Utilization of Nebulized 3% Saline in Infants Hospitalized with Bronchiolitis

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Objectives To describe utilization of 3% hypertonic saline (HTS) in hospitalized infants and to evaluate the association between HTS use and length of stay (LOS) in a real-world setting.

Study design This multicenter retrospective cohort study included infants ≤12 months hospitalized with bronchiolitis between October 2008 and September 2011 using the Pediatric Health Information System. HTS use was categorized as trial, rescue, daily, or sporadic. Differences in LOS were compared after matching daily HTS recipients and nonrecipients on propensity score.

Results There were 63 337 hospitalizations for bronchiolitis. HTS was used in 24 of 42 hospitals and 2.9% of all hospitalizations. HTS use increased from 0.4% of visits in 2008 to 9.2% of visits in 2011. There was substantial variation in HTS use across hospitals (range 0.1%-32.6%). When used, HTS was given daily during 60.6% of hospitalizations, sporadically in 10.4%, as a trial in 11.3%, and as a rescue in 17.7%. The propensity score-matched analysis of daily HTS recipients (n = 953) vs nonrecipients (n = 953) showed no difference in mean LOS (HTS 2.3 days vs nonrecipients 2.5 days; β-coefficient -0.04; 95% CI −0.15, 0.07; P = .5) or odds of staying longer than 1, 2, or 3 days. Daily HTS recipients had a 33% decreased odds of staying in the hospital >4 days compared with nonrecipients (OR 0.67; 95% CI 0.47, 0.97; P = .03).

Conclusions Variation in HTS use and the lack of association between HTS and mean LOS demonstrates the need for further research to standardize HTS use and better define the infants for whom HTS will be most beneficial. *(J Pediatr 2015;166:1168-74)*.

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants and the most frequent cause of hospitalization in this age group.[1-3] The pathogenesis of bronchiolitis is characterized by acute inflammation, edema, and necrosis of airway epithelium, excess mucus production, and bronchospasm, ultimately leading to airway obstruction and impaired gas exchange.[4,5] Despite the high incidence of bronchiolitis and a growing understanding of its pathogenesis, currently available therapies have failed to show consistent benefit, and supportive care remains the mainstay of bronchiolitis therapy.[5] Nebulized hypertonic saline (HTS) has been proposed as a therapy that may benefit patients through reduction of airway edema, diminished plugging, and improved clearance of mucus.

Over the last decade, a growing number of randomized trials suggest that early and repeated doses of nebulized HTS improve clinical outcomes in hospitalized children compared with 0.9% normal saline (NS). The most recent Cochrane Library meta-analysis examined 6 inpatient trials of 500 infants with acute bronchiolitis and concluded that nebulized 3% saline may significantly reduce the hospital length of stay (LOS) among infants hospitalized with mild-to-moderate bronchiolitis and improve postinhalation clinical severity scores during the first 3 days of hospitalization.[6] Despite the rapid growth in literature and inconsistent benefit of HTS in children hospitalized with bronchiolitis, no official recommendations were made prior to publication of the November 2014 American Academy of Pediatrics clinical practice guideline for bronchiolitis and little is known about how HTS is utilized in practice.[5,7] In addition, even though the efficacy of HTS has been studied in randomized trials, there have been no studies of its effectiveness in reducing LOS in a broad population of infants hospitalized with bronchiolitis. The objectives of this study were: (1) to characterize the current patterns of HTS utilization in hospitalized patients at children's hospitals across the US; and (2) to evaluate the association between HTS use and LOS in a real-world setting.

APR-DRG	All Patient Refined-Diagnosis Related Group
HTS	Hypertonic saline
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IV	Intravenous
LOS	Length of stay
NS	Normal saline
PHIS	Pediatric Health Information System

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Methods

This multicenter retrospective observational study included inpatient visits of children diagnosed with bronchiolitis. Data were from the Pediatric Health Information System (PHIS), an administrative database of 43 not-for-profit, tertiary care pediatric hospitals in the US affiliated with the Children's Hospital Association (Overland Park, Kansas). Data quality and reliability are assured through a joint effort between Children's Hospital Association and participating hospitals. The database accounts for ~20% of annual pediatric hospitalizations in the US. Hospitals provide discharge/encounter data including demographics, procedures, and diagnoses in *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) format; 42 of these hospitals also submit resource utilization data (eg, pharmaceuticals, imaging, and laboratory tests) and, thus, were included in this study. For the current study, data were included from October 1, 2008, 1 year after publication of the first Cochrane meta-analysis suggesting benefit of HTS, through December 31, 2011, which were the most recent data available at time of analysis.

Patients 12 months of age and younger were eligible if they were discharged from a participating hospital between October 2008 and December 2011 with diagnosis of bronchiolitis. Bronchiolitis was defined as an ICD-9-CM discharge diagnosis code for bronchiolitis (466.11, 466.19) and an All Patient Refined-Diagnosis Related Group (APR-DRG) code for bronchiolitis (138) to minimize misclassification.[8] Children with cystic fibrosis (ICD-9-CM code, 227), spinal muscular atrophy (ICD-9-CM code, 335), or bronchiectasis (ICD-9-CM codes, 494, 748.61) were excluded, as HTS is routinely used in patients with these conditions.

Exposure and Outcome Measures

The outcome of interest for the first objective was utilization of nebulized 3% saline. Receipt of HTS was identified using PHIS-specific Clinical Transaction Classification billing codes. These codes identify if HTS was given on a particular day of hospitalization, but cannot quantify the number of times HTS was administered in a single day. Receipt of HTS was categorized into 4 use patterns: trial, rescue, daily and sporadic. Trial use was defined as use for a single day on day 0 or 1 of hospitalization, but no use for the remainder of the hospitalization. Rescue use was defined as initiation of HTS on the third day of hospitalization or beyond. Daily use was defined as initiation of HTS within the first 2 days of hospitalization and repeated administration throughout the admission. For daily use with LOS longer than 2 days, we allowed for no HTS use on the final day of hospitalization or no use for an isolated single day during the hospital stay provided that it was administered every other day consecutively. Finally, sporadic use was defined as HTS use in a random pattern that did not meet one of the first 3 categories. For the second objective, daily use of HTS was the primary exposure and the outcome of interest was hospital LOS.

Covariates

The following patient- and visit-level demographic covariates were included: age, sex, race, insurance payer category, season, and year. Patient severity was examined using intensive care unit admission, noninvasive positive-pressure ventilation, mechanical ventilation, supplemental oxygen, receipt of blood gas, and an APR-DRG severity subclass score of major or extreme. The APR-DRG severity score consists of 4 categories from mild to extreme and represent illness severity of hospitalized patients.[9,10] Finally, several diagnostic and adjunct therapeutic resources were examined: albuterol, racemic epinephrine, corticosteroids, continuous nebulized therapies, intravenous (IV) fluids, IV antibiotics, and chest radiographs.

Statistical Analyses

Unadjusted frequency distributions were developed to explore HTS use patterns by hospital and by year. A bivariable analysis was conducted by characterizing differences in covariates and hospital LOS by pattern of HTS use across all PHIS hospitals. Percentages for categorical variables, means for age in months, and means/medians for LOS in days were developed. To account for clustering within hospitals, SAS PROC SURVEY (SAS Institute, Cary, North Carolina) was used to generate tests of significance by HTS use. Similarly, general estimating equations assuming a negative binomial distribution were used to test for differences in LOS because of the highly skewed LOS data.

Because clinical trials have found benefit in using HTS in a daily fashion, infants who received HTS daily were compared with those for whom HTS was not utilized at all to examine differences in covariates and hospital LOS between these 2 groups. To ensure adequate numbers of patients in each hospital who received HTS daily, only hospitals with overall rates of daily HTS use in more than 5% of all patients with bronchiolitis were included in these analyses. The same bivariable analysis described above was conducted. In addition, a propensity score-matched analysis was conducted to test for differences in LOS, the primary outcome, between infants receiving HTS daily or not at all in these hospitals.

Propensity scores were developed to account for potential confounding by observed baseline characteristics. A propensity score estimates the probability of receiving HTS daily given the observed set of baseline covariates. The following variables were included as risk factors for HTS receipt in a multivariable logistic regression model to generate the propensity score for HTS receipt: age, sex, race, insurance, asthma diagnosis at visit, season, year, APR-DRG severity score. In addition, we included a variable denoting the hospital to account for practice variation between hospitals. Finally, the management and severity variables listed above were included as indicator variables denoting whether or not they occurred within 2 days of hospital admission. The model's C-statistic was 0.877, indicating that the model provided a better estimate than expected by chance alone.[11,12]