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Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators (Review)

Mitra AAD, Bassler D, Watts K, Lasserson TJ, Ducharme FM

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[Intervention Review]

Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators

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ABSTRACT

Background

Since the advent of inhaled β_2 -agonists, anticholinergic agents and glucocorticoids, the role of aminophylline in paediatric acute asthma has become less clear. There remains some consensus that it is beneficial in children with acute severe asthma, receiving maximised therapy (oxygen, inhaled bronchodilators, and glucocorticoids).

Objectives

To determine if the addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma receiving conventional therapy.

Search methods

The Cochrane Airways Group register of trials was used to identify relevant studies. The latest search was carried out in February 2007.

Selection criteria

Randomised-controlled trials comparing intravenous aminophylline with placebo in addition to usual care in children met the inclusion criteria.

Data collection and analysis

Two reviewers independently assessed studies and extracted data. Disagreement in the selection of trials was resolved by consensus. Attempts were made to contact authors to verify accuracy of data.

Main results

Seven trials met the inclusion criteria (380 participants). Methodological quality was high. All studies recruited children with acute severe asthma and requiring hospital admission. Six studies sought participants who were unresponsive to nebulised short-acting beta-agonist and administered systemic steroids to study participants. In two studies where some children were able to perform spirometry, baseline FEV₁ was between 35 and 45% predicted. The addition of aminophylline to steroids and β_2 -agonist significantly improved FEV₁% predicted over placebo at 6-8 hours, 12-18 hours and 24 hours. Aminophylline led to a greater improvement in PEF% predicted over placebo at 12-18 hours. There was no significant difference in length of hospital stay, symptoms, frequency of nebulisations and mechanical ventilation

rates. There were insufficient data to permit aggregation for oxygenation and duration of supplemental oxygen therapy. Aminophylline led to a three-fold increase in the risk of vomiting. There was no significant difference between treatment groups with regard to hypokalaemia, headaches, tremor, seizures, arrhythmias and deaths.

Authors' conclusions

In children with a severe asthma exacerbation, the addition of intravenous aminophylline to β_2 -agonists and glucocorticoids (with or without anticholinergics) improves lung function within 6 hours of treatment. However there is no apparent reduction in symptoms, number of nebulised treatment and length of hospital stay. There is insufficient evidence to assess the impact on oxygenation, PICU admission and mechanical ventilation. Aminophylline is associated with a significant increased risk of vomiting.

PLAIN LANGUAGE SUMMARY

Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators

Acute asthma is a common paediatric emergency prevalent in many countries. Treatment aims to reverse asthma by opening up the airways and targeting the underlying inflammation of the airways. Beta-agonists, anticholinergic agents and glucocorticoids are currently the most commonly used strategies. In the past, aminophylline has been extensively used for the management of acute asthma, despite side effects. However, its use has declined with the availability of effective inhaled bronchodilators and glucocorticoids. The purpose of this review was to assess whether the use of intravenous aminophylline in children receiving maximised inhaled bronchodilators and glucocorticoids produced additional beneficial effects. We identified a small number of good quality trials which compared aminophylline with placebo in children given inhaled bronchodilators and glucocorticoid therapy. This review found evidence that children treated with aminophylline had a greater improvement in lung function than children treated with placebo, when both groups received inhaled bronchodilators and steroids and they responded incompletely to these initial therapies. However, aminophylline use also resulted in greater risk of vomiting. Aminophylline use in children may be appropriate if children have a role in severe acute exacerbations of asthma where response to maximised therapy (inhaled bronchodilators and glucocorticoids) is poor. These results are based on small numbers and further work in this area is required.

BACKGROUND

Intravenous aminophylline produced effective bronchodilation in children with acute severe asthma and was the drug of choice for many years (May 1974). The therapeutic effects of aminophylline in asthma include bronchodilation (Wolfe 1978) and improved diaphragmatic contraction (Wanke 1994). It also has inotropic and chronotropic effects on myocardium (Conrad 1981) and improves mental alertness. Therapeutic effects occur at blood levels of 10-20 mg/dl and perhaps at levels of below 10 mg/dl. Levels above this narrow therapeutic range may occur and cause toxic effects. These include diuresis, hypokalaemia, insomnia, tachycardia, cardiac dysrhythmias, convulsions and sudden death (Emerman 1990). In many centres it has become supplanted by the use of beta-2 agonists for the treatment of acute severe asthma.

More recently there has been renewed interest in intravenous aminophylline. Current guidelines assert that there may be a role for aminophylline in particularly severe asthma (BTS 2003). This review addresses the following question: "Do children with severe asthma who have a sub-optimal response to maximised treatment with oxygen, inhaled bronchodilators and glucocorticoids receive additional benefit following aminophylline?"

OBJECTIVES

We wish to determine if the addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma who are already receiving oxygen, maximised inhaled bronchodilators and oral/intravenous glucocorticoids. Benefits of interest include lung function, symptoms, oxygenation, needs for inhaled bronchodilators, ICU admission, mechanical ventilation, length of hospitalisation, and side effects.

In addition, we wished to examine whether any beneficial effect of aminophylline may be influenced by the intensity of concomitant therapy, i.e., amount of inhaled bronchodilators and/or late administration of glucocorticoids.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised-controlled trials comparing intravenous aminophylline with placebo were considered for this review.

Types of participants

Children aged between 2 to 17 years with acute severe asthma or status asthmaticus (acute, severe, refractory exacerbations) attending emergency departments, or in hospital wards or intensive care units were included.

Children with other chronic lung diseases (such as cystic fibrosis, bronchopulmonary dysplasia) were excluded.

Types of interventions

Children had to receive a loading dose of intravenous aminophylline followed by maintenance infusion, intravenous aminophylline boluses or oral theophylline.

Co-interventions included inhaled β_2 -agonists, glucocorticoids and oxygen.

Types of outcome measures

Primary outcomes

Improvement of lung function such as peak expiratory flow rates, FEV₁, FVC, respiratory resistance, etc.

Secondary outcomes

1. Oxygenation in room air (SaO₂ and PaO₂)
2. Requirement inspired oxygen concentration
3. Length of hospital admission
4. Clinical symptom scores measured at various points in time after receiving treatment.
5. The number of nebulisers (inhaled bronchodilators or inhaled short-acting β_2 agonists) required (aminophylline v placebo) in the first 24 hours.
6. Rates of admission to hospital wards, intensive care and intubation rates were also included.
7. Adverse events: vomiting, headache, tremor, seizures, tachycardia, arrhythmias, hypertension, the magnitude of diuresis and incidence of hypokalaemia, and death were examined.

For the studies based in emergency department, the endpoints also included admission rates to ICU/wards, intubation and relapse rates. For inpatient studies, endpoints included the rate and duration of intubation and the duration of ICU/hospital admission.

Search methods for identification of studies

Electronic searches

The standard Cochrane Airways Group methodology was used.

The Cochrane Airways Group asthma register was searched using the following terms

[child* OR adolescen* OR ped* OR paed* OR preschool OR pre-school OR young] AND [emerg* OR acute* OR severe* OR intensive* OR status] AND [aminophylline* OR intravenous theophylline* OR xanthin* OR methylxanthin*] AND [asthma OR asthmaticus]

A search of CENTRAL was also carried out using the same search terms.

Each abstract was reviewed by one reviewer and annotated as:

- (1) RCT
- (2) Possible RCT
- (3) Clearly not an RCT.

Searching other resources

The full-text publications of all references, irrespective of language of publication, identified as "RCTs" or "possible RCTs" were obtained and reviewed by both reviewers. Secondly, bibliography of all RCTs and review articles identified above, were checked to identify potentially relevant citations. Thirdly, the pharmaceutical companies producing aminophylline were contacted. Enquiries regarding other published or unpublished studies known and/or supported by the companies involved were made so that relevant

trials could be included. Finally, personal contact with colleagues working in the field of paediatric asthma were made to identify potentially relevant trials. The last search was carried out in February 2007.

Data collection and analysis

Selection of studies

Selection of included studies and assessment of study quality were performed on the full text article, by two reviewers masked to the authors' names and affiliation, name of journal, date of publication, and sources of financial support for the study. Disagreement was resolved by consensus.

Inter-reviewer agreement in the selection of relevant studies and in the assessment of methodological quality was calculated using the kappa statistics and the weighted kappa with quadratic means.

Data extraction and management

Attempts were made to contact an author of each RCT, by mail, fax and/or electronic mail, on at least three occasions to verify the accuracy of the extracted data and to provide additional data, if necessary.

Assessment of risk of bias in included studies

The methodological quality of eligible controlled trials was assessed by two different methods. The quality of blinding was ranked using the Cochrane Approach and recorded under "Allocation Concealment"

A referred to adequate concealment

B referred to uncertainty about adequacy of concealment

C referred to clearly inadequate concealment.

Jadad's 5-point instrument was used to evaluate the reported quality of randomisation and blinding, and the description of withdrawals and dropouts (Jadad 1996). This blind assessment has been shown to be valid and associated with high inter-rater reliability. Whenever possible, authors of relevant publications were asked to confirm these assessments of study methodology.

Assessment of heterogeneity

Where the I square statistic exceeded 0%, we also applied Random Effects modelling. However, we present the results of both models where this re-analysis affected the direction of the pooled effect estimate. In such instances we have also attempted to explain the sources of observed heterogeneity.

Data synthesis

Continuous variables

For continuous data variables we have calculated a Fixed Effect Weighted Mean Difference (WMD) for data measured on the same scale. For data measured on different scales which could not be converted to a WMD, we have pooled using a Fixed Effect Standardised Mean Difference (SMD).

Dichotomous variables

For outcomes where data are reported as binary event data, we have pooled studies with a Fixed Effect Risk Ratio (RR). However, where studies have reported no events occurring and

thus contribute zero event rates to analyses, we reported the risk differences, in addition to relative risk, to incorporate their estimates in the analysis.

Data were pooled with a fixed effect model using Review Manager software.

Subgroup analysis and investigation of heterogeneity

We intended to perform the following subgroup analyses in the presence of heterogeneity:

1. Baseline severity of asthma exacerbation as determined by lung function tests (severity based upon BTS 2003).
2. Intensity of bronchodilator therapy prior to aminophylline infusion, determined by cumulative dose/Kg of beta2-agonists with/without anticholinergic agents. Intensity of bronchodilator will serve to stratify trials in three groups:
 - Maximised β_2 -agonist therapy - more than 0.45 mg/Kg/hr of salbutamol equivalent i.e. three doses of 0.15 mg/kg/hr
 - Maximised β_2 -agonist therapy combined with anticholinergic agents
 - Sub-maximal bronchodilation
3. Aminophylline levels < 15mcg/ml compared with levels $\geq$ 15mcg/ml

The secondary aim is to test the hypothesis that children receiving maximised amounts of inhaled bronchodilators and early glucocorticoids showed minimal benefit from the addition of intravenous aminophylline compared with children receiving sub-optimal bronchodilators and late glucocorticoids. Adverse effect outcomes were stratified by aminophylline levels in the lower (<15mcg/ml) and higher ($\geq$ 15mcg/ml) part of the therapeutic range. Heterogeneity of effect size was assessed with the Chi square analysis test (Matthews 1996).

Sensitivity analysis

A sensitivity analysis based on methodological quality and publication status was carried out for these areas. An additional sensitivity analysis considered the timing and intensity of treatment with glucocorticoids.

RESULTS

Description of studies

Results of the search

Search results from February 2006-February 2007

For an archive of the searches for this review Table 1. For the update of this review three references were retrieved from a total of 19 references. One of these was an unpublished conference abstract from a study already excluded from the review (Ream 2001). Two additional references pertained to assessment of aminophylline in the acute setting, one of which was in adults (Nakano 2006) and one was not randomised (Yamauchi 2005), therefore neither met the review entry criteria.

Included studies

Seven studies met the inclusion criteria of the review. Five were from the USA, one from Australia and one from Turkey.

Design

All included trials were placebo controlled, double blind and randomised.

Participants

All studies pertained to children with acute severe asthma who required hospital admission. Failure to respond to 2-3 successive nebulizations of albuterol was a prerequisite in all studies except for [Strauss 1994](#), in which failure to respond to bronchodilator was not a stipulated entry criterion. In two studies where ability to perform spirometry was an inclusion criterion (FEV₁ - [Carter 1993](#) or PEF - [Strauss 1994](#)), baseline mean predicted FEV₁ and PEF at randomisation were respectively 41% ([Carter 1993](#)), and 37.5% ([Strauss 1994](#)). Prior treatment with theophylline was an exclusion criterion for all studies. The mean age of the children in all the studies was between 5 years and 9 years, except for [Strauss 1994](#) where children were slightly older (mean age aminophylline group 11.5 years, placebo group 10.7 years). Baseline severity for each trial (including details of concomitant therapies used) is reported in Table 02.

Settings

All studies were conducted in a hospital setting. Six studies were conducted in emergency departments. [Carter 1993](#) was conducted in an in-patient setting.

Intervention

Intravenous aminophylline was given as an initial bolus, followed by a continuous infusion with serum levels checked to ensure "therapeutic levels" in all eight studies. "Therapeutic levels" were considered to be 10-20 mcg/ml in 4 studies ([Bien 1995](#); [Carter 1993](#); [Needleman 1995](#); [Strauss 1994](#)), 10.5-14.3mcg/ml in 1 study ([Nuhoglu 1998](#)), 12-20 mcg/ml in another trial ([Di Giulio 1993](#)), while [Yung 1998](#) aimed for higher levels of 15-20 mcg/ml. Children were given oxygen, regular beta agonists and glucocorticoids from the outset in all the studies. Only children in [Yung 1998](#) also received nebulized ipratropium as well as beta agonists. In all studies aminophylline was compared to placebo.

Outcomes

All the studies used similar and validated clinical scores except for [Strauss 1994](#). Three studies reported lung function ([Carter 1993](#), [Strauss 1994](#); [Yung 1998](#)). Three studies reported the number of nebulized bronchodilators required ([Di Giulio 1993](#); [Nuhoglu 1998](#); [Strauss 1994](#)). Three studies reported on length of stay in hospital ([Needleman 1995](#); [Strauss 1994](#); [Yung 1998](#)). One study also reported oximetry and ventilator rates ([Yung 1998](#)). Seven studies reported side effects ([Needleman 1995](#)) did not. Admission rates to PICU and mechanical ventilation were not always recorded as some trials excluded children who required PICU admission.

Excluded studies

See [Characteristics of excluded studies](#).

Risk of bias in included studies

The overall risk of bias was low, with a number of studies employing adequate procedures to minimise the risk of bias in allocating participants to treatment groups, and masking treatment group assignment. All the studies had adequate concealment of allocation. Inclusion and exclusion criteria were clearly reported in trials, as were withdrawals and dropouts. Statistical methods used for analysis were explained in the studies. Confirmation of methodology and study design was obtained for three of the seven studies ([Carter 1993](#); [Nuhoglu 1998](#); [Yung 1998](#)).

Effects of interventions

Data were stratified on the basis of β_2 -agonist treatment (submaximal inhaled β_2 (<45 mg/kg/hr); maximized inhaled β_2 (≥ 0.45 mg/kg/hr); maximised β_2 (≥ 0.45 mg/kg/hr) + anticholinergics). This is because other subgroup analyses to examine the impact of baseline severity, intensity of bronchodilator therapy prior to randomisation and aminophylline serum levels on study results could not be done because of the small number of trials reporting these values. In addition, the impact on the timing and intensity of treatment with glucocorticoids on study results could not be examined because all trials used adequate early doses of parenteral glucocorticoids.

Lung function

Patients receiving aminophylline displayed significant greater improvement in % predicted FEV₁ compared to placebo at 6-8 hours (8.37% predicted, 95% CI: 0.82, 15.92; 2 trials, [Analysis 1.2](#)), 12-18 hours (8.15% predicted, 95% CI: 1.04, 15.27; 2 trials, [Analysis 1.3](#)), and 24 hours (8.87% predicted, 95% CI: 1.25, 16.50; 2 trials, [Analysis 1.4](#)).

Patients receiving aminophylline displayed significantly greater improvement in PEF compared with placebo at 6-8 hours (SMD 0.62, 95% CI 0.04 to 1.2; or around 14% predicted based upon the pooled deviation of [Yung 1998](#), [Analysis 1.6](#)) 12-18 hours (SMD 0.75, 95% CI 0.25 to 1.26; or around 9% predicted based upon the standard deviation of [Yung 1998](#), [Analysis 1.7](#)), but was not significant at 24 hours (SMD 0.39, 95% CI -0.51 to 1.30, [Analysis 1.8](#)). The interpretation of the SMD expressed as % improvement PEF does assume that the pooled standard deviation of [Yung 1998](#) applies to the other studies.

There were insufficient data to permit aggregation of FEV₁ and PEF at other points in time. Clearly, the weight carried by [Yung 1998](#) markedly influenced the lung function results. Due to the small numbers it was also not possible to carry out Chi square testing for heterogeneity.

Symptoms

There was a significant difference in favour of aminophylline at 6-8 hours (SMD: -0.42 (95% CI: -0.70, -0.14; 2 trials). However, at 24 hours there was no significant difference between treatment groups (SMD -0.13 95% CI: -0.52, 0.25; submaximal subgroup). Note that although [Yung 1998](#) did not present data at 24hours, the authors reported that there was no significant difference.

Medication Usage

There was no significant difference between aminophylline and placebo in terms of the number of nebulized bronchodilators required in 24 hours (WMD = 0.15, 95% CI: -0.52, +0.83; 2 trials).

There were no data to analyse in terms of oxygenation, or reduction in supplemental oxygen therapy.

Length of stay in hospital

There was no significant difference in length of stay between aminophylline and placebo (WMD = -2.1 hours, 95% CI: -9.45, +5.25; 3 trials). These findings included the data from [Yung 1998](#) after we calculated treatment and control group data from a published length of stay ratio given as 0.94 (95% CI 0.77, 1.14, $p = 0.53$).

PICU admission rates

[Yung 1998](#) did not report whether the difference in admission to PICU rates between aminophylline and placebo was significant (42% versus 51% respectively), but did report a significant effect in favour of aminophylline in terms of the number of children intubated (0 versus 5 in the aminophylline and placebo groups respectively, $p = 0.027$). However the children in the aminophylline group were all intubated prior to receiving aminophylline, and no children who had been loaded with aminophylline subsequently required intubation.

Length of Stay in PICU

There was no data reported on length of stay in PICU.

Adverse Effects & Withdrawals

There was a statistically significant increased risk of vomiting in the aminophylline group compared to placebo (RR = 3.59, 95% CI: 2.15, 6.33; 5 trials). There was no significant difference in the incidence of headache (RR = 1.24 95% CI: 0.71, 2.17; 4 trials), tremor (RR = 0.71, 95% CI: 0.71, 1.52; 3 trials), or seizures (RD = 0.00 (95% CI -0.03, 0.03; 4 trials).

No data were reported for tachycardia, hypertension, and diuresis. No deaths were reported.

There were low withdrawal rates in the studies, and there was no significant risk difference in rates of withdrawal due to adverse events (RD = 0.01 95% CI -0.03, 0.04; 7 trials), poor asthma control (RD = 0.00 95% CI -0.04, 0.03) or withdrawal for any reason (RD = 0.02 95% CI -0.02, 0.07, 7 trials).

DISCUSSION

In children with sub-optimal response to one hour of treatment with maximised beta-agonists and systemic glucocorticoids, with or without inhaled anticholinergics, the addition of aminophylline improved lung function (FEV₁) within six hours of treatment, and the favourable effect persisted for 24 hours. Subgroup analyses were inadequately powered to detect the impact of baseline severity, serum aminophylline levels and intensity of co-treatment on the magnitude of effect. The early improvement in lung function did coincide with an improvement in symptoms at 6-8 hours, but the sustained effect on FEV₁ was not matched by that of PEF or symptoms at 24 hours. There was no significant difference in the number of nebulised treatment in the initial 24 hours, admission

rate to ICU or the length of hospital stay. There were no or insufficient data to examine any effect of treatment on oxygenation and avoidance of mechanical ventilation. Other than a three-fold increase in the risk of vomiting, the addition of aminophylline was not associated with apparent increase in other side effects or in withdrawals.

In children with very severe asthma exacerbations, not responding to maximised inhaled therapy and glucocorticoids, admission to intensive care and possibly intubation may be required. In these children, even a small improvement in lung function might be important clinically; thus, the observed increased in lung function associated with theophylline use may translate in a clinical benefit that could not be captured by aggregated outcomes. [BTS 2003](#) recommend that IV aminophylline at a loading dose of 5mg/kg over 20 minutes followed by a continuous infusion of 1mg/kg, should be *considered* in a high dependency setting where children over two years of age are unresponsive to β_2 -agonist and steroid therapy. The trial from which this recommendation is mainly derived did detect significant differences in terms of lung function, and there was a slightly lower ICU admission rate favouring the aminophylline group ([Yung 1998](#)). The findings of this study are noteworthy, not least due to the intensive β_2 -agonist regime initiated by the trialists. Failure to respond to a β_2 -agonist was an inclusion criterion in this study, and as such the positive effect of aminophylline would have been more easily detected as the sample was carefully selected. In contrast [Strauss 1994](#) did not detect significant differences on any clinical outcome. In this study particularly severe children were not included and initial response to a bronchodilator was not assessed. The lower threshold for clinical scores as an exclusion criterion may have rendered the sample less severe, and therefore less likely to benefit from the addition of aminophylline.

Whilst improvements in lung function did not always correlate with improvements in symptoms, some clinical assessment undertaken did incorporate lung function assessment. [Yung 1998](#) reported significant changes in both clinical assessment scores and lung function; the remaining studies which reported both outcomes did not report improvements in either. The absence of a significant effect on symptom scores after 6-8 hours may be related to the small number of trials with low numbers of their participants reporting these outcomes. The censored nature of spirometric outcomes in paediatric trials (where only a subset of participants are able to provide data on FEV₁ or PEF) may prevent a clearer picture emerging from the data. In future studies, stratification of data between those able and those unable to perform spirometry would facilitate better scrutiny of the relationship (if any) between lung function and symptoms in the acute setting. One further explanation for this could be that the association between changes in clinical scores remain largely unvalidated against changes in lung function. There may be different sensitivities in the symptom scores used, and between-observer reproducibility may also vary ([Chalut 2000](#)).

Data from only two trials did not identify a difference in the number of nebulised bronchodilators which children required in the first 24 hours after admission and length of hospital admission. Insufficient data prevented aggregation of data for more clinically important outcomes such as risk of ICU admission and mechanical ventilation.

In one small study which did not meet the inclusion criteria of the review ([Ream 2001](#)), aminophylline did lead to faster clinical

improvement. Whilst not in itself a reason to recommend routine use of aminophylline, the study does justify further work in this subgroup of patients, and in particular those who have been mechanically ventilated.

Several adverse events classically associated with this therapy that did not occur with greater frequency in the actively treated group (such as headache, tremor and seizures). However, use of aminophylline was associated with a 3.7 fold increased in the risk of vomiting. While aminophylline appears otherwise safe, the discomfort associated with increased vomiting should be acknowledged.

Firm conclusions regarding any differences in the response to aminophylline between children who have failed to respond to β_2 -agonists and those who improve after administration of these drugs could not be drawn. The largest trial (Yung 1998) which showed a positive effect of aminophylline clearly influenced the results of this meta-analysis, and was conducted in a quite carefully selected sample of children. Whilst this study was not the only one to maximise the dose of β_2 -agonists, it was the largest one and therefore had the greatest statistical power of the assembled studies to detect differences. Further trials would help to clarify the validity of the findings of this review and could help to determine more clearly the role of aminophylline in acute severe asthma in comparison with other therapies currently recommended in this setting, including IV MgSO_4 (BTS 2003).

AUTHORS' CONCLUSIONS

Implications for practice

In children with a severe asthma acute exacerbation, unresponsive to maximised bronchodilation, supplemental oxygen and systemic steroids, the addition of aminophylline improves lung function within six to eight hours of treatment with an improvement in symptoms up to eight hours after therapy. The addition of

aminophylline was not associated with a significant reduction in the number of nebulised bronchodilator treatments and length of hospital stay. There is insufficient evidence to confirm whether these benefits translate in more important outcomes such as improved oxygenation, and reduction in the rate and length of intensive care admission and mechanical ventilation.

Implications for research

Due to the promising findings in several small trials, larger paediatric studies involving children aged 1 to 17 years with severe acute asthma are needed. Randomised controlled trials should compare aminophylline with placebo as add-on therapy to maximised inhaled/nebulised β_2 -agonists and anticholinergics with early intravenous glucocorticoids. The trials should be sufficiently powered to examine the rate of intubation and mechanical ventilation in children with acute severe asthma, and therefore be preferably multicentre trials.

We urge trialists to measure and report changes in lung function, symptoms (using validated and responsive symptom scores), saturation, oxygen requirement, intensive care admission rates, intubation rates and side effects at various points in time (e.g., 4, 6, 12 and 24 hours).

Studies comparing aminophylline with other alternative treatments such as MgSO_4 and IV β_2 -agonists would be useful in establishing the relative efficacies of these treatments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bien 1995

Methods	DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial OUTCOME ASSESSOR BLINDING: Adequate WITHDRAWAL/DROPOUTS: All patients accounted for
Participants	ELIGIBLE: No comment. We are not told about people who were approached but declined the study

Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators (Review)

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Bien 1995 (Continued)

RANDOMISED: 44 (Aminophylline Group 22, Placebo Group 22, 5 withdrawals)
COMPLETED : 39 (Aminophylline Group 19, Placebo Group 20)
MEAN AGE : Aminophylline Group 5.7 years, Placebo Group 4.1 years (statistically significant)
Sex; Aminophylline Group Male:14 (74%), Female 5 (26%)
Placebo Group Male 12 (60%), Female 8 (40%)
ASTHMA DIAGNOSIS: American Thoracic Society Definition of Asthma
RECRUITMENT: Children aged 2 - 10 years admitted to Children's Hospital Medical Center in Cincinnati, Ohio requiring admission for acute severe asthma.
Children were excluded if they required intensive care, had a diagnosis of pneumonia, a pyrexia above 101.5 Fahrenheit, a chronic illness other than asthma, a history of adverse reaction to study medications, current usage of systemic corticosteroids or medication which alters theophylline metabolism, a serum level of theophylline above 2.5micrograms/mL or previous admission to the study.

Interventions	<p>SETTING: Hospital admissions for acute severe asthma</p> <p>PRIOR TREATMENT: Nebulised albuterol.</p> <p>MODE:Children received an intravenous infusion or placebo</p> <p>CO-INTERVENTIONS:</p> <p>1.Oxygen to maintain saturations above 94%, 2.Methylprednisolone 2mg/Kg at enrolment followed by 1mg/kg of methylprednisolone intravenously every 6 hours,</p> <p>3. Nebulised albuterol 2.5mg with a maximum interval of 6 hours</p> <p>DURATION: The first 24 hours after admission</p>
Outcomes	<p>Pulmonary index clinical score incorporating, respiratory rate, wheeze, inspiratory/expiratory ratio and accessory muscle usage.</p> <p>Oxygen saturation in room air</p> <p>Peak flows in children able to cooperate 6 - 10 years</p> <p>Theophylline levels</p> <p>Aerosol Requirement</p> <p>Toxicity ie nausea, vomiting, insomnia, headache, irritability and seizures</p> <p>Measurements were taken at baseline, 8hours, 16 and 24 hours after admission</p>
Notes	<p>JADAD SCORE = 5</p> <p>Randomisation = 1 point Double Blind = 1 point Description of withdrawals = 1 point</p> <p>Method of randomisation is described = 1 point Method of blinding was appropriate = 1 point</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation from a computer generated sequence
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-blind, placebo controlled trial

Carter 1993

Methods	<p>DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial</p> <p>OUTCOME ASSESSOR BLINDING: Not Stated</p> <p>WITHDRAWAL/DROPOUTS: All patients accounted for</p>
Participants	<p>ELIGIBLE: No comment. We are not told about people who were approached but declined the study</p> <p>RANDOMISED: 25 (4 withdrawals)</p> <p>COMPLETED : 21 (Aminophylline Group 12, Placebo Group 9)</p> <p>MEAN AGE : Aminophylline Group 12 years, Placebo Group 11 years</p>

Carter 1993 (Continued)

Sex; Aminophylline Group Male:8 (66%), Female: 4 (33%)
 Placebo Group Male: 6 (66%), Female: 3 (33%)
 ASTHMA DIAGNOSIS: American Thoracic Society Definition
 RECRUITMENT: Children aged 5 - 18 years admitted to Shands Hospital, University of Florida for treatment of severe asthma. Lack of response to 3 albuterol nebulisers of 5mg at 20mt intervals. Excluded children had an underlying illness or PCO₂ >50mmHg after the nebulisers or couldn't perform pulmonary function tests

Interventions	SETTING: Hospital admissions for acute severe asthma PRIOR TREATMENT: 5mg of nebulised albuterol given every 20 mts on three occasions. MODE:Children received an intravenous infusion or placebo CO-INTERVENTIONS: 1. Oxygen to maintain saturations above 92%, 2.Methylprednisolone(1mg/Kg of iv) 6 hourly, 3.Nebulised albuterol 2.5mg - 5mg every 20 mts - 6 hourly depending on FEV1. DURATION: 36 hours after entry into study
Outcomes	CLINICAL SCORE incorporating, respiratory rate, wheeze, inspiratory/expiratory ratio and accessory muscle usage. FEV1 as percentage of predicted normal values for age and height Nausea, Headache, Palpatations and Tremor
Notes	JADAD SCORE = 5 Randomisation = 1 point Double - Blind = 1 point Description of Dropouts = 1 point Randomisation, by computer generated numbers in envelopes(author contacted) = 1 points Double Blinding was appropriate = 1 point

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated numbers in envelopes (author contacted)
Allocation concealment?	Low risk	Aminophylline and placebo solutions prepared by the pharmacy service
Blinding? All outcomes	Low risk	Identically presented treatments

Di Giulio 1993

Methods	DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial OUTCOME ASSESSOR BLINDING: Not Stated WITHDRAWAL/DROPOUTS: All patients accounted for
Participants	ELIGIBLE: No comment. We are not told about people who were approached but declined the study RANDOMISED: 34 (5 withdrawals) COMPLETED : 29 (Aminophylline Group 16, Placebo Group 13) MEAN AGE : Aminophylline Group 6.9 years, Placebo Group 7.4 years Sex; Aminophylline Group Male:11 (69%), Female: 5 (31%) Placebo Group Male: 9 (69%), Female: 4 (31%) ASTHMA DIAGNOSIS: Physician definition of recurrent wheezing responsive to bronchodilators RECRUITMENT: Children aged 2 - 18 years in the paediatric emergency Department. Insufficient improvement to allow discharge following 3 nebulisers of albuterol 2.5mg every 20 mts Exclusion criteria - No theophylline products in the previous 48 hours or a theophylline level less than 5.0mg/L (27.5micromol/L)

Di Giulio 1993 (Continued)

Asthma score less than or equal to 3 after emergency treatment
Presentation outside 8am and 11pm
Exclusions included intensive care admissions, corticosteroids in the fortnight prior to admission or pregnancy

Interventions	<p>SETTING: Emergency department for acute severe asthma PRIOR TREATMENT: 2.5mg of nebulised albuterol given every 20 mts on three occasions. MODE: Children received an intravenous infusion or placebo CO-INTERVENTIONS: 1. Oxygen to maintain saturations above 92%, 2. Methylprednisolone (2mg/Kg of iv) initially followed by 0.5mg/Kg every 6 hours, 3. albuterol 2.5mg, 3 - 4 hourly as directed by the physician DURATION: Until discharge</p>
Outcomes	<p>CLINICAL SCORE incorporating, respiratory rate, wheeze, inspiratory/expiratory ratio and accessory muscle usage. Number of hours to reach a clinical score of 2 or less Number and dose of albuterol administered Effects such as Pulse, Blood Pressure, Emesis and Tremor</p>
Notes	<p>JADAD SCORE = 4 Randomisation = 1 point Double - Blind = 1 point Description of Dropouts = 1 point Randomisation, no comment on method = 0 points Double Blinding was appropriate = 1 point</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical placebo and theophylline preparations

Needleman 1995

Methods	<p>DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial OUTCOME ASSESSOR BLINDING: Not Stated WITHDRAWAL/DROPOUTS: All patients accounted for</p>
Participants	<p>ELIGIBLE: No comment. We are not told about people who were approached but declined the study RANDOMISED: 45 (3 withdrawals) COMPLETED : 42 (Aminophylline Group 22, Placebo Group 20) MEAN AGE : Aminophylline Group 8.5 years, Placebo Group 7.0 years Sex; Aminophylline Group Male: 5 (23%), Female: 17 (77%) Placebo Group Male: 8 (40%), Female: 12 (60%) ASTHMA DIAGNOSIS: A previous diagnosis of asthma or reactive airways disease and were actively wheezing at presentation to the emergency department RECRUITMENT: Children aged 2 - 18 years admitted to University of Maryland Medical Center, Baltimore, for the treatment of acute severe asthma. Lack of clinical improvement after three albuterol nebulisations at 20 minute intervals was determined by the senior pediatric resident and the pediatric emergency department attending physician.</p>

Needleman 1995 (Continued)

Patients were excluded if they had taken theophylline within 48 hours of admission or had a serum level above 2.5 micromoles/litre, had underlying cardiac disease or were admitted to intensive care.

Interventions	<p>SETTING: Hospital admissions for acute severe asthma</p> <p>PRIOR TREATMENT: Nebulised albuterol given every 20 mts on three occasions.</p> <p>MODE: Children received an intravenous infusion or placebo</p> <p>CO-INTERVENTIONS:</p> <p>1. Oxygen to maintain saturations above 94%, 2. Methylprednisolone 2mg/Kg per day (maximum of 125mg), 3. Nebulised 2 hourly albuterol 2.5mg, with the interval increased as tolerated.</p> <p>DURATION: Until Discharge</p>
Outcomes	<p>CLINICAL SCORE incorporating, respiratory rate, wheeze, inspiratory/expiratory ratio and accessory muscle usage.</p> <p>Length of Stay</p> <p>Spirometry</p> <p>Pulse Oximetry</p>
Notes	<p>JADAD SCORE = 4</p> <p>Randomisation = 1 point Double - Blind = 1 point Description of Dropouts = 1 point</p> <p>Randomisation was appropriate = 0 points Double Blinding was appropriate = 1 point</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Low risk	Sealed envelopes prepared by the pharmacy service
Blinding? All outcomes	Low risk	Identically presented treatments

Nuhoglu 1998

Methods	<p>DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial</p> <p>OUTCOME ASSESSOR BLINDING: Yes</p> <p>WITHDRAWAL/DROPOUTS: All patients accounted for</p>
Participants	<p>ELIGIBLE: Children who did not respond to two nebulisers of salbutamol 2.5mg, 20mts apart or who had an asthma score above 3</p> <p>RANDOMISED: 38 children (Aminophylline Group 18, Placebo Group 20)</p> <p>COMPLETED : 36 (Aminophylline Group 17, Placebo Group 19)</p> <p>MEAN AGE : Aminophylline Group 5.9 years, Placebo Group 5.2 years</p> <p>Sex; Aminophylline Group Male: 6 (35%), Female: 11 (65%)</p> <p>Placebo Group Male: 7 (37%), Female: 12 (63%)</p> <p>ASTHMA DIAGNOSIS: American Thoracic Society Definition</p> <p>RECRUITMENT: Children aged 2 to 16 years unresponsive to 2 doses of salbutamol 2.5mg. Lack of clinical improvement after two salbutamol nebulisations at 20 minute intervals was determined by the attending paediatrician in the emergency department. Patients were excluded if they had taken theophylline within 48 hours of admission or had no improvement after 6 hours of therapy</p>
Interventions	<p>SETTING: Hospital admissions for acute severe asthma in Istanbul, Turkey</p> <p>PRIOR TREATMENT: 2 doses of nebulised salbutamol 2.5mg given 20 mts apart.</p> <p>MODE: Children received an intravenous infusion or placebo</p> <p>CO-INTERVENTIONS:</p> <p>1. Oxygen to maintain saturations above 92%,</p>

Nuhoglu 1998 (Continued)

2. Methylprednisolone (2mg/Kg)
3. Nebulised salbutamol 2.5mg was given every 20 - 30mts if the asthma score was 9 - 12 or the FEV1 was <40% predicted of normal. Nebulised salbutamol 2.5mg was given every 2- 3hrs if the FEV1 was 40 - 50% predicted of normal or if the asthma score was 6 - 9. Nebulised salbutamol 2.5mg was given every 3- 6hrs if the FEV1 was > 50% predicted or if the asthma score was 3 - 6.
DURATION: The first 24hours and then patients were reviewed in outpatients

Outcomes	Number of salbutamol nebulisers needed in the first 24hours CLINICAL SCORE incorporating breathing rate, wheeze, lung auscultation and accessory muscle usage at baseline and 2.6.12 and 24 hours after entering study. Peak Flow recordings at baseline, 2, 6, 12 and 24 hours after entering study. Adverse effects such as headache, nausea, vomiting, irritability, tremor, seizures
Notes	JADAD SCORE = 5 Randomisation = 1 point Double - Blind = 1 point Description of Dropouts = 1 point Author contacted - If patients were allocated an even number they received aminophylline Rand Double Blinding was appropriate = 1 point. Author contacted and assessors were blinded as well as patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	High risk	If patients were allocated an even number they received aminophylline (author contacted)
Blinding? All outcomes	Low risk	Identically presented treatments

Strauss 1994

Methods	DESIGN: Prospective, Randomised, Double - Blind, Placebo - Controlled Trial OUTCOME ASSESSOR BLINDING: Not blinded WITHDRAWAL/DROPOUTS: All patients accounted for
Participants	ELIGIBLE: No comment. We are not told about people who were approached but declined the study RANDOMISED: 31 (Aminophylline Group 14, Placebo Group 17) COMPLETED : 26 (Aminophylline Group 11, Placebo Group 15, 5 withdrawals) MEAN AGE : Aminophylline Group 11.5 years, Placebo Group 10.7 years Sex; Aminophylline Group Male:8 (57%), Female 6 (43%) Placebo Group Male 10 (59%), Female 7 (41%) ASTHMA DIAGNOSIS: American Thoracic Society Definition of Asthma RECRUITMENT: Children aged 5 - 18 years, admitted with an acute exacerbation of asthma, via the emergency department of Schneider Children's Hospital of the Long Island Jewish Medical Center or Queens Hospital Center. Ability to perform a reproducible peak flow was required. Patients with a Wood-Downes score of >5 and patients admitted to intensive care were excluded. Patients with a theophylline level >5mcg/ml at entry or who had taken a slow release dose 4 hours prior to arrival in casualty were excluded. Children who had systemic diseases, who were too mild to require intravenous aminophylline or who were on medications that might affect aminophylline metabolism were excluded. Children could withdraw from the study at any time at their request, at their parents' request or if the attending physician felt it appropriate.
Interventions	SETTING: Hospital admissions for acute severe asthma PRIOR TREATMENT: Three doses of nebulised albuterol, each of 1.25mg if the child weighed less than 30Kg or 2.5mg if above 30Kg.

Strauss 1994 (Continued)

MODE:Children received an intravenous infusion or placebo

CO-INTERVENTIONS:

1. Oxygen, 2.methylprednisolone (1mg/Kg intravenously every 6 hours),
3. Nebulised albuterol was given at the above doses four hourly but the paediatricians could increase how frequently it was given.

DURATION: The length of admission

Outcomes	<p>LENGTH OF HOSPITAL STAY</p> <p>PEAK FLOW RATES using a Wright flow meter before and after nebulisations and expressed as a percentage of the predicted peak flow, the value obtained from a standard table</p> <p>ADVERSE EFFECTS i.e. nausea, vomiting, headache, abdominal pain, seizure, arrhythmias, palpitations</p> <p>NUMBER OF ADDITIONAL ALBUTEROL NEBULISERS IN FIRST 24 HOURS</p>
Notes	<p>JADAD SCORE = 4</p> <p>Randomised = 1 point, Double-blind = 1 point, Description of withdrawals and dropouts = 1 point</p> <p>No comment on method of randomisation = 0, Method of blinding was appropriate = 1 point</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomisation stated but not described
Allocation concealment?	High risk	The pharmacy and study investigators knew which drug the child was receiving during administration
Blinding? All outcomes	Low risk	Identically presented treatments

Yung 1998

Methods	<p>DESIGN:Prospective, Randomised, Double - Blind, Placebo - Controlled Trial</p> <p>OUTCOME ASSESSOR BLINDING: No</p> <p>WITHDRAWAL/DROPOUTS: All patients accounted for</p>
Participants	<p>ELIGIBLE: 1300 admissions with asthma, 191 eligible for study. Most of 1300 were not eligible for study as they were not sick enough. 163 consented for the study</p> <p>RANDOMISED: 163 (4 withdrawals)</p> <p>COMPLETED : 159 (Aminophylline Group 81, Placebo Group 78)</p> <p>MEAN AGE : Aminophylline Group 6.3 years, Placebo Group 6.2 years</p> <p>Sex; Aminophylline Group Male:43 (53%), Female: 38 (47%)</p> <p>Placebo Group Male: 46 (56%), Female: 36 (44%)</p> <p>ASTHMA DIAGNOSIS: A previous diagnosis of asthma or reactive airways disease and were actively wheezing at presentation to the emergency department</p> <p>RECRUITMENT: Children aged 1 - 19 years unresponsive to 3 doses of salbutamol 5mg. Lack of clinical improvement after three albuterol nebulisations at 20 minute intervals was determined by the senior pediatric resident and the pediatric emergency department attending physician.</p> <p>Patients were excluded if they had taken theophylline within 48 hours of admission or had a serum level above 2.5 micromoles/litre, had underlying cardiac disease or were admitted to intensive care.</p>
Interventions	<p>SETTING: Hospital admissions for acute severe asthma in Australia</p> <p>PRIOR TREATMENT: Nebulised albuterol given every 20 mts on three occasions.</p> <p>MODE:Children received an intravenous infusion or placebo</p> <p>CO-INTERVENTIONS:</p> <ol style="list-style-type: none"> 1. Oxygen to maintain saturations above 94%, 2.Methylprednisolone (1mg/Kg) 6 hourly ,

Yung 1998 (Continued)

3. Nebulised salbutamol 5mg as determined by medical staff and 4. Nebulised ipratropium 250mcg 4 to 6 hourly.
DURATION: Until Discharge

Outcomes	Length of Stay in hospital Spirometry Peak Flow CLINICAL SCORE incorporating, heart rate, wheeze and accessory muscle usage. Pulse Oximetry Heart Rate Supplemental oxygen Total Dose of Salbutamol used Effects such as headache, nausea, vomiting, irritability, tremor, seizures Duration of mechanical ventilation
Notes	JADAD SCORE = 5 Randomisation = 1 point Double - Blind = 1 point Description of Dropouts = 1 point Randomisation was appropriate = 1 point Double Blinding was appropriate = 1 point

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomisation stated but not described
Allocation concealment?	Low risk	Sequentially numbered boxes containing aminophylline or placebo according to a computer generated code
Blinding? All outcomes	Low risk	Identically presented treatments

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baba 2002	RCT comparing aminophylline with a water soluble forskolin derivative (NKH477). This study was excluded as it was conducted in adults, and it did not have a placebo control group.
Evans 1979	RCT comparing aminophylline with salbutamol or combination of the two. This study was excluded as it did not have a placebo arm.
Hambleton 1979	This double blind trial compares intravenous salbutamol with intravenous aminophylline. The purpose of the meta analysis is to determine if intravenous aminophylline gives additional effect following maximal inhaled bronchodilators. Consequently this study does not fit the inclusion criteria as it is not looking at the two agents together.
Kato 2004	Not randomised.
Matsubara 1998	This was a before and after study and compared the effect of intravenous aminophylline administered after saline had been infused as a control. The study was neither randomised nor of parallel design and so could not be considered for inclusion in the review.

Study	Reason for exclusion
Nakano 2006	Study conducted in adults
Pierson 1971	<p>This trial compares subcutaneous adrenaline as a bronchodilator, instead of inhaled beta 2 agonists. Furthermore the aminophylline dosage was sub-optimal</p> <p>Firstly, as the study by Zvi Ben-Zvi et al: An Evaluation of the Initial Treatment of Acute Asthma. Paediatrics Vol 70, no 3 September 1982, pages 348 - 353 shows, the subcutaneous adrenaline is a much less effective bronchodilator than nebulised agents in children. Thus it might be expected that aminophylline makes a difference in this study but might not in clinical practice with the bronchodilators in common use today. Thus this study does not fit the inclusion criteria of the meta analysis which is looking at whether aminophylline has benefit following maximal inhaled bronchodilators.</p> <p>Secondly, at 24 hours, 11 patients in the aminophylline group had serum levels below 7.5mcg/ml and 8 of these 11 had levels below 5mcg/ml. With such low levels it makes it difficult to ascribe their clinical improvement to the theophylline they received.</p>
Ream 2001	RCT conducted in PICU without a placebo control.
Roberts 2003	RCT comparing aminophylline with beta-agonists. This study was excluded due to the absence of a placebo group.
Tomac 1996	This study was a randomised trial, but compared aminophylline with corticosteroids as a control instead of comparing it with placebo. This study could not be considered for inclusion in the review.
Wang 2004	Study of the effects of theophylline in chronic asthma
Yamauchi 2005	Study conducted in adults

DATA AND ANALYSES

Comparison 1. Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 - Change in % Predicted FEV1 within 4hrs of enrolment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Maximised inhaled beta2 (>=0.45 mg/kg/hr)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV1 - Change in % Predicted FEV1 6-8 hrs after enrolment	3	65	Mean Difference (IV, Fixed, 95% CI)	8.37 [0.82, 15.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Submaximal inhaled beta 2 (<.45mg/Kg/hr)	1	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Maximised inhaled beta 2 (>=.45mg/kg/hr)	1	21	Mean Difference (IV, Fixed, 95% CI)	5.45 [-6.33, 17.23]
2.3 Maximised beta 2 (>=0.45mg/kg/hr) and anticholinergics	1	42	Mean Difference (IV, Fixed, 95% CI)	10.40 [0.57, 20.23]
3 FEV1 - Change in % Predicted FEV1 at 12-18hrs after enrolment	3	57	Mean Difference (IV, Fixed, 95% CI)	8.15 [1.04, 15.27]
3.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	1	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Maximised inhaled beta2 (>=0.45 mg/kg/hr)	1	20	Mean Difference (IV, Fixed, 95% CI)	5.74 [-6.14, 17.62]
3.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	1	35	Mean Difference (IV, Fixed, 95% CI)	9.50 [0.62, 18.38]
4 FEV1 - Change in %Predicted FEV1 at 24hrs after enrolment	3	62	Mean Difference (IV, Fixed, 95% CI)	8.87 [1.25, 16.50]
4.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	1	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Maximised inhaled beta2 (>=0.45 mg/kg/hr)	1	21	Mean Difference (IV, Fixed, 95% CI)	7.36 [-7.61, 22.33]
4.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	1	39	Mean Difference (IV, Fixed, 95% CI)	9.4 [0.54, 18.26]
5 Peak Flow - Change in % Predicted PEF within 4 hrs of enrolment	0		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Maximised inhaled beta2 (>=.45 mg/kg/hr)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Peak Flow - Change in PEF at 6-8hrs after enrolment (SMD)	2	50	Std. Mean Difference (IV, Fixed, 95% CI)	0.92 [0.32, 1.52]
6.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	1	8	Std. Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.96, 1.98]
6.2 Maximised inhaled beta2 (>=0.45 mg/kg/hr)	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	1.00 [0.35, 1.66]
7 Peak Flow - Change PEF at 12-18hrs after enrolment (SMD)	3	67	Std. Mean Difference (IV, Fixed, 95% CI)	0.75 [0.25, 1.26]
7.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	2	32	Std. Mean Difference (IV, Fixed, 95% CI)	0.73 [-0.01, 1.48]
7.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	1	35	Std. Mean Difference (IV, Fixed, 95% CI)	0.77 [0.08, 1.47]
8 Peak Flow - Change PEF at 24 hrs after enrolment (SMD)	3	70	Std. Mean Difference (IV, Random, 95% CI)	0.39 [-0.51, 1.30]
8.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	2	31	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-1.39, 2.04]
8.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	1	39	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.01, 1.31]
13 Oxygenation (SaO2 or PaO2) within 4hrs of enrollment	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Oxygenation (SaO2 or PaO2) at 6-8hrs after enrollment	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Oxygenation (SaO2 or PaO2) at 12-18hrs after enrollment	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Oxygenation (SaO2 or PaO2) at 24hrs after enrolment	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Supplemental Oxygen, reduction within 4hrs of enrolment	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
17.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Maximised inhaled beta2 (>=.45 mg/kg/hr)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Supplemental Oxygen, reduction at 6-8hrs after enrolment	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Supplemental Oxygen, reduction at 12-18 hrs after enrolment	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
19.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)t	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Supplemental Oxygen, reduction at 24hrs after enrolment	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
20.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Change in symptom scores within 4hrs of enrolment - SMD (Standardised Mean Difference)	0		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Change in symptom scores 6-8hrs after enrolment - SMD (Standardised Mean Difference)	3	215	Std. Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.70, -0.13]
22.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	1	39	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.94, 0.32]
22.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	1	21	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	1	155	Std. Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.77, -0.13]
23 Change in symptom scores 12-18hrs after enrolment - SMD (Standardised Mean Difference)	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
23.1 Submaximal inhaled beta2 (< 0.45 mg/kg/hr)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Maximised inhaled beta2 (≥ 0.45 mg/kg/hr)	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.3 Maximised Beta 2 (≥ 0.45 mg/kg/hr) + anticholinergics	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24 Change in symptom scores 24hrs after enrolment - SMD (Standardised Mean Difference)	4	127	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.52, 0.25]
24.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)	3	106	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.52, 0.25]
24.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	1	21	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Number of nebulisers required in 24hours	2	69	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.52, 0.83]
25.1 Submaximal inhaled beta 2 (<0.45mg/Kg/hr)	2	69	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.52, 0.83]
25.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 ICU Admission Rates	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
26.1 Submaximal inhaled beta2 (<.45 mg/kg/hr) over first 2 hrs	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Maximal inhaled Beta 2 (>=.45mg/kg/hr) over first 2 hours	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Rates of Patients Mechanically Ventilated in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
27.1 Submaximal inhaled beta2 (<.45 mg/kg/hr) over first 2 hrs	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.2 maximized inhaled beta2 (>=0.45 mg/kg/hr) over first 2 hrs	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Length of Hospital Stay	3	231	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-9.45, 5.25]
28.1 Submaximal Beta 2 (<0.45mg/Kg/hr)	1	26	Mean Difference (IV, Fixed, 95% CI)	6.00 [-20.49, 32.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.2 Maximised beta 2 (>0.45mg/Kg/hr)	1	42	Mean Difference (IV, Fixed, 95% CI)	4.10 [-13.73, 21.93]
28.3 Submaximal Beta 2 (<0.45mg/kg/hr) + anticholinergics	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.4 Maximised Beta 2 (>= 0.45mg/Kg/hr) + anticholinergics	1	163	Mean Difference (IV, Fixed, 95% CI)	-4.32 [-12.79, 4.15]
29 Vomiting	5	305	Risk Ratio (M-H, Fixed, 95% CI)	3.69 [2.15, 6.33]
29.1 Mean Theophylline Levels < 15mg/L (mcg/ml)	4	142	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.17, 6.39]
29.2 Mean Theophylline Levels >= 15mg/L (mcg/ml)	1	163	Risk Ratio (M-H, Fixed, 95% CI)	4.43 [2.19, 8.95]
30 Headache	3	238	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.70, 2.33]
30.1 Mean Theophylline level < 15mg/L (mcg/ml)	2	75	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [0.67, 44.61]
30.2 Mean Theophylline level >= 15mg/L (mcg/ml)	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.53, 1.93]
31 Tremor	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.88, 2.07]
31.1 Mean Theophylline level < 15mg/L (mcg/ml)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.3 [0.56, 3.02]
31.2 Mean Theophylline level >= 15mg/L (mcg/ml)	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.84, 2.23]
32 Seizures	4	274	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.03, 0.03]
32.1 Mean Theophylline Level < 15mg/L (mcg/ml)	2	88	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.06, 0.06]
32.2 Mean Theophylline level >= 15mg/L (mcg/ml)	2	186	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.03, 0.03]
33 Hypokalaemia	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
33.1 Mean Theophylline Levels < 15mg/L (mcg/ml)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.2 Mean Theophylline levels >= 15mg/L (mcg/ml)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Arrhythmias	2		Risk Difference (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
34.1 Mean Theophylline level < 15mg/L (mcg/ml)	2		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
34.2 Mean Theophylline level >= 15mg/L (mcg/ml)	0		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
35 Blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
35.1 Mean Theophylline level < 15mg/L (mcg/ml)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Mean Theophylline level >= 15mg/L (mcg/ml)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Magnitude of diuresis	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
36.1 Mean Theophylline levels < 15mg/L (mcg/ml)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.2 Mean Theophylline level >= 15mg/L (mcg/ml)	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 Incidence of hypokalaemia	0		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
37.1 Mean Theophylline levels < 15mg/L (mcg/ml)	0		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.2 Mean Theophylline level >=15mg/L (mcg/ml)	0		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38 Death	6		Risk Difference (M-H, Random, 95% CI)	Totals not selected
38.1 Mean Theophylline level < 15mg/L (mcg/ml)	4		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
38.2 Mean Theophylline level >= 15mg/L (mcg/ml)	2		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
40 Withdrawal due to adverse health events	7	370	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.03, 0.04]
40.1 Mean Theophylline levels < 15mg/L (mcg/ml)	5	186	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.05, 0.07]
40.2 Mean Theophylline level >=15mg/L (mcg/ml)	2	184	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
41 Withdrawal due to poor asthma control	7	370	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.04, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Mean Theophylline levels < 15mg/L (mcg/ml)	5	186	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.07, 0.05]
41.2 Mean Theophylline level >=15mg/L (mcg/ml)	2	184	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
43 Withdrawal (any cause)	7	371	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.02, 0.07]

Analysis 1.1. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 1 FEV1 - Change in % Predicted FEV1 within 4hrs of enrolment.

Study or subgroup	Aminophylline		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.1.1 Submaximal inhaled beta2 (<.45 mg/kg/hr)						
Nuhoglu 1998	1	6 (0)	1	-11 (0)		Not estimable
1.1.2 Maximized inhaled beta2 (>=0.45 mg/kg/hr)						
Carter 1993	12	6 (15)	9	3.9 (11)		2.08[-9.04,13.2]
1.1.3 Maximised Beta 2 (>=0.45mg/kg/hr) + anticholinergics						
					Placebo better	Aminophylline better

Analysis 1.2. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 2 FEV1 - Change in % Predicted FEV1 6-8 hrs after enrolment.

Study or subgroup	Aminophylline		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.2.1 Submaximal inhaled beta 2 (<.45mg/Kg/hr)							
Nuhoglu 1998	1	12 (0)	1	15 (0)			Not estimable
Subtotal ***	1		1				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.2.2 Maximised inhaled beta 2 (>=.45mg/kg/hr)							
Carter 1993	12	5.7 (15)	9	0.2 (12.5)		41.08%	5.45[-6.33,17.23]
Subtotal ***	12		9			41.08%	5.45[-6.33,17.23]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							
1.2.3 Maximised beta 2 (>=0.45mg/kg/hr) and anticholinergics							
Yung 1998	25	14.1 (16)	17	3.7 (16)		58.92%	10.4[0.57,20.23]
Subtotal ***	25		17			58.92%	10.4[0.57,20.23]
Heterogeneity: Not applicable							
Test for overall effect: Z=2.07(P=0.04)							
					Placebo better		Aminophylline better

Analysis 1.3. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 3 FEV1 - Change in % Predicted FEV1 at 12-18hrs after enrolment.

Analysis 1.4. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 4 FEV1 - Change in %Predicted FEV1 at 24hrs after enrolment.

Analysis 1.6. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 6 Peak Flow - Change in PEF at 6-8hrs after enrolment (SMD).

Analysis 1.7. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 7 Peak Flow - Change PEF at 12-18hrs after enrolment (SMD).

Analysis 1.8. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 8 Peak Flow - Change PEF at 24 hrs after enrolment (SMD).

Analysis 1.22. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 22 Change in symptom scores 6-8hrs after enrolment - SMD (Standardised Mean Difference).

Analysis 1.23. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 23 Change in symptom scores 12-18hrs after enrolment - SMD (Standardised Mean Difference).

Analysis 1.24. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 24 Change in symptom scores 24hrs after enrolment - SMD (Standardised Mean Difference).

Analysis 1.25. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 25 Number of nebulisers required in 24hours.

Analysis 1.26. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 26 ICU Admission Rates.

Analysis 1.27. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 27 Rates of Patients Mechanically Ventilated in ICU.

Analysis 1.28. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 28 Length of Hospital Stay. **Analysis 1.29. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 29 Vomiting.**

Analysis 1.30. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 30 Headache.

Analysis 1.31. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 31 Tremor.

Analysis 1.32. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 32 Seizures.

Analysis 1.34. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 34 Arrhythmias.

Study or subgroup	Aminophylline n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.34.1 Mean Theophylline level < 15mg/L (mcg/ml)				
Bien 1995	0/22	0/22		0[-0.08,0.08]
Strauss 1994	0/14	1/17		-0.06[-0.22,0.1]
1.34.2 Mean Theophylline level $\geq$ 15mg/L (mcg/ml)				
Favours treatment -1000 -500 0 500 1000 Favours control				

Analysis 1.35. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 35 Blood pressure.

Study or subgroup	Aminophylline		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.35.1 Mean Theophylline level < 15mg/L (mcg/ml)						
Di Giulio 1993	1	135 (0)	1	135 (0)		Not estimable
1.35.2 Mean Theophylline level $\geq$ 15mg/L (mcg/ml)						
Favours treatment -10 -5 0 5 10 Favours control						

Analysis 1.38. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 38 Death.

Study or subgroup	Aminophylline n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.38.1 Mean Theophylline level < 15mg/L (mcg/ml)				
Bien 1995	0/22	0/22		0[-0.08,0.08]
Di Giulio 1993	0/16	0/13		0[-0.13,0.13]
Nuhoglu 1998	0/17	0/19		0[-0.1,0.1]
Strauss 1994	0/14	0/17		0[-0.12,0.12]
1.38.2 Mean Theophylline level $\geq$ 15mg/L (mcg/ml)				
Carter 1993	0/12	0/11		0[-0.15,0.15]
Yung 1998	0/81	0/82		0[-0.02,0.02]
Favours treatment -1000 -500 0 500 1000 Favours control				

Analysis 1.40. Comparison 1 Aminophylline + β 2-agonists & systemic steroids versus placebo + β 2-agonists & systemic steroids, Outcome 40 Withdrawal due to adverse health events.

Study or subgroup	Aminophylline n/N	Placebo n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.40.1 Mean Theophylline levels < 15mg/L (mcg/ml)					
Bien 1995	0/22	0/22		11.93%	0[-0.08,0.08]
Di Giulio 1993	0/16	0/13		7.78%	0[-0.13,0.13]
Aminophylline better -1 -0.5 0 0.5 1 Placebo better

Analysis 1.41. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 41 Withdrawal due to poor asthma control.

Analysis 1.43. Comparison 1 Aminophylline + β_2 -agonists & systemic steroids versus placebo + β_2 -agonists & systemic steroids, Outcome 43 Withdrawal (any cause).

ADDITIONAL TABLES

Table 1. Characteristics of Included Studies by Subgroups

Study	Baseline Severity	Prior B2 dosage	Timing of Steroids	Steroid Dosage
Bien 1995	Pulmonary Index of 6.5 - 7.0		At enrollment then 6 hourly intravenously	Methyl prednisolone 2mg/Kg at enrollment then 1mg/ kg qds iv
Carter 1993	Mean Predicted FEV1 of 40% - 42%	Three nebulisers of albuterol 5mg at 20mt intervals	At enrollment then 6 hourly intravenously	Methyl prednisolone 1mg / Kg
Di Giulio 1993	Clinical Asthma score of 6	Three nebulisers of albuterol 2.5mg at 20 mt intervals	At enrollment then 6 hourly intravenously	Methyl prednisolone 2mg/Kg at enrollment then 0.5mg/Kg every 6 hours
Needleman 1995	Asthma Score of 6.96 - 7.0	Three nebulisers of albuterol at 20 mt intervals	At enrollment then not stated but at least daily	Methyl prednisolone 2mg/Kg per day (maximum of 125mg),
Nuhoglu 1998	Asthma Score 6.7 - 6.9	Two albuterol nebulisers 2.5mg at 20 mt intervals	At enrollment	Methyl prednisolone 2mg/Kg

Table 1. Characteristics of Included Studies by Subgroups *(Continued)*

Strauss 1994	Mean predicted PEF of 35% -40%	Three nebulisers of al-butanol at 20 mt intervals	At enrollment then 6 hourly intravenously	Methyl prednisolone 1mg/Kg
Yung 1998	Mean Predicted FEV1 of 36% - 39%	Three albuterol nebulisers 5mg at 20mt intervals	At enrollment then 6 hourly intravenously	Methyl prednisolone 1mg/Kg

WHAT'S NEW

Date	Event	Description
31 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 4, 2001

Date	Event	Description
20 January 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dirk Bassler and Andy Mitra reviewed the abstracts and selected the trials that possibly met the inclusion criteria. We obtained the full text of any possible trials and then agreed whether the trial should be included or not. We agreed a methodological quality score for each trial. Disagreement was resolved by consensus. Andy Mitra worked on the methodology and analysis and sent updated copies of the review to Dirk Bassler for comments. Francine Ducharme supervised the review and gave much helpful guidance and advice. Toby Lasserson and Kirsty Watts assessed studies and wrote-up findings for the updated version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Inhalation; Aminophylline [*administration & dosage] [adverse effects]; Asthma [*drug therapy]; Bronchodilator Agents [*administration & dosage] [adverse effects]; Injections, Intravenous; Randomized Controlled Trials as Topic; Vomiting [chemically induced]

MeSH check words

Adolescent; Child; Child, Preschool; Humans