



Allergic diseases and the effect of inhaled epinephrine in children with acute bronchiolitis: follow-up from the randomised, controlled, double-blind, Bronchiolitis ALL trial

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Summary

Background Although use of inhaled bronchodilators in infants with acute bronchiolitis is not supported by evidence-based guidelines, it is often justified by the belief in a subgroup effect in individuals developing atopic disease. We aimed to assess if inhaled epinephrine during acute bronchiolitis in infancy would benefit patients with later recurrent bronchial obstruction, atopic eczema, or allergic sensitisation.

Methods In the randomised, double-blind, multicentre Bronchiolitis ALL trial, 404 infants with moderate-to-severe acute bronchiolitis were recruited from eight hospitals in Norway to receive either inhaled epinephrine or saline up to every second hour throughout the hospital stay. Randomisation was done centrally, and the two study medications (20 mg/mL racemic epinephrine or 0.9% saline) were prepared in identical bottles. The dose given depended on the infant's weight: 0.10 mL, less than 5 kg; 0.15 mL, 5–6.9 kg; 0.2 mL, 7–9.9 kg; and 0.25 mL, 10 kg or more; all dissolved in 2 mL of 0.9% saline before nebulisation. The primary outcome was the length of hospital stay. In this follow-up study, 294 children were reinvestigated at 2 years of age with an interview, a clinical examination, and a skin prick test for 17 allergens, determining bronchial obstruction, atopic eczema, and allergic sensitisation, on which subgroup analyses were done. Analyses were done by intention to treat. The trial has been completed and is registered at ClinicalTrials.gov (number NCT00817466) and EUDRACT (number 2009-012667-34).

Findings Length of stay did not differ between patients who received inhaled epinephrine versus saline in the subgroup of infants who developed recurrent bronchial obstruction by age 2 years (143 [48.6%] of 294 patients; $p_{\text{interaction}}=0.40$). However, the presence of atopic eczema or allergic sensitisation by the age of 2 years ($n=77$) significantly interacted with the treatment effect of inhaled epinephrine ($p_{\text{interaction}}=0.02$); the length of stay (mean 80.3 h, 95% CI 72.8–87.9) was significantly shorter in patients receiving inhaled epinephrine versus saline in patients without allergic sensitisation or atopic eczema by 2 years (–19.9 h, –33.1 to –6.3; $p=0.003$). No significant differences were found in length of hospital stay in response to epinephrine or saline in children with atopic eczema or allergic sensitisation by 2 years (+16.2 h, –11.0 to 43.3; $p=0.24$).

Interpretation Contrary to our hypothesis, hospital length of stay for bronchiolitis was not reduced by administration of inhaled epinephrine in infants who subsequently developed atopic eczema, allergic sensitisation, or recurrent bronchial obstruction. The present study does not support an individual trial of inhaled epinephrine in acute bronchiolitis in children with increased risk of allergic diseases.

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Introduction

Acute bronchiolitis in infants, mainly caused by seasonal epidemics of respiratory syncytial virus, frequently leads to admission to hospital.^{1,2} The disease presents with respiratory distress and sometimes requires fluid, nutrition, oxygen, and ventilatory support.³

We showed that inhaled epinephrine had no effect compared with inhaled saline on the length of hospital stay or the use of supportive care in 404 infants (mean age 4.2 months, 95% CI 3.9–4.5) with acute bronchiolitis,⁴ contributing to the October 2014 recommendations by The American Academy of Pediatrics against the use of any inhaled bronchodilator in such patients.⁵

In our study,⁴ subgroup analyses did not reveal effects related to the presence of atopic eczema or a positive family

history of atopic disease at the time of acute bronchiolitis. Yet the question remains whether or not inhalations with epinephrine might be effective in patients who develop asthma or allergic disease, a practice that has been implemented in some clinical practice guidelines.⁶ Thus, more than half of infants in the USA, Finland, and Sweden with acute bronchiolitis receive inhaled bronchodilators.^{7,8}

Subgroups defined by asthma risk factors at the time of acute bronchiolitis are imprecise for classifying children who later develop disease. Results from follow-up studies of sufficiently large clinical trials, which are necessary for correct disease classification and retrospective analyses, are lacking. Most schoolchildren with asthma or atopic eczema develop the diseases in the first few years of life.^{9,10} Therefore, disease classification at about 2 years of

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Research in context

Evidence before this study

Only a few major trials have reported the effect of inhaled bronchodilators in infants with acute bronchiolitis with outcomes important to clinicians: the length of hospital stay and the use of supportive care. Furthermore, a trial of bronchodilators has been suggested for some patients with acute bronchiolitis, and possibly children with a risk of asthma. However, none of the reports have done subgroup analyses based on subsequent development of recurrent bronchial obstruction, atopic eczema, or allergic sensitisation.

Added value of this study

By contrast with our hypothesis, the presence of recurrent bronchial obstruction at age 2 years did not modify the response to inhaled racemic epinephrine in acute bronchiolitis,

whereas allergic sensitisation and atopic eczema interacted significantly. In patients without allergic sensitisation or atopic eczema by age 2 years, the length of original hospital stay was significantly shorter in patients receiving inhaled epinephrine versus saline. No significant differences were found in children with atopic eczema or allergic sensitisation by age 2 years.

Implications of all the available evidence

Our results show that compared with infants without allergic disease by age 2 years, infants who subsequently developed atopic eczema, allergic sensitisation, or recurrent bronchial obstruction did not benefit from inhaled racemic epinephrine during acute bronchiolitis. The present study does not support an individual trial of inhaled epinephrine in acute bronchiolitis for children with increased risk of allergic diseases.

age might provide a reasonable time for classifying children as having atopic eczema or recurrent obstructive airways episodes, indicative of asthma.

In this follow-up study of children from our randomised clinical trial, we aimed to assess if the treatment response to inhaled racemic epinephrine in moderate-to-severe bronchiolitis in infancy differed in patients with recurrent bronchial obstruction, atopic eczema, or allergic sensitisation by the age of 2 years.

Methods

Study design and participants

The Bronchiolitis ALL study, a multicentre, randomised, factorial designed clinical trial, compared inhalations with racemic epinephrine versus saline and two inhalation strategies (on-demand vs fixed schedule; figure 1) in infants in Norway in two consecutive winter seasons from Jan 15, 2010, to May 10, 2011.⁴ Inclusion criteria were age less than 12 months and clinical signs of moderate-to-severe bronchiolitis.³ A clinical score of more than 4 on a scale from 1 to 10 (10 worst, see appendix) was used to determine moderate-to-severe illness. Exclusion criteria were severe underlying disease, more than one previous episode of wheeze, more than 4 weeks of continuous lower airway symptoms (eg, cough), and the use of inhaled or systemic steroids in the previous 4 weeks.

Written informed consent was obtained from a parent of each child before the start of therapy. The study was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Medicines Agency, and is registered in the Norwegian Biobank Registry. The study was audited by the Norwegian Medicines Agency in 2011.

Randomisation and masking

Randomisation of the participants to receive either inhaled epinephrine or saline up to every second hour throughout the hospital stay is described in detail elsewhere.⁴ Briefly, randomisation was done centrally in blocks of eight and the

randomisation codes were communicated to the pharmacy that prepared doses of the two study medications (20 mg/mL racemic epinephrine or 0.9% saline) in identical bottles, each labelled with a numerical code showing the type of medication. The study centres were provided with a list of study numbers for use in the consecutive assignment of medication to enrolled children. Both investigators and parents were masked at inclusion, through the randomised controlled trial, and at the follow-up study.

Procedures

The dose of epinephrine given depended on the infant's weight: 0.10 mL, less than 5 kg; 0.15 mL, 5–6.9 kg; 0.2 mL, 7–9.9 kg; and 0.25 mL, 10 kg or more; all dissolved in 2 mL of 0.9% saline before nebulisation.

The use of supportive care was recorded daily and verified in patient record reviews. This re-investigation at 2 years of age, planned before the commencement of the randomised controlled trial, included a structured parental interview, a clinical examination, and a skin prick test for allergic sensitisation.

The structured interview of one or both of the patient's caregivers was done by a specially trained physician, focusing on respiratory, allergy, and atopic eczema symptoms.

Skin prick testing was done on the volar side of both lower arms with 11–17 relevant allergens (egg, peanut, almond, dog epithelium, cat epithelium, *Dermatophagoides pteronyssinus*, prawns, milk, birch, wheat, timothy grass, hazelnut, soy, cod, *Cladosporium herbarum*, and *Alternaria tenuis*), and positive and negative controls. A skin reaction of 3 mm or more, after subtraction of the negative control, was defined as a positive test, and allergic sensitisation was defined as a positive skin prick test to at least one allergen.

Episodes of bronchial obstruction were registered by the research physician at trial inclusion (one previous obstructive episode was allowed for inclusion) and at follow-up at age 2 years, based on previous patient

See Online for appendix

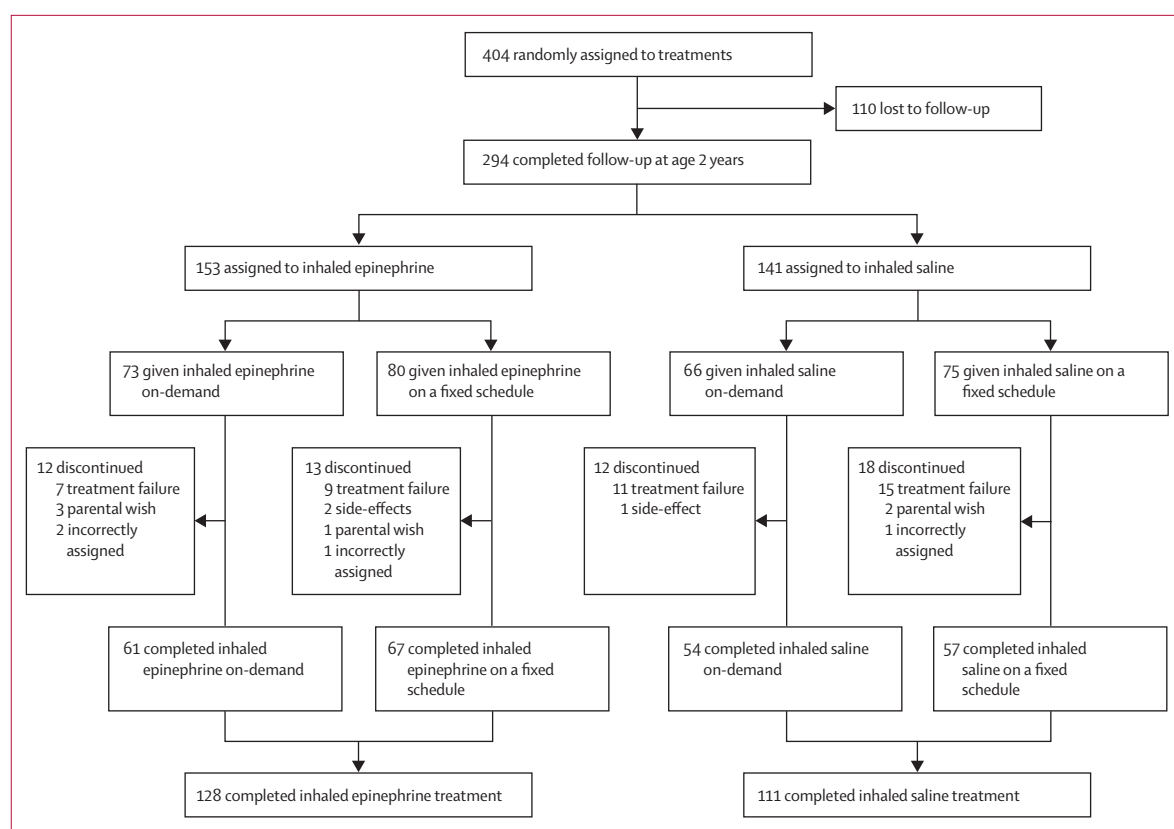


Figure 1: Trial profile

In four children, the study medication was discontinued because of administrative failures, including administration of open inhaled racemic epinephrine, suspected pertussis infection, delayed biological sampling, and administration of a dose of the study medication that was too high.

records and physician-led parental interview. The specific questions to determine recurrent bronchial obstruction were: Has the child had episodes of wheezing and/or chest tightness? If yes: specify the number of episodes during the first and second year of life. Recurrent bronchial obstruction was defined as the presence of at least three separate episodes of bronchial obstruction at any time, including the episode reported during enrolment into the clinical trial, when applicable.

At the follow-up study at age 2 years, atopic eczema was defined as either the presence of atopic eczema according to the criteria of Hanifin and Rajka, requiring the presence of a minimum of three of four major criteria and a minimum of three of 23 minor criteria,¹¹ or previously reported physician-diagnosed atopic eczema.

Outcomes

As detailed in the study protocol,⁴ the main outcome was the difference in response to inhaled epinephrine versus saline in terms of length of hospital stay and the use of supportive care, in the subgroups of patients with and without recurrent bronchial obstruction, atopic eczema, and allergic sensitisation by the age of 2 years.

The secondary outcomes were the difference in response to inhaled epinephrine versus saline in terms

of change in clinical score after the first inhalation and the difference in response to treatment on-demand versus on a fixed schedule in terms of length of hospital stay in the subgroups of patients with and without recurrent bronchial obstruction, atopic eczema, and allergic sensitisation by the age of 2 years.

Statistical methods

Continuous data are presented as means (95% CIs), and categorical data are presented as numbers and percentages. Categorical data were assessed with the use of the Pearson χ^2 test. Because data on length of stay had a non-normal distribution, comparisons between groups were assessed with the use of robust, two-sample t tests and Huber's M-estimator, with 95% CIs. Comparison of change in clinical score was assessed using t tests.

The power analysis was based on the length of stay of about 450 children admitted to hospital at the main study site during a 12-month period before the start of the study. Assuming that clinically relevant improvement would be shown by a length of stay that was reduced by at least 5 h in the group receiving inhaled racemic epinephrine, we calculated that a total of 176 children in each medication group would provide

a power of at least 80% at a two-sided α level of 0.05. Because of the inclusion of secondary outcomes and subgroup analyses, we increased the enrolment target to a total of 500 children. To assess the effects in subgroups defined by clinical outcomes at age 2 years, we did interaction analyses between the predictors (recurrent bronchial obstruction, atopic eczema, and allergic sensitisation) and the response of inhaled epinephrine versus saline on the outcomes (length of stay, with the use of robust linear regression and Huber's M-estimator; and the use of oxygen, nasogastric feeding, and ventilatory support with the use of logistic regression). Secondary survival analyses for potential differences in treatment effect related to clinical outcomes at 2 years of age were done by Cox regression on length of stay with interaction and stratified analyses. The length of stay by treatment is presented as Kaplan-Meier plots.

Stratified results of the difference in length of stay in subgroups are presented in a horizontal error bar plot. *p* values of subgroup effects are presented, acknowledging the limitations of such *p* values.^{12,13}

The level of significance was set at 0.05, and analyses were done using Stata software, version 13.1. Analyses were done by the intention-to-treat principle. The study is registered at ClinicalTrials.gov (number NCT00817466) and EUDRACT (number 2009-012667-34).

Role of the funding source

The funder had no role in study design, collection, analyses, interpretation of data, or writing the report. HOS, PM, K-HC, and KCLC had access to the raw data. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

The trial included 404 infants admitted to hospital with moderate-to-severe bronchiolitis, of which 294 (73%) were reinvestigated at follow-up at age 2 years. The mean age was 4.1 months (95% CI 3.8–4.5) at inclusion and 24.6 months (24.3–25.0) at the follow-up appointment. 181 (61.6%) of 294 patients were boys. Mean length of hospital stay was 80.3 h (95% CI 72.8–87.9). Baseline characteristics were comparable in the patients that attended and did not attend the follow-up study (table) and in the treatment groups (appendix). Baseline characteristics and length of hospital stay were similar in the four groups related to recurrent bronchial obstruction and atopic eczema or allergic sensitisation at follow-up at age 2 years (appendix). No serious adverse events were reported.

Length of stay (figures 2, 3) was not significantly modified by treatment with inhaled epinephrine versus saline in the subgroup of infants who developed recurrent bronchial obstruction by age 2 years (143 [48.6%] of 294; $p_{\text{interaction}}=0.40$). The use of oxygen, nasogastric tube feeding, or ventilatory support also did not differ (all $p_{\text{interaction}}>0.1$). In stratified analyses of

	Attended follow-up (n=294)	Lost to follow-up (n=110)
Males	181 (61.6%)	59 (53.6%)
Age, days	124 (85)	134 (95)
Father, white	272 (92.5%)	100 (90.9%)
Mother, white	267 (90.8%)	101 (91.7%)
Atopic eczema	29/271 (10.7%)	11/103 (10.7%)
One previous episode of bronchial obstruction	69/260 (26.5%)	29/102 (28.4%)
More than 1 week of persistent respiratory symptoms	34/249 (13.7%)	11/99 (11.1%)
Parental asthma	59/235 (25.1%)	22/90 (26.7%)
Parental rhinoconjunctivitis	84/258 (32.6%)	29/98 (29.6%)
Clinical score	4.9 (1.0)	4.9 (0.9)
SpO ₂ (%)	96.0% (3.2)	96.0% (3.4)
Respiratory rate (breaths per min)	54.0 (11.3)	51.9 (10.4)
Heart rate (beats per min)	153.7 (18.0)	153.5 (19.6)

Values are n/N (%) or mean (SD). SpO₂=peripheral capillary oxygen saturation.

Table: Baseline characteristics of children enrolled during acute bronchiolitis who did and did not attend follow-up visit at age 2 years

patients without recurrent bronchial obstruction by age 2 years, the difference in length of stay if receiving inhaled epinephrine versus saline was –15.8 h (95% CI –33.1 to 1.6; $p=0.08$). In children with recurrent bronchial obstruction, the difference in length of stay was –5.3 h (95% CI –22.8 to 12.3; $p=0.55$).

Recurrent bronchial obstruction did not significantly modify the response to the first inhalation of epinephrine measured by change in clinical score ($p_{\text{interaction}}=0.24$).

By 2 years of age, atopic eczema was diagnosed in 68 (23.1%) of 294 children, either previously by a doctor ($n=48$) or by meeting Hanifin and Rajka's criteria¹⁴ at follow-up ($n=38$). Allergic sensitisation (positive skin prick test) was present in 23 (8.0%) of 294 individuals (allergens: peanut, $n=9$ [3.1%]; cat, $n=7$ [2.4%]; egg, $n=5$ [1.7%]; almond, $n=4$ [1.4%]; dog, $n=4$ [1.4%]; *D pteronyssinus*, $n=1$ [0.4%]; prawn, $n=1$ [0.4%]; and cow's milk, $n=1$ [0.4%]).

The presence of atopic eczema or allergic sensitisation by the age of 2 years ($n=77$) significantly interacted with the treatment effect of inhaled epinephrine in terms of length of hospital stay when analysed by robust linear regression analyses ($p_{\text{interaction}}=0.02$) and by Cox regression analyses ($p_{\text{interaction}}=0.03$), and the use of supplementary oxygen ($p_{\text{interaction}}=0.03$). In patients without atopic eczema or allergic sensitisation by the age of 2 years ($n=217/294$, 73.8%), inhaled epinephrine significantly reduced length of stay versus saline (–19.9 h, 95% CI –33.1 to –6.3; $p=0.003$) but did not affect the need for additional oxygen support (46/106, 43.4% vs 54/103, 52.4%; rate ratio 0.83 [0.62 to 1.10]; $p=0.19$). In patients with atopic eczema or allergic sensitisation ($n=77/294$, 26.2%) there was no statistically significant effect of inhaled epinephrine versus saline on length of stay

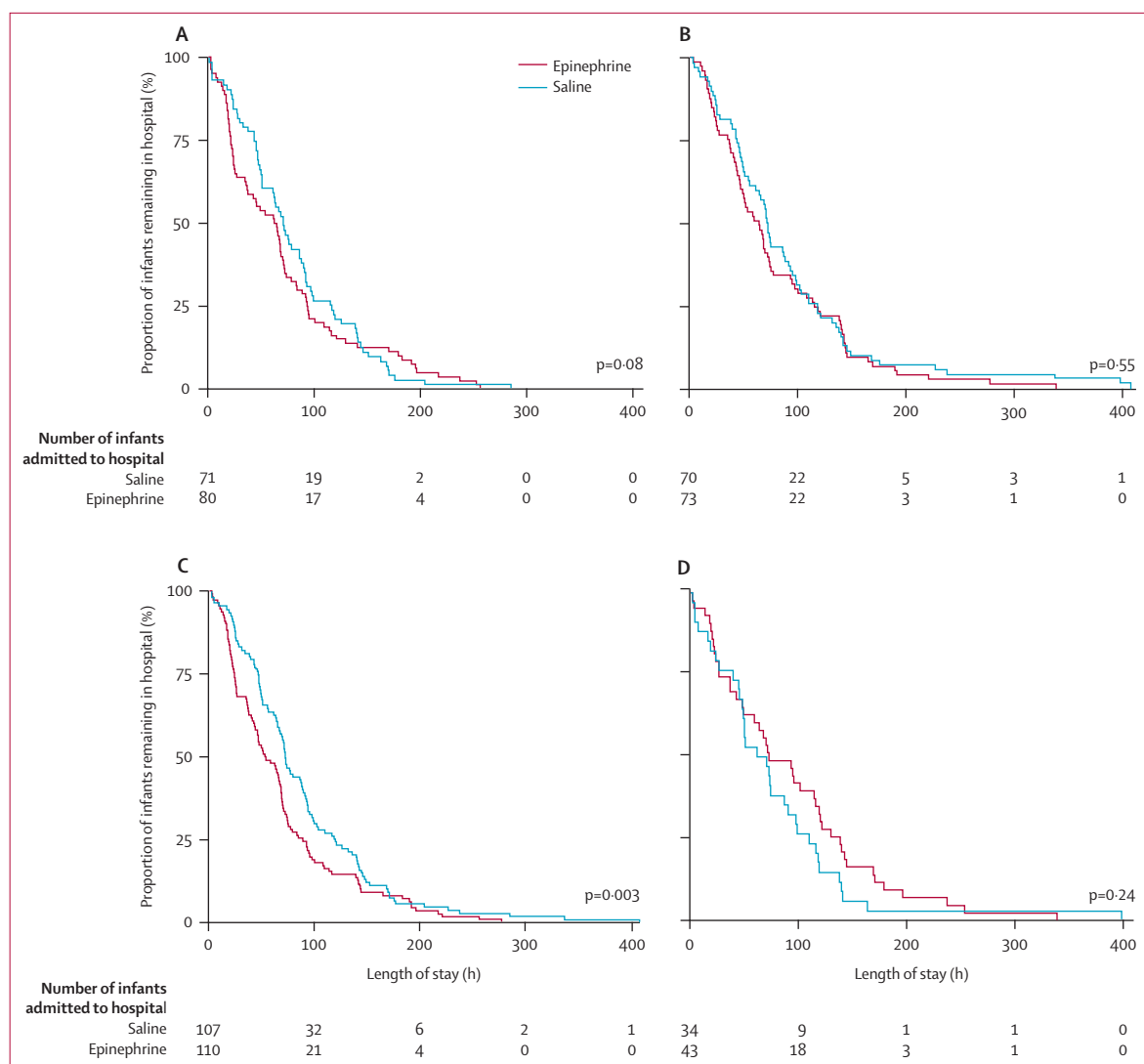


Figure 2: Length of hospital stay according to study treatment

Kaplan-Meier plots show the proportion of infants remaining in hospital according to whether they were treated with inhaled racemic epinephrine or inhaled saline in patients at the age of 2 years: (A) without recurrent bronchial obstruction (after secondary survival analysis: hazard ratio [HR] 1.13, 95% CI 0.82–1.57; $p=0.45$); (B) with recurrent bronchial obstruction (HR 1.15, 0.83–1.61; $p=0.39$); (C) without atopic eczema or allergic sensitisation (HR 1.38, 1.05–1.81; $p=0.02$); and (D) with either atopic eczema or allergic sensitisation (HR 0.77, 0.48–1.22; $p=0.26$). p values are from robust linear regression analyses.

(+16.2 h, 95% CI –11.0 to 43.3; $p=0.24$; figures 2, 3) or on the need for additional oxygen support (17/40, 42.5% vs 7/31, 22.6%; rate ratio 1.88 [95% CI 0.89–3.96]; $p=0.09$). Secondary stratified survival analyses showed that children who received inhaled epinephrine without atopic eczema or allergic sensitisation had a hazard ratio (HR) of 1.38 (95% CI 1.05–1.81; $p=0.02$) for being discharged from hospital, compared with 0.77 (0.48–1.22; $p=0.26$) for being discharged from hospital for children with atopic eczema or allergic sensitisation.

Atopic eczema or allergic sensitisation did not significantly modify the response to the first inhalation of epinephrine measured by the change in clinical score ($p_{\text{interaction}}=0.37$).

There was no interaction between inhalant strategy (on-demand vs fixed schedule) and recurrent bronchial obstruction ($p_{\text{interaction}}=0.29$) or atopic eczema and allergic sensitisation ($p_{\text{interaction}}=0.59$) on the length of stay. Stratified analyses are presented in the appendix.

Discussion

The present study assessed if the effect of inhaled racemic epinephrine during hospital admission with moderate-to-severe acute bronchiolitis in infancy differed in patients with recurrent bronchial obstruction, atopic eczema, or allergic sensitisation, by the age of 2 years. We found that patients without atopic eczema or allergic sensitisation by the age of 2 years had a significantly

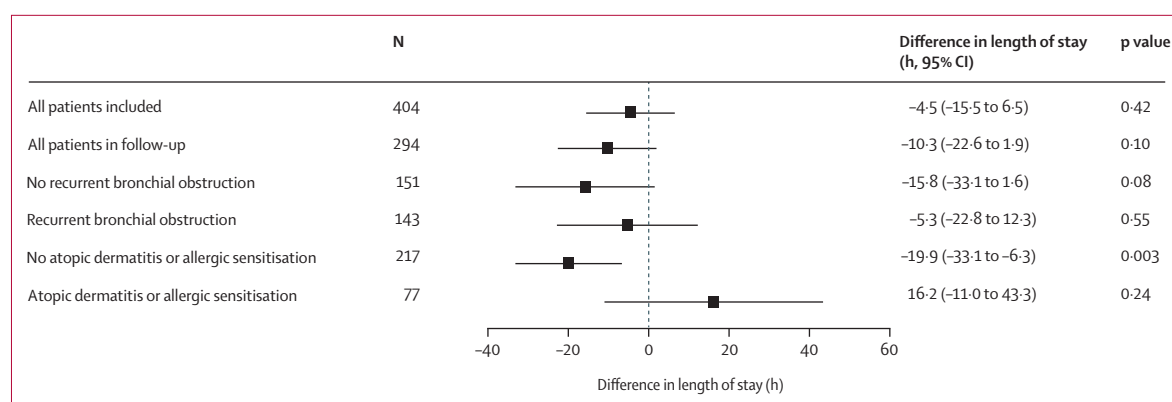


Figure 3: Treatment response to inhaled racemic epinephrine versus saline in infants with acute bronchiolitis, shown as difference in length of stay in hospital in subgroups based on the presence of recurrent bronchial obstruction, atopic eczema, or allergic sensitisation by the age of 2 years

Error bars are 95% CIs for the difference in estimated length of stay between patients who received inhaled epinephrine versus saline analysed by robust linear regression.

shorter length of stay if treated with inhaled epinephrine versus saline.

The effect of bronchodilators in acute bronchiolitis has been the subject of debate. Major guidelines recommend a restrictive approach,^{5,14,15} based on evidence showing no effect of any bronchodilator on the most clinically relevant parameters such as length of stay and the use of supportive care.^{4,16–18} Despite this, inhaled bronchodilators (including epinephrine) are still used in most patients in several countries, including the USA, Sweden, and Finland.^{7,8} Sustained frequent use of inhaled bronchodilators is presumably due to a belief in the existence of one or more subgroup(s) of patients that benefit from such treatment.

The present study to our knowledge is the first to report a potential treatment effect in subgroups of patients with recurrent bronchial obstruction, allergic sensitisation, or atopic eczema up to the age of 2 years. Our findings show that not only was there a lack of effect of inhaled epinephrine in children who went on to have recurrent bronchial obstruction episodes, atopic eczema, or allergic sensitisation, but rather that children without these diseases appeared to benefit from inhaled racemic epinephrine. The findings in our study contrast with the hypothesis that inhaled epinephrine might be beneficial in children developing asthma, atopic disease, or allergy,⁶ which has wide support among clinicians. It is not clear why children without atopic eczema or allergic sensitisation responded to inhaled epinephrine, whereas those with one or both of these conditions did not. The rationale for the use of the nonselective adrenergic agonist epinephrine has been the potential effect on vascular engorgement and mucosal swelling that adds to the dilating effect of β -2-adrenergic selective agonists on bronchial smooth muscle. However, it is not clear when chronic inflammation starts in the airways of children with asthma, although it has been suggested that some children with pre-school wheezing develop airway remodelling at a very early stage.^{19–21} Airway obstruction in

acute bronchiolitis usually occurs in the distant bronchioles involving exaggerated cytopathology with neutrophil-dominated inflammatory changes with subsequent shedding of infected epithelium and sub-mucosal oedema.²² However, we speculate that children who develop atopic disease might already have an altered airway response to the viral infection,²⁰ with chronic inflammatory changes possibly adding to the reduced airway calibre in response to the viral infection. A possible reduction in airway oedema by racemic epinephrine might attenuate airway obstruction and speed recovery in children without chronic inflammatory responses associated with allergic sensitisation or atopic eczema. However, findings from a randomised controlled trial have shown that palivizumab, a monoclonal antibody against respiratory syncytial virus, reduced subsequent episodes of wheeze, suggesting that a viral infection in infancy might cause epithelial damage and itself contribute to the pathogenesis of recurrent wheeze.²³

Our results suggest that the differential response to epinephrine might show differences in underlying pathophysiological mechanisms in children with and without allergic disease developing by 2 years of age. High genomic load of respiratory syncytial virus has been associated with severity in clinical studies, including a large multicentre study²⁴ that corroborated the involvement of Th-2 (IL-4 and IL-6) cytokines²⁵ and interferon²⁶ in severe acute bronchiolitis. However, we can only speculate that the shorter length of stay in children without atopic disease who received inhaled epinephrine could be associated with a less pronounced Th-2 type inflammatory response to the virus, but we do not have any evidence to support this hypothesis.

As with other studies and the definition of asthma described in the Nordic consensus report on asthma management,²⁷ our definition of recurrent bronchial obstruction was set to at least three episodes. It is possible that subgroups of patients have transient response to epinephrine that is not reflected in hospital length of

stay. However, the lack of initial response to epinephrine as a secondary outcome supports our finding that the treatment does not seem to be effective in children with recurrent bronchial obstruction.

We believe the follow-up rate of 73% (294/404) of children was acceptable due to the nature of the study, including moderately to severely ill infants. The study population is reasonable for subgroup analyses in terms of major outcomes. Loss to follow-up is unlikely to bias the results because the parents were masked, and the characteristics of the randomisation groups were similar.

Racemic epinephrine did not show benefit in children with an increased risk of asthma. In the present study we were not able to identify relevant subgroups at the time of acute bronchiolitis thus restricting the clinical applicability of choosing individuals who would potentially benefit from inhaled racemic epinephrine. We found no significant treatment differences based on allergic disease risk at the time of hospital admission,⁴ possibly because atopic eczema had not yet developed for most infants. Our study does not support a trial of inhaled epinephrine in children with increased risk of allergic diseases.

Contributors

HOS conceptualised and designed the study, coordinated and supervised data collection, analysed data, drafted the initial manuscript, and approved the final manuscript as submitted. LBR, TLB, HE, BK, and JOGH, contributed to design of the study and acquisition of data, revised the manuscript, and approved the final manuscript as submitted. ED, CM, MHA, and KESB contributed to acquisition of data and revised the manuscript. PM contributed to design of the study, did the statistical analyses and interpretation of data, reviewed and revised the manuscript, and approved the final manuscript as submitted. K-HC conceptualised and designed the study, analysed data, reviewed and revised the manuscript, and approved the final manuscript as submitted. KCLC was the Principal Investigator, conceptualised and designed the study, analysed data, drafted the initial manuscript, and approved the final manuscript as submitted. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

K-HC reports personal fees from Boehringer Ingelheim, Novartis, Takeda Nycomed, and Meda, outside of the submitted work. The other authors declare no competing interests.

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