# A multicentre, randomised, double-blind, placebo-controlled trial of aminophylline for bronchiolitis in infants admitted to intensive care

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## ABSTRACT

**Objective:** To determine whether aminophylline reduced the duration of respiratory support in children admitted to intensive care with bronchiolitis.

**Design:** A multicentre, randomised, double-blind, placebo-controlled trial.

**Setting:** Paediatric intensive care units in teaching hospitals.

**Participants:** Forty-five children with severe bronchiolitis.

**Intervention:** Patients were randomly assigned to receive an infusion of aminophylline (23) or placebo (22). The primary outcome measure was the number of hours of respiratory support required in the 120 hours after randomisation; respiratory support was defined as either nasal continuous positive airways pressure or mechanical ventilation.

**Results:** The trial was stopped early due to poor recruitment. Respiratory support was required for a median of only 1.5 days (interquartile range [IQR], 0.4–3.5 days) in the aminophylline group compared with 1.9 days (IQR, 0.3–3.5) days in the placebo group. However, more patients in the placebo group were receiving respiratory support at the time of randomisation and, after adjustment for this, there was no suggestion of a beneficial effect of aminophylline among the small number of patients studied ($P = 0.54$, exact log-rank test stratified by respiratory support at the time of randomisation and censored at the time of death in one child in the aminophylline group).

**Conclusion:** Not enough children were recruited for the study to test the hypothesis that aminophylline reduces the need for respiratory support in severe bronchiolitis. Consequently, the role of aminophylline in the management of severe bronchiolitis remains unknown.


Crit Care Resusc 2014; 16: 220–224

Bronchiolitis is the most common severe lower respiratory tract infection in infancy.[1] It is usually caused by respiratory syncytial virus (RSV), often affects previously well children and is associated with substantial morbidity, accounting for up to 20% of hospitalisations in children aged less than 5 years.[2] From 2001 to 2004, 1272 children were admitted to paediatric intensive care units (PICUs) in Australia and New Zealand with severe bronchiolitis. Mechanical ventilation was required in 49% of these bronchiolitis admissions (Slater A, Australian and New Zealand Paediatric Intensive Care Registry, personal communication, May 2005).

The treatment of bronchiolitis is supportive. Several trials and meta-analyses have examined the use of pharmacological agents, but the results have been inconclusive. Agents studied have included oral dexamethasone,[3] nebulised adrenaline,[4,5] combination therapy with both dexamethasone and nebulised adrenaline,[6,7] nebulised hypertonic saline[8] and antibiotics.[9] Although a randomised trial has suggested that treatment with systemic corticosteroid and nebulised adrenaline may be effective,[8] national guidelines emphasise that the main treatment is supportive therapy.[10,11]

There is some evidence that aminophylline may improve the management of bronchiolitis by improving respiratory function. Aubier and colleagues studied the effect of aminophylline on normal diaphragmatic function and found that aminophylline improved the contractility of the fatigued diaphragm.[12] There have been no studies of adequate size analysing the clinical effect of aminophylline in patients with bronchiolitis. Outwater and Crone, and Schena and colleagues prospectively studied three and four patients, with bronchiolitis, respectively, who were given aminophylline.[13,14] Measurements were made of tidal volume, airway pressure and peak flow rates. Total respiratory resistance decreased, tidal volume increased, and the arterial partial pressure of carbon dioxide ($PaCO_2$) decreased. There was a trend towards improved respiratory function, but the sample sizes were too small for statistically significant results. Mezey treated nine bronchiolitis patients with aminophylline;[15] all clinical and blood gas indicators improved, and it was concluded that aminophylline improved the outcome and reduced the need for ventilator support, but again, the sample size was small. Labbe and colleagues studied the use of oral theophylline solution[16] and found no statistical difference between the outcome of children given theophylline and control patients; the study included 62 patients, but only 26 received theophylline, and only 10 had theophylline concentrations above the lower limit of the therapeutic range. There is, therefore, some

evidence that aminophylline may improve the outcome of bronchiolitis, but it is insufficient for aminophylline to be considered a standard therapy.

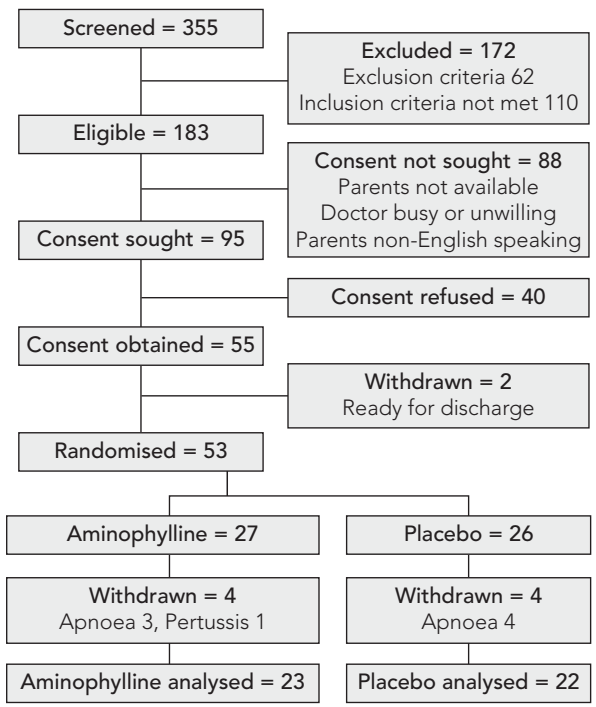
We performed a multicentre, randomised, double-blind, placebo-controlled trial of aminophylline infusion versus placebo to determine whether aminophylline reduced the requirement for respiratory support in children with bronchiolitis in intensive care.

## Methods

### Participants

Patients were recruited from 2002 to 2009 from the PICUs at the Royal Children's Hospital, Melbourne (35 patients), and in 2008 and 2009 from Royal Children's Hospital, Brisbane (eight patients), Princess Margaret Hospital for Children, Perth (one patient), and Starship Children's Hospital, Auckland (one patient). All the PICUs are members of the Australian and New Zealand Paediatric Intensive Care Society Study Group. The study was funded by a grant from the Australian and New Zealand Intensive Care Foundation. Written informed consent was obtained from the parents or guardians of all patients included in the trial. Ethics approval for the trial was obtained from each centre's local ethics committee. The trial was coordinated by a research coordinator (C D) who collated the data. The trial was overseen by a data and safety monitoring committee.

**Figure 1. Enrolment and randomisation of children in the trial**




To be eligible for recruitment, patients had to meet all the following criteria: age less than 24 months (12 months after 2008); a clinical diagnosis of bronchiolitis (defined as a first or second episode of wheezing or respiratory distress associated with an upper respiratory tract infection); admission to a PICU; no previous admission to the study; and no episodes of apnoea requiring treatment with aminophylline or caffeine. Children with a contraindication to aminophylline were excluded; this was defined as a previous history of a severe reaction; a previous history of atrial or ventricular arrhythmia; a previous history of seizures; a previous history of liver dysfunction; or a resting heart rate > 200 beats per minute. If the admission criteria were satisfied, written consent was sought by the research coordinator or a PICU physician. If consent was obtained, patients were randomly allocated to control or intervention groups online by the European Academic Trials Data Centres Service (TENALEA), with stratification by PICU and by the amount of respiratory support at the time of allocation, defined as spontaneous breathing, or nasal continuous positive airway pressure (NCPAP), or ventilation. Allocation codes were blinded to parents, staff and all investigators other than one nominated unblinded investigator at each site.

### Baseline assessment

Baseline measures obtained at the time of recruitment included demographic data, weight, gestational age, previous medical history, time of admission and randomisation, level of respiratory support, heart rate at the time of randomisation, and RSV status.

### Patient management

Management between study groups, other than the study drug, was identical. Total fluids were restricted to 60 mL/kg/day. All patients had a nasopharyngeal aspirate collected for immunofluorescence for common respiratory viruses, including RSV. Samples were screened for *Bordetella pertussis* if clinically indicated. Emphasis was placed on minimal handling and nursing the child in a neutral thermal environment. Transcutaneous oxygen saturations ($SpO_2$) and electrocardiograms were monitored in all patients. Oxygen was given via mask or nasal prongs if the $SpO_2$ was < 95%. If the child became exhausted, or had an $SpO_2$ < 90% despite oxygen, NCPAP was administered at a level of 8–12 cm $H_2O$. If the child became exhausted, or had an $SpO_2$ < 90% despite NCPAP, endotracheal intubation and mechanical ventilation were undertaken. Salbutamol and corticosteroids were not given unless the child was already on these for another indication.

### Intervention

Patients were allocated at random to receive an infusion of either aminophylline or placebo (0.9% saline); staff caring

for the patient were blinded as to which infusion the patient was receiving. Study drugs (standard vials of aminophylline 250 mg in 10 mL, or 0.9% saline 10 mL) were sourced from a single provider (Stenlake Compounding Chemist), and each vial of study drug was assigned a random number; all the vials were of identical volume and odour, and covered in black heat wrap so they were not identifiable. The dose of study drug was infused according to a predetermined protocol: patients received a loading dose of 7 mg/kg of aminophylline (< 7 kg) or 10 mg/kg (≥ 7 kg) or the equivalent volume of placebo, followed by a continuous infusion for 72 hours or until discharge from PICU, whichever was sooner. Drug monitoring was performed by checking serum theophylline concentrations 1 hour after completion of the loading dose, 12–18 hours after commencement of the maintenance infusion, then daily for 2 days. The theophylline concentration results were reported to the unblinded investigator, who then instructed staff to make appropriate changes to the rate of the drug infusion according to the protocol. The target therapeutic theophylline levels were 60–80 µmol/L (10–15 µg/mL) in neonates and 60–110 µmol/L (10–20 µg/mL) in older children. Arbitrary changes to the placebo infusion rate were suggested to maintain blinding.

### Assessment

In the 5 days (120 hours) after randomisation, the research nurse recorded: any change in the level of respiratory support; total hours of spontaneous breathing (neither NCPAP nor mechanical ventilation); total hours of NCPAP; total hours of mechanical ventilation; presence or absence of RSV in nasopharyngeal aspirate; number of hours of test-drug administration; length of PICU stay; length of hospital stay; and adverse events.

**Table 1. Baseline characteristics of the patients**

| | Aminophylline ($n = 23$) | Placebo ($n = 22$) |
|---|---|---|
| Age in months, median (IQR) | 3.0 (1.9–4.6) | 2.6 (1.4–5.1) |
| Weight in kg, median (IQR) | 5.5 (4.5–7.2) | 6.2 (4.6–9.1) |
| Male sex, no. (%) | 15 (65) | 13 (59) |
| Born premature, no. (%) | 7 (30) | 6 (27) |
| Ventilatory support at time of randomisation, no. (%) | | |
| None | 7 (30) | 3 (14) |
| NCPAP | 11 (48) | 13 (59) |
| Invasive ventilation | 5 (22) | 6 (27) |

IQR = interquartile range. NCPAP = nasal continuous positive airway pressure.

### Adverse events

If adverse events occurred during test-drug administration they were recorded as one of: sinus tachycardia; arrhythmia; hypotension; irritability; tremor; seizures; nausea or vomiting; fever; rash; or other. Within each category the level of adverse event was documented as minor, moderate or severe according to predetermined criteria. If a severe adverse event occurred, the test-drug infusion was stopped and the event reported to the data and safety monitoring committee.

### Outcome measures

The primary outcome measure was the number of hours of respiratory support (NCPAP or ventilation) required from the time of admission to the study until 120 hours (5 days) after admission. Secondary outcome measures included the length of stay in the PICU and the length of stay in hospital.

### Statistical analysis

From analysis of previous PICU admissions of children with bronchiolitis in Australia and New Zealand we calculated that, to detect a reduction of 24 hours or more in the duration of respiratory support with a power of 90% and $P \leq 0.05$, 87 respiratory-supported patients would be needed in the treatment group and 87 in the control group. Historically, in our institutions only 63.6% of children admitted to the PICU received respiratory support; therefore, 137 children would need to be randomly allocated to the treatment group and 137 to the control group. Exact log-rank survival tests, stratified by ventilatory support at the time of randomisation and censored at the time of death, were performed using StatXact, version 4 (Cytel).

## Results

### Recruitment and baseline characteristics

A total of 53 patients were randomly allocated to control or intervention groups before the study was stopped owing to poor recruitment (Figure 1). Eight patients were subsequently withdrawn, all at the Royal Children's Hospital, Melbourne: one was diagnosed with pertussis, and seven had only apnoea (soon after starting the trial it was decided to limit recruitment to children with wheezing or respiratory distress). The baseline characteristics of the aminophylline (23 patients) and placebo (22 patients) groups were similar (Table 1), but there was a trend towards more patients requiring respiratory support in the placebo group.

### Interventions and outcomes

Aminophylline and placebo were infused for similar durations: aminophylline for a median of 1.8 days (IQR, 0.8–2.9 days) and placebo for a median of 2.3 days (IQR, 1.7–4.2 days; $P = 0.35$). Results analysed by exact log-rank tests,

**Table 2. Duration of positive pressure support, time in intensive care and time in hospital, median no. of days (IQR)**

| | Ventilatory support at time of randomisation | | | | |
|---|---|---|---|---|---|
| | None | NCPAP | Ventilation | Total | *P** |
| Aminophylline group, *n* | 7 | 11 | 5 | 23 | |
| Placebo group, *n* | 3 | 13 | 6 | 22 | |
| **Days of NCPAP or ventilation** | | | | | |
| Aminophylline | 0.0 (0.0–1.5) | 1.6 (0.9–3.5) | 5.8 (3.1–7.8) | 1.5 (0.4–3.5) | 0.54 |
| Placebo | 0.0 (0.0–0.2) | 1.9 (1.3–2.9) | 4.4 (2.0–7.7) | 1.9 (0.3–3.5) | |
| **Days of NCPAP** | | | | | |
| Aminophylline | 0 (0.0–1.5) | 1.6 (0.9–3.5) | 0.0 (0.0–1.0) | 1.0 (0.0–2.0) | 0.76 |
| Placebo | 0 (0.0–0.2) | 1.9 (1.3–2.9) | 1.1 (0.0–1.7) | 1.5 (0.2–2.8) | |
| **Days of ventilation** | | | | | |
| Aminophylline | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 3.8 (2.1–7.8) | 0.0 (0.0–0.0) | 0.16 |
| Placebo | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 3.5 (2.0–6.0) | 0.0 (0.0–1.3) | |
| **Days in intensive care** | | | | | |
| Aminophylline | 2.0 (1.3–2.8) | 3.0 (2.3–4.3) | 8.6 (6.5–8.9) | 2.8 (2.0–6.5) | 0.69 |
| Placebo | 1.2 (1.1–4.7) | 3.1 (2.0–5.6) | 8.8 (6.5–11.9) | 4.4 (2.0–9.0) | |
| **Days in hospital** | | | | | |
| Aminophylline | 5.1 (3.4–27.1) | 6.7 (4.1–8.2) | 13.9 (12.5–15.1) | 6.8 (4.1–15.1) | 0.71 |
| Placebo | 4.0 (2.4–9.9) | 6.2 (5.1–10.0) | 11.8 (10.4–14.9) | 8.4 (4.8–12.7) | |

IQR = interquartile range. NCPAP = nasal continuous positive airway pressure. * Exact log-rank test, stratified by ventilatory support at the time of randomisation and censored at the time of death for one child in the aminophylline group.

stratified by ventilatory support at the time of randomisation and censored at the time of death for one child in the aminophylline group, are presented in Table 2. Respiratory support was required for a median of only 1.5 days (IQR, 0.4–3.5 days) in the aminophylline group compared with 1.9 days (IQR, 0.3–3.5 days) in the placebo group, but the difference was not statistically significant when adjusted for respiratory support at the time of admission ($P = 0.54$). Similarly, the differences in the duration of NCPAP, mechanical ventilation, PICU stay and hospital stay were not statistically significant when adjusted for respiratory support at the time of randomisation (Table 2). One patient in the aminophylline group died, and was included in the analysis; the cause of death was severe hypoxic respiratory failure on a background of chronic lung disease and congenital heart disease. Because of hypokalaemia, aminophylline had been discontinued 12 hours before death, and there was no suggestion that aminophylline contributed to the child's death.

### Complications

The main complications experienced were sinus tachycardia (aminophylline, five patients; placebo, one patient); irritability (aminophylline, three; placebo, zero); arrhythmia (aminophylline, one; placebo, zero); and death (aminophylline, one; placebo, zero). Aminophylline administration was ceased in three patients because of sinus tachycardia, and in one patient with frequent ventricular ectopic beats; no serious adverse events were caused by aminophylline. Nausea and vomiting were reported in one child who was receiving aminophylline. Adverse events were reported to the data and safety monitoring committee.

## Discussion

Bronchiolitis remains a condition with few treatment options apart from supportive therapy. In this trial, we attempted to determine whether aminophylline should be used to treat this common condition. Aminophylline is used in the management of acute severe asthma unresponsive to maximal doses of bronchodilators plus steroids, and aminophylline or caffeine are often used to treat apnoea in infants with bronchiolitis. There have not been any randomised trials of aminophylline for the treatment of bronchiolitis in children in intensive care, but a randomised trial has suggested that aminophylline confers benefit to children with asthma in intensive care.[17]

Children in the aminophylline group had a slightly shorter duration of respiratory support compared with the placebo group; however, more patients in the placebo group were receiving respiratory support at the time of randomisation

and, after adjustment for this, there was no suggestion of a beneficial effect of aminophylline in the small number of patients studied ($P = 0.54$, exact log-rank survival test stratified by respiratory support at the time of randomisation and censored at the time of death in one child in the aminophylline group).

This trial is a multicentre double-blind placebo-controlled trial, but the results are inconclusive. The biggest problem is the small number of subjects (target number, 274; actual, 45). Slow recruitment led to the trial being stopped early, with 35 of the 45 subjects being recruited in one PICU. This was probably owing to difficulties in obtaining informed consent for randomised trials among children in intensive care units; insufficient clinical research staff; concerns about the side effects of aminophylline; another concurrent trial of treatment for bronchiolitis; and the complexity of the trial, with aminophylline concentrations being kept secret and the infusion rates being adjusted by a designated unblinded investigator at each site. Another potential problem is that blinding may have been compromised by the emergence of tachycardia and agitation in the aminophylline group, but it is highly unlikely that this influenced management decisions such as the time to try cessation of NCPAP or mechanical ventilation.

This trial illustrates the very great difficulties in doing randomised trials of drugs that are already licensed, especially in children. Despite the importance of finding an effective drug therapy for the treatment of severe bronchiolitis, drug companies are reluctant to fund randomised trials of drugs that are out of patent.[18] This is compounded by the increasingly onerous conditions being imposed by ethics committees for obtaining consent for research in children, conditions that are often designed to protect the interests of the institutions involved rather than the subjects.[19] Consequently, the role of aminophylline in the management of severe bronchiolitis remains unknown.

## Competing interests

None declared.

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