Acutectomy bronchiolitis is commonly a cause for admission to hospital in infants during winter. Current management is supportive, utilising fluids and oxygen, with no specific therapy to influence the natural history or progression of the disease.1

Affected infants become increasingly dyspnoeic and hypoxic for three to four days, after which most improve spontaneously.2 During the convalescent phase, respiratory secretions and debris become thicker and more abundant, occasionally blocking lower airways with segmental atelectasis in severe cases. Although the hallmark of bronchiolitis is airway narrowing, this has been shown to be unresponsive to bronchodilator therapy,3 including specifically the airway blockage that characterises the recovery phase.7

Adrenaline has a number of advantages over β2 adrenergic selective bronchodilators that ensure its efficacy with fewer side effects: (1) α adrenergic vasoconstrictor action that can decongest the mucosa, limit its own absorption, and regulate pulmonary blood flow, with little effect on ventilation-perfusion matching; (2) β2 adrenergic bronchial muscle relaxant effect; (3) β1 adrenergic action to suppress release of chemical mediators; (4) physiological antihistamine effect that can reverse histamine effects, such as oedema; and (5) it reduces catarrhal secretions.9

β2 Adrenergic bronchodilators have mucosal and pulmonary vasoconstrictor effects. The former increase mucosal absorption rates with resultant direct tachycardic effects, by virtue of the residual inherent β1 adrenergic activity effects. The latter enhance ventilation-perfusion mismatching which results in hypoxia and hypoxia induced tachyarrhythmia. Airway obstruction increases work of breathing and precipitates hypoxia; both are associated with tachycardia. The vasoconstrictor and bronchodilator activities of adrenaline protect against its direct as well as hypoxia induced arrhythmogenicity. It is therefore not surprising that in clinical studies, drugs such as salbutamol, with minimal residual β2 adrenergic activity, have more potential to cause tachycardia than adrenaline, which in spite of its potent β2 adrenergic activity might reduce heart rate.10

Many recent studies have reported on the efficacy of inhaled adrenaline (epinephrine) in the treatment of bronchiolitis, but were subject to criticism over patient selection10–12 and study design,12–14 in particular the use of bronchodilators for comparison. In this study, with continued standard supportive care, we compared the efficacy and safety of nebulised adrenaline against saline as placebo in infants less than 1 year of age presenting with moderately severe acute bronchiolitis.

**Patients and Methods**

**Patients**

We studied infants aged 30 days to 1 year within the first four days of their respiratory illness who had clinically, rather than virologically diagnosed bronchiolitis, as defined by Court,14 of sufficient severity that oxygen therapy was required to keep saturations >94% or with tachypnoea of ≥50 breaths/min. Patients were studied at presentation to hospital, having been referred by their general practitioners to our paediatric assessment and admission unit. Infants were not eligible if the disease duration was greater than four days, as we were interested in studying responsiveness during the progressive phase of the disease. Thereafter mucoid secretions assume a more important role in airway blockage at the convalescent stage. Subjects were further excluded if they had a history of a previous wheezy episode, or chronic lung, cardiac, or neuromuscular disease. In addition, recruitment was delayed for 24 hours if the infant had received oral steroids, or for 2 hours if they had received inhaled bronchodilators.

**Intervention**

The infants were stabilised with antipyretics if necessary (temperature >38°C) and/or nasal suction if the nose was blocked. Facial oxygen was removed if the oxygen saturation (SpO2) was >90% in air; if not, it was provided to maintain SpO2 at 90–92%. This situation was maintained for at least 30 minutes before the patients received any study treatment and

**Results**

No improvement was shown with inhaled adrenaline in acute bronchiolitis, when compared with supportive care or placebo. Improvements noted pretreatment question whether prior noted improvements were through supportive care or pharmacological interventions.

**Conclusion**

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was left unaltered throughout the study. After stabilisation, the infants received minimal handling to allow them to settle or sleep.

Infants were studied in a double blind placebo controlled manner with randomisation in balanced blocks of eight. The infants were randomised to a single dose (3 ml) of either levoadrenaline (3 mg), the commonly available form in the UK, or 0.9% saline placebo. Treatment was nebulised in 100% oxygen at 6 l/min for three minutes using a Pari-BABY nebuliser and soft silicon rounded facemask held gently to make a tight seal around the nose and the mouth. The adrenaline dose is based on the maximum dose used in a previous study. We chose a single large dose of 3 mg in preference to repeated smaller doses, as is the practice in the treatment of croup, to avoid frequent handling of these infants might invalidate the study, should discrepancy within subjects or between groups become evident.

Assessment
The infants were assessed five times: twice before treatment (times -20 minutes and zero), and three times thereafter, at 20, 40, and 60 minutes. Assessments prior to treatment evaluated changes with supportive therapy and stabilisation alone.

Assessments at each point were:
(1) Respiratory rate: counted manually, by both palpation and visual observation of chest excursion, for a complete minute on two occasions; average recorded.
(2) Heart rate: taken from pulse oximeter reading five times during a one minute period; average of five recordings recorded.
(3) SpO2: taken from pulse oximeter reading five times during a one minute period; average of five readings recorded.
(4) Respiratory clinical status was assessed using the Respiratory Distress Assessment Instrument (RDAI) developed by Lowell and colleagues.
(5) The infant’s status of activity (four levels: asleep, quiet, agitated, and crying) during assessments was documented.

To study the safety of nebulised adrenaline, all subjects were admitted at least for a day, even though many were expected to improve and to be ready for discharge. The aim was to observe adequately for adverse effects such as vomiting, pallor, tremor, or arrhythmia.

Informed consent was obtained from parents. The local ethics committee approved the study.

**Sample size**
As an assessment of treatment efficacy, a reduction in respiratory rate of 7 breaths/min was regarded as important. Assuming a standard deviation of the respiratory rate of 7 breaths/min, with an α error of 0.05 (two tailed test) and power of 90%, a sample size of 21 infants per group would be sufficient to detect an important treatment effect.

As an assessment of treatment safety, an increase in heart rate by 15 beats/min was considered important. Assuming a standard deviation of the heart rate of 15 beats/min, an α error of 0.05 (two tailed test) and power of 90%, a sample size of 21 infants per group would be sufficient.

Primary outcome measure was the changes in respiratory and heart rates, as compared between the groups, before any nebulised treatment and 20 minutes after either saline or adrenaline nebulisation.

**Statistical analysis**
Statistical analysis used the Statistical Package for Social Sciences, version 10. The investigator and statistician were blinded to treatment allocation, with treatment groups randomised to groups 1 and 2. Non-parametric data were analysed using Pearson’s χ²; Fisher’s exact test, or the Mann–Whitney test; parametric data were analysed using the paired t test and general linear model for repeated measurements analyses.

**RESULTS**
The study period was from mid December 1998 to the end of May 2000 and thereby encompassed two winters. All infants admitted to the Leicester Royal Infirmary Children’s Hospital during this time with a clinical diagnosis of bronchiolitis, who were thought to be suitable for the study, were referred for assessment.

We assessed 109 infants and recruited 38 (35%) into the study. The remaining 71 were not recruited, either through failure to obtain parental consent (n = 22) or ineligibility (n = 49). Reasons for rejection were: disease too mild (n = 21), recurrent wheeze (n = 9), symptoms more than four days duration (n = 9), recent systemic steroids (n = 4), lobar collapse (n = 2), mechanical ventilation required (n = 2), neurological disease (n = 1), and chronic lung disease (n = 1).

The two treatment groups were similar for age, gender, respiratory virology, radiology, and clinical signs at baseline assessment (table 1).

Although activity status changed in some infants as a result of nebulisation, it generally returned to the prenebulisation state by the time of the first post-nebulisation assessment (at 20 minutes). Therefore, during the study period the activity status was on average similar between groups, excluding its influence on the five points of assessments (χ² = 44.69, 0.92, 0.26, and 0.94); for example, a decrease in activity might decrease an infant’s heart rate.

Stabilisation and pretreatment supportive care resulted in significant falls from baseline in both respiratory rate (mean
which is well established in bronchiolitis; and secondly, to compare the study treatment to its vehicle as the vehicle itself may be beneficial. Previous studies compared adrenaline with salbutamol and failed to account for the effects of supportive care and improvement with time. A possible criticism of this study might be the failure to recruit the projected number of subjects into each treatment arm. However, although the study was short of two patients per treatment arm, the amount of overlap in confidence intervals made this shortfall statistically insignificant and thereby negated the possibility of missed differences.

A further criticism might be the insufficiency of the delivered adrenaline dose. Although we used the highest dose, 3 mg, reported in such studies, an increase in heart rate by 6.7 beats/min on average was noted in the treatment group at 40 minutes; this had resolved by 60 minutes. This suggests that the small range of aerosol particle size produced by the Pari-BABY nebuliser ensured minimal oropharyngeal deposition and absorption, while lung deposition occurred. The α adrenergic activity of adrenaline ensured local respiratory tract vasoconstriction and delayed its own systemic absorption. This is the main reason for choosing: (a) the Pari-BABY nebuliser, to minimise side effects by eliminating non-targeted organ absorption (upper respiratory tract); (b) the mucosal vasoconstrictor adrenaline (rather than the vasodilator salbutamol), which limits its own absorption and hence its direct cardiac effects; and (c) the pulmonary vasoconstrictor adrenaline, which does not induce perfusion–ventilation mismatching and hypoxia, which has an indirect arrhythmogenic potential.

Nebulised adrenaline cannot be recommended as treatment for infants with a moderately severe first attack of bronchiolitis on the results of this study. However, as it was found non-deleterious to patients it might be considered for its bronchodilator properties in infants over 1 year of age with recurrent wheeze.

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Authors’ affiliations
A Abul-Ainine, D Luyt, Children’s Hospital, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, UK

REFERENCES
2 Price JF. Acute and long-term effects of viral bronchiolitis in infancy. Lung 1990;168(suppl), 141–21.

Identifying risk of blindness

Complications of uveitis can be predicted early in children with idiopathic arthritis—an important advance, as this is the commonest form of anterior uveitis in children. Edelsten et al in the UK have reported risk factors associated with complications and remission based on a retrospective case review of children with painless anterior uveitis diagnosed between 1982 and 1998. They analysed endpoints for complications—cataract surgery, glaucoma, and loss of vision to <6/24—and for remission—inactive uveitis requiring no treatment for six months or more—against baseline characteristics on initial presentation. Children who had received treatment from onset at the study institute and had complied were assigned together to the standard cohort. Those who had initially been treated elsewhere, were poor compliers, had uveitis with another disease or uveitis presenting first with juvenile idiopathic arthritis were included in the non-standard cohort.

Overall, about a fifth (21%, 34/163) of children developed complications. Severe disease at onset of uveitis was a significant risk factor in both cohorts, multivariate analysis showed. For remission, it was mild onset. In all, 6% of children had severe sight loss (4% in the standard cohort) and 11% (6%) sustained moderate or severe loss respectively. Severe disease at first visit predicts poor outcome and calls for aggressive immediate treatment. However, Edelsten et al also advocate earlier diagnosis—ultimately universal screening—and better treatment for and characterisation of those children with mild symptoms at onset whose uveitis nevertheless progresses to complications—almost half the total developing complications in this study.