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Oral Dexamethasone for Bronchiolitis: A Randomized Trial



WHAT IS KNOWN ON THIS SUBJECT: Some infants presenting with bronchiolitis are later diagnosed with asthma. Corticosteroid treatment of all infants with bronchiolitis is not clearly efficacious.



WHAT THIS STUDY ADDS: We used infant eczema or asthma history in a first-degree relative to select patients with bronchiolitis for dexamethasone or placebo blinded treatment. Dexamethasone treatment of 5 days led to significantly earlier readiness for discharge from inpatient treatment.

abstract

OBJECTIVE: Determine whether dexamethasone treatment added to salbutamol reduces time to readiness for discharge in patients with bronchiolitis and possible asthma.

METHODS: We compared efficacy and safety of dexamethasone, 1 mg/kg, then 0.6 mg/kg for 4 more days, with placebo for acute bronchiolitis in patients with asthma risk, as determined by eczema or a family history of asthma in a first-degree relative. All patients received inhaled salbutamol. Time to readiness for discharge was the primary efficacy outcome.

RESULTS: Two hundred previously healthy infants diagnosed with bronchiolitis, median age 3.5 months, were enrolled. Five placebo recipients needed admission to intensive care unit during inpatient treatment ($P = .02$). Among 100 dexamethasone recipients, geometric mean time to readiness for discharge was 18.6 hours (95% confidence interval [CI], 14.9 to 23.1 hours); among 90 control patients, 27.1 hours (95% CI, 21.8 to 33.8 hours). The ratio, 0.69 (95% CI, 0.51 to 0.93), revealed a mean 31% shortening of duration to readiness for discharge favoring dexamethasone ($P = .015$). Twenty-two dexamethasone and 19 control patients were readmitted to the short stay inpatient in the week after discharge ($P = .9$). No hospitalizations or side effects were reported during 7 days of surveillance.

CONCLUSIONS: Dexamethasone with salbutamol shortened time to readiness for inpatient discharge during bronchiolitis episodes in patients with eczema or a family history of asthma in a first-degree relative. Inpatient and clinic visits in the subsequent week occurred similarly for the 2 groups. *Pediatrics* 2013;132:e810–e816

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KEY WORDS

bronchiolitis, dexamethasone therapy, respiratory syncytial virus, length of stay, respiratory infections

ABBREVIATIONS

CI—confidence interval

PEC—pediatric emergency center

Drs Alansari, Alsakran, and Davidson did the literature search, study design, data analysis and interpretation, and primary drafting of the manuscript; Drs Alansari, Alsakran, Ibrahim, Alrefai, and Zakaria recruited patients for the study; and all authors contributed manuscript content and revisions and approved the final manuscript as submitted.

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Bronchiolitis is the most common serious lower respiratory tract illness in young infants, affecting mainly children between 2 and 5 months of age.^{1,2} The highest incidence in temperate climates is reported in winter.^{3,4} It is a common cause for inpatient admissions, especially in infants less than 6 months of age,⁵ but is usually self-limited and lasts about a week in previously healthy children. The proportion of presenting patients needing admission varies depending on many factors. A recent multicenter prospective cohort study from the United States found 43% were admitted,⁶ whereas a single-center study from the United Kingdom reported a 36% admission rate.⁷ In a recent US study of term, otherwise healthy infants, the rates of emergency department visits and admissions were 77 and 71 per 1000 patient-years, respectively.⁸

Recent meta-analyses do not support the routine use of bronchodilators,⁹ steam or nebulized normal saline,¹⁰ anticholinergics,¹¹ or steroids¹² to treat bronchiolitis. After years of research, the mainstay of treatment remains supportive care, with supplemental oxygen and hydration therapy.^{13–15} Five percent nebulized saline appears superior to placebo for improving the Wang bronchiolitis severity score,¹⁶ as does 3% nebulized saline,¹⁷ and the combination of nebulized hypertonic saline with other therapies may also have promise.¹⁸

The evidence linking atopic asthma to bronchiolitis is complex, and the relationship remains as perplexing now as when summarized more than a decade ago.¹⁹ The challenge in distinguishing the first attack of asthma in infants, usually first associated with viral lower respiratory tract infection and later presenting as unremitting wheezing, from the episodic wheezing of infant bronchiolitis due to repeated viral infections, has been highlighted

previously.²⁰ Because steroid use is known to decrease admission rate and length of emergency stay in children with asthma²¹ but failed to do so in bronchiolitis,²² identifying asthmatic or preasthmatic patients and targeting them with steroid treatment early might improve symptoms and hasten recovery. A shorter stay and possibly a lower chance of needing return visits or subsequent hospitalization are desirable goals of better bronchiolitis therapy. We reasoned that we might focus steroid treatment on an atopic population, enriched for possible asthma and presenting with bronchiolitis, if we targeted infants and young children with eczema or first-degree relatives (a parent or sibling) with asthma²³ and that for them, dexamethasone could be safe and effective, alleviating severe symptoms and decreasing the length of hospitalization or inpatient confinement. Therefore, we compared blinded oral dexamethasone to placebo in acute infant bronchiolitis in patients with eczema or a first-degree relative with asthma, all of whom also received salbutamol.

METHODS

Setting and Participants

The study was conducted between February 2010 and March 2012 in the short stay unit of the Pediatric Emergency Center (PEC) of Hamad General Hospital, the only pediatric emergency facility in the State of Qatar. The PEC serves an average of 280 000 patients annually and manages 42 beds in a short stay inpatient unit, to which patients are admitted if they are too ill to be sent home but do not need the intensive care unit. Patients admitted to the unit are assessed at least every 6 hours by a pediatrician to determine readiness for discharge. The length of stay in the unit for bronchiolitis ranges from 6 to 168 hours. In 2011, we saw 8718 infants and young children in 10 666 visits for bronchiolitis.

Infants aged ≤ 18 months presenting to the unit for treatment of moderate to severe viral bronchiolitis who had a positive history for eczema or were known to have a parent or a full sibling with a prior physician diagnosis of asthma were eligible for the study. Consecutive patients were recruited except when a study nurse was unavailable or the unit was too busy to recruit. Eczema was considered present if there was a prior physician diagnosis or the patient had rash consistent with eczema on presentation. Moderate to severe bronchiolitis was defined as a prodromal history consistent with viral upper respiratory tract infection followed by wheezing or crackles on auscultation and a Wang bronchiolitis severity score²⁴ of ≥ 4 on presentation. The Wang bronchiolitis severity score ranges from 0 to 12 and has 4 variables, each receiving a score from 0 to 3, with higher scores denoting worse status. Patients were excluded from the study if they had 1 or more of the following characteristics: preterm birth ≤ 34 weeks' gestation, previous history of wheezing, steroid use within 48 hours of presentation, obtundation and progressive respiratory failure necessitating intensive care unit admission, history of apnea within 24 hours before presentation, oxygen saturation $\leq 85\%$ on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease, and immunodeficiency or exposure to varicella within 21 days before enrollment. Written, informed consent, sought from a parent or legal guardian for consecutive eligible patients as soon as the patient was admitted to the unit, was obtained for all participants. The study was approved by the hospital institutional review board and registered.

Study Procedures

Patients were examined on presentation in the examination area of the center, and those needing additional

treatment or observation were admitted to the short stay infirmary unit. Consecutive patients with bronchiolitis were assessed for study eligibility within 2 hours of the initial physician assessment. Patients for whom written informed consent was obtained underwent plain chest radiography, and nasopharyngeal swabs were taken for respiratory syncytial virus detection (Quick Vue RSV-Strip; Quidel, San Diego, CA). Then, the enrolling physicians accessed a sealed envelope in consecutive order containing a random number corresponding to a recently prepared package of blinded study medication identified with the same number. The study pharmacist and study statistician had the randomization list, containing generated random numbers with 1 of 2 codes identifying sterilely prepared dexamethasone or placebo (vehicle) for oral administration, which had the same color, smell, and taste. At least 3 packages of blinded study medication were prepared to be available for each day during the bronchiolitis seasons. Dexamethasone was prepared at a concentration of 1 mg/mL. Study medications were administered orally after enrollment at a dosage of 1 mL/kg for the first day and then 0.6 mL/kg once daily for 4 days starting from the second day after enrollment, a regimen previously tested in a less selective patient population.²⁵ Patients who vomited the medicine within half an hour after administration had a similar dose repeated.

All patients received 2.5 mg salbutamol nebulization mixed with 2 mL normal saline at 0, 30, 60, and 120 min and then every 2 hours until ready for discharge, which is standard treatment in our unit for bronchiolitis. Inhaled therapies were delivered through a tight-fitted face mask by pressurized oxygen with the flowmeter set at 10 L/min. Nebulized epinephrine (0.5 mL/kg) at a minimum dose of 2.5 mL and maximum dose of 5

mL was allowed to be administered with 2 mL of normal saline at a maximum frequency of every hour, and additional treatment (eg, supplementary oxygen, hydration) were given at the discretion of the treating physician. Patients were to be withdrawn from study drug dosing if clinical deterioration was determined to warrant intensive care admission. Patients were judged ready for discharge when the treating physician determined the patient did not need supplementary oxygen, was feeding adequately without intravenous fluids, and had minimal or absent wheezing, crackles, and chest retractions, provided the patient had an oxygen saturation $\geq 94\%$ and severity score < 4 . At discharge, patients were sent home with salbutamol metered-dose inhalers with an appropriately sized Aero-chamber with mask attachment (Forest Laboratories, Dublin, Ireland). Daily follow-up by study nurse by telephone was mandatory for 1 week after discharge. The patient could return to the pediatric emergency center earlier if needed.

Study Measurements and Outcomes

The primary outcome, elapsed time from randomization until the treating physician decided the patient was clinically ready for discharge, was documented for all patients. We also recorded the number of patients using as-needed epinephrine nebulization. For the week after infirmary discharge, we noted patients needing hospital admission, patients needing readmission to the short stay infirmary unit (site of initial treatment) but not hospital admission, and patients visiting a clinic or revisiting the emergency center briefly for the same illness. Daily calls from the study nurse recorded information on general well-being, work of breathing, feeding intolerance, vomiting, diarrhea, and need for physician visits and hospitalization.

Statistical Analysis

Time to readiness for discharge was plotted by univariate Kaplan–Meier survival analysis to depict the proportion of patients remaining in the PEC infirmary in each group. The accelerated failure time model with log logistic function analysis was used to calculate and compare the geometric mean times to readiness for discharge for each treatment group by their ratio.^{26,27} This model uses all patient values to provide geometric means, their ratio and its 95% confidence interval (CI), and a *P* value for the log-transformed data. We compared follow-up data collected for each group and proportion of patients medically ready for discharge at 12, 18, 24, 36, and 48 hours. To estimate sample size, we started with a prestudy survey of duration of stay in the PEC for 28 patients meeting our study inclusion criteria, which showed that approximately 39% were discharged by 12 hours. We believed a difference of $\sim 20\%$ between treatment groups for percentage discharged at 12 hours would be clinically significant. With a sample size of 93 patients per group, there would be 80% power to find a significant difference ($P < .05$, 2-sided) if 30% were the result in the control therapy group. To compensate for dropouts, we planned to recruit 200 patients altogether.

Categorical and continuous variables were expressed as frequency (percentage) and mean \pm SD. Descriptive statistics were used to summarize all baseline demographic and clinical characteristics of the patients. Quantitative variable means between the 2 independent groups were analyzed by using unpaired *t* and Wilcoxon rank sum tests. Associations between 2 or more qualitative and categorical variables were assessed by using the χ^2 test. For small cell frequencies, χ^2 test with a continuity correction factor was used. Significant values were reported

with their corresponding 95% CI. $P < .05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical software package (SPSS, version 19.0; IBM SPSS Statistics, IBM Corporation). Data were transferred from the SPSS package to Stata SE 11.0 (StataCorp, College Station, TX) for accelerated failure time model analysis.

Role of the Funding Source

Hamad Medical Corporation approved US\$ 51 000 for the project. No other support was provided by any source. Hamad provided care to the patients, and its institutional review board approved the study and consent form but played no other role in the study. Hamad employed all the physicians except Dr Davidson.

RESULTS

Two hundred previously healthy infants diagnosed with viral bronchiolitis, median age 3.5 months (range, 29 days–12.1 months) were enrolled in the study during bronchiolitis seasons, between February 2010 and March 2012 (Fig 1). Consecutive eligible patients were recruited, and informed consent was obtained from at least 1 parent. Ten infants were excluded from the analysis: 3 should have been excluded from enrollment (1 had a history of apnea just before admission, and 2 did not meet the inclusion criteria of the study). Five infants in the control group and none in the dexamethasone group ($P = .02$, Fisher's exact test) needed intensive care admission at 26, 36, 86, 140, and 141 hours, respectively, and 2 more infants were electively removed by their parents. Of the 190 infants remaining, 100 were randomly assigned to receive dexamethasone and 90 to receive placebo. Subjects' baseline characteristics were similar in the 2 treatment arms before enrollment (Table 1).

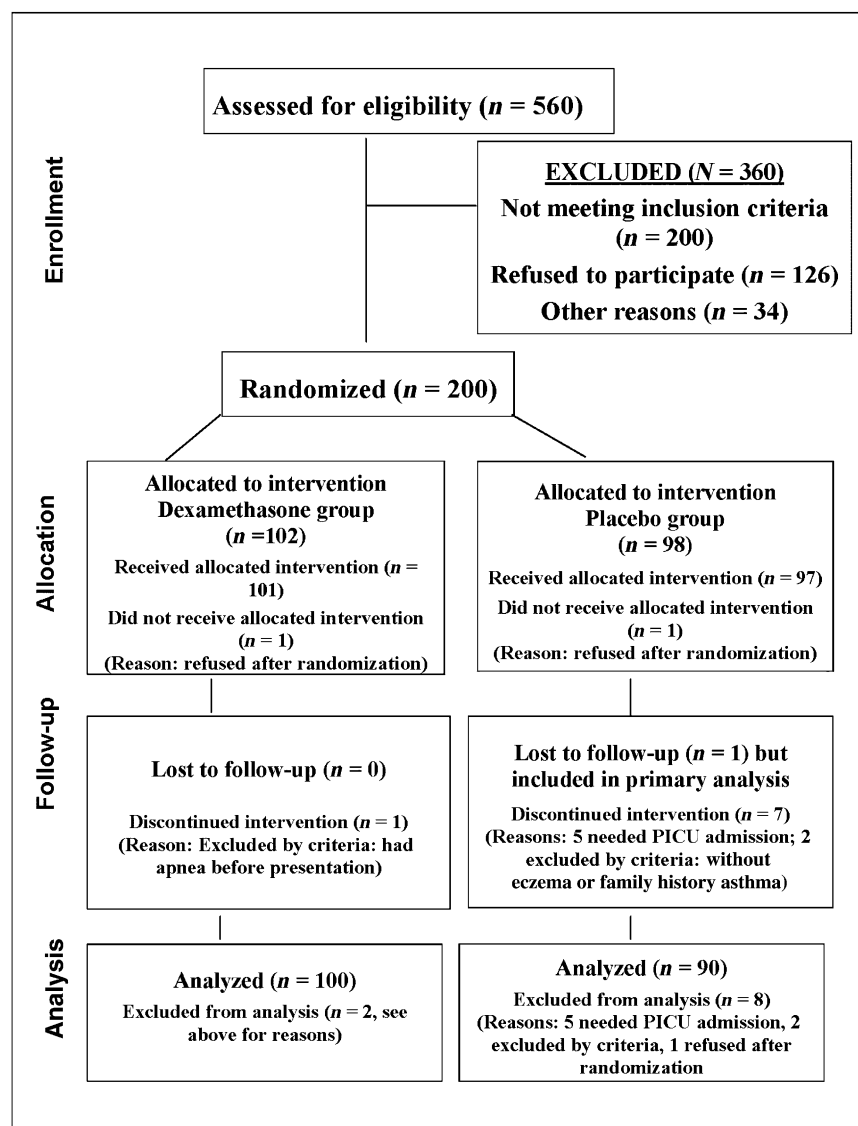


FIGURE 1
Study flowchart of enrolled patients.

Efficacy

The dexamethasone group was ready for discharge earlier, with a mean duration 69% (95% CI, 51% to 83%) of the mean duration for the placebo group, $P = .015$. Geometric mean durations until readiness for discharge were 18.6 hours (95% CI, 14.9 to 23.1 hours) and 27.1 hours (95% CI, 21.8 to 33.8 hours) for dexamethasone and placebo, respectively (Table 2). Among the secondary outcomes, 19 dexamethasone and 31 placebo recipients received nebulized epinephrine ($P = .03$). The proportions of patients needing hospital

admission or making outpatient visits in the week after discharge were similar in the 2 groups (Table 2). Daily telephone surveillance revealed no particular side effect concerns in either treatment group. A significant difference in proportion of patients ready for discharge became evident in this sample size by 18 hours and disappeared by 48 hours (Table 2, Fig 2).

In the 7 days after discharge, inpatient care was needed for 22 (22%) of the dexamethasone group, with an average stay of 17 hours, and 19 (21%) of the placebo group, with an average stay of 18

TABLE 1 Baseline Characteristics of Enrolled Infants

Characteristics	Dexamethasone, <i>n</i> = 102	Placebo, <i>n</i> = 98	<i>P</i> Value
Age, months, mean ± SD	3.4 ± 2.2	3.9 ± 2.0	.8
Duration of symptoms before enrollment, days, mean ± SD	4.5 ± 3.3	4.4 ± 2.7	.8
Male/female, <i>n</i>	70/32	57/41	
Baseline Wang severity score, mean ± SD	6.45 ± 3.34	6.84 ± 1.62	.09
Baseline O ₂ saturation, %, mean ± SD	97 ± 1.4	97 ± 1.5	.9
Respiratory syncytial virus positivity, <i>n</i> (%)	39 (38%)	38 (39%)	.9
Chest x-ray, <i>n</i> (%)			
Normal	39 (38%)	35 (36%)	.7
Collapse or lobar consolidation	15 (15%)	16 (16%)	.8
Lesser infiltrates	48 (47%)	47 (48%)	.9
Atopic history, <i>n</i> (%)			
Eczema in patient	31 (30%)	31 (32%)	.9
First-degree patient relative with asthma, <i>n</i> (%)			
Mother with asthma	19 (19%)	22 (22%)	.5
Father with asthma	22 (22%)	22 (22%)	.9
Both parents with asthma	5 (4.9%)	5 (5%)	1.0
Full sibling with asthma	77 (76%)	70 (71%)	.5
Patient with eczema and a first-degree relative with asthma	19 (19%)	20 (20%)	.5

hours, *P* = .9. Nineteen dexamethasone and 11 placebo recipients made a clinic or brief PEC visit (*P* = .2). No inpatient-discharged patients needed hospitalization in the week after discharge.

DISCUSSION

A literature review showed that a previous history of eczema in the patient or

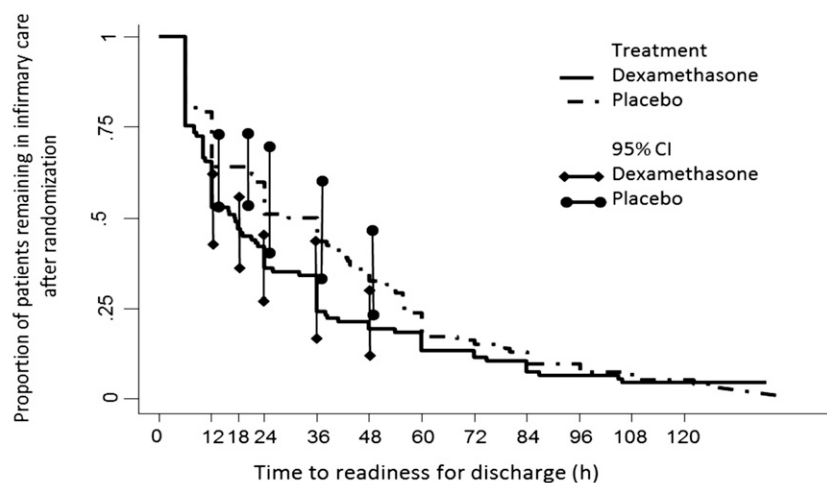
asthma in a parent or full sibling appears to identify a population of infants and young children with bronchiolitis who will have a clinically significant benefit of earlier (by 31%) readiness for discharge without undue risk from early steroid administration. Because the criteria we tested were present in 66% of a similar population of patients with a first episode of bronchiolitis,²² applying this

generalizable treatment could alleviate the overall burden of this disease in many clinical settings.

We built our study question and methods on the work of many others. When atopic manifestations were prevalent in patients with bronchiolitis, a single dose of dexamethasone showed improvement in respiratory assessment scores in 1 small study.²⁸ A subgroup analysis for patients with atopic family histories suggested the possibility of dexamethasone effect (*P* = .07) in an otherwise negative study in which dexamethasone 1 mg/kg intramuscularly or placebo was given for 3 days.²⁹ In other studies, a lower dose daily of dexamethasone (0.15 mg/kg) in unselected patients with bronchiolitis³⁰ and somewhat higher daily doses administered multiple times (0.5 mg/kg, then 0.3 mg/kg) to hospitalized patients³¹ were not superior to placebo, so we chose higher dosages. A previously reported multicenter randomized controlled trial comparing just a single dose of dexamethasone with placebo showed no difference between the 2 groups in the decision about hospital admission at 4 hours and the length of hospital stay.²² Although we also found no difference in readiness

TABLE 2 Primary and Secondary Outcomes

Primary Outcomes				
Outcome	Dexamethasone (95% CI), <i>N</i> = 100		Placebo (95% CI), <i>N</i> = 90	
Geometric mean time to readiness for discharge	18.6 h (14.9 to 23.1 h)		27.1 h (21.8 to 33.8 h)	
Ratio of geometric means	0.69 (0.51 to 0.93), <i>P</i> = .015			
Secondary Outcomes				
Percentage of Patients Ready for Discharge in Each Treatment Group at Time After Enrollment				
Time (h)	Dexamethasone % (95% CI), <i>N</i> = 100	Placebo % (95% CI), <i>N</i> = 90	Difference (95% CI)	<i>P</i> Value
12	48.0 (38.5 to 57.7)	36.6 (27.4 to 46.7)	11.3 (−2.6 to 25.3)	.11
18	54.0 (44.3 to 63.4)	36.6 (27.4 to 46.9)	17.3 (3.4 to 31.3)	.01
24	65.0 (55.2 to 73.7)	50.0 (39.9 to 60.1)	15.0 (1.1 to 28.9)	.03
36	77.0 (67.8 to 84.2)	57.7 (47.5 to 67.5)	19.2 (6.1 to 32.3)	.005
48	82.0 (73.2 to 88.4)	68.8 (58.7 to 77.5)	13.1 (0.9 to 25.3)	.03
Outcome	Dexamethasone %, <i>N</i> = 100		Placebo %, <i>N</i> = 90	<i>P</i> Value
Patients using as-needed epinephrine nebulization	19		31	.03
Patients needing hospital admission in the week after discharge	0		0	—
Patients needing inpatient care but not hospital admission in the week after discharge	22		19	.9
Patients with clinic visits but not hospital admission in the week after discharge	19		11	.2



Number remaining										
Dexamethasone	102	55	37	25	20	14	12	8	7	5
Placebo	92	59	47	40	30	17	14	9	7	5

FIGURE 2

Bronchiolitis discharges from the PEC.

for discharge at 4 hours, we found an overall geometric mean shorter length of stay for patients treated with dexamethasone (and salbutamol), probably because the treatment was targeted to patients with eczema or a first-degree relative with asthma, rather than the entire population with bronchiolitis.

Another recent bronchiolitis treatment study²⁵ found with marginal statistical significance that with repeated daily dosing of dexamethasone for 6 days altogether, with 2 doses of epinephrine in the emergency department, hospital admission within the subsequent 7 days could be reduced. We found no

significant difference in subsequent need for postdischarge readmission to inpatient care or outpatient clinic visits, and no inpatient-discharged patient needed hospital admission. It might be that postdischarge revisits are unavoidable. All our study patients in both groups received salbutamol inhalations, probably providing comparable effect to the epinephrine received in the aforementioned study. However, in light of the data of Plint and colleagues,²⁵ perhaps a more prolonged or less abruptly tapered dexamethasone regimen could not only allow earlier discharge but also reduce the need for postdischarge visits and

hospitalization and still be safe. Our positive findings take advantage of prior trials of dexamethasone dosage and dose frequency, and we selected for randomization an especially potentially responsive and proportionally plentiful patient subset.

Our study is limited in its detail of safety reporting. Study nurses asked questions from a checklist, but we collected general rather than specific responses. We did not measure the prevalences of patient eczema or atopy in the first-degree family in our bronchiolitis population during the study, but subsequent surveying suggests it is more than half, perhaps nearly as many as two-thirds of acute bronchiolitis presentations.

CONCLUSIONS

Oral dexamethasone administered with salbutamol significantly reduced the duration until clinical readiness for discharge in the treatment of bronchiolitis in patients with eczema or a family history of asthma in a first-degree relative. We speculate that a somewhat more prolonged dosing regimen may also reduce the need for postdischarge visits.

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