ORIGINAL ARTICLE

Racemic Adrenaline and Inhalation Strategies in Acute Bronchiolitis

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ABSTRACT

BACKGROUND

Acute bronchiolitis in infants frequently results in hospitalization, but there is no established consensus on inhalation therapy — either the type of medication or the frequency of administration — that may be of value. We aimed to assess the effectiveness of inhaled racemic adrenaline as compared with inhaled saline and the strategy for frequency of inhalation (on demand vs. fixed schedule) in infants hospitalized with acute bronchiolitis.

METHODS

In this eight-center, randomized, double-blind trial with a 2-by-2 factorial design, we compared inhaled racemic adrenaline with inhaled saline and on-demand inhalation with fixed-schedule inhalation (up to every 2 hours) in infants (<12 months of age) with moderate-to-severe acute bronchiolitis. An overall clinical score of 4 or higher (on a scale of 0 to 10, with higher scores indicating more severe illness) was required for study inclusion. Any use of oxygen therapy, nasogastric-tube feeding, or ventilatory support was recorded. The primary outcome was the length of the hospital stay, with analyses conducted according to the intention-to-treat principle.

RESULTS

The mean age of the 404 infants included in the study was 4.2 months, and 59.4% were boys. Length of stay, use of oxygen supplementation, nasogastric-tube feeding, ventilatory support, and relative improvement in the clinical score from baseline (preinhalation) were similar in the infants treated with inhaled racemic adrenaline and those treated with inhaled saline (P>0.1 for all comparisons). On-demand inhalation, as compared with fixed-schedule inhalation, was associated with a significantly shorter estimated mean length of stay — 47.6 hours (95% confidence interval [CI], 30.6 to 64.6) versus 61.3 hours (95% CI, 45.4 to 77.2; P=0.01) — as well as less use of oxygen supplementation (in 38.3% of infants vs. 48.7%, P=0.04), less use of ventilatory support (in 4.0% vs. 10.8%, P=0.01), and fewer inhalation treatments (12.0 vs. 17.0, P<0.001).

CONCLUSIONS

In the treatment of acute bronchiolitis in infants, inhaled racemic adrenaline is not more effective than inhaled saline. However, the strategy of inhalation on demand appears to be superior to that of inhalation on a fixed schedule. (Funded by Medicines for Children; ClinicalTrials.gov number, NCT00817466; EudraCT number, 2009-012667-34.)

Acute bronchiolitis in infants, which frequently leads to hospitalization[1,2] and sometimes requires ventilatory support, is occasionally fatal[3]; it is usually viral in origin, with respiratory syncytial virus[4] being the most common cause. The clinical disease is characterized by nasal flaring, tachypnea, dyspnea, chest retractions, crepitations, and wheezing.[5]

Bronchodilators are not recommended[6,7] but are often used in the treatment of bronchiolitis,[8-10] as are saline inhalations. Adrenaline reduces mucosal swelling,[11] giving it an edge over the β_2-adrenergic agonists,[12] and has led to the frequent use of inhaled adrenaline,[13] which has improved symptoms[12,14-20] and reduced the need for hospitalization in outpatients with acute bronchiolitis.[12] Among inpatients, however, inhaled adrenaline has not been found to reduce the length of the hospital stay.[12,20-22] Assessment of the possible influences of age, sex, and status with respect to an asthma predisposition[23] on the effect of inhaled adrenaline requires large multicenter studies.[12,24]

Inhaled nebulized solutions can be prescribed for use on demand or on a fixed schedule. We were unable to find documentation on the comparative efficacy of these two strategies in children with acute bronchiolitis.

We tested the hypothesis that inhaled racemic adrenaline is superior to inhaled saline in the treatment of acute bronchiolitis in infancy and that administration on a fixed schedule is superior to administration on demand. We also assessed whether age, sex, or status with respect to allergic diseases influenced treatment efficacy.

METHODS

STUDY DESIGN

This multicenter, double-blind, randomized clinical trial (the Bronchiolitis All-study, SE-Norway) included infants with acute bronchiolitis who were admitted to the pediatric departments of eight hospitals in southeastern Norway from January 2010 through May 2011. In accordance with a 2-by-2 factorial design, children were randomly assigned to receive inhaled racemic adrenaline or inhaled saline and to receive the assigned treatment on demand or on a fixed schedule (Fig. 1).

The study was approved by the Regional Committees for Medical and Health Research Ethics and by the Norwegian Medicines Agency and is registered in the Norwegian Biobank Registry. Written informed consent was obtained from a parent of each child before the start of therapy. The study was audited by the Norwegian Medicines Agency in 2011. All authors vouch for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol (available with the full text of this article at NEJM.org).

The inclusion criteria were clinical signs of bronchiolitis as defined by Court[5] (see the Supplementary Appendix, available at NEJM.org), an age of less than 12 months, and an overall clinical score of at least 4 on a scale of 0 to 10. The clinical score was the sum of points allotted, from 0 (indicating normal findings) to 2 (indicating severe illness), for each of the following: general condition, skin color, findings on auscultation, respiratory rate, and retractions[15,25] (Table S1 in the Supplementary Appendix). The study physicians performing the clinical scoring were trained at investigator meetings as well as on site by the first author and by local primary investigators. The exclusion criteria were the presence of any serious cardiac, immunologic, neurologic, or oncologic disease or any serious pulmonary disease other than bronchiolitis; more than one previous episode of obstructive airway disease; symptoms of disease of the lower airway (e.g., coughing) for more than 4 weeks; and receipt of any glucocorticoid therapy in the preceding 4 weeks.

Children were enrolled in the study on admission to the hospital as long as attending personnel (a physician and a nurse) were available. Clinical scoring was performed by a pediatrician. After written informed consent was obtained from a parent, children underwent randomization, and the assigned study medication was administered. The baseline characteristics of the children were obtained on admission, and the assessment included a pediatrician-guided, structured interview of one or both parents. Viral analyses of nasopharyngeal aspirates were performed at the largest hospital involved in the study (Oslo University Hospital) with the use of a polymerase-chain-reaction assay for nine common airway viruses. (See the Supplementary Appendix for further information on the biologic specimens gathered.)

Randomization was performed centrally in blocks of eight, with assignment to one of the four study groups, with the use of SAS software, version 9.3. The randomization codes were com-

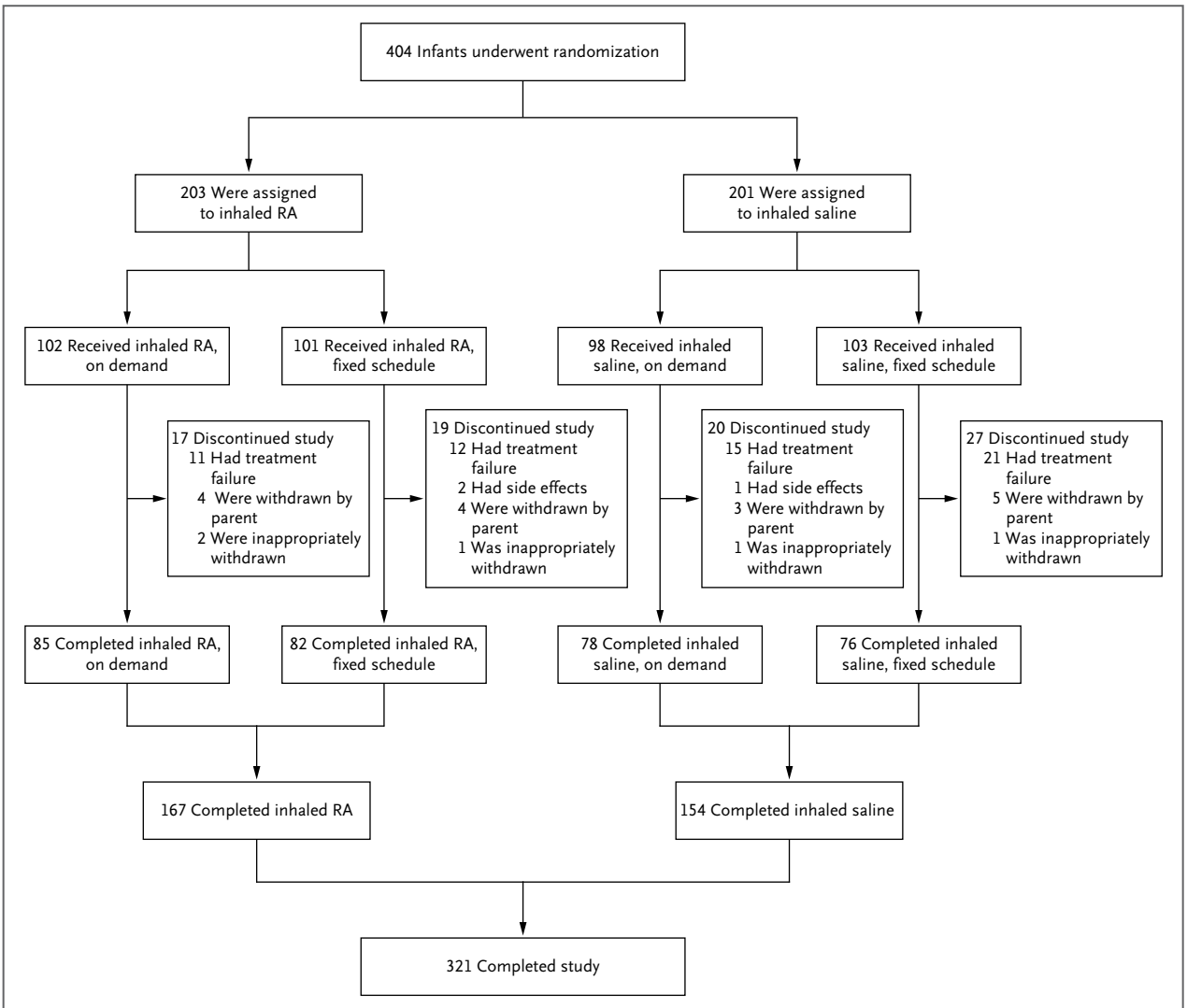

Figure 1. Randomization of the Study Patients.

In five children, the study medication was discontinued because of the following administrative failures: administration of open inhaled racemic adrenaline (RA), suspected pertussis infection, delayed biologic sampling, administration of a dose of the study medication that was too high, and insufficient supply of study medication.

municated directly by the study statistician to the pharmacy, where doses of the two study medications (10 ml of racemic adrenaline dissolved in 0.9% saline to form a solution of 20 mg per milliliter or 0.9% saline alone) were prepared in identical bottles, each labeled with a numerical code indicating the type of medication and timing of administration (on demand or fixed schedule). The study centers, which were not aware of the randomization block size, were provided with a list of study numbers for use in the consecutive assignment of medication to enrolled children.

The dose administered was based on the infant's weight: 0.10 ml for infants weighing less than 5 kg, 0.15 ml for those weighing 5 to 6.9 kg, 0.20 ml for those weighing 7 to 9.9 kg, and 0.25 ml for those weighing 10 kg or more.[15] The medications were diluted in 2 ml of saline before nebulization and were administered through a Sidestream Reusable Nebulizer with a Respironics Facemask (both from Philips Respironics), driven by 100% oxygen at a rate of 6 liters per minute. No other inhaled medications, with the exception of 0.9% inhaled saline (which was an option in both study groups, to be administered

at the discretion of the attending physician), could be administered during the period when the infant was participating in the trial. Supportive therapy and any other treatments were provided in accordance with routine care. In accordance with national guidelines, glucocorticoids and β_2-adrenergic agonists were not administered.[13]

OUTCOMES

The primary outcome, length of hospital stay, was defined as the time from the first study inhalation until discharge from the hospital, as recorded in the medical record for each patient. Secondary outcomes were the change in the clinical score 30 minutes after the first inhalation and the use of nasogastric-tube feeding, oxygen supplementation, or ventilatory support, all of which were recorded throughout the patient's hospital stay. Adverse events during hospitalization were monitored and reported within 24 hours.

Clinical scores, oxygen saturation as measured by pulse oximetry, heart rate, respiratory rate, the use of nasogastric-tube feeding, the use of ventilatory support, and the time at which each inhalation occurred were recorded from one to four times daily during hospitalization (see the Supplementary Appendix for details). Treatment with supplemental oxygen and the performance of chest radiography were also recorded.

STATISTICAL ANALYSES

Continuous data are presented as means (±SD), and categorical data are presented as numbers and percentages. Categorical data were assessed with the use of the Pearson chi-square test. Because data on length of stay had a non-normal distribution, comparisons between groups were assessed with the use of a robust, two-sample t-test and Huber's M-estimator, with 95% confidence intervals.

Interactions were assessed for inhaled racemic adrenaline versus inhaled saline and on-demand versus fixed-schedule administration, as well as for treatment and site, with the use of robust linear regression and Huber's M-estimator. The Jonckheere–Terpstra test was used to assess interactions between age (at 3-month intervals) and interventions. Local regression smoothing was applied to assess the effect of age on length of stay.

The power analysis was based on the length of stay of approximately 450 children hospitalized at the main study site during a 12-month period before the start of the study. Assuming that clinically relevant improvement would be indicated by a length of stay that was reduced by at least 5 hours in the group receiving inhaled racemic adrenaline,[26] we calculated that a total of 176 children in each medication group would provide a power of at least 80% at a two-sided alpha level of 0.05. Owing to the inclusion of secondary outcomes and subgroup analyses, we increased the enrollment target to a total of 500 children. The level of significance was set at 0.05, and analyses were performed with the use of SAS software, version 9.3, and IBM SPSS software, version 19.

RESULTS

STUDY PATIENTS

The study included 404 children (59.4% of whom were boys) with a mean age of 126 days (4.2 months) (Table 1). The number of children enrolled at each study center ranged from 22 to 136 (mean, 51) (Table S2 in the Supplementary Appendix). The study medication was discontinued in 83 children (20.5%) for the reasons listed in Figure 1.

The mean (±SD) length of stay for all infants was 80±67 hours; most children were discharged between 8 a.m. and 11 p.m. (Fig. S1 in the Supplementary Appendix). Baseline characteristics did not differ significantly among the four study groups (Table 1).

Routine respiratory viral assays were performed in 123 of the 136 children admitted to Oslo University Hospital; 99 of those 123 children (80.5%) were positive for respiratory syncytial virus and 21 of 123 children (17.1%) were positive for another virus; 5 of 123 (4.1%) children were positive for two viruses.

RACEMIC ADRENALINE VERSUS SALINE

There was no significant difference in length of hospital stay between children treated with inhaled racemic adrenaline and those treated with inhaled saline (P=0.43) (Table 2 and Fig. 2A). There were also no significant between-group differences in the use of nasogastric-tube feeding, supplemental oxygen, or ventilatory support; clinical scores before and after the first inhalation of the study medication; or the number of children in whom the study medication was discontinued (36 children in the group receiving inhaled racemic adrenaline and 47 in the group receiving inhaled saline) (Table 2).

Table 1. Baseline Characteristics of the Study Patients.*

Characteristics	Inhaled Racemic Adrenaline		Inhaled Saline	
	On Demand (N=102)	Fixed Schedule (N=101)	On Demand (N=98)	Fixed Schedule (N=103)
Male sex — no. (%)	63 (61.8)	60 (59.4)	54 (55.1)	63 (61.2)
Mean age — days	134.9±91.6	116.9±87.8	117.8±68.1	136.0±97.0
Parental race — no./total no. (%)†				
Father white	79/87 (90.8)	85/90 (94.4)	75/83 (90.4)	83/91 (91.2)
Mother white	79/88 (89.8)	85/92 (92.4)	78/84 (92.9)	83/92 (90.2)
Medical history — no./total no. (%)				
Atopic eczema	12/92 (13.0)	8/96 (8.3)	6/90 (6.6)	14/96 (14.6)
Allergies	4/87 (4.6)	0/96 (0)	1/90 (1.1)	2/96 (2.1)
1 previous wheeze	24/88 (27.3)	23/91 (25.3)	20/90 (22.2)	31/93 (33.3)
Respiratory symptoms for >1 wk — no./total no. (%)	8/75 (10.7)	12/90 (13.3)	10/86 (11.6)	15/89 (16.9)
Parental medical history — no./total no. (%)				
Asthma	17/78 (21.8)	22/83 (26.5)	23/80 (28.8)	21/84 (25.0)
Rhinoconjunctivitis	23/88 (26.1)	33/89 (37.1)	23/87 (26.4)	34/92 (37.0)
Clinical characteristics before study inclusion				
Clinical score‡	4.9±1.0	5.0±1.0	4.9±1.0	4.9±1.0
SpO_2§	96.0±3.6	96.0±3.3	96.0±3.4	96.1±2.8
Respiratory rate — breaths/min	53.1±11.8	53.6±10.5	53.8±11.3	53.4±11.1
Heart rate — beats/min	154.5±17.5	156.0±18.7	155.2±19.9	153.7±17.7

* Plus–minus values are means ±SD. No significant differences in baseline characteristics were found among the four groups.
† Race was determined by the investigator.
‡ A clinical score of 4 or higher (on a range of 0 to 10, with 0 being the best score) was required for study inclusion.
§ SpO_2 denotes oxygen saturation as measured by pulse oximetry.

ON-DEMAND VERSUS FIXED-SCHEDULE ADMINISTRATION

The mean length of the hospital stay was significantly shorter for children in the group receiving treatment on demand than in the group receiving treatment on a fixed schedule (P=0.01) (Table 2 and Fig. 2B). Children in the on-demand group received a mean of 5.0 (30%) fewer inhalations than those in the fixed-schedule group (P<0.001). Children receiving inhalations on demand also had a lower probability of being treated with ventilatory support (P=0.01) or supplemental oxygen (P=0.04), and inhalations given on demand were not associated with nasogastric-tube feeding or treatment discontinuation (Table 2).

There was no interaction between the two treatment interventions (inhaled racemic adrenaline vs. inhaled saline and on-demand vs. fixed schedule), with an estimated interaction term of 1.4 hours (95% confidence interval [CI], –20.1 to 22.8; P=0.90) (Table S4 in the Supplementary Appendix.)

INFLUENCE OF AGE, ALLERGIC DISEASE, AND SEX

Age (in 3-month periods) had a significant effect on length of hospital stay with regard to both medication type and inhalation strategy, as estimated with the use of the Jonckheere–Terpstra test (P<0.001). The stay was longer in the younger infants (<8 weeks of age) than in the older infants (≥8 weeks of age) in the group receiving inhaled racemic adrenaline group, as indicated with a curve showing the median at every time point (Fig. S2A and S2B in the Supplementary Appendix).

In subgroup analyses comparing children younger than 3 months of age (177, or 43.8% of the study population) with those 3 months of age or older, there was no significant difference between the effect of inhaled racemic adrenaline

Table 2. Length of Stay and Use of Supportive Therapy According to Medication and Inhalation Strategy.

Variable	Inhaled Racemic Adrenaline (N=203)	Inhaled Saline (N=201)	Difference or Rate Ratio (95% CI)*	P Value	On Demand (N=200)	Fixed Schedule (N=204)	Difference or Rate Ratio (95% CI)*	P Value
Length of stay — hr†								
Mean	78.7	81.8			73.9	86.5		
Range	69.2 to 88.1	72.6 to 91.0			64.6 to 83.2	77.1 to 95.8		
Estimated length of stay — hr†								
Mean	63.6	68.1			47.6	61.3		
Range	46.2 to 81.0	49.8 to 86.4			30.6 to 64.6	45.4 to 77.2		
Mean difference			4.5 (−6.5 to 15.5)	0.42			13.7 (2.9 to 24.4)	0.01
Change in clinical score after 1 inhalation‡								
Mean	−1.26	−1.08			−1.18	−1.16		
Range	−1.44 to −1.08	−1.23 to −0.92			−1.35 to −1.02	−1.33 to −0.98		
No. of inhalations								
Mean	13.9	15.2			12.0	17.0		
Range	12.1 to 15.7	13.2 to 17.2			10.3 to 13.6	15.0 to 19.1		
Supportive therapy — no./total no. (%)								
Oxygen	83/192 (43.2)	83/189 (43.9)	0.98 (0.78 to 1.24)		72/188 (38.3)	94/193 (48.7)	0.79 (0.62 to 0.99)	0.04
Nasogastric-tube feeding	57/201 (28.4)	59/199 (29.6)	0.96 (0.70 to 1.30)		52/198 (26.3)	64/202 (31.7)	0.83 (0.61 to 1.13)	
Ventilatory support	15/203 (7.4)	15/201 (7.5)	0.99 (0.50 to 1.97)		8/200 (4.0)	22/204 (10.8)	0.37 (0.17 to 0.81)	0.01
Discontinued treatment — no./total no. (%)	36/203 (17.7)	47/201 (23.4)	0.76 (0.52 to 1.12)		37/200 (18.5)	46/204 (22.5)	0.82 (0.56 to 1.21)	

* Rate ratios are shown for supportive therapy.
† The mean given for "Length of stay" was an unweighted mean. The mean given for "Estimated length of stay" was a weighted mean estimated with the use of robust linear regression analysis.
‡ There were 377 children with clinical scoring before and after the first inhalation at the time of study enrollment.

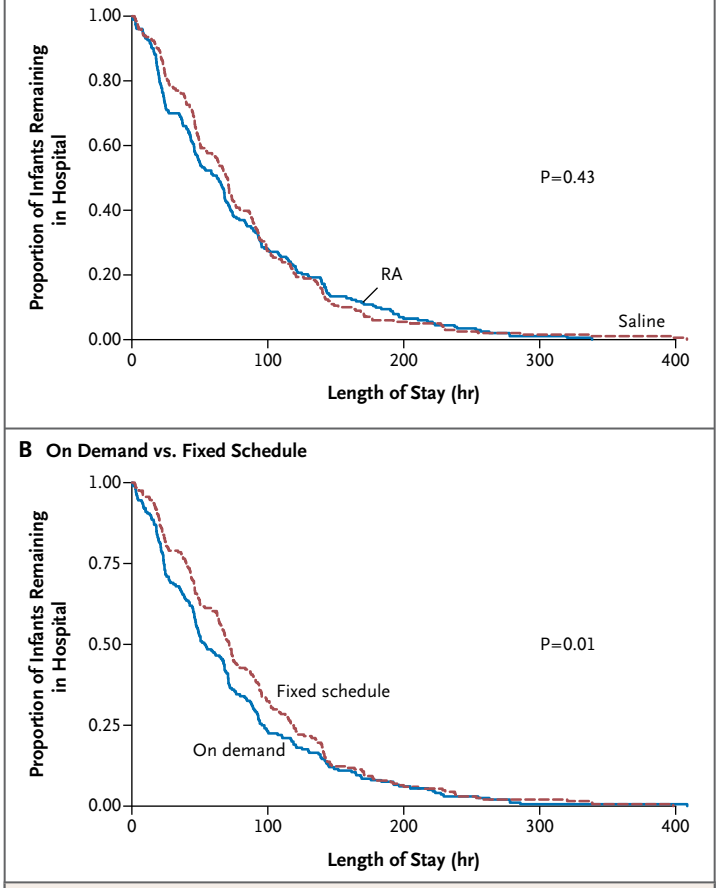

Figure 2. Length of Hospital Stay According to Study Treatment and Schedule of Administration.

Kaplan–Meier plots show the proportion of infants remaining in the hospital according to whether they were treated with inhaled racemic adrenaline or inhaled saline (Panel A) and according to whether the inhalations were administered on demand or on a fixed schedule (Panel B).

as compared with that of inhaled saline. In the youngest children only, inhalations given on demand were associated with a significantly shorter hospital stay than were inhalations given on a fixed schedule (Table S3 in the Supplementary Appendix). Status with respect to a history of atopic eczema or wheezing, status with respect to a family history of atopic disease, and sex were not found to have a significant influence on treatment response.

ADVERSE EVENTS

No serious adverse events were reported. Three children (including one who was receiving inhaled saline) discontinued treatment because of moderate tachycardia, which may have been due to the study medication.

DISCUSSION

In infants with acute bronchiolitis, treatment with inhalations of racemic adrenaline was not associated with a shorter hospital stay than treatment with inhaled saline. However, the administration of inhalations on demand was found to be superior to administration on a fixed schedule in reducing the length of stay and in reducing the use of ventilatory support, supplemental oxygen therapy, and nasogastric-tube feeding. There was an interaction between age and either medication type or inhalation strategy.

The lack of effect of inhaled racemic adrenaline on length of hospital stay confirms similar findings on length of stay for albuterol and saline[21] and for albuterol alone.[22] There was a similar lack of effect of these medications on the clinical score and oxygen saturation according to a Cochrane meta-analysis,[12] including the findings in 292 patients from two trials[20,21] reviewed in the meta-analysis.

Our data show that inhalations given on demand are superior to those administered on a fixed schedule in children younger than 12 months of age, with the mean length of stay 13.7 hours shorter for those receiving inhalations on demand. This difference was both clinically and statistically significant and has substantial financial implications. Although not previously shown, the possibility that saline may have a bronchoconstrictive effect in the youngest infants (younger than 3 months of age) cannot be ruled out. Thus, the superiority of the on-demand schedule, in which fewer inhalations were administered, supports the goal of "minimal handling" (allowing infants to sleep, with minimal interruption)[27] in acutely ill infants.

The significant interaction we noted between age and inhaled racemic adrenaline is of interest. The tendency for the youngest infants receiving inhaled racemic adrenaline to have a longer hospital stay does not support the reported effectiveness of inhaled racemic adrenaline for reducing vascular engorgement and edema in children with asthma.[11] Also unlike the findings in children with asthma,[28] in our study population of children with bronchiolitis, status with respect to a parental history of allergic disease, status with respect to atopic eczema, and sex were not associated with symptomatic treatment efficacy.

Our study of two inhalation solutions was sufficiently powered to allow detection of a

5-hour difference in length of stay and to perform subgroup analyses for the major outcomes. The study included a nationally representative patient cohort with the expected patterns of viral infection.[4] In addition, the study was managed in accordance with local and national guidelines, and the baseline characteristics were similar in all four treatment groups (Table S1 in the Supplementary Appendix).

Despite the limited power of the study to detect an interaction between the interventions, the observed interaction was approximately one third of the 5-hour length of stay selected a priori as a clinically relevant difference.[26] The initially planned end point for length of stay, which was the time at which the child was deemed ready for discharge, was not recorded for 83 children (Fig. 1). We therefore used the actual time of discharge for all children. The results were similar with the use of these two end points (Table S5 in the Supplementary Appendix).

In conclusion, our study showed that for hospitalized infants with acute bronchiolitis, inhaled racemic adrenaline was not superior to inhaled saline with regard to length of hospital stay, use of supportive treatment, or clinical score. However, the administration of inhalations on demand, as compared with a fixed schedule of inhalations, was associated with a shorter hospital stay and with a reduced need for supportive treatment.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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