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Hypertonic Saline and Acute Wheezing in Preschool Children

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KEY WORDS
wheezing, preschool children, asthma, controlled clinical trial, hypertonic saline

ABBREVIATIONS
AR—admission rate
ASL—airway surface liquid
CS—clinical severity score
ED—emergency department
HS—hypertonic saline 5%
LOS—length of stay
MC—mucus clearance
NS—normal saline
PCR—polymerase chain reaction
RSV—respiratory syncytial virus

Dr Mandelberg conceived of the study; Drs Mandelberg and Ater designed the protocol, planned the statistical analysis, and provided intellectual input to the study design; Drs Mandelberg, Ater, Shai, Bar, Fireman, and Dalal supervised and acquired the study data; Dr Tasher was responsible for virology studies; all authors contributed to the interpretation of study results and critically reviewed the manuscript; and Dr Mandelberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

This trial has been registered at www.clinicaltrials.gov (identifier NCT01073527).

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WHAT'S KNOWN ON THIS SUBJECT: Most acute wheezing episodes in preschool children are associated with rhinovirus, which decreases extracellular adenosine triphosphate levels, leading to airway surface liquid dehydration and submucosal edema, which cause failure of mucus clearance. These children respond poorly to available treatments.

WHAT THIS STUDY ADDS: Hypertonic saline inhalation, a pro–airway surface liquid hydration therapy, significantly decreases both length of stay by 33% (1 day) and the absolute risk of hospitalization by 30% in preschool children presenting with acute wheezing episode to the emergency department.

abstract

BACKGROUND: Most acute wheezing episodes in preschool children are associated with rhinovirus. Rhinovirus decreases extracellular adenosine triphosphate levels, leading to airway surface liquid dehydration. This, along with submucosal edema, mucus plaques, and inflammation, causes failure of mucus clearance. These preschool children do not respond well to available treatments, even oral steroids. This calls for pro–mucus clearance and prohydration treatments such as hypertonic saline in wheezing preschool children.

METHODS: Randomized, controlled, double-blind study. Forty-one children (mean age 31.9 ± 17.4 months, range 1–6 years) presented with wheezing to the emergency department were randomized after 1 albuterol inhalation to receive either 4 mL of hypertonic saline 5% (HS) (n = 16) or 4 mL of normal saline (NS) (n = 25), both with 0.5 mL albuterol, twice every 20 minutes in the emergency department and 4 times a day thereafter if hospitalized. The primary outcome measured was length of stay (LOS) and the secondary outcomes were admission rate (AR) and clinical severity score.

RESULTS: The LOS was significantly shorter in the HS than in the NS group: median 2 days (range 0–6) versus 3 days (range 0–5) days (P = .027). The AR was significantly lower in the HS than the NS group: 62.2% versus 92%. Clinical severity score improved significantly in both groups but did not reach significance between them.

CONCLUSIONS: Using HS inhalations significantly shortens LOS and lowers AR in preschool children presenting with an acute wheezing episode to the emergency department. *Pediatrics* 2012;129:e1397–e1403

Most wheezing episodes causing hospitalization or emergency department (ED) visits in preschool children are associated with viral respiratory tract infections.[1] The most common are rhinoviruses, detected in the lower airways and leading to lower airway inflammation.[2] There is no satisfactory treatment of these virus-induced wheezing episodes in preschool children, who often do not respond to either bronchodilators or oral prednisone, the most potent anti-inflammatory treatment.[3,4] In a recent review, Guilbert noted that novel and effective treatments are critically needed for study in this population.[5]

Over the past several years, new insights into the pathophysiology of virus-associated wheezing illnesses in small children, as well as exacerbations of pulmonary symptoms in chronic airway diseases in all age groups, have evolved.[6] It has been suggested that these virus-triggered airway illnesses result from intermittent catastrophic failure of mucus clearance (MC) due to dehydration of the airway surface liquid (ASL). Recently, it was found that rhinovirus in the lower airways induces a change in electrolyte and water movement on the luminal surface of the epithelial cells, similar to the effects observed during respiratory syncytial virus (RSV) infection: both increase extracellular adenosine triphosphate–ase levels, resulting in a concomitant decrease in extracellular adenosine triphosphate levels. This decrease in turn lowers chloride secretion and increases sodium absorption from the ASL. As water moves with the electrolytes, it is transported from the ASL into the mucosa. These changes in electrolytes and water movement cause dehydration of the ASL and edema of the submucosa and adventitia.[7]

In addition, viral illnesses in the lower airways cause increased mucus secretion and epithelial sloughing, sometimes with mucus plug formation. These factors, along with ASL dehydration, contribute to MC failure and airway lumen narrowing, leading to the clinical picture of respiratory distress with wheezing.

Thus, it has been suggested that therapy to maintain hydration of the ASL, decrease submucosal edema, and improve the rheological properties of the mucus can benefit children during acute viral wheezing illnesses.[6–8]

Hypertonic saline 5% (HS) may, in theory, reverse some of the pathophysiologic abnormalities attributed to virus-induced acute wheezing episodes in small children. It may hydrate the ASL, decrease submucosal edema, and improve the rheological properties of the mucus, thereby improving both cough- and non-cough-dependent MC.[6]

Indeed, it has been recently confirmed that wheezing hospitalized infants <2 years old with virus-induced bronchiolitis respond favorably to an HS/albuterol combination. Length of stay (LOS) has been shown to decrease, and clinical scores (CS) have been shown to improve.[9]

The evolving understanding of the pathophysiology of virus-induced airway disease in small children and the positive documented effect of HS in infants and children <2 years old with bronchiolitis led us to investigate the use of HS/albuterol in virus-induced acute wheezing attacks in preschool children.

METHODS

A prospective, randomized double-blind controlled trial to investigate the efficacy of inhaled HS treatment of 1- to 6-year-old children presented to the ED with acute wheezing episodes from January 2009 to January 2011.

Signed informed consent was obtained from the parents of each child, and the Helsinki Committee of our hospital approved the study.

Inclusion criteria were children aged 1 to 6 years who presented to Wolfson Medical Center with acute wheezing illness and a CS ≥6.[10] This CS is a validated score used routinely in our ED for the assessment of wheezing children. Thus, the investigators are highly experienced in using this score. This scoring system is a modification of 1 published by the National Institutes of Health, which rates the severity of an episode according to the signs and symptoms. This system has confirmed good interrater reliability, tested in 98 wheezing children in the ED (Pearson correlation statistics: .92).[10] Five investigators (DA, HS, BB, NF, and AM) participated in the outcome assessment of CS.

During RSV season, we recruited 2- to 6-year-old children to better exclude infants with RSV bronchiolitis. Additional exclusion criteria were cardiac disease, chronic respiratory disease, and children presenting with severe disease requiring intensive care admission.

On admission to the ED, all children received 1 inhalation of normal saline (NS) with albuterol (5 mg/mL), 15 minutes after inhalation a CS (Table 1) was obtained. Eligible patients whose parents agreed to enter the study and signed an informed consent were randomly assigned in double-blind fashion to 1 of 2 treatment groups: Group I, the treatment group, received 2 more inhalations of HS (4 mL each) with 0.5 mL albuterol at 20-minute intervals in the ED, and Group 2, the control group, received 2 inhalations of NS (4 mL each) with 0.5 mL of albuterol in the same manner. A second CS was obtained after the third inhalation.

After this assessment the decision to hospitalize the children was made at the discretion of the attending physician according to the usual policy of our ED and based on clinical grounds: no or insufficient improvement after the third inhalation, posttreatment CS ≥8, and/or saturation ≤94%. Patients who were admitted to the pediatric ward continued treatment of ≥4 inhalations per day as needed with either study drug (HS or NS

with albuterol). The statistician delivered 2 random allocation sequence lists (computer generated): 1 for children <3 years old and another for children >3 years old. The content of the therapeutic solution (NS or HS) was blinded to the investigators and the medical personnel. There was no detectable difference in color, smell, or other physical properties between the NS and HS solutions. The code was deposited with the pharmacist. One of the investigators (DA, HS, BB, NF, and AM) enrolled the patients at the ED and assigned them to their groups according to a random allocation sequence list.

In the ward, CS was obtained daily by 1 of the investigators 15 minutes after the morning inhalation. The children were defined as ready for discharge by 1 of the investigators when the CS was ≤6, even if the child remained hospitalized for nonmedical reasons.

Systemic steroids, oral prednisone, or intravenous methylprednisolone (2 mg/kg per day), were added according to the common practice in our institution at that time.

For each patient, a questionnaire was completed listing demographic data, history of past wheezing illnesses, atopic measures, smoking exposure, and current illness history.

Delivery System

We used a nebulizer (Micro-Mist; Hudson Respiratory Care Inc, Temecula, CA) routinely available in our ward connected to a source of pressurized oxygen from the wall, set to a flow rate of 8 L/min. This device has a mass output of 0.26 mL/min and produces particles of 4.2 μm mass median aerodynamic diameter with geometric SD of 1.8.

Test for Viral Respiratory Tract Infections

Samples for viral detection were obtained from 30 of the 41 (73%) children (those whose parents' approval was obtained specifically for this test). Respiratory specimens were obtained by the induced sputum technique modified from Zar et al[11] and tested by polymerase chain reaction (PCR). Sputum induction was undertaken on the day of enrollment after and during the HS/NS inhalations by 1 of the investigators trained in the technique. Induced sputum was obtained either by expectoration (in children able to cooperate) or by suctioning through the oropharynx using a sterile mucus extractor (catheter size 6). Those children who did not cough were gently stimulated to cough with the tip of the catheter at the oropharynx before suctioning after Zar et al.[11] Specimens were transported directly to the laboratory for processing and tested by PCR. DNA and RNA were coextracted from 200-mL sample supernatant using QIAamp viral DNA/RNA kit (Qiagen, Hidden, Germany). RNA and DNA were extracted according to the manufacturer's protocol before PCR analysis. Amplification was performed in an ABI Prism 7500 Sequence Detection System (PE Applied Biosystems, Carlsbad, CA) for 15 minutes at 500c, 10 minutes at 950c, following by 40 cycles of 8 seconds at 950c and 34 seconds at 600c. Multiplex reverse-transcription PCR was performed for the detection of 20 respiratory pathogens by FTD Respiratory Pathogens kit (PE Applied Biosystems, Carlsbad, CA). These pathogens included influenza viruses A and B, H1N1, rhinovirus, CoVs (OC43, NL63, 229E, HKU1), parainfluenza 1 to 4, and RSV A and B. Additional primer probe sets were used for detection of hBoV, adenovirus, *Mycoplasma* pneumonia, parechovirus, enterovirus, and human metapneumovirus. PCRs with RNA targets used 10 μL nucleic acid from QIAamp viral DNA/RNA kit (Qiagen). Results were analyzed by sequence detection software (PE Applied Biosystems, Carlsbad, CA).

Statistics

One major outcome of interest was measured: LOS, measured from time of presenting to the ED until ready to discharge (CS ≤6). Additionally, 2 secondary outcomes were measured: admission rate (AR) and CS improvement between the 2 treatment groups. Analysis of data were carried out using SPSS 11.0 statistical analysis software (SPSS Inc, Chicago, IL). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cutoff at $P = .01$). Continuous variables with approximately normal distribution are reported as mean ± SD. Continuous variables with distribution significantly deviating from normal, such as LOS, are reported as a median (range). Categorical variables such as gender were described using frequency distributions and are presented as frequency (%). Continuous variables were compared by using the paired or unpaired *t* test as appropriate. A P value <.05 for the 2-tailed t test was considered statistically significant. When variables, such as LOS, were highly skewed, comparisons were made using the Mann-Whitney nonparametric U test. Categorical variables were compared by using the χ^2 test (exact as needed) or by Fisher exact test when appropriate.

Power Calculations

We considered a reduction in LOS of 1 day to be clinically significant. With a sample size of $n = 40$ (both arms), this study was designed to have 80% power to detect a true, between-group difference of 1.0 ± 1.1 days in LOS using the t test for independent samples. This assumption is based on the mean LOS of the preschool children with wheezing episodes at our institution of 3.1 ± 1.1 days. This calculation assumes a 2-sided hypothesis with an α of .05.

RESULTS

Forty-one children presenting to the ED with an acute wheezing episode, aged 17.4 ± 31.9 months (range 1–6 years), were enrolled in the study between January 2009 and January 2011. Of the

TABLE 1 Asthma Clinical Severity Score

	1 Point	2 Point	3 Point
Respiratory rate (breath/min)			
2–3 y	≤34	35–39	≤40
4–5 y	≤30	31–35	≤36
Oxygen saturation (%), room air	>95	90–95	<90
Auscultation	Normal or end-expiratory wheezing	Expiratory wheezing	Inspiratory and expiratory wheezing, diminished breath sounds, or both
Retractions	Non or intercostals	Intercostals and substernal	Intercostals, substernal and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts
Asthma score	5–7 (Mild)	8–11 (Moderate)	12–15 (Severe)

Modified from Qureshi et al.[10]

41 children in the ED, 25 were allocated to the NS group and 16 to HS group. Epidemiologic and baseline characteristics of the 2 groups were similar (Tables 2 and 3). The overall flow of participants during the study period is given in Fig 1. PCR tests were successful in 29 of the 30 patients who agreed to the procedure (overall 70% of the 41 children). Twenty-four of the samples (83%) were positive for ≥1 respiratory virus with the most common being rhinovirus (11/29; 38%) and no significant differences between groups (Table 3). In 6/29 (21%) more than one virus was detected; in two cases, three viruses were detected. Virus detections and distributions did not vary significantly between the groups (Table 3).The LOS was significantly shorter in the HS than the NS group: median 2 days (range 0–6), versus 3 days (range 0–5; $P = .027$; Fig 2, Table 4). The AR was significantly lower in the HS than the NS group: 62.2% vs 92% (Fig 2, Table 4). Repeated-measures models indicate that the CS improved significantly postinhalation during hospitalization days in both groups but did not reach significance between the groups ($P = .1$, in favor of the treatment group). A similar result was obtained when evaluating CS postinhalations on the first day: the CS improved significantly in both groups from 11.0 ± 2.3 to 9.6 ± 1.6 (12.7%) for the NS group and from 10.3 ± 2.3 to 8.7 ± 3.0 (15.5%) for the HS (treatment) group but did not reach significance between the groups.

The median LOS was 2.7 days (range 0–6), and the AR was 33 of 41 patients (80%) for the whole population. No adverse effects were observed in either of the groups.

DISCUSSION

This article is the first to try to determine the effect of inhaled an HS bronchodilator combination in preschool children presenting to the ED with an acute wheezing episode. Our study shows that adding HS inhalations to common practice treatment significantly shortens LOS by 33% (1 day) and significantly decreases the absolute risk of hospitalization (AR) by 30% in preschool children presenting to the ED with acute wheezing. The mean LOS decreased by 1.1 days, from 3.1 to 2 days; however, because the LOS distribution significantly deviated from normal, it is reported and should be considered as a median LOS decrease of only 1 day.

These results could have an important clinical impact on the way we treat many wheezing preschool children. However, it is noteworthy to point out several patient characteristics that could be interpreted as risk factors for a wheezing episode severe enough to require ED visits and hospitalizations. First, the majority (92%) of the control group necessitated hospitalization, which is a higher rate than was previously reported from our own hospital in the years 1997 and 1998.[12] This high admission rate can be explained by the following reasons: although the minimal inclusion criteria was CS ≥6, all the children who were recruited to our study had CS ≥8 (10.7 ± 2.3, range 8–15), which is moderate to severe disease. Children with milder disease and lower CS were not recruited because of obvious improvement after the first prerandomization albuterol inhalation. This may explain our relatively high admission rate. Additional possible explanation for the high AR is that during the years after

TABLE 2 Epidemiologic Characteristics

	HS $n = 16$	NS $n = 25$	All $N = 41$	P
Age (mo)	30 ± 13.4	19.7 ± 33.1	17.4 ±3 1.9	.6
Gender (female/male)	9:7	19:6	28:13	.3
Parent with asthma	37.5%	40%	39%	1.0
Atopic dermatitis	18.8%	8%	12.2%	.35
Wheezing in the past	75%	84%	80.5%	.7
Multiple-trigger past wheezing	43.8%	48%	46.3%	1.0
Age of first wheeze (mo)	9.4 ± 9.2	13.4 ± 12.3	11.7 ± 11	.482
Number of ED visits in past year	± 0.751.1	0.88 ± 1	0.82 ± 1	1.0
Smoking in the family	68.8%	52%	58.5%	.34

TABLE 3 Baseline Characteristics

	HS $n = 16$	NS $n = 25$	All $N = 41$	P
CS, baseline	10.3 ± 2.3	11 ± 2.3	10.7 ± 2.3	.308
Saturation baseline	95% ± 0.03	95% ± 0.03	95% ± 0.03	.828
IgE (IU/mL)	200 ± 407	212 ± 246	207 ± 326	.904
WBC count 1000/μL	13.3 ± 6.1	16.2 ± 5.6	15 ± 5.9	.155
Eosinophils/μL	226 ± 246	205 ± 407	215±326	.861
Eosinophilia, >500	13.3%	13%	13.1%	1
Bronchodilator treatment	68.8%	80%	75.6%	.472
Inhaled steroid treatment	50%	52%	51.2%	1
Oral steroid treatment	37.5%	33.3%	35%	1
URI symptoms and signs	93.8%	84%	87.8%	.632
Positive viral PCR	8	16	24	.5
Rhinovirus	4	7	11	1.00
Adenovirus	2	4	6	1.00
Bocavirus	0	5	5	.14
Enterovirus	2	3	5	1.00
Coronavirus	0	1	1	1.00
PIV	1	0	1	1.00
Influenza A	1	0	1	1.00
Influenza B	0	1	1	1.00
RSV	1	0	1	1.00

IgE, immunoglobulin E; PIV, parainfluenza; URI, upper respiratory tract infection; WBC, white blood cell.

our previous publication,[12] ambulatory health care services developed its own emergency care facilities, encouraging their insured patients to present to these facilities first. Patients who fail to improve in these facilities are referred to our hospital ED. Therefore, these children suffered from a relatively more severe acute wheezing attack, and most were hospitalized. Thus, generalization of our conclusions to milder cases should be taken with caution until tested in a blinded randomized trial in ambulatory populations.

Second, although our design was intended to include children as old as 6 years, our patients were relatively young (32 ± 17 months), and these conclusions might not be applicable to older children, in particular, those over 4 or 5 years, which were underrepresented in the current study. Third, most of these children (80.5%) wheezed in the past, and almost half (46.3%) reported multiple-trigger wheezing episodes. Because our study was designed as a blinded randomized nonselective trial intended to include unselected wheezing preschool children presenting to the ED, we believe that our population correctly represents the usual patient population of preschool children presenting to the ED: young, with previous wheezing episodes. This is compatible with recent published data that wheezing preschool children <4 years old experience nearly triple the rate of hospitalization than older children.[13] Considering this, we believe that our results and conclusions could be generalized to preschool children presenting to the ED with at least moderate to severe wheezing episode.

We believe that viral bronchiolitis cases were properly excluded in our study: using PCR, RSV was found in only 1 patient (Table 3). Moreover, during the RSV season, we recruited only children aged >2 years in which RSV bronchiolitis is less prevalent. Additionally, any child suspected clinically to suffer from viral bronchiolitis was excluded. Thus, we believe that our population represents nonbronchiolitis, mostly virus-triggered wheezing, sometimes referred practically as "asthmatic" attacks in preschool children.

A weakness of our study is that the repeated-measures models indicate that the CS improved only nominally postinhalation during hospitalization days in favor of the treatment group but contrary to our hypothesis, did not reach significance between the groups ($P = .1$). However, more children of the treatment group, which were obviously those with a better CS, were sent home. Moreover, we believe that the LOS and the AR are much "harder" and objective

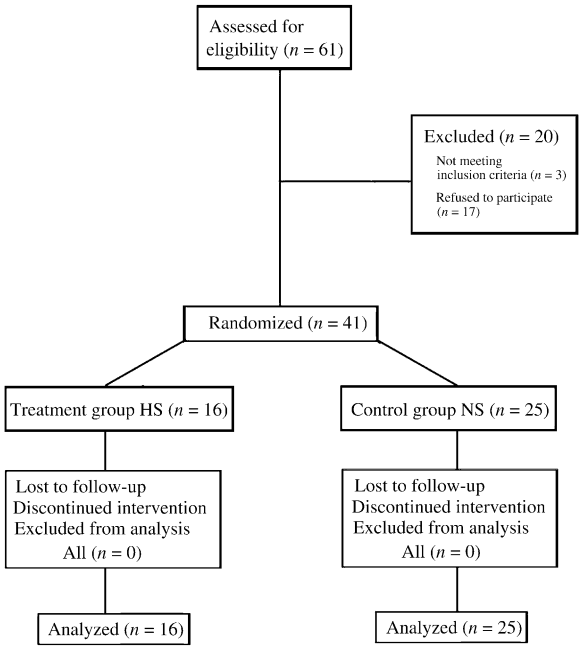

FIGURE 1
Flow of participants.

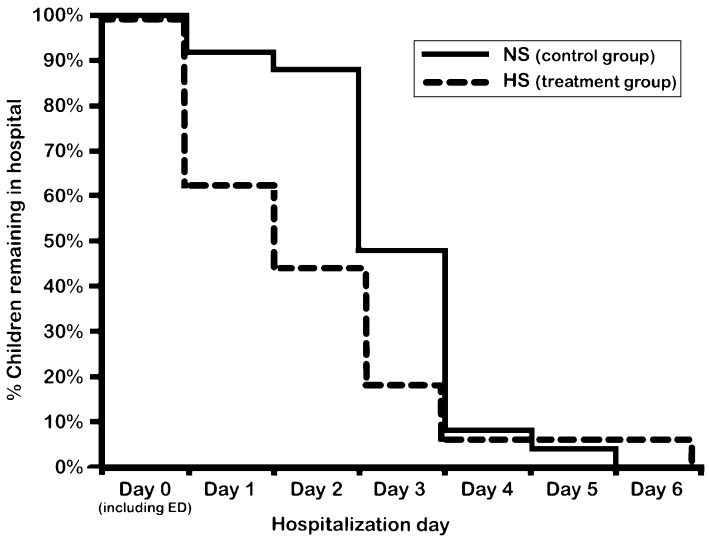

FIGURE 2
Kaplan-Meier graph for length of stay.

TABLE 4 Hospitalization Rate

Outcomes	HS $n = 16$	NS $n = 25$	P HS vs NS	All Patients $N = 41$
Admission rate (%)	10 (62.2%)	23 (92%)	$<.05$	33 (80%)
Discharged from the hospital (%)	6 (38.8%)	2 (8%)		8 (20%)
LOS, Median (range)	2 (0–5)	3 (0–6)	$<.03$	2.7 (0–6)

measurements than the CS and are fundamentally less influenced by the smaller numbers of children remaining in the hospital after the second, third, fourth, and fifth days.

HS Acts in the Airways Through Several Mechanisms

HS induces an osmotic flow of water into the mucus layer, rehydrating secretions and improving mucus rheology. HS reduces edema of the airway wall by absorbing water from the mucosa and submucosa. It stimulates cilial beat via the release of prostaglandin E2[14] and increases mucociliary clearance. It breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion. HS can cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction.[5] Indeed, many of the hypertonic saline responding elements described here may play a role in virus-induced wheezing, such as mucosal and submucosal edema, peribronchial infiltrate of inflammatory cells, necrosis and desquamation of ciliated epithelial cells, and excess mucus secretion. The combination of an airway wall swelling, sloughing of necrotic debris, increased mucus production, and impaired secretion clearance eventually contribute, in addition to bronchospasm, to airway obstruction, gas trapping, atelectasis, and impaired gas exchange. Moreover, in the more severely affected children who respond less favorably to conventional treatment such as bronchodilators and therefore, present to the ED, the relative contribution of these "nonspasmodic" pathologic and pathophysiologic consequences of viral and asthmatic inflammation to airway obstruction, gas trapping, atelectasis, and impaired gas exchange become even more important.

We focused on the HS (with albuterol) effect compared with NS control (with albuterol). Indeed, we cannot rule out a possible contribution of HS effect on increasing albuterol action. However, this has not been studied so far.

CONCLUSIONS

This is the first study to look into HS treatment in preschool children with a wheezing episode. Our study shows that adding HS to common treatment significantly shortens LOS by 33% (1 day) and lowers the absolute AR by 30% in preschool children presenting to the ED with moderately to severe acute wheezing episode.

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