase-2 trial, was [stopped](#) early because of [safety concerns](#).<sup>2</sup>

$\beta$ -agonists had been an appealing therapeutic option for ARDS in view of extensive clinical experience, low cost, and an [excellent safety](#) profile when used for patients with [obstructed airways](#). Stimulation of the  $\beta$ -2 receptor increases cyclic adenosine monophosphate and active transport of sodium and chloride across type-1 and type-2 alveolar epithelial cells, creating an [osmotic gradient](#) for [reabsorption of water](#) from the injured lung.<sup>3</sup> [Clearance](#) of epithelial [fluid is impaired](#) in patients with [ARDS](#), more so in fatal cases.<sup>4</sup> A [phase-2](#) study of [intravenous salbutamol \(BALTI-1\)](#) showed [reductions](#) in

extravascular lung water, reduced alveolar capillary leak, and improved lung function in a single-centre trial with 40 patients, providing strong proof of concept.<sup>2</sup>

The BALTI-2 investigators designed a high-quality pragmatic [multicentre](#) trial of [1334](#) patients to determine if a [7-day continuous infusion of salbutamol](#) would improve 28-day mortality versus placebo (0.9% sterile sodium chloride). The Data Monitoring and Ethics Committee (DMEC) recommended that the study stop after the second interim analysis of 273 patients because of a significant increase in [mortality](#) ([risk ratio 1.55](#), 95% CI 1.07–2.24;  $p=0.02$ ). The BALTI-2 Steering Committee accepted this recommendation. DMECs should balance the interests of participants, who are best served by stopping recruitment when harm is apparent, against the interest of society, which could be best served by continuation of a trial until

the results are compelling enough to guide the care of future patients.<sup>5</sup> Did the BALTI-2 DMEC and Steering Committee strike the right balance, and are the results sufficient to change practice?

The findings show consistent evidence for a harmful effect of intravenous salbutamol. The infusion was poorly tolerated because of tachycardia, lactic acidosis, and arrhythmias. The risk ratio for 28-day mortality was 1.47 (95% CI 1.03–2.08). Confidence limits for ventilator-free days and organ failure-free days excluded the null in the direction of harm. Although no previously defined subset seemed to show benefit, early termination limits the power to detect such interactions and is a major drawback of early stopping. Post-hoc attempts at identification of the cause of excess mortality with death certificates were unsuccessful; however, establishment of the proximate cause of death is difficult in patients who are critically ill. Mortality was lower than expected in the placebo group, but this finding parallels those in other contemporary ARDS trials and is probably due to improved supportive care practices, such as lower tidal volume ventilation and conservative fluid therapy.<sup>6,7</sup> Thus, the findings consistently indicate harm from intravenous salbutamol at the dose studied (15 µg/kg ideal weight per h), but do not provide a clear mechanism. The findings are in line with the acute lung injury (ALTA) trial<sup>8</sup> of aerosolised salbutamol, which stopped early for futility with numerically lower ventilator-free days (p=0.087) and a significant reduction in days free of care in an intensive-care unit (p=0.023).

Injury to the epithelium during ARDS can render it unresponsive to β-agonists, leaving patients treated with salbutamol with little or no potential benefit. Possible explanations for harmful pulmonary effects have been reviewed.<sup>8,9</sup> Prolonged administration of β-agonists might downregulate β-receptors in lung epithelia and impair fluid removal. β-agonists could have a differential effect on the endothelium (harmful) versus the epithelium (beneficial if functional), and β-2 agonists could increase cardiac output thus aggravating alveolar capillary leak. Salbutamol activates the renin-angiotensin system and this might antagonise attempts at diuresis as part of conservative fluid management. More positive fluid balance was noted in the ALTA trial, in which conservative fluid management was protocolised in both groups.<sup>7</sup> These potential adverse pulmonary effects could explain part of the adverse effect on ventilator-free days in BALTI-2.



Endogenous or exogenous catecholamine exposure in critical illness, including ARDS, might have a dark side. The risk of increased adverse cardiac events in patients with cardiovascular disease is an obvious example, and salbutamol, although relatively β-2 selective, is a partial β-1 agonist.<sup>10</sup> Plasma catecholamine concentrations increase with critical illness and might contribute to the pathogenesis of septic myocardial injury and cardiac failure during septic shock.<sup>11</sup> This hyperadrenergic state might cause pernicious adverse effects, including skeletal muscle catabolism, altered glucose homeostasis and innate immunity, increased β-oxidation of lipids, altered mitochondrial and myocardial function, enhanced gastrointestinal bacterial translocation, and the promotion of bacterial growth.<sup>12,13</sup> β-blockade prevents or reverses many of these adverse effects in experimental animals and in patients with extensive burns, major cardiovascular surgery, and sepsis.<sup>13,14</sup>

Much work needs to be done, but the BALTI-2 results should encourage research on approaches to reduce adrenergic upregulation and catecholamine exposure during critical illness and ARDS to identify if these approaches improve outcomes. For now, the results of the truncated BALTI-2 trial are sufficient to change practice. β-2 agonist treatment in patients with ARDS should be limited to the treatment of clinically important reversible airway obstruction and should not be part of routine care.

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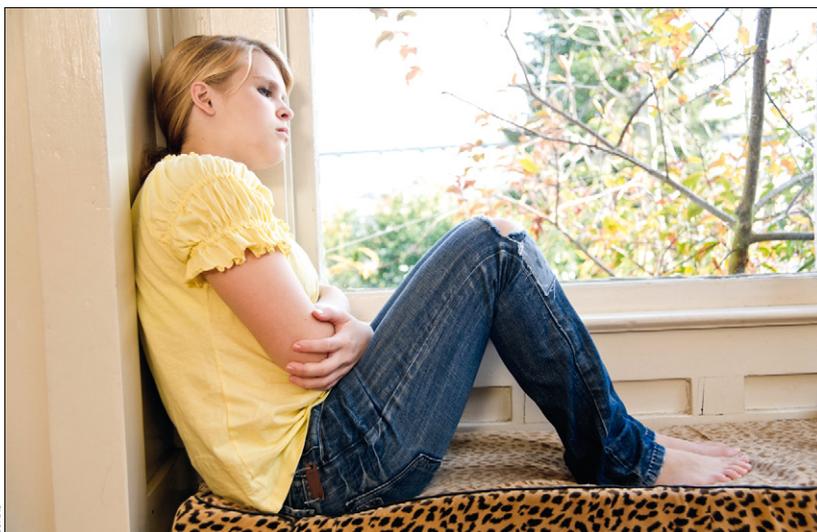
## Self-harm in adolescence and future mental health

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See [Articles](#) page 236

Results of several school-based community studies have shown that self-harm (intentional self-injury or self-poisoning) is very common in adolescents, being reported by around 10% of 15 and 16 year olds,<sup>1–3</sup> although with some international variation in prevalence.<sup>4</sup> In *The Lancet* Paul Moran and colleagues<sup>5</sup> report a study in which they found that about 8% of adolescents in a sample of nearly 2000 Australian pupils, recruited from schools in the state of Victoria, said they had self-harmed. As in other studies, self-harm was more frequent in girls than boys (risk ratio 1.6, 95% CI 1.2–2.2), and the most common method was

self-cutting, which is by stark contrast with the pattern in samples presenting to hospitals, in which overdoses predominate.<sup>6</sup> Factors associated with adolescent self-harm in Moran and colleagues' study were much the same as those found in other community studies<sup>1–3,7</sup> and included anxiety and depression, heavy alcohol use, smoking, and antisocial behaviour.

Self-harm by an adolescent understandably causes great concern for parents and friends, and for school staff and clinicians. A crucial issue that is often raised is about the relevance of this behaviour in adolescence for future mental health, including possible persistence and worsening of self-harm. Moran and colleagues' study makes a special contribution to this topic. The authors repeatedly surveyed their study participants in nine waves between ages 14–15 years and young adulthood; data on self-harm were collected in waves three (mean age 15.9 years) to nine (mean age 29.0 years). Of the participants who self-harmed in adolescence, nine out of ten reported no self-harm in young adulthood, although young women were more likely than young men to continue to self-harm. Self-cutting in particular became less common. Persistence of self-harm into young adulthood was associated with reporting of self-harm at several assessment points during adolescence. Although the numbers are small, the data seem to show that the proportion of individuals self-harming with suicidal intent increased



# Effect of intravenous $\beta$ -2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial



Fang Gao Smith, Gavin D Perkins, Simon Gates, Duncan Young, Daniel F McAuley, William Tunnicliffe, Zahid Khan, Sarah E Lamb, for the BALTI-2 study investigators

## Summary

**Background** In a previous randomised controlled phase 2 trial, intravenous infusion of salbutamol for up to 7 days in patients with acute respiratory distress syndrome (ARDS) reduced extravascular lung water and plateau airway pressure. We assessed the effects of this intervention on mortality in patients with ARDS.

**Methods** We did a multicentre, placebo-controlled, parallel-group, randomised trial at 46 UK intensive-care units between December, 2006, and March, 2010. Intubated and mechanically ventilated patients (aged  $\geq 16$  years) within 72 h of ARDS onset were randomly assigned to receive either salbutamol (15  $\mu\text{g}/\text{kg}$  ideal bodyweight per h) or placebo for up to 7 days. Randomisation was done by a central telephone or web-based randomisation service with minimisation by centre, pressure of arterial oxygen to fractional inspired oxygen concentration ( $\text{PaO}_2/\text{F}_i\text{O}_2$ ) ratio, and age. All participants, caregivers, and investigators were masked to group allocation. The primary outcome was death within 28 days of randomisation. Analysis was by intention-to-treat. This trial is registered, ISRCTN38366450 and EudraCT number 2006-002647-86.

**Findings** We randomly assigned 162 patients to the salbutamol group and 164 to the placebo group. One patient in each group withdrew consent. Recruitment was stopped after the second interim analysis because of safety concerns. Salbutamol increased 28-day mortality (55 [34%] of 161 patients died in the salbutamol group vs 38 (23%) of 163 in the placebo group; risk ratio [RR] 1.47, 95% CI 1.03–2.08).

**Interpretation** Treatment with intravenous salbutamol early in the course of ARDS was poorly tolerated. Treatment is unlikely to be beneficial, and could worsen outcomes. Routine use of  $\beta$ -2 agonist treatment in ventilated patients with this disorder cannot be recommended.

**Funding** UK Medical Research Council, UK Department of Health, UK Intensive Care Foundation.

## Introduction

Acute respiratory distress syndrome (ARDS) occurs in about 14% of mechanically ventilated patients, and causes a mortality of 40–60%<sup>1–3</sup> and a substantial reduction in survivors' quality of life.<sup>4,6</sup>  $\beta$ -2 agonists could be a potential pharmacological intervention because they act on the many pulmonary cellular pathways thought to be associated with the pathophysiology of ARDS. These drugs reduce neutrophil sequestration, activation, and production of inflammatory cytokines,<sup>7,8</sup> and activate  $\beta$ -2 receptors on alveolar type-1 and type-2 cells, which increases intracellular cyclic adenosine monophosphate, leading to increased sodium transport and acceleration of alveolar fluid reabsorption.<sup>9–11</sup> In patients with ARDS given salbutamol, we reported in vivo evidence of reduced permeability of alveolar capillaries, and in vitro evidence of enhanced wound repair in epithelial monolayers.<sup>12</sup> These data suggest that  $\beta$ -2 agonists could maintain alveolar-capillary integrity, thereby reducing alveolar flooding.

Findings from the  $\beta$ -agonist lung injury trial (BALTI)<sup>13</sup>—a single-centre, randomised controlled trial in 40 patients with ARDS—showed that an infusion of

salbutamol for 7 days caused significant reductions in extravascular lung water and plateau airway pressure. However, this trial was not designed to assess the potential effects on mortality. We therefore assessed whether treatment with salbutamol in the early course of ARDS would improve clinical outcomes.

## Methods

### Study design and participants

We undertook a multicentre, pragmatic, double-blind, placebo-controlled, parallel-group, randomised trial at 46 UK intensive-care units between December, 2006, and March, 2010. Eligible participants were intubated and mechanically ventilated adults aged 16 years and older within 72 h of ARDS onset. Patients were identified and recruited by local investigators at each site. We defined ARDS in accordance with the American European Consensus criteria:<sup>14</sup> a pressure of arterial oxygen to fractional inspired oxygen concentration ( $\text{PaO}_2/\text{F}_i\text{O}_2$ ) ratio of 200 mm Hg or less, bilateral pulmonary infiltrates consistent with oedema, and the absence of clinically evident left atrial hypertension. Exclusion criteria were pregnancy; current treatment

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See [Comment](#) page 196

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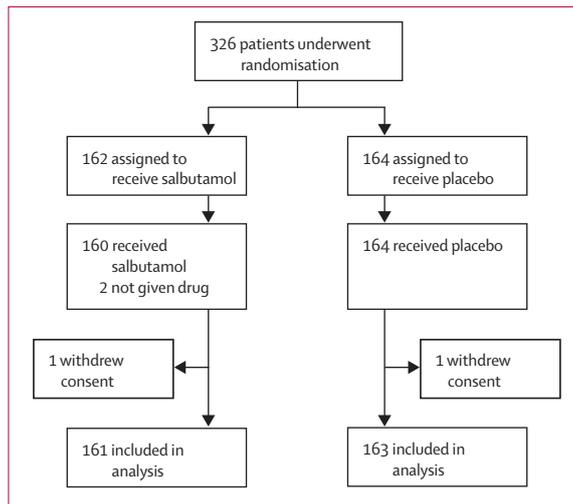


Figure 1: Trial profile

with intravenous  $\beta$ -2 agonist or need for continuous, regular, aerolised  $\beta$ -2 agonists; current treatment with  $\beta$ -adrenergic antagonists; imminent withdrawal of medical treatment; chronic liver disease, defined as Child-Pugh grade C; and enrolment in another clinical trial of an investigational medicinal product within the previous 28 days.

Sedated patients did not have capacity to give consent; therefore, consistent with requirements of the EU clinical trial directive,<sup>15</sup> we obtained written informed consent from a personal or professional legal representative before randomisation. All surviving patients were informed about the trial at the earliest opportunity after regaining competence and consent to continue in the trial was sought. The study protocol<sup>16</sup> was approved for all centres by the Oxfordshire Research Ethics Committee A. Site specific approval was obtained at each site. The trial was monitored for safety by an independent Data Monitoring and Ethics Committee.

### Randomisation and masking

Study drug packs were prepared by Bilcare Global Clinical Supplies (Europe; Powys, UK). The active and placebo drug components of the infusions were packaged identically into numbered treatment packs, each containing 5 mL of either salbutamol sulphate BP (1 mg/mL in a sterile isotonic solution, GlaxoSmithKline, Middlesex, UK) or placebo (0.9% sterile sodium chloride). We used a computer-generated randomisation sequence with a block size of eight. Patients were randomly assigned in a 1:1 ratio by a centralised 24 h telephone or web-based randomisation service (University of Aberdeen, UK). Randomisation was minimised by centre,  $\text{PaO}_2/\text{F}_i\text{O}_2$  ratio ( $\leq 50$ , 51–99, or  $\geq 100$  mm Hg), and age (<64, 65–84,  $\geq 85$  years). Participants, care providers, and investigators were masked to group assignment.

### Procedures

We obtained acute physiology and chronic health evaluation II (APACHE II) scores from Intensive Care National Audit and Research Centre (ICNARC) for sites ( $n=36$ ) that participate in the ICNARC's Case Mix Programme or, for non-participating sites (ten), we obtained data necessary for calculation of the scores. We used the APACHE II score to calculate the mortality risk, which we used for subgroup analysis.

The most likely cause of ARDS was identified by the treating clinician and categorised as direct lung injury (smoke or toxin inhalation, aspiration of gastric content, near drowning, thoracic trauma, pneumonia, or other) or indirect lung injury (sepsis, cardiopulmonary bypass, pancreatitis, non-thoracic trauma, other). The protocol recommended use of a lung protective ventilation strategy on the basis of ideal bodyweight,<sup>17</sup> fluid restriction,<sup>18</sup> and appropriate high positive end-expiratory pressure.<sup>19</sup> Compliance with recommendations for protective ventilation were assessed at baseline only (tidal volumes per kg ideal bodyweight). All other treatments were delivered in accordance with local clinical practice.

Before the start of recruitment, the intensive-care unit nurse was trained to monitor side-effects of the treatment and to inform the research team as necessary. Infusion syringes were prepared immediately before use by the nurse and contained two ampoules of the blinded solutions (salbutamol or placebo) diluted with 40 mL of saline in a 50 mL syringe. Salbutamol and placebo were administered through a dedicated intravenous line at a rate of 0.075 mL/kg ideal bodyweight per h (equivalent to 15  $\mu\text{g}$  salbutamol per kg ideal bodyweight per h). The patient was measured from heel to vertex with a soft tape measure, and the ideal bodyweight and infusion rate obtained from the conversion table.<sup>17</sup> If any patient developed a tachycardia (heart rate  $>140$  beats per min), new arrhythmia, or lactic acidosis, we adjusted the infusion rate according to a prespecified dose-adjustment schedule.<sup>15</sup> Infusion of the study drug was stopped at 7 days, or earlier if clinically indicated.

### Study outcomes

The primary outcome was 28-day mortality, defined as death up to the end of calendar day 28 after randomisation. Secondary outcomes were mortality in the intensive-care unit or hospital before first discharge; ventilator-free and organ failure-free days from randomisation to day 28; length of stay in intensive-care unit and hospital; and tachycardia, new arrhythmia, or other side-effects sufficient to stop treatment with trial drug. We defined ventilator-free days as the number of calendar days after patients started unassisted breathing until day 28 after randomisation for patients who survived at least 48 consecutive hours after start of unassisted breathing.<sup>20</sup> The number of ventilator-free days was zero for patients who died without start of unassisted breathing or before 48 consecutive hours of unassisted breathing.<sup>20</sup> We defined

organ failure-free days as the number of days in the first 28 days after randomisation that the patient received no cardiovascular, renal, liver, or neurological support as defined by the Critical Care Minimum Dataset.<sup>21</sup>

We did not plan to collect data for cause of death in the original trial protocol; however, after early termination of the trial because of the increased 28-day mortality in the salbutamol group, the data for the main cause of death were ascertained for all participants dying within 28 days of randomisation. We requested causes of death as recorded on the death certificate for the disorder directly leading to death. Patients who remained alive and in critical care after randomisation were monitored daily until discharged to a ward, or until day 28.

### Statistical analysis

We based the sample-size calculation on our BALTI trial<sup>13</sup> and on 2005 data from the Intensive Care National Audit and Research Centre. The target sample size of 1334 gave 90% power at  $p < 0.05$  to detect a risk ratio (RR) of 0.8 for 28-day mortality between the salbutamol and placebo groups with a 3% loss of patients for the primary outcome, with the assumption that the 28-day mortality in the placebo group was 44%. We planned interim analyses every 12 months, or more frequently if requested by the Data Monitoring and Ethics Committee. The committee used the Haybittle-Peto<sup>22</sup> stopping guideline: a difference of three standard errors would be needed before considering recommending trial cessation for benefit at an interim analysis.

All analyses were based on intention-to-treat analyses. We compared the primary outcome and other dichotomous outcomes using RRs and 95% CIs. We compared continuous outcomes with mean differences and their 95% CIs. We analysed 28-day mortality with survival analysis, and by comparison of the two groups with hazard ratios and 95% CIs and the Kaplan–Meier curve. All reported  $p$  values are two-sided and were not adjusted for multiple comparisons. We used prespecified subgroup analyses to investigate the effects of age, severity of hypoxaemia at study entry, cause (direct vs indirect causes of ARDS), and the APACHE II mortality risk, on the effect of salbutamol. All subgroup analyses used interaction tests; we either calculated the ratio of RRs between the subgroups, or used interaction terms in logistic regression models. We did a post-hoc analysis for the main causes of death as recorded on the death certificates of participants who died within 28 days of randomisation. This trial is registered, ISRCTN38366450 and EudraCT number 2006-002647-86.

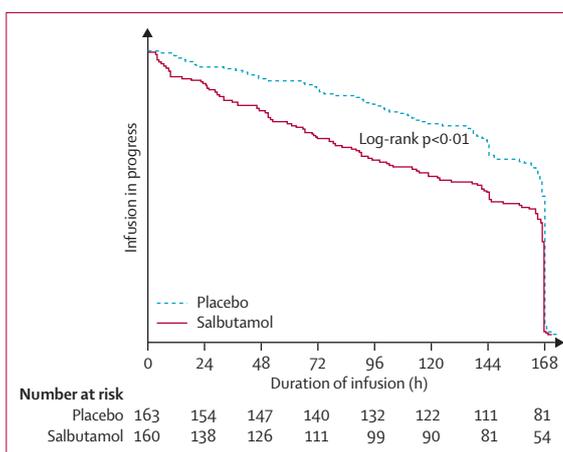
### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FGS, SG, GDP, and SEL had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

	Salbutamol (n=162)	Placebo (n=164)
Age (years)	55.8 (17.2)	54.2 (17.5)
Male sex	102 (63%)	110 (67%)
Height (cm)	168.8 (10.8)	169.0 (12.2)
APACHE II score	19.5 (6.2)	18.9 (6.7)
APACHE II predicted mortality	0.43 (0.20)	0.42 (0.21)
Tidal volume (mL/kg ideal bodyweight)	8.0 (1.7)	8.3 (1.9)
PaO <sub>2</sub> /F <sub>2</sub> O <sub>2</sub> ratio (mm Hg)	103.5 (36.75)	103.5 (36.75)
100–200	82 (51%)	81 (49%)
51–99	74 (46%)	78 (48%)
≤50	6 (4%)	4 (2%)
Missing data	0	1
Cause of ARDS		
Direct lung injury	103 (64%)	105 (64%)
Smoke or toxin inhalation	1	2
Gastric content aspiration	6	9
Near drowning	1	0
Thoracic trauma	5	9
Pneumonia	86	79
Drug related	2	1
Other	2	5
Missing data	1	0
Indirect lung injury	58 (36%)	59 (36%)
Sepsis	39	47
Cardiopulmonary bypass	1	1
Pancreatitis	6	4
Non-thoracic trauma	2	6
Transfusion related	6	1
Other	4	0
Time from ICU admission to randomisation (days)	2.7 (2.9)	2.5 (2.6)
Missing data	1	0

Data are mean (SD) or number (%), unless otherwise stated. PaO<sub>2</sub>/F<sub>2</sub>O<sub>2</sub>=pressure of arterial oxygen to fractional inspired oxygen. APACHE II=acute physiology and chronic health evaluation II. ARDS=acute respiratory distress syndrome. ICU=intensive-care unit.

**Table 1: Baseline characteristics**



**Figure 2: Kaplan-Meier curves for duration of infusions**

Duration of salbutamol and placebo infusions from 28 days after randomisation. HR=hazard ratio.

	Salbutamol (n=161)	Placebo (n=163)	RR* or difference† (95% CI)
Mortality 28 days after randomisation	55 (34%)	38 (23%)	1.47* (1.03 to 2.08)
Death before discharge from ICU	58 (36%)	45 (28%)	1.31* (0.95 to 1.80)
Death before discharge from hospital	62 (39%)	53 (33%)	1.18* (0.88 to 1.59)
Ventilator-free days	8.5 (8.8, 0-26)	11.1 (9.3, 0-27)	-2.7† (-4.7 to -0.7)
Organ failure-free days	16.2 (10.7, 0-28)	18.5 (9.8, 0-28)	-2.3† (-4.5 to -0.1)
Tachycardia sufficient to stop treatment with study drug	23 (14%)	2 (1%)	11.71* (2.81 to 48.88)
New arrhythmia sufficient to stop treatment with study drug	14 (9%)	3 (2%)	4.75* (1.39 to 16.23)
New lactic acidosis sufficient to stop treatment with study drug	10 (6%)	1 (<1%)	10.73* (1.36 to 84.82)
Duration of ICU stay (days)	17.6 (14.3, 0-85)	17.1 (14.0, 0-91)	0.5† (-2.6 to 3.6)
Duration of hospital stay (days)	32.5 (35.9, 0-191)	34.9 (36.3, 0-243)	-2.4† (-10.3 to 5.5)
Duration of ICU stay with exclusion of deaths‡	20.5 (15.3, 3-85)	17.1 (12.6, 1-82)	3.4† (-0.3 to 7.1)
Serious adverse events recorded	9 (6%)	4 (2%)	..
Related to study drug	4 (3%)	0	..
Related to study drug and unexpected	1 (<1%)	0	..

Data are number (%) or mean (SD, range). RR=risk ratio. ICU=intensive-care unit. \*Data are risk ratio. †Data show the difference. ‡Salbutamol group, n=103; placebo group, n=118.

Table 2: Primary and secondary outcomes

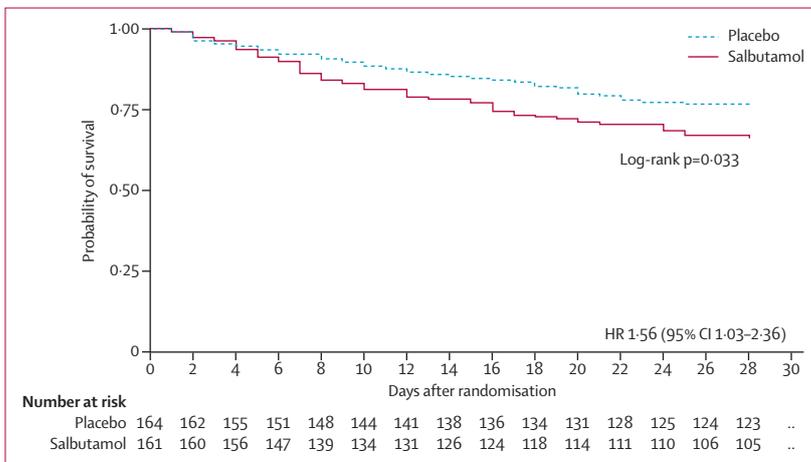


Figure 3: Kaplan-Meier curves for mortality. Rate of death in the two study groups up to 28 days after randomisation.

Results

46 study sites participated in recruitment; a further 25 sites obtained approval to start the trial, but were unable to do so before recruitment was stopped. Recruitment was stopped after the second interim analysis, when the Data Monitoring and Ethics Committee reviewed the results for 273 patients in March, 2010. The RR for the primary outcome at this time was 1.55 (95% CI 1.07–2.24). Therefore, the committee recommended suspension of recruitment to BALTI-2 because of a significant (p=0.02)

adverse effect of salbutamol on 28-day mortality, and the 99.8% CI excluded a benefit for salbutamol of the size anticipated in the protocol. Infusion was discontinued in all patients (one receiving salbutamol, two receiving placebo) receiving study drug at that time. The trial steering committee endorsed this recommendation and closed recruitment on March 23, 2010.

Figure 1 shows the trial profile. 326 patients were randomly assigned to receive either salbutamol or placebo. Two patients withdrew consent; no outcome data were available for these patients. The study drug was not given to two patients in the salbutamol group: one patient needed a β blocker between randomisation and starting the drug, the other patient’s next of kin refused to have a separate intravenous line inserted for infusion after initially giving consent.

Both groups had similar baseline characteristics (table 1). The median time from randomisation to start of the study infusion was similar in both groups (salbutamol 1.3 h, IQR 0.6–2.5; placebo 1.1 h, 0.6–2.2). Patients in the salbutamol group were more likely to have their infusion stopped early than were those in the placebo group, either because of death (14/161 vs eight of 163), or the development of significant side-effects (47/161 vs 13/163). The duration of infusion was on average 24.5 h (95% CI 12.3–36.7) shorter in the salbutamol group than in the placebo group (mean 114.1 h [SD 62.7] vs 138.6 h [47.9]; figure 2). The risks of patients developing a tachycardia, new arrhythmia, or lactic acidosis severe enough to warrant stopping of the study drug were substantially higher in the salbutamol group than in the placebo group (table 2).

More patients died 28 days after randomisation in the salbutamol group than in the placebo group (RR 1.47, 95% CI 1.03–2.08; p=0.03; table 2). Survival analysis of the primary outcome (figure 3) showed a hazard ratio of 1.56 (95% CI 1.03–2.36). Salbutamol resulted in a 10.9% (95% CI 1.0–20.4) absolute increase in 28-day mortality (table 2). One additional death occurred for every 9.2 (95% CI 4.9–100.9) patients with ARDS given salbutamol. The number of deaths before discharge from either intensive-care unit or hospital did not differ significantly between groups (p=0.10 and p=0.26, respectively; table 2). We noted an 8.4% (95% CI -1.7 to 18.3) absolute increase in intensive-care unit mortality and a 6.0% (-4.4 to 16.2) increase in hospital mortality in the salbutamol group (table 2).

Ventilator-free and organ failure-free days in the first 28 days after randomisation were both reduced in the salbutamol group (table 2). We detected no clear differences between the groups in length of stay in intensive-care units and hospitals (table 2). Surviving patients with ARDS in the salbutamol group needed a mean of 3.4 more days (95% CI -0.3 to 7.1) in intensive-care units than did those in the placebo group (table 2). Serious adverse events (other than those recorded as trial outcomes, eg, death) were reported for 13 participants (nine in salbutamol group, four in placebo group). Four of these events were

thought to be related to the study drug infusion, and only one was an unexpected effect. Subgroup analyses did not suggest that the effects of salbutamol were modified by any of the variables investigated. For cause (categorical subgrouping variable), the ratio of RRs was 0.96 (95% CI 0.46–2.01). For continuous variables the ratios of odds ratios for each variable investigated were 0.97, 0.93–1.00;  $p=0.07$  for age; 1.02, 0.92–1.14;  $p=0.66$  for severity of hypoxemia; and 1.29, 0.08–22.04;  $p=0.86$  for mortality risk. The analysis suggested weak evidence of a possible interaction effect with age. However, the effect was small and strongly affected by the oldest age stratum (>85 years), in which there were only four patients; therefore, this finding is likely to be due to chance.

Adjustment for baseline variables (age, sex, PaO<sub>2</sub>/F<sub>2</sub>O<sub>2</sub> ratio, and cause) alone or in combination made no substantial difference to the estimate of the treatment effect of salbutamol or its statistical significance (data not shown). We obtained data for cause of death for 91 of 93 patients who died by day 28 (55/55 in the salbutamol group, 36/38 in the placebo group). Because of the diversity of individual diagnoses, we grouped results for cause of death according to organ system. Diagnoses for the respiratory system were the most common primary cause of death in both groups (28 [51%] patients given salbutamol vs 20 [53%] given placebo), followed by multiorgan failure (12 [22%] vs 14 [37%]). ARDS was recorded on the death certificate for 11 (21%) patients in the salbutamol group, and eight (21%) in the placebo group.

## Discussion

Our findings show that intravenous salbutamol given to patients with early ARDS significantly increased 28-day mortality, and reduced ventilator-free days and organ failure-free days compared with those given placebo. Treatment was poorly tolerated because of tachycardia, arrhythmias, and lactic acidosis. These findings were unexpected; however, they have clarified whether intravenous infusion of  $\beta$ -2 agonists should be used in patients with ARDS (panel). The ALTA trial<sup>23</sup> of aerosolised salbutamol for treatment of acute lung injury in 282 patients was stopped because the primary endpoint, ventilator-free days, had crossed predefined futility boundaries, making the probability of a positive trial very low. Nevertheless, in that trial, clinical outcomes were worse in the salbutamol group than in the placebo group, particularly in the most severely ill patients. Because we recruited a large number of ARDS patients, with characteristics similar to other multicentre trials,<sup>2,23</sup> from 46 multidisciplinary intensive-care units in the UK, our data could be generalised to other intensive-care units.

Our trial has some limitations. First, mortality in the placebo group was much lower than anticipated. This outcome could have been caused by changes in the mortality of ARDS because of improvements in treatments.<sup>24</sup> Second, because of the nature of pragmatic trials, we did not obtain prospective data for cardiovascular

### Panel: Research in context

#### Systematic review

We searched PubMed and The Cochrane Library from Jan 1, 1960, to Aug 31, 2011, for randomised controlled trials or systematic reviews investigating the use of  $\beta$  agonists for the treatment of patients with established acute respiratory distress syndrome (ARDS). We used a combination of text ("salbutamol", "beta agonist", "ARDS") and medical subject headings terms ("adrenergic beta-agonists", "respiratory distress syndrome", "adult"). We identified two randomised controlled trials<sup>13,23</sup> and no systematic reviews. Both trials were at low risk of bias, according to the criteria of the Cochrane risk of bias method.

The  $\beta$ -agonist lung injury trial (BALTI)<sup>13</sup> recruited 40 patients and used an intravenous infusion of salbutamol. Findings from the trial showed reductions in extravascular lung water and plateau airway pressure in the group given salbutamol, but no difference in 28-day mortality (11 [58%] of 19 patients died in the salbutamol group vs 14 [67%] of 21 in the placebo group).<sup>12</sup> The aerosolised beta-2 agonist for treatment of acute lung injury (ALTA)<sup>23</sup> trial randomly assigned 282 patients with acute lung injury to receive aerosolised salbutamol (5 mg) or placebo. The trial was stopped early on grounds of futility. The number of ventilator-free days (salbutamol 14.4 days vs placebo 16.6 days; 95% CI for the difference -4.7 to 0.3 days;  $p=0.087$ ) or hospital mortality (35 [23%] of 152 patients died in the salbutamol group vs 23 [17%] of 130 in the placebo group; 95% CI for the difference -4.0 to 14.7;  $p=0.30$ ) did not differ significantly.

#### Interpretation

The effects on ventilator-free days and mortality in ALTA were consistent with those in BALTI-2, but our trial shows clearly that intravenous administration of salbutamol at 15  $\mu$ g/kg ideal bodyweight per h to patients with early ARDS was poorly tolerated, is unlikely to be beneficial, and could worsen outcomes. Routine use of  $\beta$ -2 agonist therapy in mechanically ventilated patients with ARDS cannot be recommended.

comorbidity and causes of deaths, including results of post-mortem. These data could provide useful information about possible explanations of these unexpected trial results. Third, the trial was stopped at a smaller sample size than was planned; therefore, the precision of the treatment effect estimates is lower than expected. A large sample size and narrow CIs might clarify salbutamol's effects on secondary outcomes, such as mortality rates in intensive-care units and hospitals. Fourth, although we recommended best practice for ARDS (protective ventilation, conservative fluid management), we did not measure details of clinical management. We selected the dose of salbutamol (15  $\mu$ g/kg ideal bodyweight per h) after an early dose-ranging study identified it to be the maximum dose that critically ill patients could receive without an increase in ventricular, atrial tachycardia, or ectopy. This dose was used in the BALTI study<sup>25</sup> and resulted in steady-state plasma concentrations of salbutamol ( $1 \times 10^{-6}$  M), and is associated with a 100% increase in clearance of basal alveolar fluid in animal studies of ARDS. The dose is at the high end of the manufacturer's recommended dosing regimen; as such, a beneficial effect of salbutamol could have been outweighed by its adverse effects at this dose. A lower dose of salbutamol might have produced a different outcome, so the conclusions from our study can relate only to the dose given.

The mechanisms underlying the increased mortality in the salbutamol group remain unclear. That the survival curves for salbutamol and placebo seem to continue to diverge after the end of the salbutamol infusion might be notable, so the mechanism could be complex. The ALTA investigators<sup>23</sup> explored possible explanations for the scarcity of effect of  $\beta$ -2 agonists, including poor drug delivery to injured and oedematous alveoli, inadequate alveolar epithelial response, downregulation of  $\beta$ -2 receptors, and genetic variation. Adverse effects on the cardiovascular system—eg, tachyarrhythmias, cardiomyopathy and myocardial infarction—could have been harmful.<sup>26,27</sup> Recruitment of damaged alveoli<sup>28</sup> and activation of the renin-angiotensin aldosterone system could adversely affect pulmonary fluid balance.<sup>29</sup>

Findings from this multicentre trial provide evidence that intravenous salbutamol in the early course of ARDS was poorly tolerated, is unlikely to be beneficial, and could worsen outcomes. Routine use of  $\beta$ -2 agonist therapy in mechanically ventilated patients with ARDS cannot be recommended.

#### Contributors

FGS (chief investigator), DY, GDP, and DFM conceived the study and designed it with SG (senior trialist and statistician) and SEL (director of the clinical trials unit). FGS, SG, GDP, SEL, and DY obtained the funding and managed the undertaking of the trial. DFM, WT, and ZK contributed substantially to trial recruitment. SG did all statistical analyses, and GDP, FGS, SEL, WT, ZK, DFM, and DY interpreted the data. FGS and SG drafted the report with input editing from GDP, SEL, DFM, WT, ZK, and DY.

#### BALTI-2 study group

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#### Conflicts of interest

FGS and GDP have received an investigator-led research grant from GlaxoSmithKline. GDP and DFM have consulted for, sat on advisory boards for, and received lecture fees from GlaxoSmithKline, and have received lecture fees from AstraZeneca for educational meetings (all unrelated to  $\beta$  agonists). All other authors declare that they have no conflicts of interest.

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