Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma (Review)

Travers AH, Jones AP, Camargo Jr CA, Milan SJ, Rowe BH

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[Intervention Review]

Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

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ABSTRACT

Background

Inhaled beta$_2$-agonist therapy is central to the management of acute asthma. For rapid bronchodilation in severe cases, penetration of inhaled drug to the affected small conducting airway may be impeded, and the intravenous (IV) rather than inhaled administration of bronchodilators may provide an earlier response. IV beta$_2$-agonist agents and IV aminophylline may also be considered as additional interventions in this setting and this review compares IV beta-agonist agents and IV aminophylline in the treatment of people with acute asthma.

Objectives

To compare the benefit of IV beta$_2$-agonists versus IV aminophylline for acute asthma treated in the emergency department and in patients admitted to hospital with acute severe asthma.

Search methods

Randomised controlled trials (RCTs) were identified using the Cochrane Airways Group Register, which is compiled from systematic searches of bibliographic databases as well as handsearching of respiratory journals and conference abstracts. The latest search was run in September 2012. We searched bibliographies from included studies and known reviews were also searched. Primary authors and content experts were contacted to identify eligible studies.

Selection criteria

We included RCTs of patients who presented to the emergency department with acute asthma, and patients admitted to hospital with acute severe asthma, and were treated with IV beta$_2$-agonists versus IV aminophylline. Two review authors independently selected potentially relevant articles and selected articles for inclusion. Methodological quality was independently assessed using two scoring systems and two review authors.

Data collection and analysis

Data were extracted independently by two review authors. Missing data were obtained from authors or calculated from data present in the papers. Trials were combined using a random-effects model for odds ratios (OR) or mean differences (MD) and reported with 95% confidence intervals (95% CI).

Main results

Eleven studies met our inclusion criteria and in total they included 350 patients. However, opportunities to combine these studies in meta-analyses were limited by the variations in the range of outcomes reported in the trials.

Length of stay

Two studies reported length of stay. They were both paediatric trials (with one in paediatric intensive care unit), and there was no significant difference between the two groups (MD 23.19 hours; 95% CI -2.40 to 48.77 hours; 2 studies; N = 73). Individual separate MD analyses for the two studies also indicated no significant difference between the aminophylline and beta$_2$-agonist on this outcome. However, this finding should be interpreted with caution owing to the small number of trials and participants the analysis.

Pulmonary function

There were no significant differences in the sequential or summative pulmonary function demonstrated across the studies.

Heart rate

Data for serial heart rates were reported in three studies at various points from 15 to 60 minutes and in each case there were no significant differences between people in the IV aminophylline or beta$_2$-agonist groups. The difference between the two groups with respect to final heart rate was statistically significant (MD 10.00; 95% CI 0.99 to 19.01), although these data are from a single, small study and should be interpreted with caution.

Adverse effects

The analyses for giddiness (OR 59.22; 95% CI 2.80 to 1253.05; 1 study; N = 30), nausea/vomiting (where reported as a combined outcome) (OR 14.18; 95% CI 1.62 to 124.52; 2 studies; N = 96) and nausea (OR 6.53; 95% CI 1.60 to 26.72; 2 studies; N = 49) all significantly favoured beta$_2$-agonists. In view of the very small number of studies and number of patients contributing to these analyses these results should be interpreted with caution. A closely related review considering the possible benefits of adding IV aminophylline to beta-agonists in adults with acute asthma also indicates a higher incidence of adverse effects associated with IV aminophylline.

Authors' conclusions

In the included RCTs there was no consistent evidence favouring either IV beta$_2$-agonists or IV aminophylline for patients with acute asthma. The opportunity to draw clear conclusions is limited by the heterogeneity of outcomes evaluated and the small sample sizes in the included studies. It is recommended that these data should be viewed carefully alongside the conclusions from separate Cochrane reviews comparing IV beta$_2$-agonists plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone and IV aminophylline plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone.

PLAIN LANGUAGE SUMMARY

Intravenous beta$_2$-agonists and intravenous aminophylline for acute asthma

Beta$_2$-agonist and aminophylline drugs are used for the treatment of asthma and work by opening the airways to help people breathe more easily. Both drugs can be given intravenously (IV) (directly through a vein). The question this review considered was whether there was any important difference between these drugs for patients with acute asthma. This review examined all the randomised controlled trials comparing IV beta$_2$-agonists to aminophylline.

We found 11 studies involving 350 patients (157 children and 193 adults) with acute asthma. No consistent evidence favouring either IV beta$_2$-agonists or IV aminophylline was found from randomised trials of patients with acute asthma. It is recommended that these results should be viewed carefully alongside the conclusions from separate Cochrane reviews comparing IV beta$_2$-agonists plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone and IV aminophylline plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

IV beta-agonists compared to IV aminophylline for acute asthma

Patient or population: patients with acute asthma
Settings:
Intervention: IV beta-agonists
Comparison: IV aminophylline

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV aminophylline	IV beta agonists				
Length of hospital stay	Mean stay in the trial conducted in PICU was 106 h and in 57 h in the non-PICU study	Mean length of stay in the IV beta$_2$-agonist group was 23 h longer (-2.4 lower to 48.77 higher)	MD 23.19 h (-2.4 to 48.77)	73 (2 studies)	⊕⊕⊕◯ **moderate** [1]	
PEF **(L/min) at 60 min**	Mean PEF in the aminophylline group at 60 min was 145 L/min	Mean PEF (L/min) at 60 min in the IV beta$_2$-agonist group was **3.75 lower** (42.86 lower to 35.36 higher)	MD -3.75 (-42.86 to 35.36)	59 (2 studies)	⊕⊕⊕◯ **moderate** [2]	
FEV1 (L) at 60 min	Mean FEV1 in the aminophylline group was 0.94 L	Mean FEV1 (l L) at 1 h in the IV beta$_2$-agonist group was **0.09 lower** (0.26 lower to 0.08 higher)	MD -0.09 (-0.26 to 0.08)	59 (2 studies)	⊕⊕⊕◯ **moderate**[2]	

Heart Rate at 60 min	Mean heart rate in the aminophylline group was 111 bpm	Mean heart rate at 60 min in the IV beta$_2$-agonist group was **2.54 higher** (6.28 lower to 11.36 higher)	MD 2.54 (-6.28 to 11.36)	82 (3 studies)	⊕⊕◯◯ **low**[2,3]
Clinical failure [4]	**267 per 1000**	**271 per 1000** (127 to 486)	**OR 1.02** (0.4 to 2.62)	89 (2 studies)	⊕⊕⊕◯ **moderate**[2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
bpm: beats/min; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IV: intravenous; MD: mean difference; OR: odds ratio; PEF: peak expiratory flow rate; PICU: paediatric intensive care unit

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. A point was deducted for imprecision.
2. In the following outcomes PEF **(L/min) at 60 min, FEV1 (L) at 15 min, FEV1 (L) at 60 min, FEV1 (L) at 3 h** and c**linical failure:** a point was deducted for imprecision and clinical heterogeneity between the trials.
3. In **heart rate at 60 min:** a point was deducted in relation to the level of statistical heterogeneity among the three included trials (I^2 = 58%).
4. Clinical failure here refers to the number of patients in Tribe 1976 who considered their condition had not improved, and to the inverse of treatment success reported in Singhi 2011 (an abstract where no definition of treatment success was included).

BACKGROUND

Description of the condition

Every year over 10 million people experience an asthma exacerbation in the US (Krishnan 2006) and in the UK there were 65,732 hospital admissions for asthma between 2005 and 2006 (NHS 2011). The hospital admission rate is approximately 10% to 20% for people with acute asthma. In the 80% to 90% of people who are discharged from the emergency department (ED), there is a relapse rate of 10% to 20% within the following two weeks (Griswold 2005;Rowe 2008; Rowe 2010). In the last 20 years various national (e.g. NAEPP 1997; BTS 1998; Boulet 1999; EPR3 2007; BTS/SIGN 2012) and international (e.g. NHLBI/WHO 1995; GINA 2011) clinical guidelines providing guidance on the management of acute asthma have been published.

Description of the intervention

The investigation of the role of intravenous (IV) beta$_2$-agonists in the ED treatment of asthma and in patients admitted to hospital with acute severe asthma has developed since the 1980s. Evidence-based practice guidance available in North America and Europe has recommended inhaled beta$_2$-agonist therapy for all cases of asthma presenting to the ED (Beveridge 1996; Ernst 1996; Lipworth 1997; NAEPP 1997; GINA 2011; BTS/SIGN 2012) as well as systemic corticosteroids and inhaled ipratropium bromide in more severe cases. The use of aminophylline (methylxanthine treatments more generally) in the treatment of asthma also has a long history. Worldwide, methylxanthines are used more than any other drug for asthma, and IV aminophylline has been used in the management of acute asthma despite the lack of evidence. The question of whether IV beta$_2$-agonists or IV aminophylline provide additional benefit to patients with acute asthma when given in addition to inhaled beta$_2$-agonist therapy is addressed in other Cochrane reviews (Travers 2012; Nair 2012) and we recommend that this review be considered in relation to those reviews.

How the intervention might work

Patients with acute asthma are conventionally treated with beta$_2$-agonist bronchodilators and corticosteroids. The use of inhaled aerosols delivers high drug concentrations to the affected airways, selectively treating the pulmonary system and reducing systemic adverse effects by minimising systemic drug levels (Dolovich 2005). There are a number of disadvantages of the inhaled route. First, specific inhalation techniques are necessary for the proper use of each type (e.g. nebulised aerosol, pressurised metered dose inhaler, dry powder inhaler). Second, inhaled aerosols may require longer durations of administration. Third, patients in acute respiratory distress may not be able to generate the necessary flow rates for drug delivery to the affected airways (Dolovich 2005). In this latter circumstance penetration of inhaled drug to the affected small conducting airways may be impeded by bronchospasm, mural inflammation, and impaction by mucous and other inflammatory products. In such cases, if bronchodilation occurs primarily in response to the systemic distribution of the drug, IV bronchodilators may produce an earlier clinical response compared to inhaled bronchodilators (Browne 1997). How methylxanthines work remains unclear, although the main cellular effects concern adenosine receptor blockade, the inhibition of a phosphodiesterase enzyme resulting in the accumulation of cyclic adenosine monophosphate (AMP) and the translocation of calcium. Traditionally, xanthines have been associated with weak bronchodilation; however, the effect of theophylline on airway inflammation in asthma may be beneficial (Nair 2012).

Why it is important to do this review

IV beta$_2$-agonists are sometimes used in patients unresponsive to inhaled bronchodilators and systemic corticosteroid therapy, or if the inhaled route is not practical for the patient (Beveridge 1996; Ernst 1996; Lipworth 1997; NAEPP 1997). However, uncertainties regarding the benefit of this route of delivery remain, and there are safety concerns with the intravenous route (Putland 2006; Rowe 2006). An earlier Cochrane review including this comparison (Travers 2001) concluded that "There is no evidence to support the use of IV beta$_2$-agonists in patients with severe acute asthma. These drugs should be given by inhalation. No subgroups were identified in which the IV route should be considered." The Cochrane review by Nair 2000, which is currently being updated, concluded that "in acute asthma, the use of IV aminophylline did not result in any additional bronchodilation compared to standard care with beta-agonists. The frequency of adverse effects was higher with aminophylline. No subgroups in which aminophylline might be more effective could be identified. These results should be added to consensus statements and guidelines". The current version of this review aims to compare IV beta$_2$-agonists to IV aminophylline in severe acute asthma with the inclusion of relevant randomised controlled trials (RCTs).

A separate review is available in *The Cochrane Library* for "Continuous versus intermittent beta-agonists for acute asthma" (Camargo 2011). At the time of writing, reviews evaluating the benefit of adding IV beta$_2$-agonists or IV aminophylline to standard care for acute asthma are in preparation and will be published in *The Cochrane Library* in 2012 (Nair 2012; Travers 2012). We recommend that the conclusions from this review be considered in conjunction with those reviews.

OBJECTIVES

To determine the comparative effectiveness of IV beta$_2$-agonists compared to IV aminophylline in the treatment of patients with acute asthma who present to the ED and in patients admitted to hospital with acute severe asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs.

Types of participants

We included studies of adults and children with severe acute asthma presenting to an ED (or its equivalent) and patients admitted to hospital with acute severe asthma.

Types of interventions

The target intervention was the administration of IV beta$_2$-agonists and IV aminophylline. We compared IV beta$_2$-agonists and standard of care (e.g. inhaled bronchodilators, corticosteroids, etc.) with IV methylxanthines and standard care.

Types of outcome measures

Primary outcomes

1. Hospital admission.
2. Length of hospital stay.

Secondary outcomes

1. Pulmonary function.
2. Vital signs.
3. Arterial blood gas measurement.
4. Adverse effects.
5. Evidence-based asthma severity/clinical scores.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR) of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (Appendix 1 gives full details of sources and search methods). All records in the CAGR coded as 'asthma' were searched using the terms in Appendix 2. We also conducted a search of ClinicalTrials.gov using the terms in Appendix 2. All databases were searched from their inception to the present and there was no restriction on language of publication. The searches were carried out in November 2011 and updated in September 2012.

Searching other resources

Inquiries regarding other published or unpublished studies known or supported by the authors of the primary studies were made so that these results could be included in this review. Several pathways were used to locate authors including letters to an address presented in the article, internet 'People and Hospital Searches', electronic author searches in library databases for the address on the most recent article published by the author and contact with other reviewers on the ARG. Scientific advisors of the various pharmaceutical companies (GlaxoSmithKline) that manufacture beta$_2$-agonists were contacted for any unpublished, published or interim results on beta$_2$-agonist research. Personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies. We also checked the bibliographies of included papers for additional RCTs.

Data collection and analysis

Selection of studies

The reference lists from the search strategy was independently reviewed by two review authors (AHT, SJM), and clearly irrelevant articles were discarded. If the title, abstract or descriptors suggested any potential relevance, the full-text article was retrieved. Each relevant paper was then assessed by two independent review authors (SJM, AHT) for inclusion in this review. The review authors were not blinded to the authors, journal of publication or results of the studies as investigator bias was deemed unlikely. Disagreement would have been resolved by consensus or third party adjudication (CC).

Data extraction and management

Data for the trials were independently extracted by two review authors (AHT, SJM) and entered by SJM into The Cochrane Collaboration software program, Review Manager 5.1 (RevMan 2011). In cases where tables were unavailable, graphs were enlarged and values were approximated. This technique was required for three studies (Tribe 1976; Johnson 1978; Hambleton 1979).

Assessment of risk of bias in included studies

The risk of bias of included studies was assessed using The Cochrane Collaboration's risk of bias methodology (Chapter 8 of the *Cochrane Handbook of Systematic Reviews of Interventions*; Higgins 2011). Two review authors (AHT and SJM) assessed the risk of bias for all included studies with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each item was assessed as high, low or unclear risk of bias along with relevant information reported in the RCT.

Measures of treatment effect

One review author (SJM) entered data into Review Manager (RevMan 2011).
For dichotomous variables, data were expressed as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the patient.

Dealing with missing data

We planned to contact authors if outcome data or information on trial design were missing, but this issue did not arise.

Assessment of heterogeneity

Heterogeneity was using a Chi^2 test (P value < 0.10 denoted significant heterogeneity) but interpreted with caution owing to the low power associated with this test. The I^2 statistic was also considered and interpreted in relation to the following guidance (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We planned to examine publication bias by visual inspection of funnel plots, if there had been an adequate number of trials aggregated in the analyses (10 or more). However, it is recognised that an asymmetrical funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and is therefore not necessarily a reflection of publication bias (Higgins 2011).

Data synthesis

All trials were combined using RevMan 2011 software. For continuous variables, random-effects MD and 95% CI were calculated for each study. For dichotomous variables, random-effects OR with 95% CI were calculated for individual studies. All similar studies were pooled using random-effects OR or MD and 95% CIs.

Subgroup analysis and investigation of heterogeneity

We planned that for those main outcome measures with statistical heterogeneity, a priori subgroup analyses would be divided on the following basis:

1. population: adult versus paediatric;
2. co-intervention with inhaled $beta_2$-agonists;
3. type of $beta_2$-agonist.

Sensitivity analysis

Sensitivity analyses were planned on the statistical method of analysis (random versus fixed effects) in the event of high levels of heterogeneity; however, the paucity of available data from the trials provide an opportunity to pursue this objective, and random-effects analyses were used throughout.

RESULTS

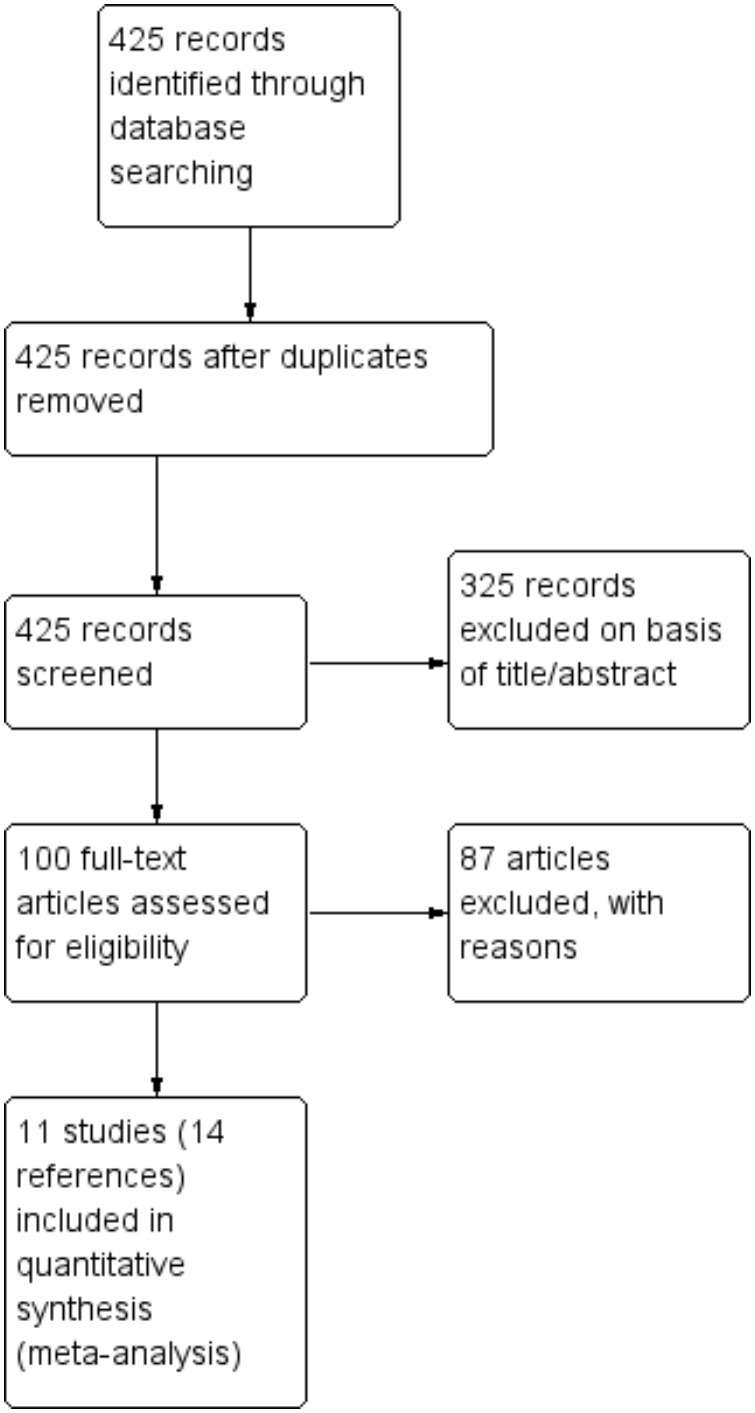
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The database searches retrieved a total of 425 references. After independent screening of titles and abstracts and retrieval of full-text papers, we identified 11 unique studies (14 references) for inclusion in the review, and 86 studies were excluded (Figure 1). The latest search was run in September 2012.

Figure 1. Study flow diagram.



Included studies

Only 11 studies (350 patients) met our inclusion criteria: Evans 1980 (13 patients), Femi-Pearse 1977 (32 patients), Hambleton 1979 (18 patients), Johnson 1978 (39 patients), Roberts 2003 (44 patients), Sharma 1984 (20 patients), Singhi 2011 (66 patients), Spiro 1976 (30 patients), Tribe 1976 (39 patients), Wheeler 2005 (29 40 patients) and Williams 1975 (20 patients). Four papers (36%, 4/11) were paediatric studies evaluating patients with severe acute asthma (157 patients): Hambleton 1979 (18 patients), Roberts 2003 (44 patients), Singhi 2011 (66 patients) and Wheeler 2005 (29 patients), with one study (Wheeler 2005) conducted with children requiring admission to the intensive care unit (ICU). The citations Hambleton 1979, Roberts 2003 and Singhi 2011 had limited opportunities for aggregating data owing to variations in the outcomes measures reported.

Seven papers (64%, 7/11) focused on adults of variable asthma severity (193 patients) (Williams 1975; Spiro 1976; Tribe 1976; Femi-Pearse 1977; Johnson 1978; Evans 1980; Sharma 1984). In four, the specific focus was on patients with acute severe asthma (Williams 1975; Femi-Pearse 1977; Johnson 1978; Evans 1980). Too few studies with sufficient similar outcomes limited any meaningful comparisons between papers. A summary of the included trials is provided in Table 1.

Excluded studies

Eighty-six studies failed to meet the eligibility criteria of this review. Forty-one (47%) were non-randomised, 21 (24%) used epinephrine (adrenaline), eight (9%) compared IV beta$_2$-agonists versus inhaled beta$_2$-agonists, three (3%) compared IV beta$_2$-agonists versus placebo, three (3%) were with patients with stable asthma, two (2%) were conducted in the laboratory setting rather than the ED or hospital, two (2%) were reviews, two(2%) used subcutaneous beta$_2$-agonists rather than IV beta$_2$-agonists, one (1%) evaluated the addition of IV aminophylline to inhaled beta$_2$ agonists, one (1%) compared IV terbutaline versus IV atrial natriuretic factor, one (1%) compared IV aminophylline versus nebulised isoproterenol and one (1%) compared IV salbutamol versus nebulised ipratropium. The reasons for their exclusion are given in the Characteristics of excluded studies table.

Risk of bias in included studies

Complete information on the risk if bias judgements can be found in the Characteristics of included studies table. Figure 2 and Figure 3 show graphical representations of our judgements across studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

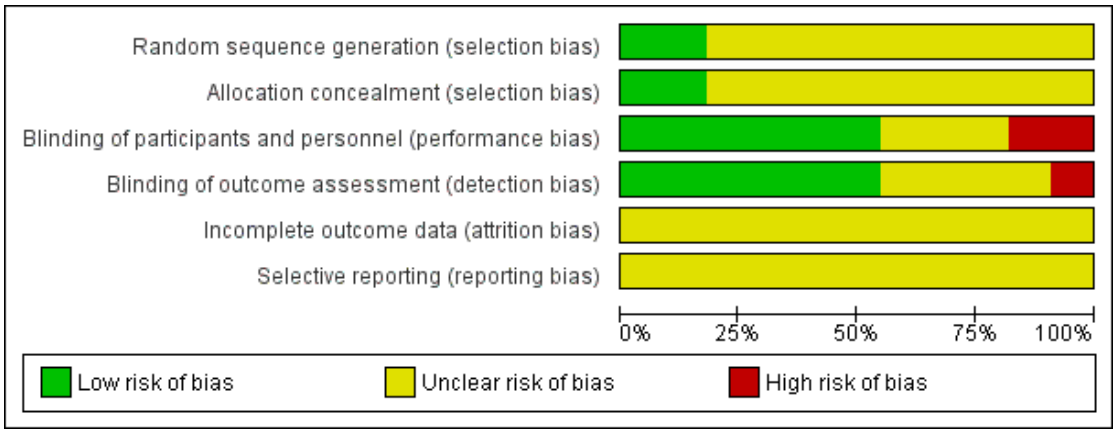
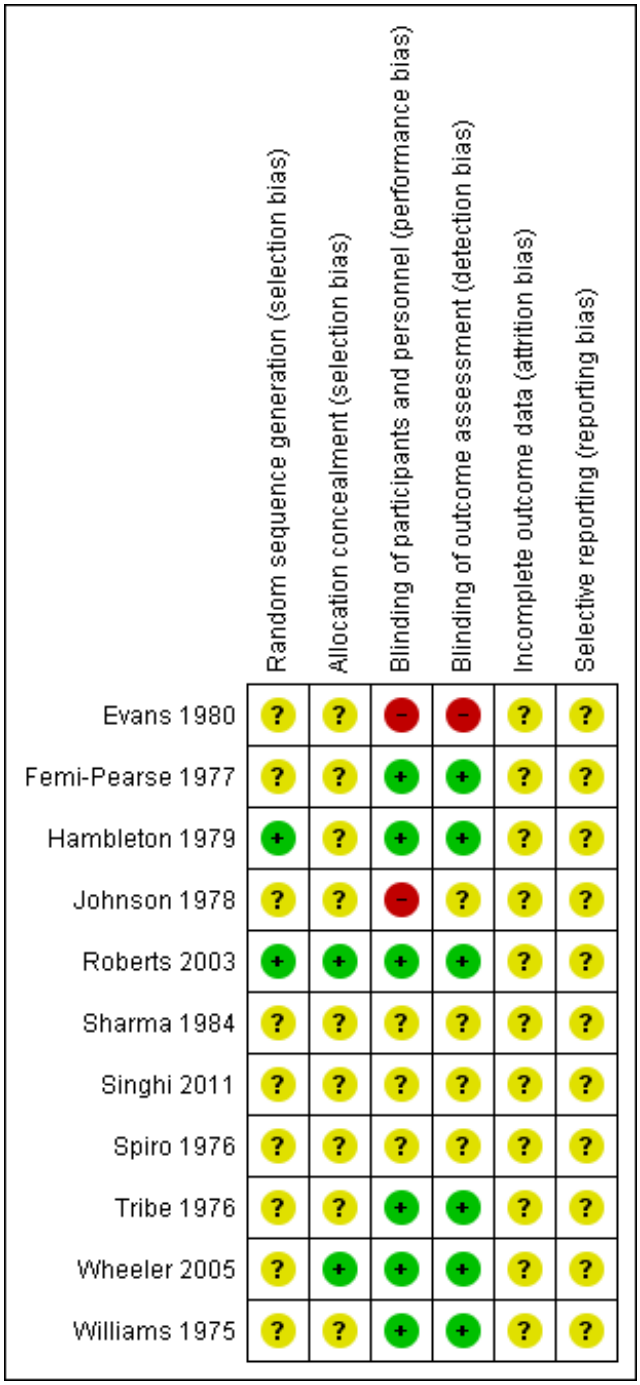


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only two of the 11 included studies (18%) were assessed as low risk of selection bias (Hambleton 1979; Roberts 2003). In the remaining nine (82%) the risk of bias was judged to be unclear.

Blinding

Six of the 11 included (54%) studies were low risk of performance and selection bias (Williams 1975; Tribe 1976; Femi-Pearse 1977; Hambleton 1979; Roberts 2003; Wheeler 2005). In the remaining five (46%) the risk of bias was considered as unclear in three (27%) (Spiro 1976; Sharma 1984; Singhi 2011) and high in the remaining two (19%, 2/11) (Johnson 1978; Evans 1980).

Incomplete outcome data

In all 11 included studies reporting bias was judged to be unclear. As these trials are very short we evaluated trials where no patients were reported as having been withdrawn to be at no higher risk of bias than those where several failed to complete the trial; in acute asthma trials it is conceivable that all participants will complete the trial.

Selective reporting

In each of the 11 included studies reporting bias was judged to be unclear. There was no apparent indication of selective reporting in any of the trials. However, it was disappointing that no trials reported data for hospital admissions.

Effects of interventions

See: **Summary of findings for the main comparison** IV beta-agonists compared to IV aminophylline for acute asthma

Hospital admissions

None of the 11 studies reported a comparison between beta$_2$-agonists and aminophylline groups with respect to hospitalisation.

Length of hospital stay

Two studies reported length of stay (Roberts 2003; Wheeler 2005). They were both paediatric trials (with one in a paediatric ICU; Wheeler 2005), and are combined in Analysis 1.1. There was no significant difference between the two groups (MD 23.19; 95% CI -2.40 to 48.77; 2 studies; N = 73). Individual separate MD analyses for the two studies also indicated no significant difference between the aminophylline and beta$_2$-agonist on this outcome. However, this finding should be interpreted with caution owing to the small number of trials and participants.

Pulmonary function

In the two papers (Williams 1975; Johnson 1978) reporting peak expiratory flow (PEF) (L/min) over various time points up to 120 minutes, no statistical differences in PEF were identified between IV beta$_2$-agonists and IV methylxanthines (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6).

Two trials (Johnson 1978; Sharma 1984) reported forced expiratory volume in one second (FEV1). In three analyses covering the periods 15 minutes, one hour and three hours there were no significant differences between IV beta$_2$-agonists and IV methylxanthines (Analysis 1.7; Analysis 1.8; Analysis 1.9).

Evans 1980 reported PEF outcomes that we were unable to aggregate in the meta-analysis: time to 50% of maximum PEF (MD 5.00; 95% CI -24.15 to 34.15), time to maximum PEF (MD 2.00; 95% CI -8.02 to 12.02) and convalescent PEF (MD -35.00; 95% CI -394.04 to 324.04). In each case there was no significant difference between the IV aminophylline or beta$_2$-agonist groups and Femi-Pearse 1977 found no difference in PEF change scores between the salbutamol and aminophylline groups in the double-blind comparison included in their trial report. In Spiro 1976 FEV1, forced vital capacity (FVC) and PEF improved in both the salbutamol and aminophylline groups within the first hour of treatment and there was no significant difference between the two groups on these outcomes.

Arterial blood gas measurements

Two papers (Johnson 1978; Williams 1975) reported arterial blood gas measurements for oxygen tensions and carbon dioxide tensions. There was no statistical difference between IV beta$_2$-agonists and IV aminophylline in either the arterial oxygen tension (Analysis 1.10), or carbon dioxide tension (Analysis 1.11). However, there was a significant difference in diastolic blood pressure at 60 minutes between IV beta$_2$-agonists and IV aminophylline groups (MD -6.85; 95% CI -13.58 to -0.11) (Analysis 1.17). Two studies (Williams 1975; Johnson 1978) indicated a significantly higher level in the IV aminophylline group, although the considerable level of heterogeneity between the two trials in this analysis (I^2 = 55%) indicates that this result should be interpreted with caution as a clear effect was observed only in Williams 1975.

Heart rate

Three trials with 98 participants (Williams 1975; Tribe 1976; Johnson 1978) reported serial heart rate data at various points from

15 to 60 minutes (Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15) and in each case there were no significant differences between the IV aminophylline or beta$_2$-agonist groups. However, the difference between the two groups with respect to final heart rate was significant (MD 10.00; 95% CI 0.99 to 19.01) (Analysis 1.16). The single study contributing to this analysis (Johnson 1978), indicated a higher rate in the salbutamol arm, although this should be viewed with caution as the trial has a modest sample size (39 patients) and the significance level is marginal.

Two additional trials reported heart rate data that could not be incorporated in these analyses. Spiro 1976 reported significantly higher heart rates in the salbutamol group compared to the aminophylline group, whereas Femi-Pearse 1977 reported no difference in pulse rate between the salbutamol and aminophylline groups. However, in Hambleton 1979 there was a significantly higher level of tachycardia in the salbutamol group than in the aminophylline group.

Adverse effects

The following adverse effects are reported as subgroups in Analysis 1.19. Data from five studies were reported relevant to at least one of the following: anxiety, creatine phosphokinase (CPK) elevation, CPK-MB elevation, dysrhythmia, giddiness, headache, hyperglycaemia, hypokalaemia, local pain at injection site, numbness, palpitation, perspiration, tremor, ventricular extrasystoles, nausea, nausea/vomiting (where reported as a combined outcome) and vomiting (Williams 1975; Tribe 1976; Sharma 1984; Wheeler 2005; Singhi 2011).

The analyses for giddiness (OR 59.22; 95% CI 2.80 to 1253.05; 1 study; N = 30), nausea/vomiting (where reported as a combined outcome) (OR 14.18; 95% CI 1.62 to 124.52; 2 studies; N = 96) and nausea (OR 6.53; 95% CI 1.60 to 26.72; 2 studies; N = 49) all significantly favoured beta$_2$-agonists. In view of the very small number of studies and patients, contributing to these analyses, these results should be interpreted with caution. There were no other significant differences in terms of the other adverse events between the two treatments (Analysis 1.19). When the data were examined in a secondary fixed-effect analysis it was revealed that there was a significantly higher incidence of palpitations in the group receiving IV beta$_2$-agonists, although this effect was seen in just one (Sharma 1984) of three trials, with another trial (Wheeler 2005) reporting an absence of palpitation in both conditions. The third trial (Tribe 1976) reported no incidence of palpitations in the 10 participants in the aminophylline group and only one case in the 11 participants in the beta$_2$-agonist group. It is also noted that the level of heterogeneity in the palpitations analysis was considerable (I^2 = 56%) (Analysis 1.19).

An additional trial reported adverse effects but not in a format that could be combined; Roberts 2003 reported that nausea, vomiting and abdominal pain were the most frequently observed adverse events; however, they reported no significant differences between the salbutamol and aminophylline groups.

Asthma severity score: clinical failure

Two trials with 105 participants reported clinical failure in a format that could be included in a meta-analysis (Tribe 1976; Singhi 2011). There was no significant difference between IV beta$_2$-agonists and IV aminophylline on this outcome (OR 1.02; 95% CI 0.40 to 2.62; 2 trials; N = 105) (Analysis 1.18). In Singhi 2011 treatment success was defined as a Clinical Asthma Severity Score of 4 or greater at the end of one hour. Treatment failure, in this review, was taken as Clinical Asthma Severity Score below 4 in this trial.

In a trial with 44 adults, a comparison of the asthma severity score at two hours revealed no significant difference between the IV beta$_2$-agonists and IV aminophylline groups (Roberts 2003). However, the requirement for supplementary oxygen was significantly longer in the salbutamol group and it is noted that in Wheeler 2005, a paediatric ICU study, the length of time to achieve a Becker Clinical Asthma Score of 3 or less was significantly shorter (MD 27.40; 95% CI 9.44 to 45.36) in the methylxanthine group.

DISCUSSION

Summary of main results

This systematic review used high-quality methods to identify trials of the comparative effectiveness of IV beta2-agnosts compared to IV aminophylline. From 11 trials, 350 patients were enrolled and the results failed to identify a clear benefit of one treatment over the other. There was little opportunity for statistically aggregating the RCTs in this review comparing IV beta$_2$-agonists and IV methylxanthines. Data were available from only two trials for length of stay (Roberts 2003; Wheeler 2005), and both were paediatric trials. There was no significant difference between the two groups. However, it is recommended that this finding should be interpreted with caution owing to the small number of trials and participants in the analysis.

No statistical differences in PEF were identified between the two groups in a range of time points up to 60 minutes in the two small trials contributing to this outcome. PEF data from an additional three trials also found no significant difference. Similarly there were no significant differences between the two interventions in terms of reported FEV1.

Heart rate data from three small trials recorded at various points from 15 to 60 minutes also indicated no significant differences between IV aminophylline or IV beta$_2$-agonist treatments. However, there was a significant the difference between the two groups in terms of final heart rate (MD 10.00 beats per minute; 95% CI

0.99 to 19.01 beats per minute), although this finding should be interpreted with caution as it is based on a single study with only 39 patients. A further two trials reported heart rate data that could not be incorporated in these analyses. Spiro 1976 also reported significantly higher heart rates in the salbutamol group compared to the aminophylline group, whereas Femi-Pearse 1977 reported no difference in pulse rate between the salbutamol and aminophylline groups. The limited evidence available therefore points towards aminophylline as less likely to cause cardiac side effects.

The analyses for giddiness, nausea/vomiting (where reported as a combined outcome) and nausea all indicated a significantly higher incidence of adverse effects with aminophylline. However, in view of the very small number of studies, and number of patients, contributing to these analyses these results should be interpreted with caution. There were no other significant differences between the two groups (Analysis 1.20).

Overall completeness and applicability of evidence

The limited opportunity for statistical aggregation in this review limits the conclusions that can be drawn from these data. Overall, the general impression is that neither treatment emerges as clearly and consistently superior in the treatment of acute asthma.

This systematic review has found 11 studies that span 37 years in total: 54% (6/11) published between 1970 and 1979 (Williams 1975; Spiro 1976; Tribe 1976; Femi-Pearse 1977; Johnson 1978; Hambleton 1979;); 18% (2/11) between 1980 and 1989 (Evans 1980; Sharma 1984); 18% (2/11) between 2000 and 2009 (Roberts 2003; Wheeler 2005) and 9% (1/11) between 2010 and the time of this review (Singhi 2011). Consequently, since the evidence-based standards of care have changed dramatically over the course of these four decades, drawing meaningful conclusions from the systematic review proves difficult. These standards not only apply to the acute-phase management of severe acute asthma, but also the controller or prophylactic phase of management of asthma.

Four of the 11 studies (36%) (Tribe 1976; Johnson 1978; Sharma 1984; Roberts 2003) described to some degree the baseline chronic asthma treatment profile of patients enrolled, but with insufficient rigor to enable meaningful comparisons across studies. No studies reported on the use of inhaled corticosteroids at baseline or use of other prophylactic regimens.

The exact location (e.g. ED, inpatient unit, or critical care unit) of patient enrolment was also unclear in the majority of cases with only 18% (2/11) precisely defining the area of enrolment: "high dependent ward" (Johnson 1978) and paediatric ICU (Wheeler 2005).

A critical factor to consider is whether IV therapies were provided to people with severe acute asthma immediately or whether they were deployed on patients who failed some form of run-in therapy. Among the included studies, 45% (5/11) of studies described various forms of 'run-in treatments' prior to study drug administration (Spiro 1976; Johnson 1978; Roberts 2003; Wheeler 2005; Singhi 2011). It is possible that patients who failed to respond to run-in treatments may constitute a greater severity asthmatic and therefore have greater opportunity to demonstrate an impact of a parenteral intervention compared those patients in whom the parenteral route was used immediately. However, the small study sizes and variations in treatments and outcomes limit any meaningful comparisons.

Lastly, the use of parenteral corticosteroids during the acute-phase management was demonstrated in 64% (7/11) of studies (Tribe 1976; Johnson 1978; Hambleton 1979; Evans 1980; Roberts 2003; Wheeler 2005; Singhi 2011), with 36% (4/11) being administered in some form of run-in treatment (Johnson 1978; Roberts 2003; Wheeler 2005; Singhi 2011).

Quality of the evidence

With regard to selection bias it is noted that only two of the 11 included studies were judged to be low in risk of bias (Hambleton 1979; Roberts 2003) and the remaining nine were assessed as unclear. In terms of performance and selection bias only six of the 11 included studies were in the low-risk category (Williams 1975; Tribe 1976; Femi-Pearse 1977; Hambleton 1979; Roberts 2003; Wheeler 2005); in the unclear category there were three (Spiro 1976; Sharma 1984; Singhi 2011) and in the high category there were two (Johnson 1978; Evans 1980). There was no apparent indication of selective reporting in any of the trials.

Potential biases in the review process

The comprehensiveness of the database searches provided by the CAGR to identify potentially relevant RCTs leads us to feel reasonably confident that we have included a very high proportion of those conducted in this area; however, there is inevitably the perennial concern associated with all systematic reviews that we may have failed to capture unpublished data that would provide additional clarity. As in Travers 2001, we recognise that any failure to identify unpublished trials may lead to a bias in the assessment of the relative clinical benefits of IV beta$_2$-agonists and IV aminophylline in the treatment of acute asthma. However, the group's very comprehensive search of the published literature, without language restrictions, for RCTs of potential relevance to our comparison was based on a systematic search strategy to guard against the likelihood of bias. As in Travers 2001 we are aware that the standardisation of reporting of outcomes would facilitate comparisons among included RCTs. We note too that the assessment of adverse effects was limited by a lack of reporting consistency among the included trials.

Agreements and disagreements with other studies or reviews

Our overview is consistent with Travers 2001 as 12 years on we are still unable to draw firm conclusions of the clinical effects IV beta$_2$-agonists and IV aminophylline may have in the treatment of acute asthma. Our conclusions are limited by the paucity of data, the evolution of evidence-based asthma treatment and a lack of standardisation in reporting outcomes. Given the question of how much benefit these treatments may give in addition to inhaled beta$_2$-agonists it is recommended that these data should be viewed carefully alongside the conclusions from separate Cochrane reviews comparing IV beta$_2$-agonists plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone (Travers 2012) and IV aminophylline plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone (Nair 2012). Importantly, these results should be reviewed in the context of the most recent version of evidence-based clinical practice guidelines on severe acute asthma. Only three studies have been conducted in the era of current treatment standards (Roberts 2003 Wheeler 2005; Singhi 2011).

For example, the British Thoracic Society (BTS): *British Guideline in the Management of Asthma* (BTS/SIGN 2012) recommends for adults the "use of high-dose inhaled beta$_2$-agonists as first line agents in acute asthma and administer as early as possible. Reserve intravenous beta$_2$-agonists for those patients in whom inhaled therapy cannot be used reliably" (GRADE A recommendation). In addition, the BTS guidelines state that "IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids. Side effects such as arrhythmias and vomiting are increased if IV aminophylline is used" (recommended best practice based on the clinical experience of the guideline development group).

For children, the BTS 2009 guidelines recommend "consider early addition of a single bolus dose of IV salbutamol in severe cases where the patient has not responded to initial inhaled therapy" (GRADE B recommendation). For paediatric patients requiring continuous infusion of beta-agonists, the guidelines recommend ongoing electrolyte and cardiac rhythm monitoring (recommended best practice based on the clinical experience of the guideline development group). In addition, the BTS 2009 *Asthma Guidelines* state, "Consider aminophylline in a High Dependency Unit or Pediatric Intensive Care Unit with severe or life threatening bronchospasm unresponsive to maximal doses of bronchodilators plus steroids" (GRADE C recommendation).

AUTHORS' CONCLUSIONS

Implications for practice

The relative clinical benefits of IV beta$_2$-agonists and IV aminophylline for the treatment of acute asthma in the paediatric and adult population remains unclear since too few clinical trials were available and it is recommended that these data should be viewed carefully alongside the conclusions from separate Cochrane reviews comparing IV beta$_2$-agonists plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone (Travers 2012) and IV aminophylline plus inhaled beta$_2$-agonists versus inhaled beta$_2$-agonists alone (Nair 2012). Clinicians must be aware that use of these agents is associated with increased risk of adverse events that must be considered in light of the lack of evidence of efficacy. In addition, clinicians must be aware that the majority of these studies were not conducted in the era of current asthma standards and that many did not have appropriate run-in therapies prior to study drug administration. Current guidelines, such as those of the BTS, recommend high-dose inhaled bronchodilators with systemic corticosteroids as the first-line therapy.

Implications for research

1. Additional clarity is required to assess whether IV beta$_2$-agonists and IV aminophylline improve outcomes when given in addition to nebulised bronchodilator (beta$_2$-agonists and anticholinergics) and corticosteroid therapy (IV, oral (PO) or inhaled).

2. Additional clarity is required as to the aetiology of the severe acute asthmatic in the form of baseline asthma management. The role of IV formulations could be considered in people with severe acute asthma who have failed both baseline therapies and initial inhaled bronchodilator therapy with corticosteroids.

3. Statistical planning and sample size calculations must be more carefully considered. Trials should be large enough to protect against type II error, and when multiple statistical tests are performed the increased risk of type I errors should be addressed.

4. Complete reporting of pulmonary function test data in a systematic and standardised fashion would assist in further work (i.e. reporting of %predicted PEF and changes in %PEF).

5. The inherent variability of these peak flow tests, particularly in acute asthma, emphasises the need for further research into alternative measures, particularly assessment of factors that are important to the patient such as those measuring the patient's experience.

6. Standardisation and complete reporting of symptom data and universal descriptions of what defines a "clinical success" using standardised asthma severity scores.

7. Standardisation and complete reporting of adverse reactions and side effects.

8. Future research on acute asthma must concentrate on well-defined outcomes that may in turn lead to more informative overviews.

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REFERENCES

References to studies included in this review

Evans 1980 *{published data only}*

Evans WV, Monie J, Crimmins J, Seaton A. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *British Journal of Diseases of the Chest* 1980; **74**:385–9.

Evans WV, Monie RDH. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *British Journal of Diseases of the Chest* 1979;**73**:423–4.

Monie R, Evans WV. Saving asthmatics. *British Medical Journal* 1979;**2**:334.

Femi-Pearse 1977 *{published data only}*

Femi-Pearse D, George WO, Ilechukwu ST, Elegbeleye OO, Afonja AO. Comparison of intravenous aminophylline and salbutamol in severe asthma. *BMJ* 1977;**1**:491.

Hambleton 1979 *{published data only}*

Hambleton G, Stone MJ. Comparison of IV salbutamol with IV aminophylline in the treatment of severe, acute asthma in childhood. *Archives of Disease in Childhood* 1979; **54**:391–402.

Johnson 1978 *{published data only}*

Johnson AJ, Spiro SG, Pidgeon J, Bateman S, Clarke SW. Intravenous infusion of salbutamol in severe acute asthma. *BMJ* 1978;**1**:1013–5.

Roberts 2003 *{published data only}*

Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. *Thorax* 2003;**58**(4): 306–10. [: 0040–6376]

Sharma 1984 *{published data only}*

Sharma TN, Gupta RB, Gupta PR, Purohit SD. Comparison of intravenous aminophylline, salbutamol, and terbutaline in acute asthma. *Indian Journal of Chest Diseases & Allied Sciences* 1984;**26**:155–8.

Singhi 2011 *{published data only}*

Singhi S, Bansal A, Chopra K, Grover S. Randomized comparison of magnesium sulfate, terbutaline and aminophylline infusion in acute severe asthma in children. *Critical Care Medicine* 2010;**38 Suppl**(12):Poster 371.

Singhi S, Bansal A, Chopra K, Grover S. Randomized comparison of magnesium sulfate, terbutaline and aminophylline infusion in acute severe asthma in children. *Pediatric Critical Care Medicine* 2011;**12**(3 Suppl):A1.

Spiro 1976 *{published data only}*

Spiro SG, Johnson AJ, Bateman S. Intravenous infusion of salbutamol and aminophylline in acute asthma. *American Review of Respiratory Disease* 1976;**113**(4):129.

Tribe 1976 *{published data only}*

Tribe AE, Wong RM, Robinson JS. A controlled trial of intravenous salbutamol and aminophylline in acute asthma. *Medical Journal of Australia* 1976;**2**:749–52.

Wheeler 2005 *{published data only}*

Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. Pediatric Critical Care Medicine 2005; Vol. 6, issue 2:142–7. [: 1529–7535]

Williams 1975 *{published data only}*

Williams SJ, Parrish RW, Seaton A. Comparison of intravenous aminophylline and salbutamol in severe asthma. *BMJ* 1975;**4**:685.

References to studies excluded from this review

Abd 1989 *{published data only}*

Abd El-Moneim MA, Hanafy HM, Gomaa K, Hussein MG. Comparison of inhaled salbutamol, inhaled reproterol and injected epinephrine in the treatment of acute asthma in children. *Alexandria Journal of Pediatrics* 1989;**3**(2): 153–60.

Aggarwal 1986 *{published data only}*

Aggarwal P, Pande JN, Guleria JS. Bronchodilators in acute bronchial asthma: a comparative study. *Indian Journal of Chest Diseases and Allied Sciences* 1986;**28**(1):21–7.

Anonymous 1978 *{published data only}*
Anonymous. Intravenous versus inhaled salbutamol. *Lancet* 1978;**1**:80.

Appel 1989 *{published data only}*
Appel D, Karpel JP, Sherman M. Epinephrine improves expiratory flow rates in patients with asthma who do not respond to inhaled metaproterenol sulfate. *Journal of Allergy & Clinical Immunology* 1989;**84**(1):90–8.

Arnaud 1977 *{published data only}*
Arnaud A, Dugue P, Orehek J, Pommier de Santi P, Vervloet D, Charpin J. Treatment of acute asthma. Comparison of the effectiveness of corticosteroids and a combination of corticosteroids and an adrenergic beta-stimulant. *Nouvelle Presse Medicale* 1977;**6**(45):4183–6.

Badatcheff 1989 *{published data only}*
Badatcheff A, Person C, Raoult J, Meslier N, Racineux JL. Effects of salbutamol and intravenous adrenaline in severe asthmatic crisis. *Revue des Maladies Respiratoires* 1989;**6** (Suppl 3):R168.

Becker 1983 *{published data only}*
Becker AB, Nelson NA, Simons FE. Inhaled salbutamol albuterol vs injected epinephrine in the treatment of acute asthma in children. *Journal of Pediatrics* 1983;**102**(3): 465–9.

Ben-Zvi 1982 *{published data only}*
Ben-Zvi Z, Lam C, Hoffman J, Teets-Grimm KC, Kattan M. An evaluation of the initial treatment of acute asthma. *Pediatrics* 1982;**70**(3):348–53.

Ben-Zvi 1983 *{published data only}*
Ben-Zvi Z, Lam C, Spohn WA, Gribetz I, Mulvihill MN, Kattan M. An evaluation of repeated injections of epinephrine for the initial treatment of acute asthma. *American Review of Respiratory Disease* 1983;**127**(1):101–5.

Beswick 1975 *{published data only}*
Beswick K, Davies J, Davey AJ. A comparison of intravenous aminophylline and salbutamol in the treatment of severe bronchospasm. *The Practitioner* 1975;**214**:561–6.

Bloomfield 1979 *{published data only}*
Bloomfield P, Carmichael J, Petrie GR, Jewell NP, Crompton GK. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. *BMJ* 1979;**1**:848–50.

Blumenthal 1979 *{published data only}*
Blumenthal I, Tormey W. Comparison of IV salbutamol with IV aminophylline in severe acute asthma. *Archives of Disease in Childhood* 1979;**54**:983–7.

Boe 1985 *{published data only}*
Boe J, Carlsson LG, Hetta L, Karlson B, Ljungholm K. Acute asthma - plasma levels and effect of terbutaline i.v. injection. *European Journal of Respiratory Diseases* 1985;**67**: 261–8.

Bogie 2007 *{published data only}*
Bogie AL, Towne D, Luckett PM, Abramo TJ, Wiebe RA. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. Pediatric Emergency Care 2007; Vol. 23:355–61.

Bohn 1984 *{published data only}*
Bohn D, Kalloghlian A, Jenkins J, Edmonds J, Barker G. Intravenous salbutamol in the treatment of status asthmaticus in children. *Critical Care Medicine* 1984;**12**: 892–6.

Brandstetter 1980 *{published data only}*
Brandstetter RD, Gotz VP, Mar DD. Optimal dosing of epinephrine in acute asthma. *American Journal of Hospital Pharmacy* 1980;**37**(10):1326–9.

Brooks 1972 *{published data only}*
Brooks SM, Mintz S, Weiss EB. Patterns of responses to bronchodilators in patients with bronchial asthma. *Journal of Laboratory & Clinical Medicine* 1972;**79**(2):267–76.

Browne 1997 *{published data only}*
Browne GJ, Penna AS, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute asthma in children. *Lancet* 1997;**349**:301–5.

Browne 2002 *{published data only}*
Browne GJ, Trieu L, Van Asperen P. Randomized, double-blind, placebo-controlled trial of intravenous salbutamol and nebulized ipratropium bromide in early management of severe acute asthma in children presenting to an emergency department. *Critical Care Medicine.* 2002;**30**(2):448–53.

Bruguerolle 1991 *{published data only}*
Bruguerolle B, Philip-Joet F, Lagier F, Pierson F, Reynaud M, Leonardelli M, et al. Unequal day-night terbutaline IV dosing in acute severe asthma: effect on nocturnal patency, heart rate, and arterial pressure. *Chronobiology International* 1991;**8**:194–202.

Chanez 1990 *{published data only}*
Chanez P, Mann C, Bousquet J, Chabrier PE, Godard P, Braquet P, et al. Atrial natriuretic factor ANF is a potent bronchodilator in asthma. Journal of Allergy & Clinical Immunology 1990; Vol. 86, issue 3 pt 1:321–4.

Cheong 1988 *{published data only}*
Cheong B, Reynolds SR, Rajan G, Ward MJ. Intravenous B-agonist in severe acute asthma. *BMJ* 1988;**297**:448–50.

Chiang 2000 *{published data only}*
Chiang VW, Burns JP, Rifai N, Lipshultz SE, Adams MJ, Weiner DL. Cardiac toxicity of intravenous terbutaline for the treatment of severe asthma in children: a prospective assessment. *Journal of Pediatrics* 2000;**137**(1):73–7.

Claybo 1985 *{published data only}*
Claybo R. Intravenous vs. nebulized salbutamol for treatment of severe status asthmaticus. *Critical Care Medicine* 1985;**13**(8):696–7.

Crompton 1990 *{published data only}*
Crompton G. Nebulized or intravenous beta-adrenoceptor agonist therapy in acute asthma. *European Respiratory Journal* 1990;**3**:125–6.

Davis 1977 *{published data only}*
Davis WJ, Pang LM, Chernack WJ, Mellins RB. Terbutaline in the treatment of acute asthma in childhood. *Chest* 1977; **72**(5):614–7.

Downes 1973 *{published data only}*
Downes J, Wood D, Harwood I. Intravenous isoproterenol infusion in children with severe hypercapnia due to status asthmaticus. *Critical Care Medicine* 1973;**1**(2):63–8.

Edmunds 1981 *{published data only}*
Edmunds AT, Godfrey S. Cardiovascular response during severe acute asthma and its treatment in children. *Thorax* 1981;**36**:534–40.

Elenbaas 1985 *{published data only}*
Elenbaas RM, Frost GL, Robinson WA, Collier RE, McNabney WK, Ryan JL, et al. Subcutaneous epinephrine vs. nebulized metaproterenol in acute asthma. *Drug Intelligence & Clinical Pharmacy* 1985;**19**(17-8):567–71.

Fanta 1986 *{published data only}*
Fanta CH, Rossing TH, McFadden ER, Jr. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxanthines indicated?. *American Journal of Medicine* 1986;**80**(1):5–10.

Fitchett 1975 *{published data only}*
Fitchett DH, McNicol MW, Riordan JF. Intravenous salbutamol in management of status asthmaticus. *BMJ* 1975;**1**:53–5.

Gotz 1981 *{published data only}*
Gotz VP, Brandstetter RD, Mar DD. Bronchodilatory effect of subcutaneous epinephrine in acute asthma. *Annals of Emergency Medicine* 1981;**10**(10):518–20.

Grant 1976 *{published data only}*
Grant I. Effect of intravenous injection of salbutamol in asthma. *British Journal of Clinical Pharmacology* 1976;**3**: 509–10.

Greif 1985 *{published data only}*
Greif J, Markovitz L, Topilsky M. Comparison of intravenous salbutamol (albuterol) and aminophylline in the treatment of acute asthmatic attacks. *Annals of Allergy* 1985;**55**:504–6.

Herman 1983 *{published data only}*
Herman JJ, Noah ZL, Moody RR. Use of intravenous isoproterenol for status asthmaticus in children. *Critical Care Medicine* 1983;**11**:716–20.

Hetzel 1976 *{published data only}*
Hetzel MR, Clark TJH. Comparison of intravenous and aerosol salbutamol. *BMJ* 1976;**2**(6014):919.

Hirsch 1979 *{published data only}*
Hirsch SR. Intravenous therapy with terbutaline. *Chest* 1979;**75**:648.

Hussein 1986 *{published data only}*
Hussein A, von der Hardt H, Muller W, Schell SM. Intravenous infusion of reproterol in the treatment of acute severe asthma in children. *Monatsschrift fur Kinderheilkunde* 1986;**134**:192–6.

Iodice 1980 *{published data only}*
Iodice F, Rufolo L, Piscione F, De Michele G. Hemodynamic and ventilatory effects of intravenous salbutamol in patients affected by cold. *Respiration* 1980;**40**:272–7.

Janson 1988 *{published data only}*
Janson C, Herala M, Sjogren I. Nebulization versus injection in ambulatory treatment of acute asthma: a comparative study. *British Journal of Diseases of the Chest* 1988;**82**(4): 347–53.

Janson 1992 *{published data only}*
Janson C, Boman D. Intravenous theophylline after beta 2-agonist treatment in severe acute asthma. Effect on patients who are not pre-treated with theophylline. *Upsala Journal of Medical Sciences* 1992;**97**:149–55.

Karetzky 1980 *{published data only}*
Karetzky MS. Acute asthma: the use of subcutaneous epinephrine in therapy. *Annals of Allergy* 1980;**44**(1):12–4.

Kornberg 1991 *{published data only}*
Kornberg AE, Zuckerman S, Welliver JR, Mezzadri F, Aquino N. Effect of injected long-acting epinephrine in addition to aerosolized albuterol in the treatment of acute asthma in children. *Pediatric Emergency Care* 1991;**7** (1): 1–3.

Lawford 1978 *{published data only}*
Lawford P, Jones BJM, Milledge JS. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. *BMJ* 1978;**1**:84.

Lebovitz 2004 *{published data only}*
Lebovitz DJ, Smith PG, O'Riordan M, Reed MD. Pharmacokinetic properties and tolerability of single-dose terbutaline in patients with severe asthma treated in the pediatric intensive care unit. *Current Therapeutic Research, Clinical & Experimental* 2004;**65**(1):98–109. [: 0011–393X]

Lin 1996 *{published data only}*
Lin YZ, Hsieh KH, Chang LF, Chu CY. Terbutaline nebulization and epinephrine injection in treating acute asthmatic children. *Pediatric Allergy & Immunology* 1996;**7** (2):95–9.

Lowell 1987 *{published data only}*
Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics* 1987;**79** (6):939–45.

Marlin 1975 *{published data only}*
Marlin G, Turner P. Intravenous treatment with rimiterol and salbutamol. *BMJ* 1975;**2**:715–9.

May 1975 *{published data only}*
May CS, Paterson JW, Spiro SG, Johnson AJ. Intravenous infusion of salbutamol in the treatment of asthma. *British Journal of Clinical Pharmacology* 1975;**2**:503–8.

Naspitz 1987 *{published data only}*
Naspitz CK, Sole D, Wandalsen N. Treatment of acute attacks of bronchial asthma. A comparative study of epinephrine subcutaneous and fenoterol inhalation. *Annals of Allergy* 1987;**59**(1):21–4.

Ngamphaiboon 1989 *{published data only}*
Ngamphaiboon J, Chumdermpadetsuk S. Nebulized salbutamol vs injected epinephrine in the treatment of acute asthma in children. *Chulalongkorn Medical Journal* 1989;**33**(9):669–73.

Nogrady 1977 *{published data only}*
Nogrady SG, Hartley JPR, Seaton A. Metabolic effects of intravenous salbutamol in the course of acute asthma. *Thorax* 1977;**32**:559–62.

Noseda 1989 *{published data only}*
Noseda A, Yernault JC. Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizer or spacer?. *European Respiratory Journal* 1989;**2**:377–82.

Nowak 2010 *{published data only}*
Nowak R, Iwaki Y, Matsuda K, Johnson K, Dunton AW. Reduced hospital admission and improved pulmonary function following intravenous mn-221 (bedoradrine), a novel, highly selective β2-adrenergic receptor agonist, adjunctive to standard of care in severe acute exacerbation of asthma. *Chest* 2010;**138**(4):166A.

O'Connell 1990 *{published data only}*
O'Connell MB, Iber C. Continuous intravenous terbutaline infusions for adult patients with status asthmaticus. *Annals of Allergy* 1990;**64**:213–8.

Pang 1977 *{published data only}*
Pang LM, Rodriguez-Martinez F, Davis WJ, Mellins RB. Terbutaline in the treatment of status asthmaticus. Chest 1977; Vol. 72, issue 4:469–73.

Parry 1976 *{published data only}*
Parry L, Martorano, Cotton E. Management of life-threatening asthma with intravenous isoproterenol infusions. *American Journal of Diseases of Children* 1976; **130**:39–42.

Pierce 1981 *{published data only}*
Pierce RJ, Payne CR, Williams SJ, Denison DM, Clark TJH. Comparison of intravenous and inhaled terbutaline in the treatment of asthma. *Chest* 1981;**79**:506–11.

Prego 2001 *{published data only}*
Prego Petit J, Sehabiague Rigau GR, De Leonardis Capelo DJ, Pujadas Ferrer MA. Treatment of asthmatic crisis with intravenous salbutamol and in continuous nebulization in an emergency. *Archivos de Pediatra del Uruguay* 2001;**72**: S5–13.

Quadrel 1995 *{published data only}*
Quadrel M, Lavery RF, Jaker M, Atkin S, Tortella BJ, Cody RP. Prospective, randomized trial of epinephrine, metaproterenol, and both in the prehospital treatment of asthma in the adult patient. *Annals of Emergency Medicine* 1995;**26**(4):469–73.

Quijada 1992 *{published data only}*
Quijada C, Galleguillos F. Alternative treatment for acute asthmatic crisis. *Revista Medica de Chile* 1992;**120**(2): 142–6.

Rodrigo 1994 *{published data only}*
Rodrigo C, Rodrigo G. Treatment of acute asthma. Lack of therapeutic benefit and increase of the toxicity from aminophylline given in addition to high doses of salbutamol delivered by metered-dose inhaler with a spacer. *Chest* 1994; **106**(4):1071–6.

Rossing 1980 *{published data only}*
Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER, Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. *American Review of Respiratory Disease* 1980;**122**(3):365–71.

Ruddy 1986 *{published data only}*
Ruddy RM, Kolski G, Scarpa N, Wilmott R. Aerosolized metaproterenol compared to subcutaneous epinephrine in the emergency treatment of acute childhood asthma. *Pediatric Pulmonology* 1986;**2**(4):230–6.

Salmeron 1994 *{published data only}*
Salmeron S, Brochard L, Mal H, Tenaillon A, Henry-Amar M, Renon D, et al. Nebulized versus intravenous albuterol in hypercapnic acute asthma: a multicenter, double-blind, randomized study. *American Journal of Respiratory & Critical Care Medicine* 1994;**149**:1466–70.

Salmeron 1995 *{published data only}*
Salmeron S, Ellrodt A, Taravella O. Sympathomimetics in severe acute asthma. *Lancet* 1995;**346**:257.

Schiavi 1987 *{published data only}*
Schiavi E. Acute effect of intravenous salbutamol in status asthmaticus [Efecto agudo salbutamol intravenosos en et astado de mal asmatico]. *Medicina* 1987;**47**:39–44.

Smith 1986 *{published data only}*
Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *British Journal of Clinical Pharmacology* 1986;**21**:451–3.

Smith 1992 *{published data only}*
Smith AP, Banks J, Buchanan K, Cheong B, Gunawardena KA. Mechanisms of abnormal glucose metabolism during the treatment of acute severe asthma. *Quarterly Journal of Medicine* 1992;**82**(297):71–80.

Subias 1989 *{published data only}*
Subias J, Manrique N, Hidalgo V. Status asthmaticus treatment: beta-agonist therapy experience in 71 cases. *Anales Espanoles de Pediatria* 1989;**31**:435–9.

Swedish Society 1990 *{published data only}*
Swedish Society of Chest Medicine, Janson C, Boe J, Boman G, Larsson S, Mossberg B, et al. High-dose inhaled versus intravenous salbutamol combined with theophylline in severe acute asthma. *European Respiratory Journal* 1990; **3**:163–70.

Tarala 1981 *{published data only}*
Tarala RA, Martyn V, Paterson JW. Effect of intravenous injection of rimiterol in asthma. *British Journal of Clinical Pharmacology* 1981;**12**(3):333–40.

Teoh 1979 *{published data only}*
Teoh P. Clinical evaluation of intravenous hexoprenaline in bronchial asthma. *Annals Academy of Medicine* 1979;**8**: 144–7.

Thiringer 1976 *{published data only}*
Thiringer G, Svedmyr N. Comparison of infused and inhaled terbutaline in patients with asthma. *Scandinavian Journal of Respiratory Diseases* 1976;**57**:17–24.

Thompson 1977 *{published data only}*
Thompson P, Friedman M. Intramuscular salbutamol in treatment of acute exacerbations of childhood asthma. *Archives of Disease in Childhood* 1977;**52**(7):551–4.

Ting 1991 *{published data only}*
Ting C. A comparative study of epinephrine injection and beta-agonist inhalation in the treatment of childhood asthma. *Chung-Hua Min Kuo Hsiao Erh Ko i Hsueh Hui Tsa Chih* 1991;**32**:372–81.

Tirot 1992 *{published data only}*
Tirot P, Bouachour G, Varache N, Harry P, Bourrier P, Chennebault JM, et al. The use of intravenous adrenaline in acute severe asthma [in French]. *Revue des Maladies Respiratoires* 1992;**9**:319–23.

Tripathi 1989 *{published data only}*
Tripathi S. Management of acute bronchial asthma - intravenous terbutaline or aminophylline?. *Journal of the Indian Medical Association* 1989;**87**:75–6.

Uden 1985 *{published data only}*
Uden DL, Goetz DR, Kohen DP, Fifield GC. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. *Annals of Emergency Medicine* 1985;**14**(3):229–32.

Van Renterghem 1987 *{published data only}*
Van Renterghem D, Lamont H, Elinck W, Pauwels R, Van Der Straeten M. Intravenous versus nebulized terbutaline in patients with acute asthma: a double-blind study. *Annals of Allergy* 1987;**59**:313–6.

Victoria 1989 *{published data only}*
Victoria MS, Battista CJ, Nangia BS. Comparison between epinephrine and terbutaline injections in the acute management of asthma. *Journal of Asthma* 1989;**26**(5): 287–90.

Williams 1977 *{published data only}*
Williams S, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma?. *Thorax* 1977;**32**:555–8.

Williams 1981 *{published data only}*
Williams SJ, Winner SJ, Clark TJH. Comparison of inhaled and intravenous terbutaline in acute severe asthma. *BMJ* 1975;**4**:685.

Wood 1972 *{published data only}*
Wood D, Downes J, Scheinkopf H, Lecks HI. Intravenous isoproterenol in the management or respiratory arrest in childhood status asthmaticus. *Journal of Allergy & Clinical Immunology* 1972;**50**:75–81.

Wood 1973 *{published data only}*
Wood D, Downes J. Intravenous isoproterenol in the treatment of respiratory failure in childhood status asthmaticus. *Annals of Allergy* 1973;**31**:607–10.

Zhang 2004 *{published data only}*
Zhang JX, Lin HQ, Chen JS. Clinical study on doxofylline injection in treatment of children with acute asthma attacks. *Zhonghua Erke Zazhi* 2004;**42**(2):143–4.

Additional references

Beveridge 1996
Beveridge RC, Grunfeld AF, Hodder RV, Verbeek PR. Guidelines for the emergency management of asthma in adults. *Canadian Medical Association Journal (CMAJ)* 1996; **155**:25–37.

Boulet 1999
Boulet L-P, Becker A, Berube D, Beveridge RC, Ernst P, on behalf of the Canadian Asthma Consensus Group. Canadian asthma consensus report. *CMAJ* 1999;**161**:(11 suppl).

BTS 1998
British Thoracic Society. The British guidelines on asthma management: 1995 review and position statement. Thorax 1998; Vol. 52:S1–20. [DOI: doi:10.1136/thx.52.2008.S1]

BTS/SIGN 2012
British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. A national clinical guideline. May 2008, revised January 2012. http://www.sign.ac.uk/guidelines/published/index.html#Respiratory. (accessed 16 October 2012).

Camargo 2011
Camargo Jr CA, Spooner C, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD001115]

Dolovich 2005
Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;**127**:335–71.

EPR3 2007
Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007.. J Allergy Clin Immunol 2007;120:S94-138..

Ernst 1996
Ernst P, Fitzgerald J, Spier S. Canadian Asthma Consensus Conference: summary of recommendations. *Canadian Respiratory Journal* 1996;**3**:89–100.

GINA 2011
Global Initiative for Asthma (GINA). GINA Report, Global Strategy for Asthma Management and Prevention, 2011. http://www.ginasthma.org. (accessed 16 October 2012).

Griswold 2005
Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr. Asthma exacerbations in North American adults: Who are the "frequent fliers" in the emergency department?. *Chest* 2005;**127**:1579–1586.

Higgins 2011
Higgins JPT, 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.

Krishnan 2006
Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, et al. Mortality in patients hospitalized for asthma exacerbations in the United States. *American Journal of Respiratory and Critical Care Medicine* 2006;**174** (6):633–8.

Lipworth 1997
Lipworth BJ. Treatment of acute asthma. *Lancet* 1997;**350**: sii18–sii23.

NAEPP 1997
National Asthma Education Program Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma. Bethesda: NIH 1997:1.

Nair 2000
Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002742]

Nair 2012
Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta2-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD002742]

NHLBI/WHO 1995
National Heart, Lung, and Blood Institute, World Health Organization. NHLBI/WHO Workshop Report. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Institutes of Health 1995.

NHS 2011
National Health Service. NHS 2011 HES Online Hospital Episode Statistics, 2011. http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=193. (accessed 15 October 2012).

Putland 2006
Putland M, KerrD, Kelly AM, Adverse Events Associated With the Use of Intravenous Epinephrine in Emergency Department Patients Presenting With Severe Asthma.. *Ann Emerg Med* 2006;**47**(6):559–563.

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

Rowe 2006
Rowe BH, Camargo CA Jr. Emergency Department treatment of severe acute asthma. *Ann Emerg Med* 2006;**47**: 564–6.

Rowe 2008
Rowe BH, Villa-Roel C, Sivilotti ML, Lang E, Borgundvaag B, Worster A, Walker A, Ross S. . Relapse after emergency department discharge for acute asthma.. *Acad Emerg Med.* 2008;**15**(8):709–17.

Rowe 2010
Rowe BH, Villa-Roel C, Abu-Laban RB, Stenstrom R, Mackey D, Stiell IG, Campbell S, Young B. Admissions to Canadian hospitals for acute asthma: a prospective, multicentre study. *Canadian Respiratory Journal* 2010;**17**: 25–30.

Travers 2012
Travers AH, Milan SJ, Jones AP, Camargo CA Jr, Rowe BH. Addition of intravenous beta$_2$-agonists to inhaled beta$_2$-agonists for acute asthma. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD010179]

References to other published versions of this review

Travers 2001
Travers AA, Jones AP, Kelly KD, Camargo CA Jr, Barker SJ, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD002988]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Evans 1980

Methods	Randomised, single-blind study comparing 15-min loading dose and 23 h 45 min infusion of medications in each treatment arm
Participants	6 patients with aminophylline infusion vs. 7 patients with salbutamol infusion and 8 patients with combined aminophylline and salbutamol infusion Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics who were enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy was on initial presentation to hospital (location not defined) . There was no description of any initial inhaled therapy on presentation. Each patient received IV hydrocortisone, but the sequencing of this therapy in relation to the study medications was not clear
Interventions	Arm A: aminophylline 0.285 mg/kg/min for 15 minutes followed by 0.014 mg/kg/min for 23 h 25 min Arm B: salbutamol 0.285 μg/kg/min followed by 0.057 μg/kg/min for 23 h 45 min Arm C: combination therapies of arms A and B
Outcomes	absolute change in mean PEF at 15 min with aminophylline (35% improvement from baseline) vs salbutamol (7% reduction from baseline) (P<0.005)
Notes	Results needed to be abstracted from the available graphs. Outcome estimates provided from extrapolation from graphs Summary reported as "Peak expiratory flow rates showed a significant improvement after 15 minutes treatment with aminophylline and the combined infusion, but this was not seen until 60 minutes with the salbutamol infusion. No synergistic bronchodilator effect was seen with the combined infusion. The results show that intravenous aminophylline is superior to intravenous salbutamol in the doses given in the initial treatment of acute asthma and that the combination when given intravenously is not better than aminophylline alone"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Allocation concealment unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blind

Evans 1980 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Single blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears to be no patients withdrawn
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Femi-Pearse 1977

Methods	Randomised, parallel protocol
Participants	32 adults (in the double blind study included in the report) Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics who were enrolled in the study 'Run-in' treatment profile and sequencing: the timing of study therapy was on initial presentation to hospital (location not defined) . There was no description of any initial inhaled therapy on presentation. There was no reporting of other adjunctive or conjunctive therapies
Interventions	IV salbutamol vs. IV aminophylline
Outcomes	Change in VS and PEF
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as single and double blind; however, details of the blinding are not included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No indication of blinding of outcome assessment in trial report. However blinding of study personnel responsible for outcome assessment in double-blind section of the study indicates the risk of detection bias would be low

Femi-Pearse 1977 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of patients having been withdrawn from trial
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Hambleton 1979

Methods	Randomised, parallel protocol
Participants	18 children Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy was on admission to hospital (location not defined). There was no description of any initial inhaled therapy on presentation. Each patient received IV hydrocortisone immediately, but the exact sequencing of this therapy in relation to the study medications was not clear
Interventions	IV salbutamol vs. IV aminophylline
Outcomes	Change in clinical scores, VS and ASE
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind; however, details of the blinding are not included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No indication of blinding of outcome assessment in trial report. However, blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of patients having been withdrawn from trial
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Johnson 1978

Methods	Randomisation: yes (mentioned briefly) Blinding: no Number excluded: 23 Withdrawals: 8 (6 from IV salbutamol because unsatisfactory response starting at 8 to 32 h and 2 from comparison at 24 h owing to no response) Baseline characteristics: heart rate (bpm): 109 (SD 4) salbutamol, 107 (SD 5) aminophylline, 110 (SD 3) control; systolic/diastolic blood pressure (mmHg): 134 (SD 5)/81 (SD 2) salbutamol, 141 (SD 6)/83 (SD 3) aminophylline, 137 (SD 3)/83 (SD 2) control; PaO_2: 8.3 (SD 0.3) salbutamol, 7.5 (SD 0.7) aminophylline, 8.0 (SD 0.4) control; $PaCO_2$: 5.1 (SD 0.2) salbutamol, 5.0 (SD 0.1) aminophylline, 5.2 (SD 0.3) control; pH 7.4 (SD 0.01) salbutamol, 7.38 (SD 0.01) aminophylline, 7.4 (SD 0.01) control; PEF/FEV1: 98 (SD 8)/0.6 (SD 0.1) salbutamol, 92 (SD 9)/1.1 (SD 0.2) aminophylline, 108 (SD 10)/1.0 (SD 0.1) control
Participants	Location: London, UK Participants: initially 62, 39 final (23 improved with run in Rx); age (years): 16 to 65 (mean: 36.2 salbutamol, 41.9 aminophylline, 36.7 control); males: 9 salbutamol, 4 aminophylline, 11 control; females: 11 salbutamol, 15 aminophylline, 12 control; height (cm): 168.2 (SD 1.9) salbutamol, 162.6 (SD 1.7) aminophylline, 167.9 (SD 1.8) control; weight (kg) 63.9 (SD 1.5) salbutamol, 60.8 (SD 2.6) aminophylline, 63.5 (SD 1.5) control Asthma definition and severity: PEF < 150 (not mentioned, abstracted from article instead), run-in phase for about 45 min of aminophylline/nebulised salbutamol/hydrocortisone, RCT Exclusion criteria: presence of cardiovascular or renal disease, improvement with run-in phase Inhaled corticosteroid use: 30 equally distributed Baseline asthma treatment characteristics: baseline asthma characteristics were reported: 30 of the 62 patients were regularly taking PO corticosteroids; 54 were receiving salbutamol by tablet or aerosol and 26 were taking methylxanthine derivatives. The distribution of patients receiving corticosteroids or salbutamol or both was distributed equally between the study groups. However, 14 (74%) patients in the aminophylline group were receiving methylxanthine derivatives compared to 6 (30%) in the salbutamol group and 6 (26%) in the no infusion group 'Run-in' treatment profile and sequencing: the timing of study therapy was on admission to hospital ("high dependence medical ward"), after a 75-min run-in treatment with: 1) aminophylline 5 mg/kg body IV, 2) supplementary oxygen, 3) 2 inhalations of nebulised salbutamol (5 mg each) given by IPPB; 4) hydrocortisone 200 mg IV and 5) prednisone 40 mg PO
Interventions	Run-in phase with inclusion and rand at 75 min, consecutive patients, parallel cohort of drug A vs. drug B, cross-over possible at doctor's discretion, compared to 'control' group Standard care: for first 75 min O_2 NPV 35%, aminophylline 5 mg/kg IV load, hydrocortisone 200 mg IV, prednisone 40 mg PO qd, salbutamol 5 mg IPPB q6h, physiotherapy Treatment group: aminophylline infusion 1 mg/min at 75 min and 'control group' of inhaled salbutamol vs. salbutamol IV infusion at 10 μg/min at 75 min Placebo: none

Johnson 1978 (*Continued*)

Outcomes	PFTs: PEF/% PEF response/FEV: salbutamol 146 (SD 10)/FVC 2 (SD 0.2)/ 0.8 (SD 0.1), 133.3/0.79, 148/1.0; control 145 (SD 15)/FVC 1.9 (SD 0.2)/0.9 (SD 0.1), 150/ 0.93, 170.8/1.07 Timing: 15, 60, 360 min Side effects: no details
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessment in trial report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 patients withdrew from salbutamol group and 2 withdrawn from the aminophylline group
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Roberts 2003

Methods	Single centre
Participants	Severe acute paediatric asthmatic patients who did not improve with 3 doses of inhaled salbutamol/ipratropium: 44 patients enrolled, 18 with IV salbutamol vs. 26 with IV aminophylline Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study. 11.8% (2/18) in the IV salbutamol and 20% (5/26) in the IV aminophylline had received treatment with nebulised beta-agonists before presentation, however the dose and number of treatments was not specified 'Run-in' treatment profile and sequencing: the timing of study therapy was on presentation to hospital (location not defined), after a 60-min run-in treatment with poor response to 3 nebulisers containing salbutamol (2.

	5 mg, 5 mg if > 5 years) and ipratropium (125 μg, 250 μg if > 5 years). All patients received systemic corticosteroids; however, the sequencing of this relative to the study drugs is unclear
Interventions	Single bolus of IV salbutamol (15 μg/kg over 20 min) followed by an infusion of saline or a continuous aminophylline infusion (bolus of 5 mg/kg over 20 min followed by an infusion of 0.9 mg/kg/h)
Outcomes	No statistically significant difference in ASS at 2 h between the 2 groups (median (IQR) 6 (6, 8) and 6.5 (5, 8) for salbutamol and aminophylline respectively, P = 0.93). A similar improvement in ASS to 2 h was seen in the 2 groups (mean difference -0.08; 95% CI -0.97 to 0.80), there was a trend (P = 0.07) towards a longer duration of oxygen therapy in the salbutamol group (17.8 h; 95% CI 8.5 to 37.5 vs. 7.0 h; 95% CI 3.4 to 14.2), and a significantly (P = 0.02) longer length of hospital stay in the salbutamol group (85.4 h; 95% CI 66.1 to 110.2 vs. 57.3 h; 95% CI 45.6 to 72.0). There was no significant difference in adverse events between the 2 groups
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Trial reported as allocation concealment; however, details are not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No indication of blinding of outcome assessment in trial report. However, blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 withdrew from aminophylline group, and 1 from the salbutamol group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Sharma 1984

Methods	Randomised, parallel protocol
Participants	30 Adults Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study; however, the authors only enrolled patients who had 'no history of bronchodilator drugs' within 24 h of the study 'Run-in' treatment profile and sequencing: the timing of study therapy was on admission to hospital (location not defined). There was no description of any initial inhaled therapy on presentation. It is not clear if adjunctive or conjunctive therapies were provided to patients in this study
Interventions	IV salbutamol (N = 10) vs. IV aminophylline (N = 10). In addition 10 patients received IV terbutaline and data from these patients have been combined with the 10 receiving IV salbutamol in the adverse effects analyses of the 2012 update of this review
Outcomes	Change in FEV1 and maximal mid-expiratory flow rate, ASE
Notes	FEV1 data obtained in original version of this review for IV salbutamol (N = 10) vs. IV aminophylline (N = 10) is included in Analysis 1.7; Analysis 1.8; Analysis 1.9

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No indication of blinding of participants and personnel included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No indication of blinding of outcome assessment in trial report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient withdrawn prematurely from the aminophylline group owing to hypotension
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Singhi 2011

Methods	Randomised trial
Participants	Paediatric severe acute asthma: 100 enrolled, 34 with IV magnesium, 33 with IV terbutaline and 33 with IV aminophylline Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy after no response to 1-h run-in treatment with: 1) supplemental oxygen, 2) 3 doses of nebulised salbutamol, budesonide and ipratropium; and 3) systemic corticosteroids. Location of enrolment was not clearly defined
Interventions	Run-in treatment phase with oxygen, 3 doses nebulised salbutamol and ipratropium, and 1 dose of systemic corticosteroids) then patients randomised to: Arm A: IV magnesium 50 mg/kg over 20 min Arm B: IV terbutaline 10 μg/kg over 30 minutes then 0.1 μg/kg/min for 1 h Arm C: IV aminophylline 5 mg/kg bolus then 0.9 mg/kg/min for 1 h
Outcomes	'Treatment success' defined as clinical ASS $\geq$ 4 at 1 h. Treatment success was noted in 33/34 in arm A, 23/33 in arm B and 23/33 in arm C (P < 0.001). 0/34 side effects in arm A vs. 2/33 arm B (symptomatic hypokalaemia) vs. 9/33 arm C (nausea/vomiting) (P < 0.001)
Notes	Available as abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear - conference abstract with limited information
Allocation concealment (selection bias)	Unclear risk	Unclear - conference abstract with limited information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Selective reporting (reporting bias)	Unclear risk	Unclear - conference abstract with limited information

Spiro 1976

Methods	Randomised trial
Participants	Acute asthmatics aged 16 to 65 years: 16 with IV salbutamol vs. 14 with IV aminophylline Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy after no response to a 30-min run-in treatment with: 1) IV aminophylline bolus 5 mg/kg; and 2) 2 serial treatments with nebulised salbutamol 5 mg. Location of enrolment was not clearly defined. It is not clear of the adjunctive or conjunctive therapies provided to patients in this study
Interventions	Run-in phase of IV aminophylline 5 mg/kg bolus and then followed at 15 min of nebulised salbutamol for 2 consecutive treatments, and then if not improved 'randomly allocated' to: Arm A: IV salbutamol 10 μg/min infusion Arm B: IV aminophylline 1 mg/min
Outcomes	Spirometry, PEF, heart rate. FEV1, FVC and PEF improved in both groups within 1 h, but all values were consistently better with aminophylline throughout the 36-h period, with increased heart rate present in the IV salbutamol group
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear - conference abstract with limited information
Allocation concealment (selection bias)	Unclear risk	Unclear - conference abstract with limited information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear - conference abstract with limited information
Selective reporting (reporting bias)	Unclear risk	Unclear - conference abstract with limited information

Tribe 1976

Methods	Randomisation: yes (method not mentioned) Blinding: double-blind Number excluded: no details Withdrawals: 2 Baseline characteristics: heart rate (bpm): 103.7 beta-agonists (IV), 114.6 aminophylline (amino); PaO_2 (kPa): 8 beta-agonists, 7.6 aminophylline; $PaCO_2$ (kPa): 4.2 beta-agonists, 4.5 aminophylline; FEV: beta-agonists 0.7 (range: 0.3 to 1.7) female, 1.7 (range: 0.3 to 3.1) male, aminophylline 0.7 (range: 0.3 to 1.3) female, 0.7 male (only 1 participant)
Participants	Location: Perth, Australia Participants: 25 eligible, 23 final (2 lost to follow-up no details given, 11 beta-agonists, 12 aminophylline); mean age (years) 42 female/ 49 male beta-agonists, 48 female/17 male aminophylline; males 2 beta-agonists, 1 aminophylline; females 9 beta-agonists, 11 aminophylline Asthma definition and severity: no specified definition, included if demonstrable wheeze or SOB Exclusion criteria: arrhythmia, $PaO_2 < 50$, $PaCO_2 > 50$, patients 'poor general condition', 'too ill to await Rx', allergy, excessive drug Rx in previous 3 h Inhaled corticosteroid use: 3 beta-agonists, 1 aminophylline Baseline asthma treatment characteristics: baseline therapy of asthmatics enrolled into the study demonstrated that 36% (4/11) of the salbutamol group and 42% (5/12) of the aminophylline group had PO/inhalational/ parenteral bronchodilator therapy given in the 3 h prior to study. 27% (3/11) of the salbutamol group and 8% (1/12) of the aminophylline group were receiving corticosteroids prior to enrolment 'Run-in' treatment profile and sequencing: the timing of study therapy was on admission to hospital (location not defined). There was no description of any initial inhaled therapy on presentation. Each patient received IV hydrocortisone 100 mg immediately prior to enrolment
Interventions	Standard care: hydrocortisone 100 mg IV, 4 had IV beta-agonists within 3 h prior, 5 had nebulised beta-agonists within 3 h prior Treatment group: theophylline 250 mg IV at 0 min over 5 min vs. salbutamol 100 μg IV at 0 min Placebo: unknown
Outcomes	PFTs: FEV salbutamol positive 26%; aminophylline positive 23% Timing: 60 min Side effects: salbutamol 'impression' - 2 (1 headache, 1 tremor and palpitations), aminophylline 'impression' - 3 (2 pain, 1 headache and vomiting)
Notes	Author correspondence: Severe co-interventions with beta-agonists prior to start of trial, questionable if IV $beta_2$-agonists started at truly 0 min
Risk of bias	

Tribe 1976 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind; however, details of the blinding are not included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No indication of blinding of outcome assessment in trial report. However, blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 patients were withdrawn (1 with raised $PaCO_2$ and the 1 developed a reaction during salbutamol administration)
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Wheeler 2005

Methods	Randomised, prospective, controlled, double-blind trial
Participants	Severe acute asthmatics in the PICU setting; 40 patients enrolled, arm A (IV theophylline) 13, arm B (IV terbutaline) 16, arm C (IV theophylline and IV terbutaline) 11 Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy was within 2-h admission to PICU. A run-in treatment consisted of standard doses of IV methylprednisolone 2 mg/kg and continuous albuterol nebulisation administered at a rate of 10 mg/h. Duration of this run-in treatment not clear from the study methods
Interventions	Supplemental oxygen delivered as needed by either nasal cannula or face mask to maintain oxygen saturation 95%, maintenance IV fluids, standard doses of IV methylprednisolone (2 mg/kg every 6 h for 24 h followed by 1 mg/kg every 6 h until discharge from the PICU), and continuous albuterol nebulisation administered at a rate of 10 mg/h. Additional therapeutics such as magnesium, ketamine, anticholinergics or helium-oxygen were administered at the discretion of the attending PICU physician and the other members of the healthcare team Arm A: IV theophylline 4.0 mL/kg (6.4 mg/kg) over 20 min, followed by a continuous infusion (age 3 to 8 years 0.6 mL/kg/h (0.96 mg/kg/h), age 9 to 12 years 0.5 mL/kg/h

	(0.80 mg/kg/h), age 12 to 15 years 0.4 mL/kg/h (0.64 mg/kg/h) Arm B: IV terbutaline 0.17 mL/kg (20 g/kg) bolus and continuous infusion at a rate of 0.2 mL/kg/h (0.4 g/kg/min) Arm C: combination of arms A and B
Outcomes	There were no significant differences among the 3 groups with respect to the primary outcome variable, improvement in CAS. The CAS improved significantly from baseline in all 3 groups (arm A: 8.8 ± 0.3 at study entry, 3.9 ± 1.0 at study completion, $P < 0.05$; arm B: 8.3 ± 0.4 at study entry, 4.3 ± 1.1 at study completion, $P < 0.05$; arm C 3: 8.7 ± 0.4 at study entry, 4.3 ± 1.1 at study completion, $P < 0.05$). There were no significant differences in the length of PICU stay among groups (arm A: 4.4 ± 2.3 days, arm B: 4.9 ± 3.0 days, arm C: 4.8 ± 3.0 days, respectively). No patients in the study required mechanical ventilation. When the 4 patients who exited the study were excluded from analysis (3 from arm A and 1 from arm C), there was a significantly shorter length of time to achieve a CAS of 3 in arm A compared with arms B and C (arm A: 24.2 ± 12.1 h, arm B: 51.6 ± 33.3 h, arm C: 47.1 ± 38.3 h, respectively; $P < 0.05$)
Notes	Unclear time lines - multiple co-interventions throughout

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Low risk	Sealed envelopes coded by patient number provided allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 patients withdrew from theophylline group, and 1 patient withdrew from theophylline/terbutaline group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Williams 1975

Methods	Randomisation: yes (method not mentioned) Blinding: double blind Number excluded: no details Withdrawals: none Baseline characteristics: heart rate (bpm): 128 (SD 11) salbutamol, 125 (SD 7) theophylline; systolic/diastolic blood pressure (mmHg): 139 (SD 17)/87 (SD 9) salbutamol, 157 (SD 20)/91 (SD 9) theophylline; PaO_2 (kPa): 7.5 (SD 1.1) salbutamol, 7.7 (SD 1.6) theophylline; $PaCO_2$ (kPa): 5.6 (SD 1.2) salbutamol, 5.3 (SD 1.6) theophylline; PEF: 75 (SD 15) salbutamol, 90 (SD 20) theophylline
Participants	Location: Penarth, South Glamorgan Participants: 20 final (11 salbutamol, 9 theophylline). Asthma definition and severity: definition not specified, included if heart rate > 120 bpm, predicted PEF < 25%, PaO_2 < 69.8 Exclusion criteria: none mentioned Inhaled corticosteroid use: no details Baseline asthma treatment characteristics: no description of baseline therapy of asthmatics enrolled into the study 'Run-in' treatment profile and sequencing: the timing of study therapy was on admission to hospital (location not defined). There was no description of any initial inhaled therapy on presentation. Each patient received IV hydrocortisone immediately, but the exact sequencing of this therapy in relation to the study medications was not clear
Interventions	Parallel study, IV salbutamol vs. IV theophylline Standard care: O2 NPV 28%, hydrocortisone 1000 mg IV Treatment group: aminophylline 500 μg IV at 0 min infused over 60 min vs. salbutamol 500 μg IV at 0 min infused over 60 min (8.33 μg/min) Placebo: none
Outcomes	PFTs: PEF salbutamol 114 (SD 27), 128 (SD 53), 161 (SD 85); theophylline 109 (SD 34), 118 (SD 43), 134 (SD 64) Timing: 15, 30, 60 min Side effects: salbutamol: 5 (3 headache, 2 tremor); theophylline: 7 (2 headache, 3 tremor, 4 nausea, 1 vomiting, 4 ventricular extrasystoles)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report

Williams 1975 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind; however, details of the blinding are not included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No indication of blinding of outcome assessment in trial report. However, blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information included in the trial report regarding patients being withdrawn from the study
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

ASE: autonomic side effects; ASS: Asthma Severity Score; bpm: beats per min; CAS: Clinical Asthma Score; FEV: forced expiratory volume; FVC: forced vital capacity; IPPB: intermittent positive-pressure breathing; IQR: interquartile range; IV: intravenous; NPV: negative pressure ventilation; PEF: peak expiratory low rate; PFT: pulmonary function test; PICU: paediatric intensive care unit; PO: oral; q6h: every six hours; qd: four times daily; RCT: randomised controlled trial; SOB: shortness of breath; VS: vital signs.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abd 1989	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Aggarwal 1986	Excluded on basis of design, patient, intervention, comparator characteristics: non RCT; unclear stability of adult patients; compared IV aminophylline vs. IV epinephrine (adrenaline) vs. SC salbutamol Exclude on basis of IV aminophylline vs. IV epinephrine vs SC salbutamol
Anonymous 1978	Non-experimental study (not an RCT)
Appel 1989	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Arnaud 1977	Not an RCT
Badatcheff 1989	Single-blind RCT; patients with severe acute asthma; compared IV salbutamol vs. IV epinephrine (adrenaline); outcome: PEF Excluded based on comparison of IV salbutamol vs. IV epinephrine (adrenaline)
Becker 1983	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Ben-Zvi 1982	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)

(*Continued*)

Ben-Zvi 1983	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Beswick 1975	Not an RCT
Bloomfield 1979	Comparison was between IV agonists vs. inhaled agonists
Blumenthal 1979	Letter, not a clinical trial.
Boe 1985	Not an RCT. IV beta-agonist use was not the primary research question (no control; compared 2 doses of terbutaline - dose-response curve)
Bogie 2007	Comparison of IV terbutaline vs. normal saline
Bohn 1984	Not an RCT
Brandstetter 1980	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Brooks 1972	Not an RCT; patients with stable chronic asthma; compared IV aminophylline vs. nebulised isoproterenol; outcome PaO_2 Excluded based design and on comparison of IV aminophylline vs. nebulised isoproterenol
Browne 1997	Comparison between IV salbutamol vs. placebo (with both groups on a background of standard care)
Browne 2002	Excluded on basis of insufficient comparison arm. RCT; patients with severe asthma admitted to paediatric emergency department; compared IV salbutamol plus standard of care vs. nebulised ipratropium plus standard of care vs. IV salbutamol plus nebulised ipratropium vs. standard care; outcome PEF
Bruguerolle 1991	Not an RCT
Chanez 1990	Excluded on basis of comparison of IV terbutaline vs. IV atrial natriuretic factor
Cheong 1988	Comparison was between nebulised salbutamol 5 mg at 30 and 120 min vs. IV salbutamol 12.5 μg/min for 4 h at 30 min
Chiang 2000	Excluded on basis of design, comparison group and outcomes: not an RCT; paediatric patients in an emergency department; IV terbutaline to all patients with no comparison group; outcomes were ECG and biomarkers
Claybo 1985	Excluded on basis of design: letter to editor only, no data available
Crompton 1990	Review
Davis 1977	Subcutaneous (rather than IV) beta$_2$ agonists
Downes 1973	Not an RCT
Edmunds 1981	Not an RCT

(*Continued*)

Elenbaas 1985	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Fanta 1986	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Fitchett 1975	Not an RCT - cohort study
Gotz 1981	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Grant 1976	Letter to editor
Greif 1985	Not an RCT - cohort study.
Herman 1983	Not an RCT - cohort study
Hetzel 1976	Not an RCT - cohort study
Hirsch 1979	Case report
Hussein 1986	Comparison between IV reproterol vs. inhaled reproterol
Iodice 1980	Not an RCT - cohort study
Janson 1988	Excluded on basis of design and patient characteristics: not an RCT; stable asthmatics in outpatient setting; compared SC terbutaline plus IV aminophylline vs. SC terbutaline plus delayed nebulised ipratropium vs. SC terbutaline SC plus concurrent nebulised ipratropium
Janson 1992	Not an RCT
Karetzky 1980	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Kornberg 1991	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Lawford 1978	Comparison was between nebulised salbutamol 10 mg at 0 min lasting for 45 min vs. IV salbutamol infusion 20 μg/min at 0 min lasting for 45 min
Lebovitz 2004	Excluded on basis of design: dose finding/pharmacokinetic study
Lin 1996	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Lowell 1987	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Marlin 1975	Patients with chronic asthma
May 1975	Not an RCT - cohort study.
Naspitz 1987	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)

(*Continued*)

Ngamphaiboon 1989	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Nogrady 1977	Case series
Noseda 1989	Review
Nowak 2010	Excluded based on comparison: RCT; patients with severe acute asthma, compared IV bedoradine plus standard care vs. standard care; outcome PEF
O'Connell 1990	Not an RCT - cohort study
Pang 1977	Excluded on basis of design and no comparison group: not an RCT, paediatric patients, SC terbutaline SC
Parry 1976	Not an RCT - cohort study
Pierce 1981	Patients were not seen in an emergency/hospital setting (study done in a laboratory setting)
Prego 2001	Excluded based on comparison: not an RCT, paediatric patients with severe asthma, compared IV salbutamol vs. nebulised salbutamol; range of outcomes
Quadrel 1995	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Quijada 1992	Excluded based on comparison: RCT; patients with severe acute asthma; compared SC salbutamol vs. nebulised salbutamol; outcome PEF
Rodrigo 1994	Addition of IV aminophylline to inhaled beta$_2$ agonists
Rossing 1980	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Ruddy 1986	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Salmeron 1994	Trial did not compare IV beta$_2$ agonists to IV aminophylline. The comparison was between nebulised albuterol 10 mg (two 5 mg nebulisations over 15 min for 1 h), then if successful continue with nebulised albuterol 5 mg every 2 h for 7 h vs. IV albuterol infusion of 8.3 μg/min for 60 min (total 500 μg) at 0 min lasting for 1 h, then if successful continue with 500 μg/h for 7 h
Salmeron 1995	Letter to editor
Schiavi 1987	Not an RCT
Smith 1986	Non-experimental study (not an RCT)
Smith 1992	Not an RCT; patients with severe acute asthma; compared IV salbutamol vs. IV aminophylline; outcome PEF
Subias 1989	Not an RCT

(*Continued*)

Swedish Society 1990	Trial did not compare IV beta$_2$ agonists to IV aminophylline. The comparison was between nebulised salbutamol 0.15 mg/kg at 0 min lasting 7 min, repeated at 30 min (total nebulised 0.30 mg/kg in 1 h) vs. IV salbutamol infusion 5 μg/kg over 10 min at 0 min
Tarala 1981	Excluded on basis of type of patients: stable adults in outpatient setting
Teoh 1979	Not an RCT - cohort study
Thiringer 1976	Non-experimental study (not an RCT). Patients were not seen in an emergency/hospital setting (study done in a laboratory setting)
Thompson 1977	Study on non-severe asthmatic patients in ambulatory setting
Ting 1991	Not an RCT
Tirot 1992	Not an RCT
Tripathi 1989	Not an RCT
Uden 1985	Epinephrine (adrenaline) (rather than IV beta$_2$ agonists)
Van Renterghem 1987	Trial did not compare IV beta$_2$ agonists to IV aminophylline. The comparison was between nebulised terbutaline 0.1 mg/kg over 5 min at 0 and 60 min vs. IV terbutaline infusion 6 μg/kg over 5 min at 0 min and 60 min
Victoria 1989	Trial compared SC epinephrine (adrenaline) and IV terbutaline. Epinephrine trials will be considered in a separate Cochrane review
Williams 1977	Non-experimental study (not an RCT)
Williams 1981	Trial did not compare IV beta$_2$ agonists to IV aminophylline. The comparison was between nebulised terbutaline 2.5 mg over 10 min (repeat twice for each time FEV1 was maximal) vs. IV terbutaline infusion 250 μg over 10 min at 0 min (repeat twice for each time FEV1 was maximal)
Wood 1972	Not an RCT
Wood 1973	Not an RCT
Zhang 2004	Not an RCT

ECG: electrocardiograph; IV: intravenous; PEF: peak expiratory flow rate; RCT: randomised controlled trial; SC: subcutaneous.

DATA AND ANALYSES

Comparison 1. IV beta-agonists versus IV aminophylline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of stay (hours)	2	73	Mean Difference (IV, Random, 95% CI)	23.19 [-2.40, 48.77]
1.1 Paediatric (non-PICU)	1	44	Mean Difference (IV, Random, 95% CI)	28.10 [-2.60, 58.80]
1.2 Paediatric (ICU)	1	29	Mean Difference (IV, Random, 95% CI)	12.0 [-34.31, 58.31]
2 PEF (L/min) at 15 min	2	59	Mean Difference (IV, Random, 95% CI)	-9.53 [-28.81, 9.75]
3 PEF (L/min) at 30 min	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 PEF (L/min) at 60 min	2	59	Mean Difference (IV, Random, 95% CI)	-3.75 [-42.86, 35.36]
5 PEF (L/min) at 45 min	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 PEF (L/min) final	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 FEV1 (L) at 15 min	2	59	Mean Difference (IV, Random, 95% CI)	0.01 [-0.09, 0.11]
8 FEV1 (L) at 1 h	2	59	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.26, 0.08]
9 FEV1 (L) at 3 h	2	59	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.24, 0.15]
10 Arterial oxygen tension (mmHg)	2	59	Mean Difference (IV, Random, 95% CI)	6.00 [-2.13, 14.13]
11 Arterial carbon dioxide tension (mmHg)	2	59	Mean Difference (IV, Random, 95% CI)	0.98 [-2.16, 4.12]
12 Heart rate at 15 min	2	59	Mean Difference (IV, Random, 95% CI)	8.13 [-0.12, 16.37]
13 Heart rate at 30 min	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Heart rate at 45 min	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Heart rate at 60 min	3	82	Mean Difference (IV, Random, 95% CI)	2.54 [-6.28, 11.36]
16 Heart rate final	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Diastolic blood pressure at 60 min	2	59	Mean Difference (IV, Random, 95% CI)	-6.85 [-13.58, -0.11]
18 Clinical failure	2	89	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.40, 2.62]
19 Adverse effects	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 Anxiety	1	30	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.08, 12.56]
19.2 Creatine phosphokinase (CPK) elevation	1	29	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.38, 9.20]
19.3 CPK-MB elevation	1	29	Odds Ratio (M-H, Random, 95% CI)	2.73 [0.22, 34.01]
19.4 Dysrhythmia	1	29	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 3.04]
19.5 Giddiness	1	30	Odds Ratio (M-H, Random, 95% CI)	59.22 [2.80, 1253.05]
19.6 Headache	3	72	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.30, 3.44]
19.7 Hyperglycaemia	1	29	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.01, 6.74]
19.8 Hypokalaemia	2	95	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.10, 7.97]
19.9 Local pain at injection site	1	23	Odds Ratio (M-H, Random, 95% CI)	5.48 [0.23, 127.73]
19.10 Numbness	1	30	Odds Ratio (M-H, Random, 95% CI)	6.47 [0.24, 174.08]
19.11 Palpitations	3	82	Odds Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.00]
19.12 Perspiration	1	30	Odds Ratio (M-H, Random, 95% CI)	6.47 [0.24, 174.08]
19.13 Tremor	4	102	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.18, 5.47]
19.14 Ventricular extrasystoles	1	20	Odds Ratio (M-H, Random, 95% CI)	18.82 [0.85, 414.97]
19.15 Nausea/vomiting	2	96	Odds Ratio (M-H, Random, 95% CI)	14.18 [1.62, 124.52]

19.16 Nausea	2	49	Odds Ratio (M-H, Random, 95% CI)	6.53 [1.60, 26.72]
19.17 Vomiting	3	72	Odds Ratio (M-H, Random, 95% CI)	3.06 [0.85, 11.06]
20 Length of stay	2	73	Std. Mean Difference (IV, Random, 95% CI)	0.41 [-0.06, 0.88]
20.1 Paediatric (non-PICU)	1	44	Std. Mean Difference (IV, Random, 95% CI)	0.57 [-0.05, 1.18]
20.2 Paediatric (ICU)	1	29	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.55, 0.91]

Analysis 1.1. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 1 Length of stay (hours).

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 1 Length of stay (hours)

Study or subgroup	IV beta agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Paediatric (non-PICU)							
Roberts 2003	18	85.4 (56)	26	57.3 (43)		69.5 %	28.10 [-2.60, 58.80]
Subtotal (95% CI)	**18**		**26**			**69.5 %**	**28.10 [-2.60, 58.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.79 (P = 0.073)							
2 Paediatric (ICU)							
Wheeler 2005	16	117.6 (72)	13	105.6 (55.2)		30.5 %	12.00 [-34.31, 58.31]
Subtotal (95% CI)	**16**		**13**			**30.5 %**	**12.00 [-34.31, 58.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.51 (P = 0.61)							
Total (95% CI)	**34**		**39**			**100.0 %**	**23.19 [-2.40, 48.77]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 1.78 (P = 0.076)							
Test for subgroup differences: Chi^2 = 0.32, df = 1 (P = 0.57), I^2 =0.0%							

Analysis 1.2. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 2 PEF (L/min) at 15 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

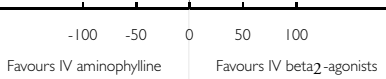
Outcome: 2 PEF (L/min) at 15 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	146 (44.7)	19	145 (65.4)		29.8 %	1.00 [-34.33, 36.33]
Williams 1975	11	90 (25)	9	104 (27)		70.2 %	-14.00 [-37.01, 9.01]
Total (95% CI)	**31**		**28**			**100.0 %**	**-9.53 [-28.81, 9.75]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.49, df = 1 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



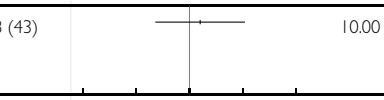
Analysis 1.3. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 3 PEF (L/min) at 30 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 3 PEF (L/min) at 30 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Williams 1975	11	128 (53)	9	118 (43)		10.00 [-32.07, 52.07]



Analysis 1.4. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 4 PEF (L/min) at 60 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

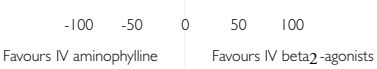
Outcome: 4 PEF (L/min) at 60 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	133.3 (46.1)	19	150 (65.8)		70.4 %	-16.70 [-52.53, 19.13]
Williams 1975	11	161 (85)	9	134 (64)		29.6 %	27.00 [-38.36, 92.36]
Total (95% CI)	**31**		**28**			**100.0 %**	**-3.75 [-42.86, 35.36]**

Heterogeneity: Tau^2 = 231.81; Chi^2 = 1.32, df = 1 (P = 0.25); I^2 =24%

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 5 PEF (L/min) at 45 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 5 PEF (L/min) at 45 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Williams 1975	11	151 (72)	9	131 (65)		20.00 [-40.11, 80.11]

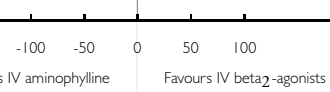
Analysis 1.6. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 6 PEF (L/min) final.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 6 PEF (L/min) final

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Johnson 1978	20	148 (46.1)	19	168 (68.4)		-20.00 [-56.80, 16.80]



Analysis 1.7. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 7 FEV1 (L) at 15 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 7 FEV1 (L) at 15 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	0.85 (0.21)	19	0.82 (0.18)		64.9 %	0.03 [-0.09, 0.15]
Sharma 1984	10	0.85 (0.19)	10	0.87 (0.19)		35.1 %	-0.02 [-0.19, 0.15]
Total (95% CI)	**30**		**29**			**100.0 %**	**0.01 [-0.09, 0.11]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.25 (P = 0.80)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 8 FEV1 (L) at 1 h.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 8 FEV1 (L) at 1 h

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	0.8 (0.27)	19	0.94 (0.4)		61.4 %	-0.14 [-0.36, 0.08]
Sharma 1984	10	0.92 (0.31)	10	0.93 (0.31)		38.6 %	-0.01 [-0.28, 0.26]
Total (95% CI)	**30**		**29**			**100.0 %**	**-0.09 [-0.26, 0.08]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.54, df = 1 (P = 0.46); I^2 =0.0%

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 9 FEV1 (L) at 3 h.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 9 FEV1 (L) at 3 h

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	0.97 (0.41)	19	1.04 (0.46)		49.6 %	-0.07 [-0.34, 0.20]
Sharma 1984	10	0.89 (0.31)	10	0.91 (0.31)		50.4 %	-0.02 [-0.29, 0.25]
Total (95% CI)	**30**		**29**			**100.0 %**	**-0.04 [-0.24, 0.15]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 10 Arterial oxygen tension (mmHg).

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

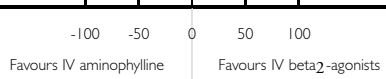
Outcome: 10 Arterial oxygen tension (mmHg)

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	62.25 (10.1)	19	56.25 (22.9)		52.6 %	6.00 [-5.21, 17.21]
Williams 1975	11	66.7 (14.2)	9	60.7 (12.7)		47.4 %	6.00 [-5.80, 17.80]
Total (95% CI)	**31**		**28**			**100.0 %**	**6.00 [-2.13, 14.13]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 11 Arterial carbon dioxide tension (mmHg).

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

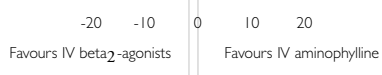
Outcome: 11 Arterial carbon dioxide tension (mmHg)

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	38.25 (6.7)	19	37.25 (3.3)		91.2 %	1.00 [-2.29, 4.29]
Williams 1975	11	39 (6.7)	9	38.2 (15)		8.8 %	0.80 [-9.77, 11.37]
Total (95% CI)	**31**		**28**			**100.0 %**	**0.98 [-2.16, 4.12]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

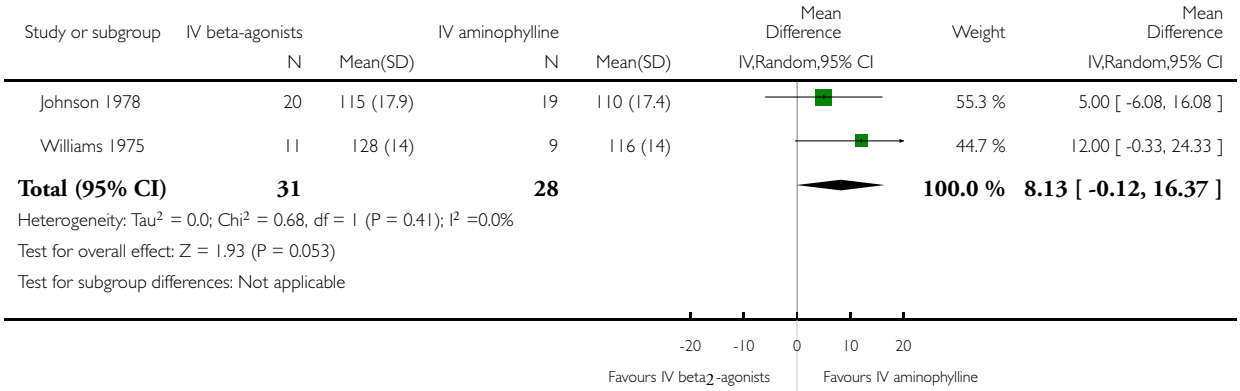


Analysis 1.12. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 12 Heart rate at 15 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 12 Heart rate at 15 min

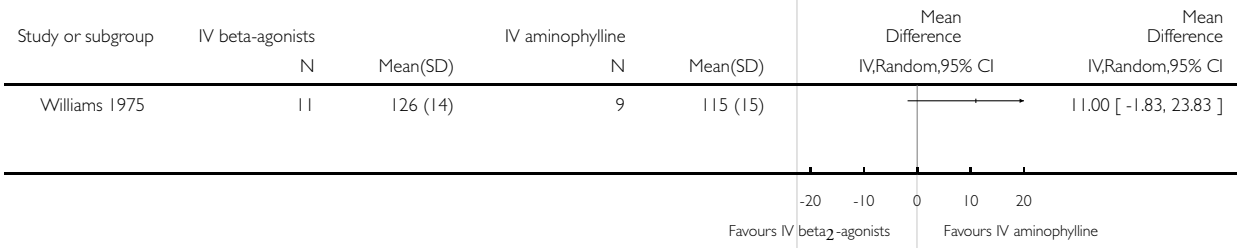


Analysis 1.13. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 13 Heart rate at 30 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 13 Heart rate at 30 min

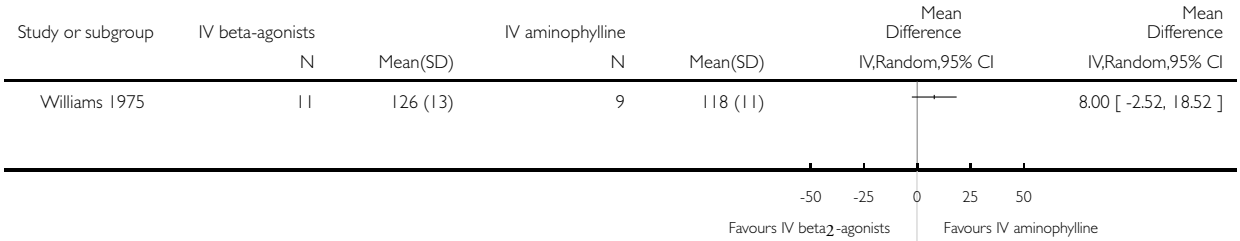


Analysis 1.14. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 14 Heart rate at 45 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 14 Heart rate at 45 min

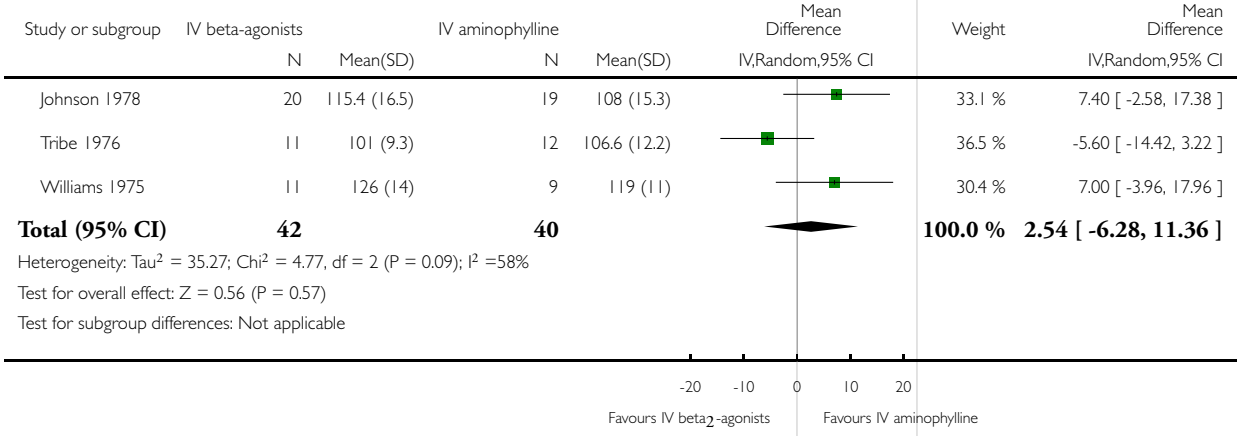


Analysis 1.15. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 15 Heart rate at 60 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 15 Heart rate at 60 min



Analysis 1.16. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 16 Heart rate final.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 16 Heart rate final

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Johnson 1978	20	114 (14.3)	19	104 (14.4)		10.00 [0.99, 19.01]

Analysis 1.17. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 17 Diastolic blood pressure at 60 min.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 17 Diastolic blood pressure at 60 min

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Johnson 1978	20	75 (8)	19	79 (7.8)		59.4 %	-4.00 [-8.96, 0.96]
Williams 1975	11	73 (7)	9	84 (10)		40.6 %	-11.00 [-18.73, -3.27]
Total (95% CI)	**31**		**28**			**100.0 %**	**-6.85 [-13.58, -0.11]**

Heterogeneity: Tau^2 = 13.52; Chi^2 = 2.23, df = 1 (P = 0.14); I^2 =55%

Test for overall effect: Z = 1.99 (P = 0.046)

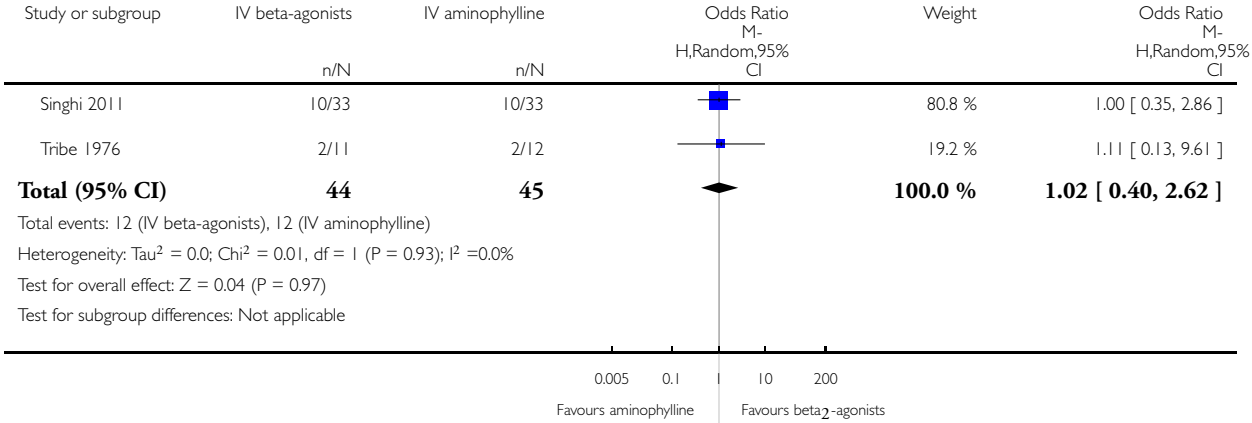
Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 18 Clinical failure.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 18 Clinical failure

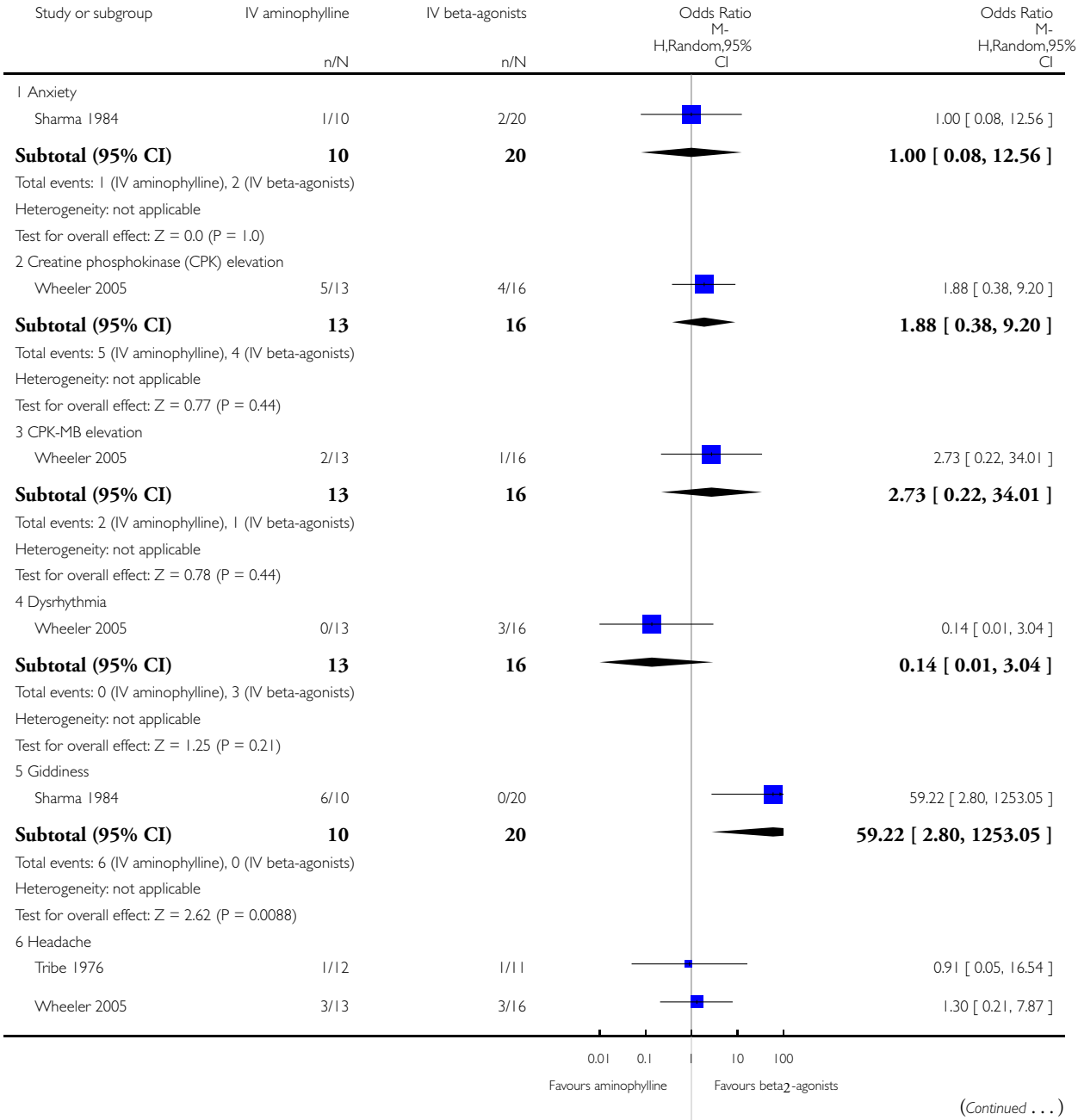


Analysis 1.19. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 19 Adverse effects.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 19 Adverse effects



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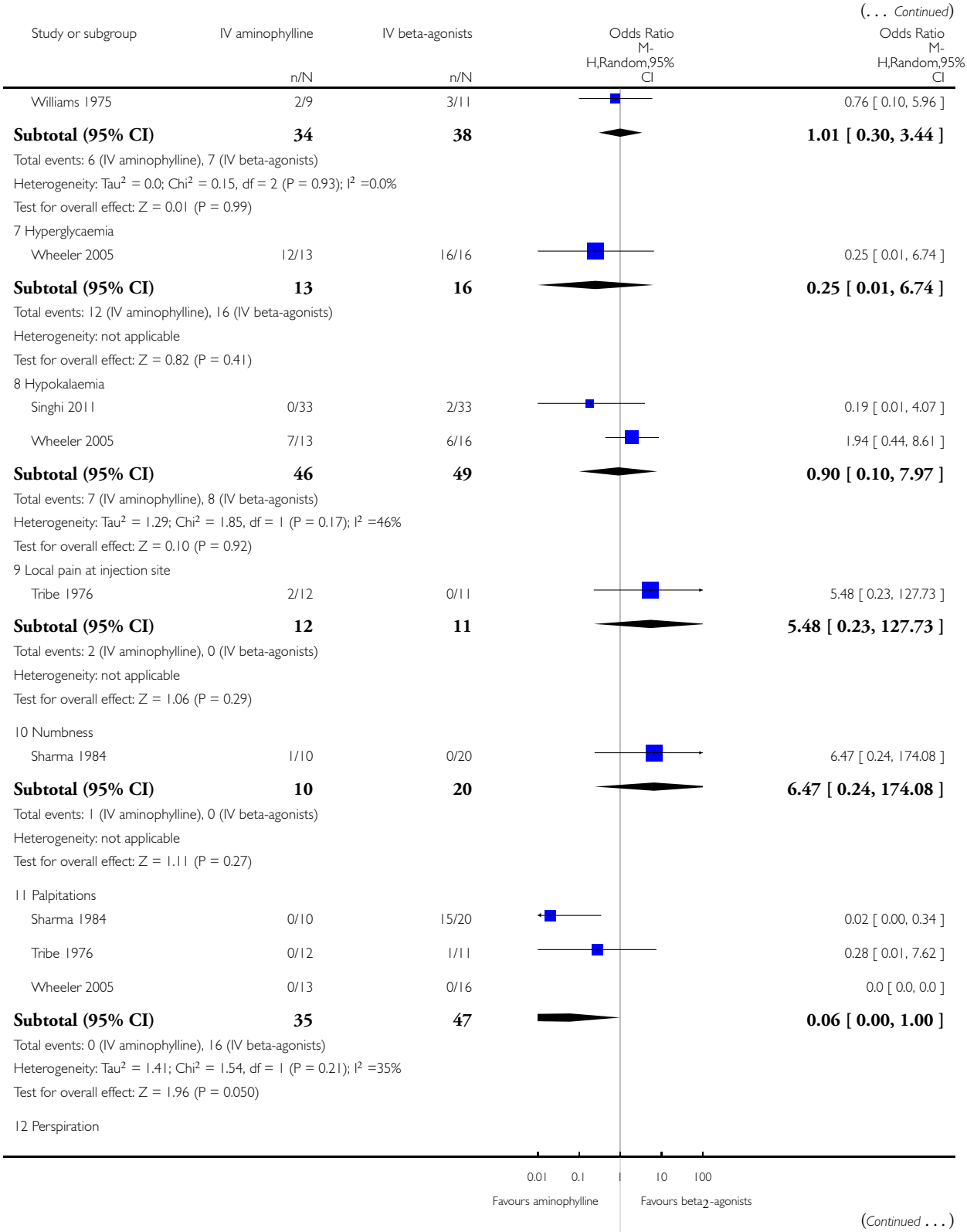

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Study or subgroup	IV aminophylline n/N	IV beta-agonists n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Sharma 1984	1/10	0/20		6.47 [0.24, 174.08]
Subtotal (95% CI)	**10**	**20**		**6.47 [0.24, 174.08]**
Total events: 1 (IV aminophylline), 0 (IV beta-agonists)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.11 (P = 0.27)				
13 Tremor				
Sharma 1984	0/10	7/20		0.09 [0.00, 1.68]
Tribe 1976	0/12	1/11		0.28 [0.01, 7.62]
Wheeler 2005	9/13	6/16		3.75 [0.79, 17.72]
Williams 1975	3/9	2/11		2.25 [0.29, 17.76]
Subtotal (95% CI)	**44**	**58**		**0.98 [0.18, 5.47]**
Total events: 12 (IV aminophylline), 16 (IV beta-agonists)				
Heterogeneity: Tau^2 = 1.59; Chi^2 = 6.44, df = 3 (P = 0.09); I^2 =53%				
Test for overall effect: Z = 0.02 (P = 0.98)				
14 Ventricular extrasystoles				
Williams 1975	4/9	0/11		18.82 [0.85, 414.97]
Subtotal (95% CI)	**9**	**11**		**18.82 [0.85, 414.97]**
Total events: 4 (IV aminophylline), 0 (IV beta-agonists)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.86 (P = 0.063)				
15 Nausea/vomiting				
Sharma 1984	1/10	0/20		6.47 [0.24, 174.08]
Singhi 2011	9/33	0/33		25.98 [1.44, 468.00]
Subtotal (95% CI)	**43**	**53**		**14.18 [1.62, 124.52]**
Total events: 10 (IV aminophylline), 0 (IV beta-agonists)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%				
Test for overall effect: Z = 2.39 (P = 0.017)				
16 Nausea				
Wheeler 2005	9/13	5/16		4.95 [1.02, 24.10]
Williams 1975	4/9	0/11		18.82 [0.85, 414.97]
Subtotal (95% CI)	**22**	**27**		**6.53 [1.60, 26.72]**
Total events: 13 (IV aminophylline), 5 (IV beta-agonists)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.58, df = 1 (P = 0.45); I^2 =0.0%				
Test for overall effect: Z = 2.61 (P = 0.0090)				
17 Vomiting				
Tribe 1976	1/12	0/11		3.00 [0.11, 81.61]
Wheeler 2005	9/13	7/16		2.89 [0.62, 13.46]

(*Continued* . . .)

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Study or subgroup	IV aminophylline n/N	IV beta-agonists n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Williams 1975	1/9	0/11		4.06 [0.15, 112.39]
Subtotal (95% CI)	**34**	**38**		**3.06 [0.85, 11.06]**
Total events: 11 (IV aminophylline), 7 (IV beta-agonists)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 2 (P = 0.98); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.71 (P = 0.088)				

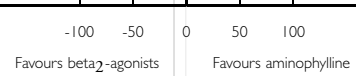
Analysis 1.20. Comparison 1 IV beta-agonists versus IV aminophylline, Outcome 20 Length of stay.

Review: Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma

Comparison: 1 IV beta-agonists versus IV aminophylline

Outcome: 20 Length of stay

Study or subgroup	IV beta-agonists N	Mean(SD)	IV aminophylline N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Paediatric (non-PICU)							
Roberts 2003	18	85.4 (56)	26	57.3 (43)		58.8 %	0.57 [-0.05, 1.18]
Subtotal (95% CI)	**18**		**26**			**58.8 %**	**0.57 [-0.05, 1.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.81 (P = 0.070)							
2 Paediatric (ICU)							
Wheeler 2005	16	4.9 (3)	13	4.4 (2.3)		41.2 %	0.18 [-0.55, 0.91]
Subtotal (95% CI)	**16**		**13**			**41.2 %**	**0.18 [-0.55, 0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)	**34**		**39**			**100.0 %**	**0.41 [-0.06, 0.88]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.63$, df = 1 (P = 0.43); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.70 (P = 0.090)							
Test for subgroup differences: $Chi^2 = 0.63$, df = 1 (P = 0.43), $I^2 = 0.0\%$							



ADDITIONAL TABLES

Table 1. Summary of included trials

Study	Aminophylline (N)	Beta$_2$-agonists (N)	Age group	Aminophylline dose	Beta$_2$-agonists dose
Evans 1980	6	7	Adults	IV Aminophylline 0.285 mg/kg/min for 15 min followed by 0.014 mg/kg/min for 23 h 25 min	IV Salbutamol 0.285 μg/kg/min followed by 0.057 μg/kg/min for 23 h 45 min
Femi-Pearse 1977	15	17	Adults	IV Aminophylline 250 mg for at least 15 min	IV Salbutamol 200 μg for at least 15 min
Hambleton 1979	*	*	18 Children	IV Aminophylline 4 mg/kg immediately and then 0.6 mg/kg/h continuously for 24 h	IV Salbutamol 4 μg/kg immediately then 0.6 μg/kg/h continuously for 24 h
Johnson 1978	19	20	Adults	IV Aminophylline infusion 1 mg/min at 75 min	IV salbutamol infusion at 10 μg/min at 75 min
Roberts 2003	26	18	Children	Continuous aminophylline infusion (bolus of 5 mg/kg over 20 min followed by an infusion of 0.9 mg/kg/h)	Single bolus of IV salbutamol (15 μg/kg over 20 min) followed by an infusion of saline
Sharma 1984	10	10	Adults	IV aminophylline 250 mg (10 mL in 10 min)	IV salbutamol 250 μg (1/2 mL) in 1 min and terbutaline 250 μg (1/2 mL diluted in normal saline) in 10 min[1]
Singhi 2011	33	33	Children	IV aminophylline 5 mg/kg bolus then 0.9 mg/kg/min for 1 h	IV Terbutaline 10 μg/kg over 30 min then 0.1 μg/kg/min for 1 h
Spiro 1976	14	16	Adults	IV aminophylline 1 mg/min	IV salbutamol 10 μg/min infusion
Tribe 1976	11	12	Adults	IV theophylline 250 mg at 0 min over 5 min	Salbutamol 100 μg iv at 0 min
Wheeler 2005	13	16	Children	IV theophylline 4.0 mL/kg (6.4 mg/kg) over 20 min,	IV terbutaline 0.17 mL/kg (20 g/kg) bolus and continuous infusion at a

Table 1. Summary of included trials (*Continued*)

				followed by a continuous infusion (age 3 to 8 years 0.6 mL/kg/h (0.96 mg/kg/h), age 9 to 12 years 0.5 mL/kg/h (0.80 mg/kg/h), age 12 to 15 years 0.4 mL/kg/h (0.64 mg/kg/h)	rate of 0.2 mL/kg/h (0.4 g/kg/min)
Williams 1975	9	11	Adults	IV aminophylline 500 μg at 0 min infused over 60 min	IV salbutamol 500 μg at 0 min infused over 60 min (8.33 μg/min)

FEV1: forced expiratory volume in 1 second; IV: intravenous.

[1]IV salbutamol (N = 10) vs. IV aminophylline (N = 10). In addition 10 patients received IV terbutaline and data from these patients have been combined with the 10 receiving IV salbutamol in the adverse effects analyses this review. FEV1 previously obtained for an earlier draft of this review for IV salbutamol (N = 10) vs. IV aminophylline (N = 10) is included in Analysis 1.7; Analysis 1.8; Analysis 1.9.

* Denotes uncertainty.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly

(*Continued*)

AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Database search strategies

Cochrane Airways Group Register (CAGR) of trials

(status* or emergenc* or ED or ER or trauma* or emergicent* or casualty or observation* or holding* or admit* or admission* or discharg* or hospitali* or outpatient* or acute* or exacerbat* or sever*) AND (bronchodilat* or "adrenergic beta-agonists" or beta-agonist or "beta agonist" or beta2* or beta-2* or albuterol or salbutamol or levalbuterol or levosalbutamol or ventolin* or proventil or ventosol or proair or isoproterenol or metaproterenol or aluprent or terbutaline or brethine or bricanyl or fenoterol or bedoradrine or reproterol or clenbuterol) AND (intraven* or IV or I.V. or bolus or infus* or inject*)
[Limited to records coded as 'asthma']

Clinicaltrials.gov

search terms = intravenous
study type = interventional studies
conditions = asthma

HISTORY

Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS

Travers A: initiated the review, wrote the protocol, performed searches, performed quality assessments, entered data and performed analysis, and primary author of review.

Jones AP: study selection, quality assessment, review of protocol.

Camargo CA Jr: protocol development, methodological input, statistical support, manuscript review at an early stage of this review's development

Rowe BH: co-authored protocol, performed selection for inclusion and quality assessment, data extraction and data entry, manuscript review, conversion to RevMan at an early stage of this review's development, and as assigned editor for the Cochrane Airways Group.

Milan SJ and Welsh E: independently selected trials for inclusion from initial searches.

Travers A and Milan SJ independently selected trials for inclusion from full trial reports and updated the 'Risk of bias' tables for trials already included in the review and similarly for any new trials identified in the update.

Milan SJ entered data and this was verified by Cates C.

Milan SJ drafted the review and further development was provided by Travers A and Cates C.

DECLARATIONS OF INTEREST

None. The authors are not involved in the primary research reported in this systematic review and have not represented the producers of these agents in the past.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2012 update of this review heterogeneity was assessed mainly in relation to the I^2 statistic. Risk of bias is assessed in accordance with Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).