RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

BETA-2-AGONIST FOR THE TREATMENT OF ACUTE LUNG INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Balwinder Singh, MD[1], Akhilesh Kumar Tiwari, MD, DNB[2], Kuljit Singh, MD, FRACP[3], Shannon K Mommer[4], Adil Ahmed, MBBS[1], Patricia J Erwin[5], Pablo Moreno Franco, MD[1, 6]

1. Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN

2. Department of Anesthesia and Critical Care, National University Hospital, Singapore

3. Department of Cardiology, Division of Medicine Queen Elizabeth Hospital, Adelaide South Australia

4. Department of General Surgery, Mayo Clinic, Rochester, MN

5. Mayo Medical Libraries, Mayo Clinic, Rochester, MN

6. Department of Medicine, Division of Transplant Critical Care Service. Mayo Clinic, Jacksonville, Florida

Correspondence and Reprint Requests to:

Balwinder Singh, MD

Department of Medicine – Division of Pulmonary and Critical Care Medicine,

Mayo Clinic College of Medicine, Rochester, MN

200 1st Street S.W.

Rochester, MN 55905

E-mail: singh.balwinder@mayo.edu

Conflict of interest: None of the authors has any disclosures or conflict of interest.

Grant support: None

Location of study: The study was performed at Mayo Clinic, Rochester, MN, USA.

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

Abstract

Background: The use of beta-2 agonist as an intervention for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) patients is controversial. Therefore, we performed a systematic review and meta-analysis of the published randomized controlled trials (RCT) using beta (β)-2-agonists to improve outcomes (mortality and ventilator free days) among patients with ALI/ARDS.

Methods: A comprehensive search of seven major databases (Ovid Medline In-Process and other non-Indexed citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus) for RCTs using β_2-agonists for ALI from their origin to March 2013 was conducted. The effect size was measured by relative-risk (RR) for dichotomous outcomes and mean-difference (MD) for continuous outcomes, with 95% confidence interval (CI). The statistical heterogeneity between the studies was assessed with the Cochran's Q test and I^2 statistic. The heterogeneity of >50% was considered significant for the analysis. Data analyses were performed using Review Manager Version 5.1. The Cochrane risk of bias tool was used to ascertain the quality of the included studies.

Results: Out of 219 studies screened, three RCTs reported mortality and ventilator-free days in 646 ALI/ARDS patients. Of the 646 patients, 334 (51.7%) received β_2-agonist and 312 (48.3%) received placebo. There was no significant decrease in 28-days and hospital mortality in the β_2-agonist group, RR (95% CI) were 1.04(0.50-2.16) and 1.22(0.95-1.56) respectively. The ventilator-free days and organ failure-free days were significantly lower for the ALI patients who received β2-agonists, MD= -2.19 days (95% CI=-3.68 to -1.99) and MD= -2.04 (95%CI= -3.74 to -0.35), respectively.

Conclusions: In patients with ALI/ARDS, β2-agonists were not only non-beneficial in improving the survival, but were harmful and increased morbidity (reduced organ-failure free days and ventilator-free days).. The current evidence discourages the use of β_2-agonist among ALI/ARDS patients.

Keywords: Acute lung injury (ALI); acute respiratory distress syndrome (ARDS); beta-2-agonist; outcomes; mortality; ventilator-free days

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

INTRODUCTION

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is characterized by the inflammation of the pulmonary vasculature resulting in increased vascular permeability, leading to non-cardiogenic pulmonary edema.[1] Beta (β)-2-agonist therapy has been traditionally considered to be beneficial in patients suffering from ALI/ARDS, because of the ability of β_2-agonists to promote salt and water transport by increasing intracellular c-AMP. Thereby, leading to improved alveolar fluid clearance (AFC).[2, 3] Impaired AFC in patients suffering from ALI has thought to contribute towards increasing mortality.[4] The other properties of β_2-agonists, which have been proposed to improve the outcomes in ALI patients, are their ability to improve the permeability of lung endothelium to proteins[5] and its anti-inflammatory properties.[6]

In a retrospective study conducted by Manocha et al.[7], inhaled β_2-agonists were found to be associated with shorter duration and low severity of ALI. However, the use of β_2-agonists as an intervention for ALI/ ARDS patients is controversial. Lack of consensus about using β_2-agonists in the treatment of ALI/ARDS patients represents one of the growing controversial issues in the critical care community.[6, 8-11] This challenging topic was addressed through the pathophysiological studies[12-15] and the randomized controlled trials (RCT)[16-18], investigating the potential role of β_2--agonists in the treatment of ALI/ARDS. However, two of the RCTs (aerosolized β-2 agonist for treatment of acute lung injury [ALTA] and β-agonist lung injury trial [BALTI]-2) were stopped before the conclusion on the account of futility and tolerability of the β_2-agonists in ALI/ARDS patients.[16, 17]

Therefore, we aimed to perform a systematic review and meta-analysis of the published RCTs, summarizing the current evidence, of use of beta-2-agonists on the outcomes (hospital mortality, 28-days mortality and ventilator free-days) among patients with ALI/ARDS.

Some of the results have been previously reported in the form of an abstract.[19]

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines for the meta-analysis.[20] The protocol for the systematic review and meta-analysis

has been registered with PROSPERO, registration number: PROSPERO 2012:CRD42012002616, available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002616.

Study eligibility and outcomes

The study eligibility criteria were-1) RCTs 2) β_2-agonists were compared against a control/placebo group, 3) reported a risk estimate or data from which it could be calculated and 4) reported following outcomes: mortality (hospital or 28-days mortality) and ventilator-free days. We did not include non-randomized controlled trials, cohort and case control studies in our meta-analysis.

The primary outcomes of our study were mortality and ventilator free-days. The secondary outcomes were organ failure-free days and adverse events. ALI and ARDS were defined as pressure of arterial oxygen to fractional inspired oxygen concentration (PaO2/FIO2) ratio of 300 mm Hg or less (for ALI) and 200 mm Hg or less (for ARDS) respectively, bilateral pulmonary infiltrates consistent with edema, and the absence of clinically evident left atrial hypertension, according to the American-European Consensus Conference Committee definition.[21] Ventilator-free days was defined as "the number of calendar days after patients started unassisted breathing until day 28 after randomization for patients who survived at least 48 consecutive hours after start of unassisted breathing".[22] Organ failure-free days were defined as "the number of days in the first 28 days after randomization that the patient received no cardiovascular, renal, liver, or neurological support".[23]

Search strategy

A comprehensive search of several databases from their origin to March 2013 (any language, any population) was conducted. The databases that were searched included: Ovid Medline In-Process and other non-Indexed citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus. The search strategy was designed and conducted by an experienced librarian (PJE) with input from the study's principle investigator (BS). Controlled vocabulary supplemented with keywords was used to search for studies using beta-2-agonist for ALI/ARDS. Two reviewers independently identified the eligible studies and extracted data. For additional information, the study authors were contacted by e-mail. The references of eligible articles, abstracts of major congresses/conferences of Pulmonary and Critical Care Medicine (Society of Critical Care Medicine, American Thoracic Society, International

Symposium on Intensive Care and Emergency Medicine, and European Society of Intensive Care Medicine) were hand searched, to minimize the publication bias.

The databases of ongoing clinical trials (e.g. http://www.controlled-trials.com/ or http://clinicaltrials.gov/) were also searched to identify potential eligible studies. The search strategy has been added as an online appendix.

Study selection

Study selection was done by two reviewers (AA and BS) independently in two phases. First, articles were screened on the basis of title and abstracts. Next, eligible articles were reviewed in full and selected according to the study eligibility criteria. The agreement between the two reviewers, was measured using Cohen's weighted kappa (κ) during both the phases.[24] Any disagreement was solved by mutual consensus in the presence of a third investigator (PMF).

Data Extraction

Two reviewers (BS and PMF), independently used standardized forms to abstract the data from all the eligible studies. The corresponding authors of eligible articles were contacted by e-mail to request for any missing data information. Following data was extracted from each study: author, country, publication year, number of patients, description of study participants, inclusion and exclusion criteria, dates of enrollment, severity of illness scores, use of β_2--agonist, outcome definition, adverse reactions (severe tachycardia leading to stoppage of the drug) by β_2-agonists, duration of follow-up and loss to follow-up.

Quality assessment

For the assessment of risk of bias in estimating the study outcomes, we used the Cochrane risk of bias tool.[25] Each study was assessed for: 1) adequate sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding for patient related outcomes and mortality, 5) incomplete outcome data addressed, 6) free of selective reporting, and 7) free of other bias. Two reviewers (BS and PMF) did the quality assessment for the study methodology, independently and in duplicate. . Any disagreement was resolved by mutual consensus in presence of the principal investigator.

Statistical analysis

Categorical variables were reported as frequency and proportion and continuous variables were reported as means ± standard deviation (SD) or medians with interquartile range (IQR). The effect size was summarized by the relative risk (RR) for mortality and mean difference for ventilator-free days, along with 95% confidence interval (CI). The statistical heterogeneity between the studies was assessed with the Cochran's Q test and I^2 statistic. A P-value <0.10 on the Cochran's Q test and an I^2 value of >50% suggest that the heterogeneity is beyond random error or chance.[26, 27] We used random DerSimonian and Laird (D–L) effects model for analysis[28], and graphically presented the results as forest plots. The heterogeneity >50% was considered significant for the analysis.[27] Cochrane risk of bias tool was used to ascertain the quality of the included studies, with each variable answered as high risk, low risk or uncertain.[25] Data analyses were performed using Review Manager Version 5.1.[29] P-value <0.05 was considered significant for all the analyses.

RESULTS

We identified 219 studies through various databases, of which 44 were excluded (duplicate studies). Another, 163 studies were excluded, as majority of them were found to be non-relevant (n= 99), not based on original research (n=59), non-RCTs (n=3) and study protocols (n=2). Twelve studies were included for the full text review, and of which three studies were finally included for the meta-analysis. Figure 1 depicts the complete flowchart for the selected studies. The interviewer agreement for study selection (from abstract and title) in phase-1 and complete article review in phase II were excellent, κ= 0.92 (95% CI= 0.80 - 1.00), and κ= 1.0 (95% CI= 1.0-1.0) respectively.

The three RCTs included 646 ALI/ARDS patients, of which 334 (51.7%) received β_2-agonist and 312 (48.3%) received placebo.[16-18] The detailed description of the included studies is given in the table 1. The three RCTs used salbutamol (albuterol) as the β_2-agonist and placebo as a control group. Two studies[16, 18] used intravenous form of salbutamol, whereas the third one[17] used the nebulized form during the trial, as a route of drug delivery. BALTI-1[18] and ALTA trials[17] included ALI patients in their study; however, BALTI-2[16] included only ARDS patients. ALTA and BALTI-2[16, 17] were multicenter trials, while the BALTI-1 was a single center study.[18]

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

Out of the three selected studies, two studies[16, 18] reported the 28-days mortality as an outcome. There was no significant decrease in 28-days mortality in the β_2-agonist group, RR (95% CI) was 1.04 (0.50 - 2.16). Significant heterogeneity was observed among the studies (I^2 = 83%). A post-hoc sub-group analysis was conducted to assess the between-study heterogeneity, based on the severity of ALI (ALI vs. ARDS). Sub-group analysis showed that there is a statistically significant difference in the 28-days mortality among the ARDS patients (RR= 1.47, 95% CI = 1.03, 2.08) as compared to the ALI patients (RR = 0.71, 95%CI= 0.44, 1.16) who were on β2-agonists (P=0.02), E Table 1. Although, this difference explains the significant heterogeneity in analysis. However, a small sample size of BALTI-1 study could be the reason behind the low 28-day mortality in ALI patients. Two studies[16, 17] reported the hospital mortality as an outcome. There was a trend towards higher hospital mortality in the patients who received β_2-agonists (RR = 1.22, 95% CI0.95-1.56) as compared to the placebo. However, it was not statistically significant, with no heterogeneity (I^2 = 0%). Figure 2 (A and B) shows the summarized evidence for the 28-days and hospital mortality, respectively.

All the studies[16-18] reported the ventilator-free days as an outcome; these were significantly lower for the patients on β_2-agonist as compared to placebo, the mean difference (95% CI) was -2.19 days (-3.68, -1.99), as shown in Figure 2C. Two studies[16, 17] reported the organ failure-free days as a secondary outcome, which were significantly lower in the patients who received β2-agonists as compared to placebo, mean difference of -2.04 days (95 % CI = -3.74, -0.35 days), I^2 =0% (Figure 2D).

Adverse events: Figure 3 (A, B and C) shows the major adverse events among the studies. The incidence of tachycardia (severe enough to stop/change the dose of medication) among patients who received β_2-agonists was significantly higher than the patients who received placebo, with the pooled risk ratios of 3.95 (95% CI, 1.41-11.06). We did observe moderate heterogeneity (I^2=44%). There was an increase in incidence of arrhythmias among the ALI patients who received β_2-agonists as compared to the patients who received placebo (RR=1.97, 95% CI = 0.70, 5.54). Significant heterogeneity was observed (I^2 = 61%, p=0.08), which could be explained by the differences in the severity of ALI and the route of drug administration (E Table 1). On sub-group analysis, there was a statistically significant difference in the arrhythmias among the ARDS patients (RR= 4.72, 95% CI = 1.38, 16.13) as compared to the ALI patients (RR = 1.41, 95%CI= 0.60, 2.17) who received β_2-agonist (P=0.04), E Table 1. The

arrhythmogenic effect of β-agonists was significantly higher in ALI patients who were given drug by IV route as compared to inhalational route. The ratio of relative risk for IV vs inhalational route was 3.57 (95% CI, 1.09, 11.67), which explained that the observed heterogeneity in the analysis. Two studies reported the heart rate variation on day 4 after the initiation of the β_2-agonists among the ARDS/ALI patients[17, 18]. There was no statistically significant mean difference in the heart rates on day 4 among the ARDS/ALI patients who received β_2-agonists or placebo.

Number needed to harm (NNH): The NNH for tachycardia and arrhythmias (severe enough to stop/change the dose of medication among patients who received β_2-agonists) were 11 (95 % CI = 8, 18) and 23 (95 % CI = 2, 38) respectively. In other words, 11 ALI patients need to be treated with β_2-agonists for one additional patient to have tachycardia. Twenty-three ALI patients need to be treated with β_2-agonists for one additional patient to have arrhythmias, in comparison to the ALI patients who received placebo.

Quality assessment: All the three studies were of high quality, with mostly low or unclear risk of biases. One study had an unclear risk of performance bias[17], and in two there was an uncertainty about the detection bias (ALTA and BALTI-1).[17, 18] The detailed quality assessment of the included studies is shown in Table-2.

DISCUSSION

ALI and ARDS are associated with non-cardiogenic pulmonary edema, and a number of pharmacological modalities have been proposed at various stages to manage these patients.[9, 30-35] In spite of all the recent advances, the mortality remains high at 30-40% or more.[36, 37] There has been an interest in the role of β_2-agonists in managing patients with ALI and ARDS. We performed a literature search and meta-analysis of the available literature, to assess the efficacy and role of β_2-agonists in improving the outcomes among patients with ALI/ARDS. Results from this meta-analysis confirm the inability of β_2-agonists in providing any benefit for ALI patients in term of mortality and ventilator free-days. Thus, adding to the list of drugs such as aspirin and statins that initially showed promise but failed to live up to the expectations.[38, 39]

In the present literature review and meta-analysis, our evidence established that the β_2-agonists were not only non-beneficial in improving the survival, but were harmful among the patients with ALI/ARDS. β_2-agonists increased morbidity (reduced organ-failure free days and ventilator-free days) and thus, added to the cost of hospitalization. Critical illness is a strong stimulator of sympathetic drive in itself, which leads to rise in the catecholamine levels.[40] Catecholamine induced myocardial stunning can reduce stroke volume and cause hypo-perfusion of various organs. Beta agonists may further accentuate the harmful effects on the cardiovascular system; excessive sympathetic drive demonstrates its harmful effects systemically and due to its arrhythmogenic properties.[41] High catecholamine levels may lead to venous and arterial thrombosis. In addition, beta stimulation can cause lactic acidosis and hypokalemia and its related effects on various systems such as ventricular arrhythmias which can be life threatening.[41-43] Beta agonists increases myocardial oxygen demand and may have a detrimental effect in the hypoxic ALI patients, and leading to increased organ failure days and lengthening the stay on the ventilator.[8, 16] Thus, the side effects of β-agonists can outweigh its benefits when it is used in a critically ill patient. The risk of arrhythmia was higher in ARDS patients as compared to ALI patients, and if the β_2-agonists were given by IV route as compared to the inhalation route. The risk of severe tachycardia (to stop or modify the dosage of medication) was almost four times higher in the patients on beta-agonist as compared to those who received placebo. The safety profile of the beta-agonist raises lot of questions on the use of β_2-agonists in the trials and as a treatment option for the critically ill ALI patients.[8]

BALTI-1 was the first phase II randomized, double blind, placebo controlled single center trial, conducted to assess the efficacy, tolerability and safety of the intravenous β_2-agonists in adult patients with ALI, to enhance the resolution of pulmonary edema.[18] Intravenous salbutamol was used in a dose of 15 µg/kg/hr among 40 patients with ALI for 7 days. The results of this study suggested that the use of salbutamol could reduce extravascular lung water (EVLW). BALTI-1 was one of the first human studies, which evaluated the role β_2-agonist had on lung water.[18] However, there was no statistically significance difference in the 28-days mortality ($p = 0.4$), among the β_2-agonist and placebo group. A rise in the heart rate at day 4 was observed among the salbutamol group (103 ± 22) as compared to placebo group (88 ± 16) in the BALTI study ($p=0.06$). In addition, five patients on salbutamol had new onset of supraventricular tachycardia as compared to the two patients in the control group ($p=0.2$), requiring dose adjustment.[18]

ALTA was a randomized, double-blinded, placebo-controlled, multicentre trial, wherein, nebulized albuterol was compared against the placebo, in patients with ALI, with ventilator–free days as the primary outcome.[17] The aerosolized route was used in ALTA[17], as the role of aerosolized route of β-2 agonist has been shown to reduce pulmonary edema.[5] The other potential benefits of this route are improved mucociliary clearance, improved respiratory mechanics and decrease in the work of breathing.[5] The ALTA trial was aimed at including 1000 patients; however, the Data Safety and Monitoring Board terminated the study after recruiting only 282 patients on the ground of futility, as the ventilator–free days difference was unfavorable and above the futility limit (-0.4 days) among the albuterol group (-2.2 days). The other variables studied in this RCT[17] were mortality and organ failure-free days among the ALI patients, however, no significant benefits were observed even in these clinical outcomes. The only benefit which albuterol offered according to this study was in the ICU free days (-2.7 days, 95% CI= -4.9 to -0.4). The authors of this RCT[17] suggested that β_2-agonist does not improve the clinical outcomes and thus, use of β_2 agonist cannot be recommended in mechanically ventilated patients with ALI diagnosis.

Following the ALTA trial[17], another trial, BALTI-2[16] was conducted by the investigators of the BALTI-1. The BALTI-2 trial was a randomized, double blind, placebo-controlled multicentre (46 centers) trial, conducted among the ARDS patients to assess the 28-days mortality.[16] The BALTI-2 trial was an extension of BALTI-1, where intravenous salbutamol (15 μg/kg/h) was used. The target sample size for this trial was to recruit 1334 ARDS patients. However, recruitment was stopped after the second interim analysis on the recommendation of the Data Monitoring and Ethics Committee, due to significant adverse effect of salbutamol on 28-day mortality (RR=1.55, 95% CI = 1.07, 2.24). For every 9 (95%CI 5-101) patients with ARDS that were treated with salbutamol, one additional death was observed. This led to the early termination of the BALTI-2 study. Furthermore, the treatment with intravenous salbutamol was poorly tolerated among the ARDS patients, thus worsening the outcomes. Patients had to ventilated for a longer duration (-2.7 days, 95% CI= -4.7 to -0.7) in the salbutamol group as compared to the placebo group. The incidence of tachycardia sufficient to stop treatment among the study group was almost ~12 times higher in the salbutamol group as compared to the placebo group.[16] There was a higher incidence of new-onset arrhythmias (RR=4.75, 95% CI = 1.4, 16.2) in the ARDS patients treated with the salbutamol as compared to those who were treated with placebo.

Results of both BALTI and BALTI-2 should attract the attention of treating physicians towards the potential side effects, which the use of salbutamol may cause, and not be blinded towards the use of salbutamol with an aim of hypothetical benefit. The results of this meta-analysis further consolidates the findings that the use of β_2-agonist for the ALI or ARDS patients cannot be recommended, on the account of no benefit in mortality and worsening of outcomes. The safety profile of β_2-agonists in this study population makes this medication unsafe and thus, further studies cannot be recommended based on these results.

Strength and limitations- The main strength of our systematic review and meta-analysis is the comprehensive search of all major databases. To find all the possible studies and reduce publication bias, we hand-searched the abstracts and proceedings of the major pulmonary and critical care conferences. We contacted the corresponding authors of the studies to identify the missing data. We performed a post-hoc subgroup analysis, to explain the between-study heterogeneity based on the severity of ALI, by which we were able to explain the heterogeneity among the results.

Our meta-analysis has certain limitations. First, due to the small numbers of studies (only 3 RCTs), we could not assess the publication bias.[44] Even after detailed searching, we could not find any more articles. However, two of the three trials were multicenter studies, thus, strengthening the external validity of the study findings. Second, the inherent limitations of the definition of ARDS, due to the variability in chest radiograph interpretation and difficulty in excluding left atrial hypertension, lack of defining acute and the sensitivity of PaO2/FIO2 to different ventilator settings. Thus, the new consensus Berlin definition of ARDS was developed to address some of these concerns.[45] The Berlin definition of ARDS[45] may serve as a better model for designing new trials, to differentiate the categories of ARDS according to the severity and create uniformity among the trials and to help in better health care services planning. Third, using VFD as an outcome has its own limitation. Weaning strategies varies according to the institution and as per physicians or intensivists preferences. There is variability among the weaning practices across the globe, with recent trials focusing on using noninvasive mechanical ventilation for weaning, but there is still no consensus on that.[46] Ventilator free days, thus as an outcome may reflect more on the effectiveness of patients ICU care than the patients' underlying disease prognosis. Nevertheless, it

provides important information especially when the severity of disease is high such as in ARDS and can still be used as a reliable outcome. Lastly, these results are not applicable to the patients under the age of 13 years, as the studies with subject <13 years of age were not included in the analysis.

Conclusions: In patients with ALI/ARDS, administration of beta-2-agonist did not improve hospital or 28-days mortality. In addition, the patients on beta-2-agonists had to be ventilated for a longer duration, and had fewer organ failure-free days, as compared to placebo. The current evidence discourages the use of beta-2-agonist among ALI/ARDS patients.

Declarations of interest: None of the authors has any disclosure or conflict of interest.

Funding source-None

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

REFERENCES

1. Perina DG. Noncardiogenic pulmonary edema. Emerg Med Clin North Am 2003;21(2):385-393.
2. Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, et al. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 2002;346(21):1631-1636.
3. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002;82(3):569-600.
4. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163(6):1376-1383.
5. McAuley DF, Frank JA, Fang X, Matthay MA. Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent airspace fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury. Crit Care Med 2004;32(7):1470-1476.
6. Lee JW. beta2 adrenergic agonists in acute lung injury? The heart of the matter. Crit Care 2009;13(6):1011.
7. Manocha S, Gordon AC, Salehifar E, Groshaus H, Walley KR, Russell JA. Inhaled beta-2 agonist salbutamol and acute lung injury: an association with improvement in acute lung injury. Crit Care 2006;10(1):R12.
8. Bassford CR, Thickett DR, Perkins GD. The rise and fall of beta-agonists in the treatment of ARDS. Crit Care 2012;16(2):208.
9. Perkins GD, McAuley DF, Richter A, Thickett DR, Gao F. Bench-to-bedside review: beta2-Agonists and the acute respiratory distress syndrome. Crit Care 2004;8(1):25-32.
10. Papazian L. Con: beta2-adrenergic agonists in ALI/ARDS--not recommended or potentially harmful? Am J Respir Crit Care Med 2011;184(5):504-506.
11. Perkins GD, McAuley DF. Pro: beta-agonists in acute lung injury--the end of the story? Am J Respir Crit Care Med 2011;184(5):503-504.

12. Pesenti A, Pelosi P, Rossi N, Aprigliano M, Brazzi L, Fumagalli R. Respiratory mechanics and bronchodilator responsiveness in patients with the adult respiratory distress syndrome. Crit Care Med 1993;21(1):78-83.

13. Morina P, Herrera M, Venegas J, Mora D, Rodriguez M, Pino E. Effects of nebulized salbutamol on respiratory mechanics in adult respiratory distress syndrome. Intensive Care Med 1997;23(1):58-64.

14. O'Kane CM, McKeown SW, Perkins GD, Bassford CR, Gao F, Thickett DR, et al. Salbutamol up-regulates matrix metalloproteinase-9 in the alveolar space in the acute respiratory distress syndrome. Crit Care Med 2009;37(7):2242-2249.

15. Perkins GD, Nathani N, McAuley DF, Gao F, Thickett DR. In vitro and in vivo effects of salbutamol on neutrophil function in acute lung injury. Thorax 2007;62(1):36-42.

16. Gao Smith F, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W, et al. Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet 2012;379(9812):229-235.

17. Matthay MA, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, et al. Randomized, Placebo-controlled Clinical Trial of an Aerosolized beta(2)-Agonist for Treatment of Acute Lung Injury. Am J Respir Crit Care Med 2011;184(5):561-568.

18. Perkins GD, McAuley DF, Thickett DR, Gao F. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006;173(3):281-287.

19. Singh B, Erwin PJ, Moreno-Franco P. Beta-2-agonist in the treatment of acute lung injury: A meta-analysis (abstract). Crit Care Med 2012;40(12S):100-101.

20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

21. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818-824.

22. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 2002;30(8):1772-1777.

23. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299(6):646-655.

24. Cohen J. A Coefficient of Agreement for Nominal Scales Educational and Psychological Measurement Educ Psychol Meas 1960;20(April):37-46.

25. Higgins JP, Green S. (editors).Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-560.

27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-1558.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-188.

29. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

30. Mitaka C, Hirata Y, Nagura T, Tsunoda Y, Amaha K. Beneficial effect of atrial natriuretic peptide on pulmonary gas exchange in patients with acute lung injury. Chest 1998;114(1):223-228.

31. Jolliet P, Bulpa P, Ritz M, Ricou B, Lopez J, Chevrolet JC. Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in acute respiratory distress syndrome. Crit Care Med 1997;25(5):786-794.

32. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. Crit Care Med 2006;34(9):2287-2293.

33. Bosma KJ, Taneja R, Lewis JF. Pharmacotherapy for prevention and treatment of acute respiratory distress syndrome: current and experimental approaches. Drugs 2010;70(10):1255-1282.

34. Papazian L, Bregeon F, Gaillat F, Thirion X, Roch A, Cortes E, et al. Inhaled NO and almitrine bismesylate in patients with acute respiratory distress syndrome: Effect of noradrenalin. Eur Respir J 1999;14(6):1283-1289.

35. Cepkova M, Matthay MA. Pharmacotherapy of acute lung injury and the acute respiratory distress syndrome. J Intensive Care Med 2006;21(3):119-143.

36. Erickson SE, Martin GS, Davis JL, Matthay MA, Eisner MD. Recent trends in acute lung injury mortality: 1996-2005. Crit Care Med 2009;37(5):1574-1579.

37. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. Am J Respir Crit Care Med 2009;179(3):220-227.

38. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. Chest 2011;139(2):289-295.

39. Kor DJ, Erlich J, Gong MN, Malinchoc M, Carter RE, Gajic O, et al. Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. Crit Care Med 2011;39(11):2393-2400.

40. Cuesta JM, Singer M. The stress response and critical illness: a review. Crit Care Med 2012;40(12):3283-3289.

41. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev 2012;64(3):450-504.

42. Scheinin M, Koulu M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: a placebo-controlled dose-response study in healthy volunteers. Br J Clin Pharmacol 1987;24(5):645-653.

43. Stratakos G, Kalomenidis J, Routsi C, Papiris S, Roussos C. Transient lactic acidosis as a side effect of inhaled salbutamol. Chest 2002;122(1):385-386.

44. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53(11):1119-1129.

45. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526-2533.

46. Burns KE, Adhikari NK, Keenan SP, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev 2010(8):CD004127.

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

Figure legends:

Figure 1. The flow chart for the selection of the studies.

Figure 2. Outcomes in the acute lung injury/acute respiratory distress patients. A) Impact of the beta-agonist on the 28-day mortality. B) Impact of the beta-agonist on the hospital mortality. C) Impact of the beta-agonist on the ventilator-free days. D) Impact of the beta-agonist on the organ failure–free days

Figure 3. Adverse events due to intervention in the acute lung injury/acute respiratory distress patients. A) Tachycardia, B) Arrhythmias and C) Change in the heart rate due to beta-agonist at day 4 of randomization.

Table 2 Quality assessment of the included studies

ONLINE SUPPLEMENT:

E Table-1: Subgroup analysis to explore the sources of heterogeneity observed in the overall analysis

Appendix- Search strategy

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

Table 1. Characteristics of the included studies

Characteristics	BALTI-1, 2006		ALTA, 2011		BALTI-2, 2012	
	β_2-agonist	Placebo	β_2-agonist	Placebo	β_2-agonist	Placebo
Country	United Kingdom		United States		United Kingdom	
Settings	Single center		Multicenter: NHLBI ARDS Clinical Trials Network		Multicentre at 46 UK ICUS	
Study design	RCT		RCT		RCT	
Inclusion criteria	Mechanically ventilated adults (> or = 18 years) within 48 h of the onset ALI or ARDS were eligible for inclusion.		Intubated and receiving mechanical ventilation, have bilateral pulmonary infiltrates consistent with edema on frontal chest radiograph, have a ratio of PaO2 to FIO2 (fraction of inspired oxygen) of 300 or less		Intubated and mechanically ventilated patients (aged ≥16 years) within 72 h of ARDS onset. ARDS defined by AECC criteria	
Blinding	Double		Double		Double	
Route for intervention	intravenous		inhaled		intravenous	
Outcome (definition)	Extravascular lung water reduction in the salbutamol group at Day 7 by thermodilution.		The primary end point was the number of ventilator-free days from randomization to Day 28		The primary outcome was 28-days mortality. Secondary outcomes were mortality in the intensive-care unit or hospital before first discharge; ventilator-free and organ failure-free days	
PF ratio*	117 (49.5)	102.8 (36.8)	170 (84)	171 (75)	103.5 (36.8)	103.5 (36.8)
Age *	68.7 (16.0)	57.0 (14.7)	52 (16)	51±16	55.8 (17.2)	54.2 (17.5)
Number of participants	21	19	152	130	161	163
Male (%)	NA	NA	85 (56%)	72 (55%)	102 (63%)	110 (67%)
APACHE II score*	24.9 (6.4)	22.5 (6.5)	NA	NA	19·5 (6·2)	18·9 (6·7)
APACHE III score*	NA	NA	94.1 (28.7)	91.5 (29.6)	NA	NA
SAPS II score*	55.6 (15.1)	49.3 (14.7)	NA	NA	NA	NA
Lung injury severity score *	2.8 (0.7)	3.0 (0.4)	NA	NA	NA	NA
28 day mortality, n (%)	11 (58%)	14 (66%)	NA	NA	55 (34%)	38 (23%)
60 day mortality, n (%)	NA	NA	35 (23.0%)	23 (17.7%)	NA	NA
90 day mortality, n (%)	NA	NA	37 (24.3%)	24 (18.5%)	NA	
ICU mortality, n (%)	NA	NA	NA	NA	58 (36%)	45 (28%)
Mortality at hospital discharge, n (%)	NA	NA	35 (23%)	23 (17%)	62 (39%)	53 (33%)
Extravascular lung water at Day 7 (ml/kg/l)*	9.2 ±6	13.2± 3	NA	NA	NA	NA
Ventilator free days*	6.2 (8.9)	5.3 (8.6)	14.4 (11.1)	16.6 (10.3)	8.5 (8.8)	11.1 (9.3)
Organ failure free days*	NA	NA	14.2 (11.1)	15.9 (11.1)	16.2 (10.7)	18.5 (9.8)
Follow-up	28d	28d	90d	90d	Until discharged to a ward, or day 28.	
Lost to Follow up %	0	0	0	0	0	0

*=all the values are presented as mean and standard deviation

ALI=acute lung injury, ARDS= acute respiratory distress syndrome, APACHE = Acute Physiology and Chronic Health Evaluation; ICU= intensive care unit, NA=not available, NHLBI=the National Heart, Lung and Blood Institute, PF= PaO2 to FIO2 ratio, RCT=randomized controlled trial, SAPS=Simplified Acute Physiology Score

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

Table 2. Quality assessment of the included studies

	Quality assessment criteria	BALTI 1_2006_UK	ALTA_2011_USA	BALTI 2_2012_UK
1	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	1	1	1
2	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	1	1	1
3	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	1	0.5	1
4	Detection bias due to knowledge of the allocated interventions by outcome assessors	0.5	0.5	1
5	Attrition bias due to amount, nature or handling of incomplete outcome data	1	1	1
6	Reporting bias due to selective outcome reporting	1	1	1
7	Bias due to problems not covered elsewhere	0.5	0.5	1

Low risk of bias =1, High risk of bias= 0, unclear = 0.5

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

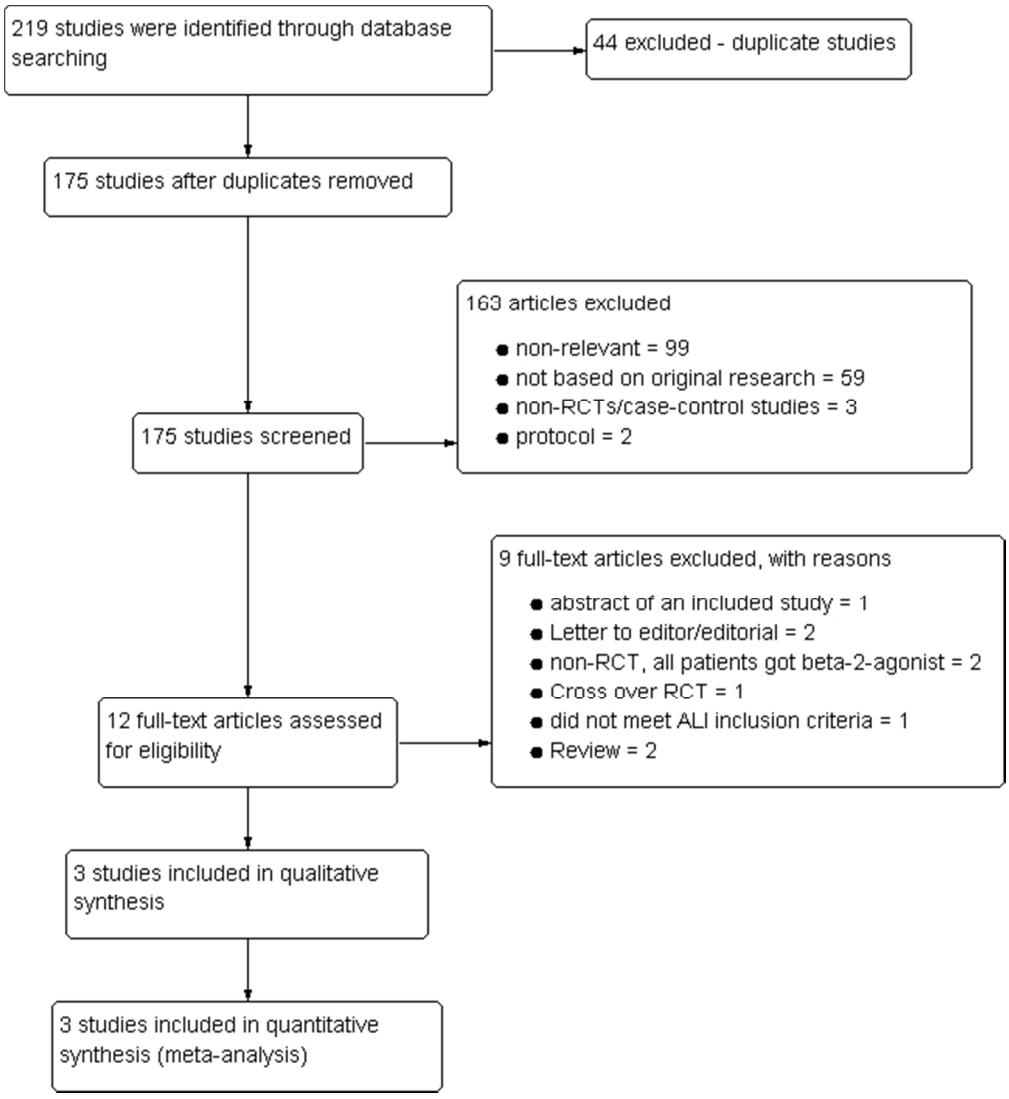

Figure 1. The flow chart for the selection of the studies.
54x59mm (300 x 300 DPI)

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

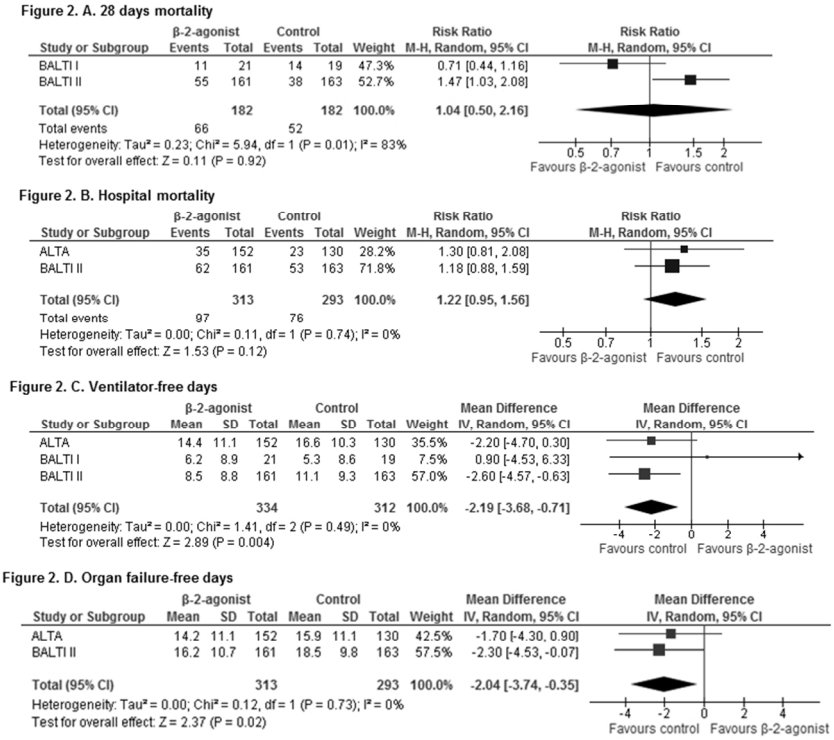

Figure 2. Outcomes in the acute lung injury/acute respiratory distress patients. A) Impact of the beta-agonist on the 28-day mortality. B) Impact of the beta-agonist on the hospital mortality. C) Impact of the beta-agonist on the ventilator-free days. D) Impact of the beta-agonist on the organ failure–free days
81x60mm (300 x 300 DPI)

RESPIRATORY CARE Paper in Press. Published on June 18, 2013 as DOI: 10.4187/respcare.02571

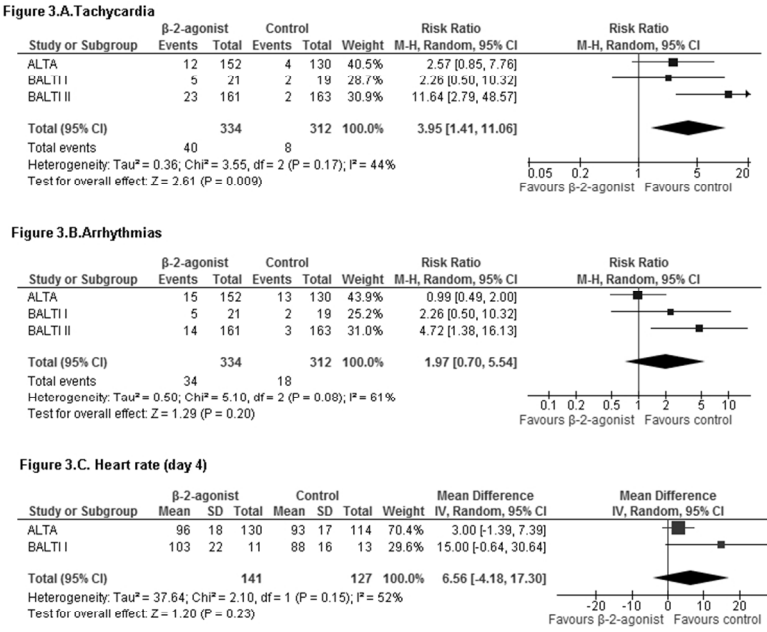

Figure 3. Adverse events due to intervention in the acute lung injury/acute respiratory distress patients. A) Tachycardia, B) Arrhythmias and C) Change in the heart rate due to beta-agonist at day 4 of randomization.

81x60mm (300 x 300 DPI)