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Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why?

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ABSTRACT

Acute, severe exacerbations of asthma present a challenge due to the significant morbidity associated with this presentation. For exacerbations that are refractory to initial treatments with inhaled and oral therapies, there is still doubt about which intravenous therapies are most likely to be helpful. β-2 agonists and aminophylline have differing mechanisms of action that also affect their adverse effects profiles and these are considered. A review of the available randomised control trials suggests that a bolus of intravenous salbutamol may reduce symptoms and hasten recovery. Aminophylline infusions may improve lung function, and in some studies have been shown to improve symptoms, but the evidence is not clear cut. Decisions about which treatment to use should include risk management considerations such as ease of prescription, preparation and administration factors and availability of high-dependency beds.

INTRODUCTION

The pathophysiology of asthma exacerbations is complex. Exposure to a trigger induces a complex interplay of factors, including eosinophil and mast cell degranulation and epithelial damage. These cause histamine, prostaglandin and leukotriene release. Continuing T cell and B cell differentiation and proliferation, promoted by cytokine release, perpetuate this cascade. Subsequent inflammation, bronchoconstriction and mucus production cause airway obstruction and impairment of gas exchange.[1]

Although most children improve after inhaled bronchodilator by nebuliser or spacer, some require intravenous treatment. Magnesium sulfate is often used as the first-line intravenous therapy for such children.[2] In children who require additional intravenous therapy, salbutamol and aminophylline are used in practice, but there is no clear consensus around which should be used first.[3] In this paper, we aim to summarise the pharmacological basis of these agents and evidence from randomised controlled trials (RCTs) relating to their efficacy and safety.

PHARMACOLOGY OF B-2 AGONISTS

Salbutamol and terbutaline are similar β-2 adrenoceptor agonists that are believed to exert their maximal therapeutic effect through bronchodilation. Stimulation of β-2 receptors in airway smooth muscle induces the cyclic AMP (c-AMP) pathway. c-AMP is a molecule with various cellular functions. Increased activity of c-AMP-dependent protein kinase A inhibits myosin phosphorylation and lowers intracellular calcium concentration, which in turn relaxes smooth muscle and causes bronchodilation.[4] Increased intracellular c-AMP may also inhibit mast cell inflammatory mediator release (figure 1; adapted from refs. 5 and 6). Severe airway obstruction may restrict delivery of inhaled salbutamol to the airway epithelium, thus providing a theoretical rationale for the use of intravenous preparations. Because adrenoreceptors are found in various organs and tissues, β-2 agonists can also cause various extrapulmonary adverse effects.

Pharmacokinetics

The half-life of salbutamol is 4–6 h, and it is excreted renally. The bronchodilatory effects of salbutamol are believed to occur at blood concentrations of between 5 and 20 ng/mL, and higher concentrations are thought to result in a greater risk of toxicity. There are limited data regarding the ideal dosing schedule for intravenous salbutamol in children.

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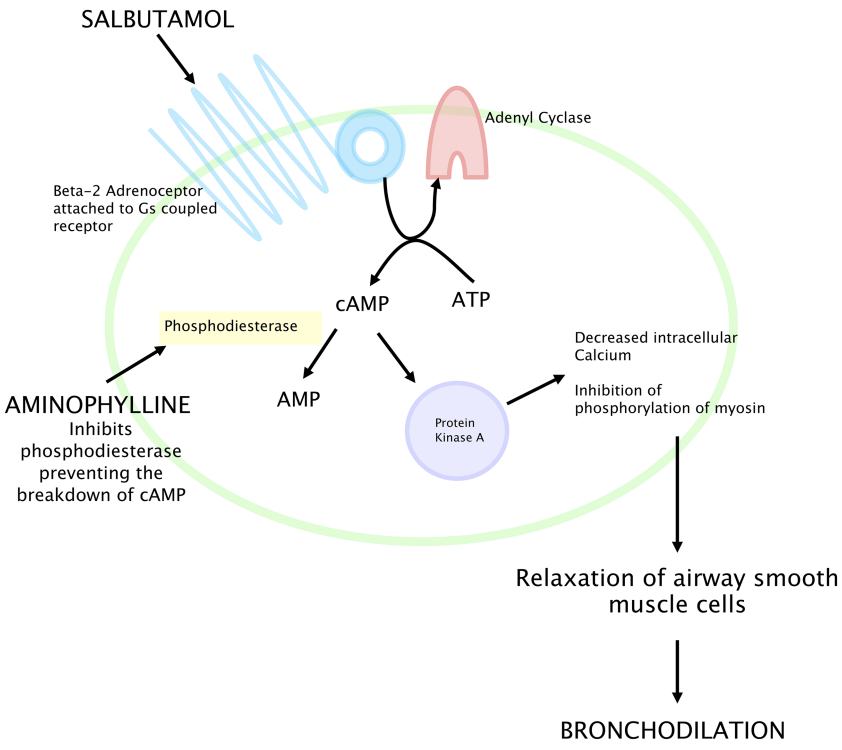

Figure 1 An illustration of the mechanisms by which salbutamol and aminophylline may cause bronchodilation through increasing intracellular cyclic AMP levels.

A recent review commented on the relatively high doses per unit of weight advised for use in children compared with adult regimens and recommended further research into the pharmacodynamics and pharmacokinetics of intravenous salbutamol in the paediatric population.[7]

Cardiovascular effects

Salbutamol stimulates both β-1 and β-2 receptors in the heart and can reduce afterload through vasodilation and a drop in vascular resistance.[8 9] These effects can cause significant tachycardia, postural hypotension and myocardial ischaemia.

Muscle tremors

Stimulation of β-2 receptors in skeletal muscle may cause tremors, which can be uncomfortable for children.

Metabolic effects of β-2 agonists

β-2 agonists can cause hypokalaemia, in a dose-dependent fashion, because β-2 receptors are linked to membrane bound Na^+/K^+ ATPase pumps. They can stimulate β-2 receptors in both pancreatic islet cells and hepatocytes, causing increased insulin secretion (which can exacerbate hypokalaemia) and increased glycogenolysis, respectively.[10 11] Patients treated with intravenous salbutamol may develop lactic acidosis because of β-2-stimulated anaerobic glycolysis in muscle. This has been demonstrated in healthy subjects[12] and has been observed in asthmatic individuals.[13 14] There are reports of the subsequent metabolic acidosis contributing to a perception of increased respiratory distress with a concomitant and unnecessary treatment escalation or continuation. There do not seem to be reports of the lactic acidosis having any directly harmful consequences.

Tolerance

There is evidence that regular use of inhaled β-2 agonists can modify the response of the β-2 receptor resulting in reduced efficacy.[15] This may make the use of intravenous salbutamol less beneficial in some cases, but the clinical significance of this finding in the management of acute exacerbations of asthma remains unclear.

PHARMACOLOGY OF AMINOPHYLLINE

Aminophylline is a methylated xanthine derivative. It is a combination of theophylline (the active component) and ethylenediamine, which is a compound that increases the solubility of theophylline but has no known intrinsic pharmacological effects.

The mechanisms of action of aminophylline are not completely understood. Beneficial effects may result from both bronchodilation and reduced airway hypersensitivity, but the extent to which each mechanism confers benefit at therapeutic doses is unclear.[16 17] Effective use of the drug also requires a consideration of its pharmacokinetics

Pharmacokinetics

Aminophylline has a narrow therapeutic range, and the associations between elevated levels and unwanted effects are important to consider. The bronchodilator

Table 1 A comparison of factors affecting prescription, administration and monitoring when using intravenous aminophylline and intravenous salbutamol infusions and boluses[W20—25]

		Aminophylline	Salbutamol infusion	Salbutamol bolus
Administration details	Reconstitution Dilution	▶ No, solution ▶ Yes: suggested concentrations 1 mg/mL ▶ Has been used neat (25 mg/mL) in fluid restriction (central line preferred as highly irritant)	▶ No, solution ▶ Yes, suggested concentration of 200 μg/mL for central line and 10–20μg/mL for peripheral line ▶ Has been used neat (1 mg/mL) in fluid restriction (central line only)	▶ No, solution ▶ Yes, suggested concentration of 200 μg/mL for central line and 10–20 μg/mL for peripheral line ▶ Has been used neat (1 mg/mL) in fluid restriction (central line only)
	Calculation complexity	▶ Yes: multistep calculation for dilution and rate	▶ Yes: multistep calculation for dilution and rate ▶ Conversion between milligrams and micrograms ▶ Conversion between hours and minutes	▶ Yes: multistep calculation for dilution and rate ▶ Conversion between milligrams and micrograms
	Therapeutic risk	▶ High: narrow therapeutic index drug	▶ High	▶ High
	Need to use part vials	▶ Yes: for loading dose ▶ Yes/no: for maintenance infusion depending on house recommendations	▶ Yes ▶ Also for larger patients need to use multiple vials to avoid multiple bag changes	▶ Yes
	Different strengths available	▶ No	▶ Yes	▶ Yes
	Need for infusion pump	▶ Yes	▶ Yes	▶ Yes
	Other	▶ Loading dose and maintenance rate will have different rates and potentially different concentrations ▶ Stable for 24 h once dilutes	▶ Protect from light ▶ Stable for 24 h once diluted	▶ Protect from light ▶ Stable for 24 h once diluted
	Risk score	▶ Amber: moderate risk	▶ Amber: moderate risk	▶ Amber: moderate risk
Fluid compatibility	Additive	▶ Sodium chloride 0.9% and 0.45% ▶ Dextrose 5% ▶ Combination of the above ▶ Combination of the above with up to 20 mmol/500 mL of potassium chloride	▶ Sodium chloride 0.9% and 0.45% ▶ Dextrose 5% ▶ Combination of the above	▶ Sodium chloride 0.9% and 0.45% ▶ Dextrose 5% ▶ Combination of the above
	Y-site	▶ As above ▶ Aminophylline is alkaline (avoid acidic drugs)	▶ As above ▶ Salbutamol is acidic (avoid alkaline drugs)	▶ As above ▶ Salbutamol is acidic (avoid alkaline drugs)
Monitoring	Levels	▶ Yes ▶ 30 min after completion of loading dose ▶ At least daily thereafter (6–12 h after rate changes)	▶ No	▶ No
	U&Es	▶ Yes: potassium at least daily	▶ Yes: potassium, recommended twice daily ▶ Yes: blood glucose, recommended twice daily	▶ Yes: potassium ▶ Yes: blood glucose

Continued

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Table 1 Continued

		Aminophylline	Salbutamol infusion	Salbutamol bolus
	ECG	▶ Yes: during loading dose ▶ Often continues during maintenance infusion	▶ Yes	▶ Yes
	Other	▶ HDU bed recommended if available (administration should not be delayed if unavailable) ▶ BP and heart rate	▶ HDU bed recommended ▶ BP and heart rate	▶ May be given in A&E ▶ BP and heart rate
Prescription ease	Dosage	▶ Varies with age ▶ Use ideal body weight ▶ Calculate and prescribe different doses for loading dose and maintenance infusion: use standard concentration recommended ▶ 2 prescriptions, one for loading dose, one for maintenance infusion ▶ No blind loading dose recommended for patient on theophylline therapies at home or with renal/liver impairment ▶ Cap loading dose at 500 mg ▶ Adjust rates depending on levels and side effects	▶ Varies with age ▶ Vast range of doses: 0.1–10 μg/kg/min. (Although note that when prescribing for children the maximum adult dose suggested in the BNF of 20 μg/min will often be surpassed. A total dose cap should be considered for larger children) ▶ Conversion mg-micrograms ▶ Conversion hours-minutes ▶ Difficult to use a standard concentration due to variability in doses ▶ Adjust rates depending on clinical picture and side effects	▶ Set dose (may be repeated if needed) ▶ Cap dose at 250 μg ▶ Over 5–20 min
Drug particulars		▶ High metabolic interaction risk – Aciclovir, azole antifungals, macrolides, quinolones, calcium channel blockers, etc., will raise theophylline concentrations – Some antiepileptics, rifampicin, tobacco smoke will reduce theophylline concentrations ▶ Additive hypokalaemia with common concomitant treatments (steroids, salbutamol) ▶ Pharmacokinetics vary greatly with age: – Neonates and infants under 6 months slower clearance than adults – Infants and children up to 9–10 faster clearance than adults – Gender different clearance in adolescents ▶ Requires pharmacy input for dosage adjustments, how long to stop, how much to re-load with etc.	▶ Low metabolic interaction risk – Antidiabetic agents ▶ Additive hypokalaemia with common concomitant treatments (steroids, aminophylline)	▶ Low metabolic interaction risk – Antidiabetic agents ▶ Additive hypokalaemia with common concomitant treatments (steroids, aminophylline)
Licensing		▶ Licensed in children older than 6 months	▶ Licensed for children older than 12 years	▶ Licensed for children older than 12 years

A&E, accident and emergency; BNF, British National Formulary; HDU, high-dependency unit; U&E, urea and electrolytes.

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effects of theophylline are proportional to the log of its concentration—in other words, increasing theophylline plasma concentration causes a less than proportional increase in bronchodilation, such that levels higher than 20 mg/L are unlikely to offer additional therapeutic benefit but will increase the risk of toxicity. Furthermore, clearance rates are affected by factors including age and the use of cytochrome P450 inducers and inhibitors. This makes careful dosing and regular assessments of serum theophylline levels crucial.

Mechanism of bronchodilation

Aminophylline may cause bronchodilation through effects on c-AMP by inhibiting certain phosphodiesterase enzymes (figure 1). Phosphodiesterases degrade intracellular c-AMP molecules, so their inhibition may result in increased levels of intracellular c-AMP and subsequent airway smooth muscle relaxation.[18] Interestingly, however, the degree of phosphodiesterase inhibition is not particularly significant at therapeutically relevant theophylline concentrations.[19] Furthermore, other drugs that inhibit phosphodiesterases more significantly are not thought to have significant bronchodilator effects at therapeutic doses (ie, roflumilast, cilomilast). Other hypotheses around the bronchodilator effects of aminophylline are that it can act by blocking adenosine receptors (adenosine has little effect on human airway muscle in vitro but can cause bronchoconstriction in asthmatic subjects when given by inhalation) and that it induces catecholamine release with subsequent adrenergic stimulation.[20] It is possible, therefore, that aminophylline acts on more pathways than salbutamol.

Immunomodulation

Other benefits in asthma exacerbations may relate to immunomodulation and anti-inflammatory effects. Long-term use of oral theophylline can reduce the numbers and activity of eosinophils in bronchial mucosa.[21] Aminophylline might also exert anti-inflammatory effects by enhancing neutrophil apoptosis via adenosine receptor antagonism[22] or by inhibiting histones required for activation of inflammatory gene transcription.[23] These effects can occur at low or subtherapeutic plasma theophylline concentrations.

Seizures

In case series, aminophylline has been implicated in the development of seizures in children, some of whom have not had underlying epilepsy, and in some cases theophylline levels remained within the recommended therapeutic range.[24–26] Although the mechanism for this is unknown, it has been proposed that aminophylline may modulate the brain's usual seizure threshold through blocking adenosine receptors.[27]

Cardiac effects

Tachycardia is a common dose-dependent side effect of aminophylline and oral theophylline.[25] In adults, theophylline has been implicated in the development of serious atrial tachyarrhythmias. It is not clear to what extent this risk extends to the paediatric population.

Vomiting

Vomiting is a common adverse effect of aminophylline and theophylline. It can happen at any plasma concentration, but is more common at supratherapeutic levels.[25]

RCTS OF SALBUTAMOL (OR TERBUTALINE) AND AMINOPHYLLINE

We identified RCTs that assessed the use of intravenous salbutamol, terbutaline or aminophylline in the paediatric population after searching the Cochrane register of controlled trials. The identified trials have been summarised in a series of tables (see online supplementary tables S1–3), and the main findings are outlined in the text below.

In three RCTs, intravenous salbutamol or terbutaline therapy have been compared with either placebo or nebulised treatment in a total of 130 children with acute asthma. Two of these[W1 W2] were conducted in the emergency department (ED) and assessed the efficacy of a bolus of salbutamol, and one[W3] assessed the efficacy of a terbutaline infusion in a paediatric intensive care unit (PICU) setting.

Only one trial[W1] reported benefit with regards to the assessment of clinical severity. One trial showed no difference, and in one trial the outcome was not reported. No trials reported lung function outcomes. Neither of the trials conducted in ED reported the rates of admission to PICU. Length of hospital stay was improved in the group receiving intravenous salbutamol in one trial conducted in ED,[W2] but was not reported in the other.[W1] Two of these studies were included in a Cochrane review,[28] which concluded that there was very little evidence to support the addition of intravenous salbutamol to nebulised therapy in children with acute asthma exacerbations.

Aminophylline has been compared with placebo or usual treatment (one study compared a control group who were managed with continuous nebulised albuterol, inhaled ipratropium and intravenous methylprednisolone with an aminophylline group given the above plus intravenous aminophylline) in children with acute asthma exacerbations in 12 RCTs involving 586 children.[W4–15] Three were conducted in ED, seven on hospital wards, one on PICU and in one study reported as a conference abstract the setting was unclear.

Three trials found that aminophylline improved clinical severity scores, but six did not. Three trials did not report this outcome. Two trials showed improved lung function scores, two did not and eight did not report this outcome. One trial showed that aminophylline reduced PICU admission rates, but

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none of the other studies reported any results for this outcome. No trials have found any benefit of aminophylline on length of hospital or PICU stay (seven found no difference, and five did not report this outcome). Also, 7 of these 12 trials have been included in a Cochrane review.[29] The review concluded that intravenous aminophylline improved lung function within 6 h of treatment, but did not appear to reduce symptoms or length of hospital stay, and there was insufficient evidence to evaluate its impact on PICU rates.

Intravenous aminophylline and salbutamol (or terbutaline) have been compared, head-to-head, in four RCTs involving 202 children.[W16–19] Two were conducted in hospital wards, and one in PICU. In one RCT, reported as a conference abstract, the setting was unclear.

In the three trials that reported results for clinical severity scores, there was no difference between salbutamol and aminophylline. No studies reported lung function outcomes. In the one study reporting PICU admission rates, there was no difference between aminophylline and salbutamol. In two studies reporting length of hospital stay, there was no difference between groups, and in two studies this outcome was not reported. These paediatric studies have been included in a subgroup analysis in a Cochrane review.[30] The review concluded that there was no consistent evidence to help decide between aminophylline and salbutamol as the first-line intravenous therapy of choice.

It is difficult to draw clear conclusions from RCTs about the relative safety profiles of the two treatments. There is wide variability in the assessment and reporting of adverse effects associated with the two treatments in clinical trials. It would appear that salbutamol does carry a risk of cardiovascular adverse effects. In one study,[W3] 6/25 children treated with terbutaline had raised troponin-I levels and one was withdrawn because of arrhythmia. In one trial comparing salbutamol with aminophylline, the group receiving salbutamol demonstrated a significant trend towards tachycardia. Nausea and vomiting were the most commonly reported adverse effects associated with the use of intravenous aminophylline, as demonstrated in several trials and in a Cochrane review.[29] In the trials involving intravenous aminophylline assessed for this review, there was only one reported case of a seizure.

SUMMARY

Salbutamol and aminophylline cause bronchodilation in airways of children with exacerbations of asthma. Both agents probably work by inducing the c-AMP pathway, which reduces intracellular calcium concentrations, thereby relaxing airway smooth muscle.

Multiple choice questions

1. Which process is not a factor in the pathophysiology of an acute exacerbation of asthma?
   A. bronchoconstriction
   B. vasoconstriction
   C. mucus formation
   D. inflammation
   E. mast cell degranulation.
2. Which effect has not been suggested as a potential mechanism of action for aminophylline?
   A. bronchodilation through inhibition of airway smooth muscle cell phosphodiesterases and subsequent increases in intracellular c-AMP concentrations;
   B. bronchodilation via blockade of pulmonary adenosine receptors;
   C. reduction of eosinophil activity in bronchial mucosa;
   D. reduction of mucosal secretions through inhibition of epithelial sodium transporter channels;
   E. inhibition of histones required for activation of inflammatory gene transcription.
3. Which adverse effect is not associated with the use of intravenous salbutamol?
   A. lactic acidosis
   B. hypokalaemia
   C. tremor
   D. myocardial ischaemia
   E. hyponatraemia.
4. Which adverse effect is not associated with the use of intravenous aminophylline?
   A. seizures
   B. nausea
   C. hypertrichosis
   D. tachycardia
   E. headache.
5. Which statement is true?
   A. Aminophylline has a narrow therapeutic index, but reliable serum levels can always be achieved by following recommended dosing guidelines.
   B. If adverse effects occur with the use of intravenous aminophylline, the serum levels will be above the recommended limits.
   C. If serum theophylline levels are below the advised limits, the rate of the infusion should be increased immediately.
   D. If a patient takes oral theophylline, they should not receive a loading dose of intravenous aminophylline.
   E. The ethylenediamine compounds attached to theophylline in order to make aminophylline are thought to contribute to its bronchodilatory effects.

Answers after the references

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Aminophylline may have additional mechanisms of action, which are poorly understood. Both agents also have extrapulmonary adverse effects, which can be dangerous or distressing to children.

The evidence from RCTs for the intravenous administration of either drug to children during an asthma exacerbation is minimal and inconsistent. A bolus of intravenous salbutamol may reduce symptoms and hasten recovery.[W1] Aminophylline infusions may improve lung function, and in some studies have been shown to improve symptoms, but this finding is not replicated in all studies. It is unlikely that either agent reduces PICU admission rates or length of hospital stay, but these evaluations are hampered because many studies do not report these outcomes. Adverse effects were noted with the use of both treatments, but the available evidence does not enable comparison of the likelihood of adverse effects with either treatment.

Despite the minimal evidence of benefits from RCTs, intravenous therapy probably does have a role in managing certain children with either refractory or severe exacerbations of asthma, and those who have previously required PICU admission. Variation of practice at individual clinician and departmental level is likely to continue with regards which of these agents should be used first. Given that intravenous agents are likely to remain in widespread use, we suggest that the choice should take into account factors such as ease of prescription, preparation and administration (which have direct implications for risk management), availability of high-dependency beds and nursing preference. These factors are summarised in table 1.

Whichever therapy is used, we would advocate that children are assessed for objective markers of improvement of clinical status after the initial loading dose bolus to evaluate whether they really need to be treated with a subsequent infusion or not. We would also stress the importance of stringent, routine monitoring of the adverse effects that we have highlighted. Current uncertainty about these therapies, including guidelines on how drug levels and adverse effects should be monitored in children, must be addressed in future research studies.

Contributors The original idea for this article came from IS, who suggested a review of the evidence around the use of intravenous salbutamol and aminophylline focusing on their mechanisms of action, efficacy and safety. The literature search and suggestions for subheadings within the pharmacology sections came from MN, OA and RF. The literature search for randomised control trials was conducted by IS and MN. The tables in the online supplementary file were produced by MN. The first draft of the article was produced by MN and was edited by IS after discussion between all the authors. IS is the guarantor for the paper.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

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Answers to the multiple choice questions

1. B
2. D
3. E
4. C
5. D

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Aminophylline Vs. Placebo/Control group Table of Results

Key to methodological quality section of table:
RQ = randomisation quality (i.e. was sequence generation adequate), AC = Allocation Concealment, B = Blinding, MD = Missing Data, SOR = Selective Outcome Reporting.
L= low risk of bias, H = high risk of bias, U = Unclear from published information.

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Bien 1995	39 patients, aged 2 -10 years, exacerbation of asthma requiring admission to tertiary hospital. 2 groups: Aminophylline bolus followed by an infusion according to a referenced algorithm. Aiming for theophylline levels of 10-20 micrograms/ml; Placebo group. Outcomes: Primary Outcome - Clinical severity score (pulmonary Index (PI)). Secondary Outcomes - Saturations in air, PEFR, salbutamol requirements, evidence of toxicity	Clinical Severity Score: No significant difference between groups in PI. Lung function: Not reported Admission to PICU: Not reported Time to discharge: Not reported Adverse Effects: Aminophylline group experienced more nausea, vomiting and insomnia	Risk of Bias: Low although not clear if allocation concealment was adequate. -RQ: L -AC: U -B: L -MD: L -SOR: L Precision: The Pulmonary Index (PI) scoring system was used. Changes in PI have been correlated with changes in pulmonary function using spirometry. Lung function measured using standard PEFR techniques. Sample Size: Data regarding sample size calculations not provided Adverse Effects: Some attempt to assess adverse effects in a systematic way

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Carter 1993	21 patients, severe asthma requiring paediatric admission after trial of 3 albuterol nebulisers 2 groups: IV aminophylline dosing adjusted to give a concentration of 10-20 micrograms /ml (n=12); Placebo (n=9) Outcomes: Primary Outcomes - Clinical severity score (PI) and FEV1. Secondary Outcomes - Nausea, headache, palpitations, and tremor.	Clinical Severity Score: No significant differences in PI between the groups. Lung function: No significant differences between the groups in FEV1 Admission to PICU: Not reported Time to Discharge: No significant difference between the two groups. Adverse Effects: No significant differences between groups	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: The Pulmonary Index (PI) scoring system was used. Changes in PI have been correlated with changes in pulmonary function using spirometry. Lung function measured using standard spirometry techniques. Sample Size: Data regarding sample size calculations not provided Adverse Effects: Some attempt to assess adverse effects in a systematic way

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
D'Avila 2008	60 patients, 2-5 years, Admitted to paediatric ED with an acute exacerbation of asthma refractory to treatment with corticosteroids and 3 albuterol nebulisers. 2 groups; IV aminophylline (n=30) 2 doses of 5mg/Kg at 6hrly intervals; Placebo group (n=30) Primary Outcomes: Length of supplemental oxygen, number of albuterol nebulisations or puffs of inhaled albuterol, length of stay in the ED, discharge destination (admission to ward/ PICU or discharge home)	Clinical Severity Score: Not reported Lung function: Not assessed Admission to PICU: 1 patient from placebo group Time to discharge: No significant difference between groups Adverse Effects: Not reported	Risk of Bias: Low although details of randomisation process not clearly reported. -RQ: U -AC: L -B: L -MD: L -SOR: L Precision: Main outcome measures reliant on precise reporting of timings and discrete events i.e. episodes of salbutamol usage. Sample Size: Sample size calculated and required numbers of patients recruited Adverse Effects: No documentation regarding assessment of adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Di Giulio 1993	29 patients, attending paediatric ED with acute asthma not fit for discharge after initial treatment, Mean ages; aminophylline group 6.9 yrs +/-4 yrs, Placebo group 7.4 yrs +/- 3.6 yrs 2 groups: IV aminophylline (n=16) at 4.8mg/kg over 20 minutes then 0.8mg/kg/hr (2-9yrs), 0.68mg/kg/hr (>9yrs); Placebo group (n=13) Outcomes: Primary Outcome - Time to clinical asthma severity score (a modified PI) of < 2. Secondary Outcomes - Number of doses of beta-adrenergic drugs used, pulse, BP, episodes of emesis and tremor.	Clinical Severity Score: No significant difference between groups in time to PI <2. Lung function: Not assessed Admission to PICU: Not reported Time to discharge: Not reported Adverse Effects: No differences in pre-specified adverse effects were observed	Risk of Bias: Potential for bias as details regarding randomisation process and allocation concealment not clearly reported. -RQ: U -AC: U -B: L -MD: L -SOR: L Precision: A modified version of the Pulmonary Index (PI) scoring system was used. Changes in PI have been correlated with changes in pulmonary function using spirometry. It is not clear whether the modified version had been formally validated prior to use. Sample Size: Data regarding sample size calculations not provided Adverse Effects: Some data collection regarding pre-specified outcomes
Nagao 2007 (Data from abstract only)	50 patients, aged 2-15 years, not responding to initial treatment with inhaled bronchodilators with an acute exacerbation of asthma 2 groups: IV aminophylline (n=26); Placebo (n=24) Outcome: change in asthma symptom score and time to disappearance of wheeze	Clinical Severity Score: Faster time to improvement in aminophylline group (p <0.05)	Unclear: Data reviewed from abstract only

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Needlemaa n 1995 (Data from abstract only)	42 patients, 2-18 years, acute exacerbation of asthma requiring admission 2 groups: IV aminophylline infusion to maintain a serum concentration greater than 55 micrograms/L; Placebo Outcome: Length of hospital stay, Rate of improvement in clinical score	CInical Severity Score: The rate of improvement in clinical scores was similar Time to Discharge: The mean length of stay for the treatment and control groups was 52.3±32.3 hours and 48.2±26.6 hours, respectively (t=0.45, P=.65). .	Unclear: Data reviewed from abstract only

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Nuhoglu 1998	38 children, 2-16 years, admitted for exacerbation of asthma with clinical asthma score >3 2 groups: Aminophylline (n=18) at 6 mg/kg over 30 mins then an infusion at 1.0 mg/kg per hr (2-9 yrs) or 0.8 mg/kg per hr (>9 yrs); Placebo group (n=20). Outcomes: Primary Outcomes - Number of salbutamol nebulisations required, change in clinical asthma score (PI) Secondary Outcomes - Adverse effects	Clinical Severity Score: No significant difference between groups in change in PI. Lung function: Only assessed in 10 patients, significance of results not assessed Admission to PICU: Not reported Time to discharge: Not reported Adverse Effects: hyperglycaemia (n=1), nausea and vomiting (n=1)	Risk of Bias: Significant risk of bias as randomisation process not clearly described, allocation concealment not adequate and not all randomised patients accounted for in results section. -RQ: U -AC: H -B: U -MD: H -SOR: L Precision: A modified version of the Pulmonary Index (PI) scoring system was used. Changes in PI have been correlated with measures of pulmonary function using spirometry. It is not clear whether the modified version had been formally validated prior to use. Sample Size: Data regarding sample size calculations not provided Adverse Effects: No clear description of methodology for assessing adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Pierson 1971	23 patients, 5-18 years, admitted following failure to respond to 3 SC epinephrine injections, no nebulisers/inhaled therapy used. 2 groups: Aminophylline (n=11) dosing information not described; Placebo group (n=12) Outcomes: Primary Outcome - Pulmonary function studies (FEV1, FVC) at 1,3,24 hours: Secondary Outcomes - blood gases, clinical severity score (PI)	Clinical Severity Score: Results not clearly reported Lung function: Statistically significant improvements in FVC and FEV1 at 1 and 24 hours ($p<0.05$) in the aminophylline group Admission to PICU: Not reported Time to discharge: Not reported Adverse Effects: No adverse effects reported	Risk of Bias: Significant risk of bias as randomisation process not clearly described and results of pulmonary index severity scoring not clearly reported -RQ: U -AC: L -B: L -MD: L -SOR: H Precision: Reported outcomes based on pulmonary function testing. Sample Size: Data regarding sample size calculations not provided Adverse Effects: No clear description of methodology for assessing adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Ream 2001	47 admissions, 1-17 years, admitted to PICU with Wood-Downes clinical asthma score ≥5 despite ED treatment 2 groups: IV aminophylline (n=23) 7 mg/kg IV bolus then 0.5 mg/kg/h (6-12 months);, 0.8 mg/kg/h (1 to 9 years); 0.65 mg/kg/h (≥ 10 years); Control group (n=24) receiving usual care without aminophylline or placebo treatment Outcomes: Primary Outcome - Improvement in Wood-Downes clinical severity score to ≤3. Secondary Outcomes - Time to discharge from PICU, adverse effects	Clinical Severity Score: IV aminophylline resulted in a significant decrease in the time to reach a Wood-Downes clinical severity score of ≤3 (excluding ventilated patients) ($p<0.05$) Lung function: Not assessed Admission to PICU: N/A, admission to PICU part of inclusion criteria. Time to discharge: IV aminophylline did not affect the time to PICU discharge Adverse Effects: An increased incidence of vomiting in the Aminophylline group with 14/23 subjects affected ($p<0.05$)	Risk of Bias: Not a placebo controlled trial -RQ: L -AC: L -B: N/A -MD: L -SOR: L Precision: Clinical severity assessed using the Wood-Downes clinical score; a published scoring mechanism that has been correlated with physiological markers of asthma severity. Sample Size: Data regarding sample size calculations not provided Adverse Effects: A systematic methodology for assessing the presence of pre-specified adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Strauss 1994	31 patients, average age 11 years +/- 3 years, acute exacerbation of asthma, patients able to provide PEFR, tertiary and general centre, excluded patients requiring PICU or with severe asthma based on clinical severity score. 2 groups: Aminophylline group (n=14) received 7 mg/kg followed by a continuous infusion at 1.2 mL/kg/h in children <9 years old; 1.0 mL/kg/h in children 9 to 12 years old; and 0.75 mL/kg/h in children > 12 years; Placebo group (n = 17) Outcomes: Primary Outcome - Length of hospital stay. Secondary Outcomes - number of additional albuterol nebulisations, PEFR and adverse effects.	Clinical Severity Score: Not recorded after initial assessment Lung function: No significant differences in PEFR between groups. Admission to PICU: Not reported Time to discharge: No significant differences in length of hospital stay. Adverse Effects: 6/14 patients in the aminophylline group experienced adverse effects including nausea, vomiting, headache, abdominal pain, palpitations compared to 1/17 in the placebo group ($p < 0.05$). 2 patients in the aminophylline group withdrawn due to adverse effects.	Risk of Bias: Unclear due to lack of detail regarding randomisation process and problems with adequate allocation concealment. -RQ: U -AC: H -B: L -MD: L -SOR: L Precision: Primary outcome measure based on timings. Sample Size: Not clear if sample size calculated prospectively from description in methodology. Adverse Effects: Some details regarding the methodology for assessing the presence adverse effects, good detail in reporting.

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Viera 2000	43 patients, 1-7 years, Seen in Paediatric ED of a University hospital, ≥2 previous wheezy episodes, Modified Wood-Downes clinical severity score 3-6 2 groups: Aminophylline group (n=24) 6mg/kg followed by 1.2mg/kg/Hr; Placebo group (n=19) Outcomes: Primary Outcome - Time to Wood-Downes (clinical asthma severity) score ≤2. Secondary Outcomes - Increase in clinical severity score of >2 points, HR > 180, arrhythmia, convulsion	Clinical Severity Score: No significant differences in change in Wood-Downes clinical asthma severity score between groups. Lung Function: Not assessed Admission to PICU: Not reported Time to discharge: No significant difference in time to discharge. Adverse Effects: No reported convulsions, tachycardia >180 or arrhythmias. Other adverse effects not documented.	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: Clinical severity assessed using the Wood-Downes clinical score; a published scoring mechanism that has been correlated with physiological markers of asthma severity. Sample Size: Data regarding sample size calculations not provided Adverse Effects: Only reported regarding pre-specified outcomes

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Yung 1998	163 patients, aged 1-19 years,acute severe asthma, unresponsive to 3 doses of nebulised salbutamol. 2 groups: Aminophylline group (n=81); loading dose of 10 mg/kg over one hour, then continuous infusion of 1.1 mg/kg/hour <10years or 0.7 mg/kg/hour >10years; Placebo group (n=82) given infusion at the same rate. Outcomes: Primary Outcome - Length of hospital stay. Secondary Outcomes - spirometry; FEV1, FVC, oxygen saturations, clinical severity score (asthma severity score (ASS)), adverse effects.	Clinical Severity Score: Aminophylline improved the clinical severity score (ASS) at 6 hours but not at any other time. Lung Function: Aminophylline improved FEV1 and PEFR at 6,12 and 24 hours and maximum mid expiratory flow at 6 and 12 hours. Admission to PICU: 5 patients required intubation after randomisation, all were in the placebo group (p=0.027). More patients in the placebo group required escalation of treatment with IV salbutamol (18 v 32% OR = 0.49, 95% CI 0.23 to 0.99, p = 0.03) Time to discharge: No significant difference in length of stay (ratio of Aminophylline stay to placebo stay 0.94 (95% confidence interval (CI) 0.77 to 1.14, p = 0.53)) Adverse Effects:Subjects in the aminophylline group were significantly more likely to have their infusions stopped because of adverse effects than placebo subjects (32 v 5%, OR = 8.7, 95% CI 2.9 to 28.4, p < 0.0001). Subjects in the aminophylline group were significantly more likely to experience nausea or vomiting	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: Clinical severity scoring was assessed using the ASS scoring system. The ASS has been found to have reasonable sensitivity as a tool for predicting the severity of an exacerbation of asthma. Sample Size: Sample size calculations provided, 86 participants required in each group. Adverse Effects: A systematic methodology for assessing the presence of pre-specified adverse effects.

Salbutamol Vs. Placebo/Nebulised Therapy Table of Results

Key to methodological quality section of table:
RQ = randomisation quality, AC = Allocation Concealment, B = Blinding, MD = Missing Data, SOR = Selective Outcome Reporting, L= low risk of bias, H = high risk of bias, U = Unclear from published information.

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Bogie 2007	46 patients, aged 2-17 years with moderate/ severe asthma, failed standard acute asthma treatment with nebulisers and required admission to PICU. 2 groups: IV terbutaline group (n=25) loading dose of 10mcg/kg/min 10-20mins then infusion at 1-4mcg/kg/min depending on response; placebo group (n=21) Outcomes: Primary Outcome - improvement in modified clinical asthma severity score (CASS) at any point. Secondary Outcomes - hours on continuous nebulised albuterol, duration of stay in the pediatric intensive care unit.	Clinical Severity Score: No significant difference observed. Mean improvement in CASS over 24 hours 6.5 points terbutaline compared with 4.8 points in the placebo group (95% CI,0.2 – 3.5) (P=0.073) Lung Function: Not assessed Admission to PICU: N/A PICU length of stay; terbutaline 43.9 and placebo 56.85 hours respectively (P = 0.345; SD, 24.75 and 55.88) Adverse Effects: one patient receiving IV terbutaline developed a significant cardiac arrhythmia and was withdrawn from the study, 6 patients from the terbutaline group had elevated Troponin I values at 12 or 24 hours.	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: The CASS was a modified version of the Pulmonary Index score which has been correlated with measures of pulmonary function using spirometry. Sample Size: Did not recruit enough participants to meet calculated power requirement Adverse Effects: Some attempt to assess pre-specified adverse effects in a systematic way

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Browne 1997	29 patients with severe asthma, 1-12 years attending AED. 2 groups; IV salbutamol 15 mcg/kg over 10 minutes (n=15); Placebo (n=14) Outcomes: Primary Outcomes - Mean recovery time (time to no longer needing nebulised salbutamol of a given frequency); the odds of patients having moderate to severe asthma 2 h after randomisation (based on clinical severity score). Secondary Outcomes - odds of patients experiencing salbutamol-related side effects; mean respiratory rate, pulse rate, plasma potassium and glucose.	Clinical severity score: At 2h; 5 (36%) of 14 patients in the IV salbutamol group had persistent moderate to severe asthma compared with 14 (93%) of 15 control patients ($p<0.002$). Lung function: Not reported Admission to PICU: not reported Time to discharge: Patients in the IV salbutamol group were discharged from the ED 9.7 h earlier than controls ($p<0.05$) Adverse Effects: Differences in side-effects were not statistically or clinically significant except higher proportion of tremor at 2 h in the IV salbutamol group ($p<0.02$).	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: Clinical severity score based on descriptive table published in National Asthma Guideline. Not clear if systematically validated. Sample Size: Calculations completed but the study was terminated when an independent assessor calculated significant differences between the groups Adverse Effects: Some attempt to assess adverse effects in a systematic way

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Browne 2002	55 patients, 1-14 yrs, attending ED with severe acute asthma 3 groups - single 15mcg/kg bolus of IV salbutamol + saline nebs (n=21, Group IS), IV saline and nebulised ipratropium bromide 250mcg/20 mins (n=19, Group IB), IV salbutamol and nebulised ipratropium (n=15, Group IS+IB) Outcomes: Primary Outcomes - Time to no longer needing nebulised therapy of a given frequency, mean discharge time from the emergency department (on hourly nebs) and hospital (on 3 hourly nebs). Secondary Outcomes - Clinical signs of moderate to severe asthma 2 hrs after randomization; number of patients experiencing side effects; means of respiratory rate, pulse rate, plasma potassium, plasma glucose.	Clinical Severity Scores: Results at 2 hours not published. Lung Function: Not assessed PICU Admission: Not recorded Time to discharge: Children in group IS were ready for discharge from the hospital 28.0 hrs earlier than those children in group IB (48.3 hrs vs. 76.3 hrs, p = .005). There were no other significant differences between groups Adverse Effects: None reported	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: H, clinical severity score data not published Precision: Primary outcome measures related to recording of timings. Sample Size: No documentation regarding SS calculations Adverse Effects: Attempts made to record adverse effects systematically

IV Aminophylline Vs. IV Salbutamol/Terbutaline Table of Results

Key to methodological quality section of table:
RQ = randomisation quality, AC = Allocation Concealment, B = Blinding, MD = Missing Data, SOR = Selective Outcome Reporting.
L= low risk of bias, H = high risk of bias, U = Unclear from published information.

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Hambleton 1979	18 children, aged 1-7 years, requiring intensive hospital treatment for acute asthma 2 groups; IV salbutamol 4 mcg/kg bolus then 0.6mcg/kg/hr for 24 hours; IV aminophylline 4mg/kg immediately then 0.6mg/kg/hr for 24 hours Primary Outcome: A modified clinical severity scoring system	Clinical Severity Score: No significant difference between groups Lung function: Not assessed Admission to PICU: Not reported Time to discharge: Not reported Adverse Effects: A significant trend towards higher heart rates in the salbutamol group	Risk of Bias: Unclear -RQ: L -AC: U -B: U -MD: L -SOR: L Precision: No clear evidence of use of a validated clinical severity scoring system. Sample Size: Data regarding sample size calculations not provided Adverse Effects: Very limited data regarding the methodology of assessment for adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Roberts 2003	44 patients, aged 1-16, acute, severe exacerbation of asthma, refractory to combined nebulisers as measured by a limited change in asthma severity score, presenting to district hospitals in the UK 2 groups; IV salbutamol (n=18) received 15mcg/kg bolus; IV aminophylline (n=26) 5mg/kg bolus then 0.9mg/kg/hr Outcomes: Primary Outcome - Change in asthma Severity Score (ASS). Secondary Outcomes - Requirement for supplemental oxygen, time to discharge from hospital, adverse effects.	Clinical Severity Score: There were no significant differences between groups in the clinical severity score (ASS) during the study. Lung Function: Not recorded Admission to PICU: 2 subjects in the salbutamol group and 1 in the aminophylline group required intubation and ventilation. Time to Discharge: The duration of inpatient treatment for the salbutamol group was 1.49 times longer (95% CI 1.06 to 2.10, p=0.02) than the aminophylline group. Adverse Effects: There were no significant differences in the number of adverse events reported in the two groups (22.2% v 36%, p=0.50, Fisher's exact test)	Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L Precision: Clinical severity scoring was assessed using the ASS scoring system. The ASS has been found to have reasonable sensitivity as a tool for predicting the severity of an exacerbation of asthma. Sample Size: Sample size calculated and required numbers of patients recruited Adverse Effects: Limited details regarding the methodology for assessing the presence adverse effects

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Singhi 2011 (Data from table published in Cochrane review)	100 patients, severe, acute asthma. 3 groups: IV magnesium (n=34) 50mg\kg over 20 mins; IV terbutaline (n=33) 10 µg/kg over 30 minutes then 0.1 µg/kg/min for 1 h, IV aminophylline (n=33) 5 mg/kg bolus then 0.9 mg/kg/min for 1 h. Outcomes: PrimaryOutcome - Clinical asthma severity score (ASS) at 1 h. Secondary Outcomes - Adverse effects	Clinical Severity Score: (Treatment success defined as clinical ASS ≥ 4 at 1 h.) Treatment success was noted in 33/34 in magnesium group, 23/33 in terbutaline group and 23/33 in aminophylline group (P < 0.001). Lung Function: Data not available Admission to PICU: Data not available Time to Discharge: Data not available Adverse Effects: 0/34 side effects in magnesium group vs. 2/33 in tebutaline group (symptomatic hypokalaemia) vs. 9/33 in aminophylline group (nausea/vomiting) (P < 0.001).	Unclear from available data
Wheeler 2005 (Data from abstract only)	40 patients, 3-15 years, impending respiratory failure secondary to status asthmaticus 3 groups; IV aminophylline + placebo; IV terbutaline + placebo; IV theophylline and terbutaline combined Outcomes: Change in clinical asthma score, length of stay in PICU, adverse effects	Clinical Severity Score: No significant differences Lung Function: Time to discharge: No significant difference in length of PICU stay. Adverse Effects: Children who received both IV treatments had a higher incidence of nausea	Unclear from available data