BRIEF REPORT

Multicenter Observational Study of the Use of Nebulized Hypertonic Saline to Treat Children Hospitalized for Bronchiolitis From 2008 to 2014

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ABSTRACT

OBJECTIVES: Among children hospitalized for bronchiolitis, we examined temporal trends in the use of hypertonic saline (HTS) and the characteristics associated with receiving this treatment.

METHODS: We conducted a secondary analysis of data from 2 large, multicenter prospective cohort studies that included young children hospitalized with bronchiolitis during 5 winter seasons (2008–2014). Our outcome was receipt of HTS any time during the preadmission visit or hospitalization. For comparison with the observed trends in HTS use, we conducted a PubMed literature review of studies evaluating HTS use for bronchiolitis. We classified publications according to their assessment of HTS efficacy (positive, negative, or neutral).

RESULTS: Among 2709 hospitalized children, 241 (8.9%) received HTS. There was marked variability in HTS use by site (0%–91%), with use more common among children admitted to the ICU than those treated on the ward (31% vs 15%). Over the study period, administration of HTS increased from 2% during the 2008–2009 season to 27% during the 2011–2012 season, but then it decreased to 11% during the 2013–2014 season. Before 2010, the number of PubMed HTS publications ranged from 0 to 3 articles per year, with all classified as either positive or neutral. The number of positive publications increased in 2010 ($n = 5$), whereas negative publications peaked in 2014 ($n = 4$).

CONCLUSIONS: Use of HTS in children hospitalized with bronchiolitis increased during the 2008 to 2012 winter seasons and then declined. These findings paralleled trends in the HTS literature, with positive articles encouraging HTS use in early years followed by a growing number of neutral and negative articles after 2012.

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Bronchiolitis is the leading cause of hospitalization of young children in the United States.[1,2] The mean cost of these hospitalizations is $8500, with a median length-of-stay (LOS) of 2 to 3 days.[3,4] The annual direct cost of bronchiolitis hospitalizations nationwide is estimated at $543 million,[4] with total charges in excess of $1.6 billion.[5] Therefore, reducing LOS in bronchiolitis could greatly reduce health care expenditure.

Currently, the mainstay of treatment is supportive, including supplemental oxygen, nasopharyngeal suctioning, intravenous fluids, and pressure-support ventilation, when necessary.[5] Pharmacological treatment in bronchiolitis is highly variable.[6–8] Several approaches have been tried, including the use of inhaled bronchodilators, inhaled and systemic corticosteroids, and ribavirin. The American Academy of Pediatrics (AAP) recommends against all of these approaches in the routine management of bronchiolitis.[9] A more recently introduced treatment of severe bronchiolitis is the use of inhaled 3% or 5% hypertonic saline (HTS).[10,11] Although several early, small studies supported HTS use in infants with bronchiolitis, the studies differed in their inclusion criteria, concentration of HTS, and concomitant bronchodilator use.[12–14] In a 2013 Cochrane systematic review, HTS was shown to reduce inpatient LOS and clinical severity scores in both the inpatient and outpatient setting.[10] However, this same review found no significant short-term change in bronchiolitis severity when HTS was given in the emergency department (ED).[10] A recent randomized trial of hypertonic versus normal saline found no difference in LOS, severity scores, or need for supplemental oxygen among hospitalized infants with bronchiolitis.[15] Although the most recent 2014 AAP guidelines recommend against HTS use in the ED, they state that HTS may be considered for infants hospitalized with bronchiolitis.[9] The actual usage of HTS over the past decade is not known.

To address this knowledge gap, we analyzed multicenter, multiyear databases of children hospitalized with bronchiolitis to identify temporal trends in the usage of this new treatment approach for severe bronchiolitis. We also examined the demographic and clinical characteristics associated with HTS administration. Although all patients were enrolled before the release of the 2014 AAP guidelines,[9] we hypothesized that the use of HTS over time would parallel the results of published studies that either did or did not support this novel treatment. Therefore, we conducted a literature review on HTS use for bronchiolitis to compare with the temporal trends observed in our cohort studies.

METHODS

Study Design

We analyzed data from 2 large, prospective, multicenter studies of children hospitalized for bronchiolitis: the 30th Multicenter Airway Research Collaboration (MARC-30) and the 35th Multicenter Airway Research Collaboration (MARC-35)[16,17] (Appendix Tables 1 and 2). A more detailed description has been published elsewhere.[16,17] Both studies were observational in nature and data collection was coordinated by the Emergency Medicine Network in Boston, Massachusetts. The number of participating sites varied over 6 bronchiolitis seasons (November 1–April 30): 13 from 2007 to 2008 (MARC-30), 16 from 2008 to 2009 (MARC-30), 14 from 2009 to 2010 (MARC-30), 9 from 2011 to 2012 (MARC-35), 17 from 2012 to 2013 (MARC-35), and 6 from 2013 to 2014 (MARC-35).

Patient management was at the discretion of the on-site health care provider. All patients were enrolled within 24 hours of admission. Inclusion criteria were an attending physician's diagnosis of bronchiolitis, age $<$24 months (MARC-30) or $<$12 months (MARC-35), and parent or guardian informed consent. Exclusion criteria for both studies were previous enrollment, transfer to a participating hospital $>$48 hours after the original admission time, and declining the nasopharyngeal aspirate collection.[16,17] Both studies were approved by all local institutional review boards. The details of patient data collection and viral testing have been previously described.[16–21]

Literature Search

To compare the observed HTS usage to trends in the literature, we conducted a PubMed search in December 2014 using the keywords "bronchiolitis" and "hypertonic saline." We included English language articles on HTS use in bronchiolitis in all clinical settings with no date limit. A single author (J.D.) then categorized the conclusions of each HTS article as positive, negative, neutral, or noninformative. A positive article was defined as one that showed clinical benefit (eg, decreased hospitalization rate, decreased LOS, improved clinical score, positive conclusion). Inversely, a negative article was defined as one reporting clinical harm or a negative conclusion. A neutral article was one in which HTS demonstrated neither clinical benefit nor harm. Lastly, noninformative articles were those that did not primarily discuss HTS use in hospitalized children with bronchiolitis.

Statistical Analyses

The primary outcome was HTS receipt at any point during the preadmission period or inpatient stay for bronchiolitis. Data for inpatient HTS treatment was unavailable during the 2007–2008 season of MARC-30; thus, the primary analysis was restricted to the 2008–2014 study period ($n = 2709$). Of these, 2179 (80%) children had their "preadmission" visit in the enrolling hospital's ED, whereas the remaining children were directly admitted from other locations (eg, another hospital, doctor's office). All analyses were performed by using Stata 14.1 (StataCorp, College Station, TX). Data are presented as proportions and medians with interquartile ranges (IQRs).

We examined trends in the use of HTS treatment by study season and compared them with trends in the bronchiolitis literature. Unadjusted associations between receipt of HTS treatment and patient characteristics were analyzed by using χ^2, Fisher's exact test, and Wilcoxon rank sum test, as appropriate. A multivariable logistic regression was conducted to evaluate independent predictors of HTS treatment. The final regression model accounts for potential clustering by site, with

TABLE 1 Characteristics of Children Hospitalized for Bronchiolitis by Use of HTS from 2008 to 2014

Characteristics	All ($N = 2709$)		No HTS ($N = 2468$)		HTS Use ($N = 241$)		P
	n	%	*n*	%	*n*	%	
Enrollment season							<.001
2008–2009	839	31	821	33	18	7	
2009–2010	854	32	796	32	58	24	
2011–2012	148	5	108	4	40	17	
2012–2013	658	24	557	23	101	42	
2013–2014	210	8	186	8	24	10	
Site region							<.001
Northeast	519	19	439	18	80	33	
Midwest	386	14	375	15	11	5	
South	1182	44	1036	42	146	61	
West	622	23	618	25	4	2	
Age at enrollment (mo), median (IQR)	2709	3.7 (1.8–7.3)	2468	3.7 (1.7–7.4)	241	3.4 (1.8–6.0)	.18
Sex							.62
Male	1623	60	1475	60	148	61	
Female	1086	40	993	40	93	39	
Race and/or ethnicity							.04
Non-Hispanic white	1022	38	915	37	107	44	
Non-Hispanic black or African American	621	23	582	24	39	16	
Hispanic	961	36	875	36	86	36	
Other	99	4	90	4	9	4	
Insurance							<.001
Private	890	33	779	32	111	46	
Public	1712	64	1586	65	126	52	
None	88	3	84	3	4	2	
Weight (kg), median (IQR)	2694	6.2 (4.7–8.2)	2453	6.3 (4.7–8.2)	241	6.1 (4.7–7.9)	.54
Parental history of asthma	866	32	780	32	86	36	.20
Prenatal smoke exposure	401	15	371	15	30	13	.28
Premature birth (≤37 wk)	767	28	703	29	64	27	.50
ICU or special care at birth	609	23	551	22	58	24	.54
Postnatal smoke exposure (in same room)	249	9	232	9	17	7	.22
Ever attended daycare	561	21	500	20	61	25	.07
Previous overnight hospitalization	514	19	469	19	45	19	.90
History of breathing problems	593	22	544	22	49	20	.54
Breathing problem began <1 d before ED visit	130	5	113	5	17	7	.09
Child discomfort in 24 h before ED visit							.07
None/mild	498	18	464	19	34	14	
Moderate	1164	43	1065	43	99	41	
Severe	1042	39	935	38	107	45	
Took antibiotics for illness before ED visit	464	17	422	17	42	18	.89
Used inhaled bronchodilator for breathing problem before ED visit	1086	40	959	39	127	53	<.001
Used corticosteroids for breathing problem before ED visit	349	13	313	13	36	15	.32

TABLE 1 Continued

Characteristics	All (N = 2709)		No HTS (N = 2468)		HTS Use (N = 241)		P
	n	%	*n*	%	*n*	%	
Virology							
No. of infections detected							.12
0	128	5	123	5	5	2	
1	1782	66	1621	66	161	67	
≥2	799	29	724	29	75	31	
RSV	2042	75	1841	75	201	83	.002
Rhinovirus	660	24	606	25	54	22	.46
ED visit							
Initial heart rate (beats per minute), median (IQR)	2678	162 (148–176)	2441	162 (148–176)	237	164 (154–177)	.06
Initial respiratory rate per minute, median (IQR)	2675	48 (40–60)	2436	48 (40–60)	239	52 (40–62)	<.001
Initial oxygen saturation by pulse oximetry							.66
<90%	290	11	261	11	29	12	
90%–93.9%	424	16	384	16	40	17	
≥94%	1937	73	1771	73	166	71	
Initial retractions							.001
None	547	20	497	20	50	21	
Mild	1181	44	1091	44	90	37	
Moderate/severe	819	30	723	29	96	40	
Not documented/unknown	162	6	157	6	5	2	
Presence of apnea	174	6	165	7	9	4	.07
Presence of wheezing	1693	64	1554	65	139	59	.08
Inhaled bronchodilator use	1690	63	1531	63	159	66	.26
Systemic corticosteroid use	387	14	362	15	25	10	.06
Systemic antibiotic use	602	22	556	23	46	19	.19
Inpatient							
ICU admission	436	16	362	15	74	31	<.001
Continuous positive airway pressure and/or intubated	165	6	134	5	31	13	<.001
Presence of apnea	116	4	105	4	11	5	.85
Inhaled bronchodilator on first admission day	990	37	881	36	109	45	.007
Systemic corticosteroid use	434	16	398	16	36	15	.58
Systemic antibiotic use	302	30	249	29	53	32	.46
Hospital LOS, d, median (IQR)	2709	2 (1–4)	2468	2 (1–4)	241	3 (2–5)	<.001

results reported as odds ratios with 95% confidence intervals . All P values were 2-tailed, with $P < .05$ considered statistically significant.

RESULTS

HTS Use Among Children Hospitalized for Bronchiolitis

Overall, the median age of the 2709 children hospitalized for bronchiolitis was 3.7 months, and 60% were male (Table 1). In total, 241 (9%) children received HTS during their ED or inpatient stay. Of these 241 children, most (69%) received HTS during their inpatient stay only, 15% received it in the ED only, and 16% received HTS in both settings.

From the 2008–2009 season to the 2011–2012 season, administration of HTS increased from 2% of patients to 27% of patients. In the 2012–2013 season, it dropped to 15% of patients and continued to drop to 11% of patients in the 2013–2014 season ($P < .001$, Fig 1A). From 2011 to 2012, most HTS was contributed by 3 out of 9 (33%) sites. From 2012 to 2013, it was contributed by 6 out of 17 (35%) sites, with 1 site using HTS on 91% (10 out of 11) of its enrolled patients. For sites with data for both seasons (2008–2009 and 2009–2010) of MARC-30, 31% (5 out of 16) of sites increased their use of HTS between the 2 enrollment seasons. The decrease in HTS use from 2013 to 2014 was largely due to 1 site

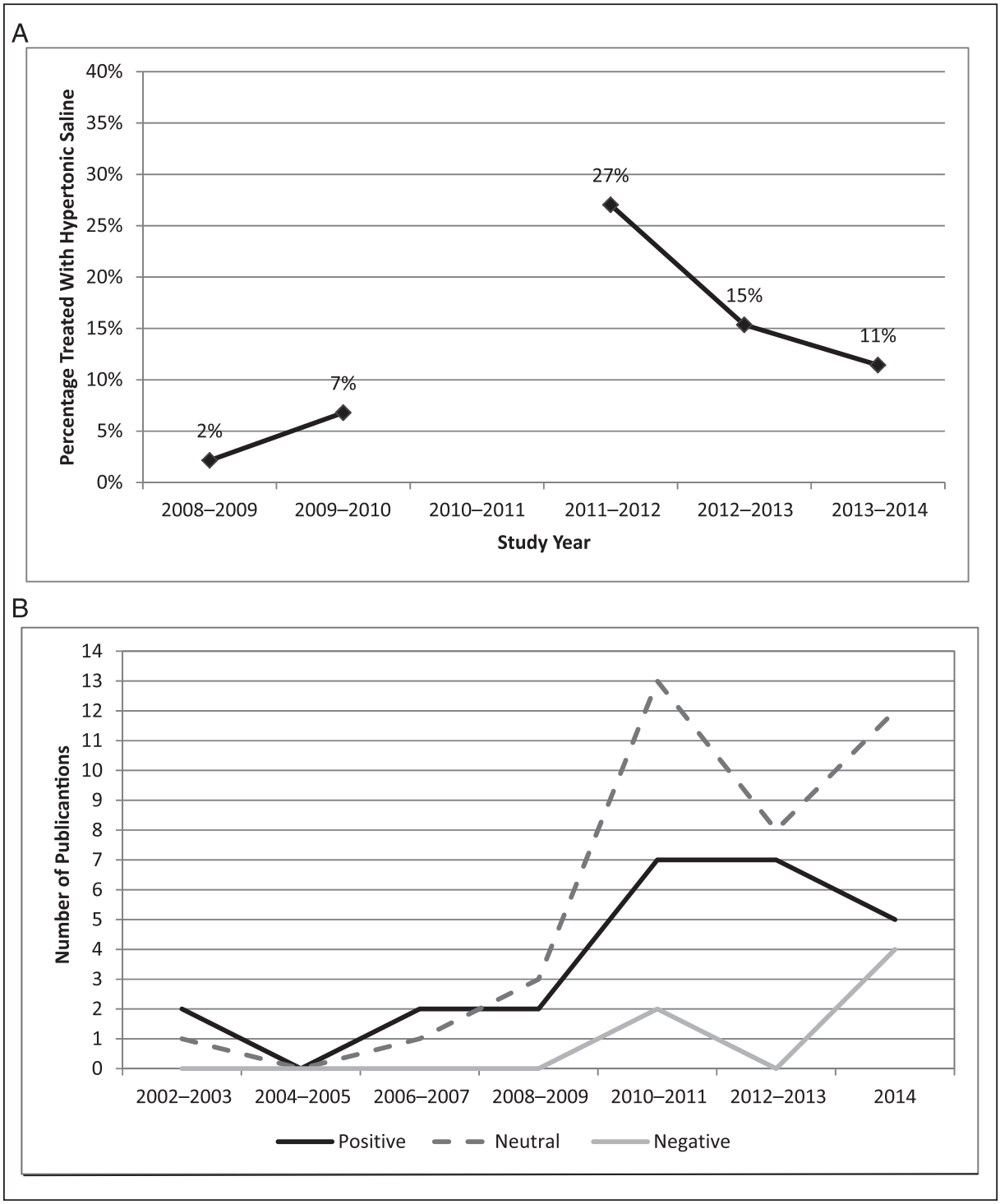

FIGURE 1 Trends in HTS use for bronchiolitis compared with relevant literature. A, HTS use among children hospitalized for bronchiolitis from 2008 to 2014. B, Number of PubMed publications evaluating HTS use for bronchiolitis from 2002 to 2014.

decreasing use from 58% to 29%. The 5 other sites with high use from 2012 to 2013 did not enroll patients in the 2013–2014 season. Although site participation varied by enrollment season, the type of sites selected for participation (eg, academic medical centers) remained relatively consistent. Among the 6 sites that participated in all 4 enrollment seasons, there was still a pronounced increase in the proportion of patients receiving HTS (2008–2009, 2%; 2009–2010, 6%;

2011–2012, 35%) and then a decline in use (2012–2013, 27%).

Of the 241 children receiving HTS, 31% were admitted to the ICU, compared with 15% of those who did not receive HTS ($P < .001$). Intubation was also more common among those receiving HTS compared with those who did not (8% vs 3%; $P = .001$). Of the patients who received HTS, 184 (77%) also received bronchodilator therapy: 75 (31%) only in the ED, 25 (10%) only in the inpatient setting, and 84 (35%) in both settings. The median LOS of patients who received HTS was 3 days (IQR, 2–5 days) vs a median of 2 days (IQR, 1–4 days, $P < .0001$) in other children.

In the multivariable model, children hospitalized during the 3 seasons from 2011 to 2014 were more likely to have received HTS compared with those enrolled in the 2008–2009 season (Table 2). Other factors associated with an increased likelihood of HTS use were ICU at birth, breathing problem started <1 day before arrival, parental rating of breathing problem as "severe," previous use of inhaled bronchodilator before arrival, and respiratory syncytial virus (RSV) infection. Also, children ≥12 months (only included in MARC-30) were less likely to receive HTS than those <2 months of age.

Literature Search

Between 1998 and 2014, 69 total articles were published evaluating HTS effectiveness for bronchiolitis; 25 (36%) positive, 38 (55%) neutral, and 6 (9%) negative. Before 2010, 1 to 3 articles were published on the topic annually (Fig 1B). However, between years 2010 and 2011, a total of 22 relevant articles were published, of which 7 were positive, 13 were neutral, and 2 were negative. Between years 2012 and 2014, 36 additional articles were published, of which 12 were positive, 20 were neutral, and 4 were negative. All of the negative studies in this period came in 2014.

DISCUSSION

In our study, 9% of children hospitalized for bronchiolitis were treated with HTS. Among children who received HTS, indicators of severe disease (ie, ICU admission, longer hospital LOS, <1 day of symptoms, and a parental rating of breathing problem as "severe") were more common compared with children who did not receive HTS. HTS use varied over season and enrolling sites, with an initial increase from 2008 to 2012 and then a decline during the 2012–2014 seasons. This variation in HTS use over time remained robust after adjustment for potential confounders in multivariable analyses.

Previous studies have noted wide practice variation in various treatments for bronchiolitis[6–8,22–27]; however, national guidelines appear to be decreasing unnecessary testing and the use of ineffective treatments.[25–28] Beyond supportive care, no treatment has been clearly established for children with

TABLE 2 Predictors of Receiving HTS among 2709 Infants Hospitalized for Bronchiolitis from 2008 to 2014

Characteristics	Odds Ratio	95% Confidence Interval		*P*
Enrollment season				
2008–2009	1.00	Reference	—	—
2009–2010	3.22	1.03	10.05	.04
2011–2012	14.17	4.52	44.38	<.001
2012–2013	7.33	2.87	18.74	<.001
2013–2014	5.02	2.20	11.46	<.001
Age at enrollment (mo)				
<2.0	1.00	Reference	—	—
2.0–5.9	1.02	0.66	1.58	.94
6.0–11.9	0.80	0.50	1.27	.34
≥12	0.39	0.19	0.79	.009
Sex				
Male	1.00	Reference	—	—
Female	0.95	0.72	1.24	.70
Race and/or ethnicity				
Non-Hispanic white	1.00	Reference	—	—
Non-Hispanic black or African American	0.69	0.43	1.11	.13
Hispanic	1.26	0.57	2.78	.58
Other	0.98	0.43	2.23	.97
Insurance				
Private	1.00	Reference	—	—
Public	0.64	0.40	1.02	.06
None	0.52	0.22	1.24	.14
Either or both parents with history of asthma	1.17	0.91	1.49	.22
Premature birth (≤37 wk)	1.06	0.79	1.43	.68
ICU or special care at birth	1.39	1.09	1.78	.008
Breathing problem began <1 d before ED visit	1.71	1.14	2.56	.01
Child discomfort in 24 h before ED visit				
None/mild	1.00	Reference	—	—
Moderate	1.09	0.78	1.52	.62
Severe	1.51	1.06	2.15	.02
Used inhaled bronchodilator for breathing problem before ED visit	1.62	1.18	2.24	.003
RSV	1.48	1.03	2.12	.03
Rhinovirus	1.06	0.72	1.55	.78

bronchiolitis. This study, however, is the first to show a rapid adoption in HTS use for bronchiolitis in parallel with literature supporting its novel use but before official sanctioning in national guidelines. The initial increase may have been due to more research publications describing HTS use in bronchiolitis patients. As time progressed, further research showed equivocal and inconsistent results for the efficacy of HTS,[8,15,29] and its overall usage subsequently declined in parallel with our findings. The quick uptake is also likely related to its negligible side effect profile, especially when coadministered with bronchodilators,[30–32] and the lack of other effective treatments. In this context, it is not surprising that sicker patients were more likely to receive HTS because clinicians would be more willing to try novel treatments in patients not improving after more established treatments failed. This can lead to confounding by severity in observational studies of medication effectiveness.[33]

More recently, a systematic review reported on all available trials of HTS up to May 2015 and concluded that nebulized HTS is associated with reduced LOS among admitted infants and reduced hospital admissions when used in the outpatient setting.[34] However, a reanalysis of 2 large meta-analyses questions these results and shows that the improvement in LOS disappears when a single outlier study is removed and the results are controlled for day of illness at presentation.[35] Although further research is needed to clarify the role of HTS in the management of bronchiolitis, it is also important to study the use and uptake of new treatments among clinicians.

This study had several potential limitations. First, the uptake and usage of HTS by clinicians could be affected by a variety of factors that we did not measure. However, our observations paralleled usage trends seen in the literature on the treatment of bronchiolitis. Our literature search strategy was limited to a single database (PubMed) and our categorization of articles relied on the assessment of 1 author. In addition, this was an observational study, which complicates the evaluation of the treatment effectiveness of HTS.[33] Also, our sample included only children hospitalized for bronchiolitis in academic medical centers and not all eligible children were enrolled, which may limit the generalizability of the results. Finally, not all study sites enrolled participants in all years; some findings might be due to site variability and not necessarily usage variability. The variability in site participation coincided with the largest changes observed in HTS use; therefore, these changes may be exaggerated. Despite these limitations, this study suggests that for severe bronchiolitis, providers are quick to trial novel therapies like HTS given the absence of other effective treatments.

CONCLUSIONS

The use of HTS in children hospitalized with bronchiolitis initially increased during the 2008–2012 seasons but then declined. The average usage over the course of our analysis was 9%, but it varied significantly across years and sites. Factors associated with HTS use included younger age, RSV infection, bronchodilator use before presentation, and need for NICU at birth; sicker patients also were more likely to receive HTS. We believe our findings are at least partially explained by the trends in HTS literature with a predominance of positive articles early on followed by an increase in negative and neutral articles after 2012. Although further research will likely clarify the role of HTS in the management of bronchiolitis, it is also important to study the use and uptake of new treatments by clinicians. By using new treatments before they are proven effective, especially when no clear alternatives are available, patients could be placed at unjustified risk for adverse events.

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APPENDIX TABLE 1 Principal Investigators at the 16 Participating Sites in MARC-30

Eugene Mowad, MD	Akron Children's Hospital, Akron, OH
Jonathan Mansbach, MD, MPH	Boston Children's Hospital, Boston, MA
John Cheng, MD and Carlos Delgado, MD	Children's Healthcare of Atlanta at Egleston, Atlanta, GA
Lisa Zaoutis, MD	Children's Hospital of Philadelphia, Philadelphia, PA
M. Jason Sanders, MD	Children's Memorial Hermann Hospital, Houston, TX
Brian Pate, MD	Children's Mercy Hospital & Clinics, Kansas City, MO
Stephen Teach, MD, MPH	Children's National Medical Center, Washington, DC
Besh Barcega, MD	Loma Linda University Children's Hospital, Loma Linda, CA
Frank LoVecchio, DO	Maricopa Medical Center, Phoenix, AZ
Paul Hain, MD and Mark Riederer, MD	Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
Dorothy Damore, MD and Nikhil Shah, MD	New York Presbyterian Hospital, New York, NY
Michelle Stevenson, MD, MS	Norton Children's Hospital, Louisville, KY
Erin Stucky Fisher, MD	Rady Children's Hospital, San Diego, CA
Haitham Haddad, MD	Rainbow Babies & Children's Hospital, Cleveland, OH
Alan Schroeder, MD	Santa Clara Valley Medical Center, San Jose, CA
Charles Macias, MD, MPH	Texas Children's Hospital, Houston, TX

APPENDIX TABLE 2 Principal Investigators at the 17 Participating Sites in MARC-35

Amy Thompson, MD	Alfred I. duPont Hospital for Children, Wilmington, DE
Federico Laham, MD, MS	Arnold Palmer Hospital for Children, Orlando, FL
Jonathan Mansbach, MD, MPH	Boston Children's Hospital, Boston, MA
Vincent Wang, MD, MHA	Children's Hospital of Los Angeles, Los Angeles, CA
Michelle Dunn, MD	Children's Hospital of Philadelphia, Philadelphia, PA
Juan Celedon, MD, DrPH	Children's Hospital of Pittsburgh, Pittsburgh, PA
Michael Gomez, MD, MS	Children's Hospital at St. Francis, Tulsa, OK
Brian Pate, MD and Henry Puls, MD	Children's Mercy Hospital & Clinics, Kansas City, MO
Stephen Teach, MD, MPH	Children's National Medical Center, Washington, DC
Richard Strait, MD	Cincinnati Children's Hospital and Medical Center, Cincinnati, OH
Ilana Wanik, MD	Connecticut Children's Medical Center, Hartford, CT
Sujit Iyer, MD	Dell Children's Medical Center of Central Texas, Austin, TX
Ari R. Cohen, MD and Wayne Shreffler, MD, PhD	Massachusetts General Hospital, Boston, MA
Michelle Stevenson, MD, MS	Norton Children's Hospital, Louisville, KY
Anne Beasley, MD	Phoenix Children's Hospital, Phoenix, AZ
Thida Ong, MD	Seattle Children's Hospital, Seattle, WA
Charles Macias, MD, MPH	Texas Children's Hospital, Houston, TX

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