

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	<p>39 patients, aged 2 -10 years, exacerbation of asthma requiring admission to tertiary hospital.</p> <p>2 groups: Aminophylline bolus followed by an infusion according to a referenced algorithm. Aiming for theophylline levels of 10-20 micrograms/ml; Placebo group.</p> <p>Outcomes: Primary Outcome - Clinical severity score (pulmonary Index (PI)). Secondary Outcomes - Saturations in air, PEFr, salbutamol requirements, evidence of toxicity</p>	<p>Clinical Severity Score: No significant difference between groups in PI.</p> <p>Lung function: Not reported</p> <p>Admission to PICU: Not reported</p> <p>Time to discharge: Not reported</p> <p>Adverse Effects: Aminophylline group experienced more nausea, vomiting and insomnia</p>	<p>Risk of Bias: Low although not clear if allocation concealment was adequate.</p> <p>-RQ: L -AC: U -B: L -MD: L -SOR: L</p> <p>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.</p> <p>Sample Size: Data regarding sample size calculations not provided</p> <p>Adverse Effects: Some attempt to assess adverse effects in a systematic way</p>

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

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

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Di Giulio 1993	<p>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</p> <p>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)</p> <p>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.</p>	<p>Clinical Severity Score: No significant difference between groups in time to PI <2.</p> <p>Lung function: Not assessed</p> <p>Admission to PICU: Not reported</p> <p>Time to discharge: Not reported</p> <p>Adverse Effects: No differences in pre-specified adverse effects were observed</p>	<p>Risk of Bias: Potential for bias as details regarding randomisation process and allocation concealment not clearly reported.</p> <p>-RQ: U -AC: U -B: L -MD: L -SOR: L</p> <p>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.</p> <p>Sample Size: Data regarding sample size calculations not provided</p> <p>Adverse Effects: Some data collection regarding pre-specified outcomes</p>
Nagao 2007 (Data from abstract only)	<p>50 patients, aged 2-15 years, not responding to initial treatment with inhaled bronchodilators with an acute exacerbation of asthma</p> <p>2 groups: IV aminophylline (n=26); Placebo (n=24)</p> <p>Outcome: change in asthma symptom score and time to disappearance of wheeze</p>	<p>Clinical Severity Score: Faster time to improvement in aminophylline group (p <0.05)</p>	<p>Unclear: Data reviewed from abstract only</p>

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Needleman 1995 (Data from abstract only)	<p>42 patients, 2-18 years, acute exacerbation of asthma requiring admission</p> <p>2 groups: IV aminophylline infusion to maintain a serum concentration greater than 55 micrograms/L; Placebo</p> <p>Outcome: Length of hospital stay, Rate of improvement in clinical score</p>	<p>Clinical Severity Score: The rate of improvement in clinical scores was similar</p> <p>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).</p>	<p>Unclear: Data reviewed from abstract only</p>

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Nuhoglu 1998	<p>38 children, 2-16 years, admitted for exacerbation of asthma with clinical asthma score >3</p> <p>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).</p> <p>Outcomes: Primary Outcomes - Number of salbutamol nebulisations required, change in clinical asthma score (PI)</p> <p>Secondary Outcomes - Adverse effects</p>	<p>Clinical Severity Score: No significant difference between groups in change in PI.</p> <p>Lung function: Only assessed in 10 patients, significance of results not assessed</p> <p>Admission to PICU: Not reported</p> <p>Time to discharge: Not reported</p> <p>Adverse Effects: hyperglycaemia (n=1), nausea and vomiting (n=1)</p>	<p>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.</p> <p>-RQ: U -AC: H -B: U -MD: H -SOR: L</p> <p>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.</p> <p>Sample Size: Data regarding sample size calculations not provided</p> <p>Adverse Effects: No clear description of methodology for assessing adverse effects</p>

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

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Ream 2001	<p>47 admissions, 1-17 years, admitted to PICU with Wood-Downes clinical asthma score ≥ 5 despite ED treatment</p> <p>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</p> <p>Outcomes: Primary Outcome - Improvement in Wood-Downes clinical severity score to ≤ 3. Secondary Outcomes - Time to discharge from PICU, adverse effects</p>	<p>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) ($p < 0.05$)</p> <p>Lung function: Not assessed</p> <p>Admission to PICU: N/A, admission to PICU part of inclusion criteria.</p> <p>Time to discharge: IV aminophylline did not affect the time to PICU discharge</p> <p>Adverse Effects: An increased incidence of vomiting in the Aminophylline group with 14/23 subjects affected ($p < 0.05$)</p>	<p>Risk of Bias: Not a placebo controlled trial -RQ: L -AC: L -B: N/A -MD: L -SOR: L</p> <p>Precision: Clinical severity assessed using the Wood-Downes clinical score; a published scoring mechanism that has been correlated with physiological markers of asthma severity.</p> <p>Sample Size: Data regarding sample size calculations not provided</p> <p>Adverse Effects: A systematic methodology for assessing the presence of pre-specified adverse effects</p>

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Strauss 1994	<p>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.</p> <p>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)</p> <p>Outcomes: Primary Outcome - Length of hospital stay. Secondary Outcomes - number of additional albuterol nebulisations, PEFr and adverse effects.</p>	<p>Clinical Severity Score: Not recorded after initial assessment</p> <p>Lung function: No significant differences in PEFr between groups.</p> <p>Admission to PICU: Not reported</p> <p>Time to discharge: No significant differences in length of hospital stay.</p> <p>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.</p>	<p>Risk of Bias: Unclear due to lack of detail regarding randomisation process and problems with adequate allocation concealment.</p> <p>-RQ: U -AC: H -B: L -MD: L -SOR: L</p> <p>Precision: Primary outcome measure based on timings.</p> <p>Sample Size: Not clear if sample size calculated prospectively from description in methodology.</p> <p>Adverse Effects: Some details regarding the methodology for assessing the presence adverse effects, good detail in reporting.</p>

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

Trial	Population Intervention and Comparison Outcomes	Results	Methodological quality
Yung 1998	<p>163 patients, aged 1-19 years, acute severe asthma, unresponsive to 3 doses of nebulised salbutamol.</p> <p>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.</p> <p>Outcomes: Primary Outcome - Length of hospital stay. Secondary Outcomes - spirometry; FEV1, FVC, oxygen saturations, clinical severity score (asthma severity score (ASS)), adverse effects.</p>	<p>Clinical Severity Score: Aminophylline improved the clinical severity score (ASS) at 6 hours but not at any other time.</p> <p>Lung Function: Aminophylline improved FEV1 and PEFR at 6, 12 and 24 hours and maximum mid expiratory flow at 6 and 12 hours.</p> <p>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)</p> <p>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))</p> <p>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</p>	<p>Risk of Bias: Low -RQ: L -AC: L -B: L -MD: L -SOR: L</p> <p>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.</p> <p>Sample Size: Sample size calculations provided, 86 participants required in each group.</p> <p>Adverse Effects: A systematic methodology for assessing the presence of pre-specified adverse effects.</p>