

## Effect of Nebulized 3% Hypertonic Saline on Intensive Care Unit Admission Rates of Infants with Moderate Acute Bronchiolitis

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### Abstract

**Objectives:** To investigate whether the use of nebulized 3% hypertonic saline in infants hospitalized for acute bronchiolitis reduces their rate of pediatric intensive care unit (PICU) admission, the mean length of PICU stay and total hospital stay.

**Methods:** Cross-sectional study including 626 infants hospitalized for moderate acute bronchiolitis comparing a group receiving nebulized 3% hypertonic saline (HS group) between September 2011 and May 2014 (n=320), with a historic control group treated with normal saline (NS group) between September 2007 and May 2010 (n=306) independently of the concomitant use of bronchodilators.

**Results:** Overall hospital stay including days at PICU, was significantly reduced in HS group (4 days (0-46) vs 5 days (1-73);  $p < 0.0001$ ). However, we did not find a significant reduction in PICU admission rate in the HS group ( $p = 0.115$ ), neither in the length of stay (LOS) in PICU (5 days (1-30) vs 6 days (1-26);  $p = 0.402$ ). Half as many admission were observed in patients with risk factors of severe disease in HS group (6.5% of those with risk factors vs 3.1% of those without risk factors), although this failure to find a difference ( $p = 0.136$ ).

**Conclusions:** Treatment with nebulized 3% hypertonic saline was not accompanied by a reduction in PICU admission. There was no difference in PICU length of stay in infants with acute bronchiolitis, and admission rates in infants with risk factors for serious bronchiolitis; it was also associated with a significantly shorter mean hospital stay.

**Keywords:** 3% hypertonic saline; Admission; Bronchiolitis; Pediatric intensive care unit

### Abbreviations

RSV: Respiratory Syncytial Virus; WDF: Wood-Downes Clinical Scoring System Modified by Ferres

### Introduction

Acute bronchiolitis is the most common lower respiratory tract infection in infants [1]. It is most frequently caused by the respiratory syncytial virus (RSV), and most cases are self-limited and may be treated symptomatically on an outpatient basis. A small proportion of patients however, require hospital admission, although this rate varies widely between series, mainly due to substantial variations in admission criteria [1]. Following a considerable increase between 1980 and 1996 [2], admission rates began to stabilize and are now approximately 2-5% [3,4]. Similar rates have been reported in our setting [5].

The proportion of hospitalized infants with acute bronchiolitis requiring pediatric intensive care also varies between groups, with rates ranging from 3% to 15% [6-10]. However, when analyzing the

infant population with increased risk for serious disease, their PICU admission rates increase as much as to 50% [11,12]. One likely explanation for such variations is the lack of scientific evidence on the criteria for PICU admission. Standard criteria include severe or rapidly progressing respiratory failure, blood oxygen saturation  $< 90\%$  with a fraction of inspired oxygen ( $FiO_2$ ) of over 40%, consciousness impairment, apneas, and severe acidosis [1]. Although an age below 3 months, and particularly 6 weeks, is not an absolute criterion for PICU admission, it has been found to be a factor for developing serious disease and therefore the need of hospitalization [13].

Treatment with nebulized 3% hypertonic saline may rehydrate the airway surface liquid and increase mucociliary clearance, so it has emerged as a novel treatment for acute bronchiolitis in recent years. Most studies and systematic reviews have demonstrated that it shortens length of hospital stay and contributes to faster clinical improvement based on disease severity scales [14-16]. Reduced hospitalization rates were also reported in a recent meta-analysis [17]. The last clinical practice guideline, recommends clinicians to administer nebulized hypertonic saline to inpatient infants as a safe and effective measure at improving symptoms and reducing hospital LOS in moderate acute bronchiolitis [18]. However, to the best of our knowledge, there are yet no studies analyzing PICU admission rates with the use of nebulized 3% hypertonic saline.

The aim of this work was to investigate whether the use of nebulized 3% hypertonic saline, with or without bronchodilators, in hospitalized infants with moderate acute bronchiolitis reduces PICU admission rates as compared to the use of normal saline. Secondly, we aimed to compare PICU admission rates in the subgroup of infants with risk factors of developing severe disease, the need for mechanical ventilation, and mean lengths of PICU and total hospital stays.

## Patients and Methods

We performed a comparative study with a historical control group, using data collected retrospectively during 3 epidemic years (September 2007 to May 2010, NS group), and prospectively during the following 3 epidemic years (September 2011 to May 2014, HS group).

### Patients

We included all infants under 2 years of age, admitted to our pediatric ward at Hospital Universitario Puerta del Mar in Cádiz (Spain), with a diagnosis of moderate acute bronchiolitis according to the International Diseases Classification, Ninth revision, code 466.1, during both study periods (2007-2010 and 2011-2014). The diagnosis of bronchiolitis was based on a first episode of respiratory distress with wheezing, preceded by an infection of the upper respiratory airways. We excluded patients with previous episodes of wheezing or a diagnosis of asthma. To analyze the effect of 3% hypertonic saline nebulization on admission to the PICU, we registered as admitted to PICU only those who had received more than three nebulizations prior to PICU admission. The criteria for admission to PICU were the same in both periods: severe respiratory failure (score >7 according to the Wood-Downes Clinical Scoring System modified by Ferres [WDF] (Table 1) [19], blood oxygen saturation below 90% whilst receiving a FiO<sub>2</sub> of over 40%, consciousness impairment, apneas, respiratory acidosis (pH < 7.1), or rapidly progressing disease at any time during hospitalization.

	0	1	2	3
<b>Wheezing</b>	None	End expiration	Entire expiratory phase	Inspiration and expiration
<b>Retractions</b>	None	Subcostal or lower intercostal	1+superclavicular +nasal flaring	2+suprasternal +lower intercostal
<b>Respiratory rate, breaths/min</b>	<30	31-45	46-60	>60
<b>Heart rate, beats/min</b>	<120	>120		
<b>Inspiratory breath sounds</b>	Normal	Regular, equal	Markedly equal	Silent thorax, no wheezing
<b>Cyanosis</b>	No	Yes		

\*A score of 1-3 points denotes mild bronchiolitis; 4-7 moderate bronchiolitis; and 8-14 severe bronchiolitis.

**Table 1:** Wood-Downes clinical scoring system scale modified by Ferres\*.

We excluded those admitted to the PICU directly from the pediatric emergency department, or referred from different hospitals, and those from our own department who had been on the ward for less than 24 hours or had received fewer than three nebulization.

### Study design

For the first period of the study (retrospective phase), we performed a chart review of all infants who met the study inclusion criteria and were discharged with a diagnosis of acute bronchiolitis between September 2007 and May 2010 (NS group). These patients had been treated mainly with bronchodilators (salbutamol or epinephrine) nebulized in saline, in addition to standard support measures. The interval between nebulization varied according to the criteria of the attending pediatrician. The following additional data were recorded for each patient: age, sex, risk factor(s) for serious disease, length of hospital stay, WDF score at hospital admission, RSV infection (based on the detection of antigen in nasopharyngeal aspirate), treatment received for this episode prior to admission (salbutamol, corticosteroids, or antibiotics), and treatment during admission (nebulized saline with salbutamol or epinephrine). We also recorded the reason for admission to the PICU, the use of mechanical ventilation, and the duration of both of these.

Starting on September 2011, our institution adopted a new treatment protocol for infants with acute moderate bronchiolitis, changing the use of normal saline to 3% hypertonic saline with or without added bronchodilators, according to the incipient evidence favouring the newer therapy [1]. For the prospective part of the study, we collected the same variables for all infants with a diagnosis of acute bronchiolitis who met the inclusion criteria between September 2011 and May 2014 (HS group). These patients were treated with nebulized 3% hypertonic saline with or without bronchodilators (salbutamol or epinephrine), in addition to the same standard support measures. The interval between nebulizations was also left to the discretion of the attending pediatrician.

We excluded all patients of the 2010-2011 season, considering it a transition period in which it was possible for a patient to receive both types of nebulizations within the same admission.

The nebulized solution was administered in both groups using an ultrasonic hospital nebulizer (Shinmed model Sw918, Shining world health care CO, LTD, New Taipei City, Taiwan). We registered as risk factors for serious disease to have been born preterm, to suffer a congenital cardiopathy, or bronchopulmonar dysplasia, immunodeficiency disorder, or any neuromuscular disorder.

### Statistical Analysis

We used the  $\chi^2$  test to analyze differences between qualitative variables. Where appropriate, the Fisher exact test was used for binary variables. We applied the Kolmogorov-Smirnov test to test for normal distribution of quantitative variables. Parametric and nonparametric quantitative variables were compared using Student's T-test and the Mann-Whitney U test, according to their distribution. Significance was considered at a p value of <0.05.

### Ethics

The study was approved by the research ethics committee of Hospital Universitario Puerta del Mar, and signed informed consent

was obtained from the parents or legal representatives of the infants who participated in the prospective stage of the study.

## Results

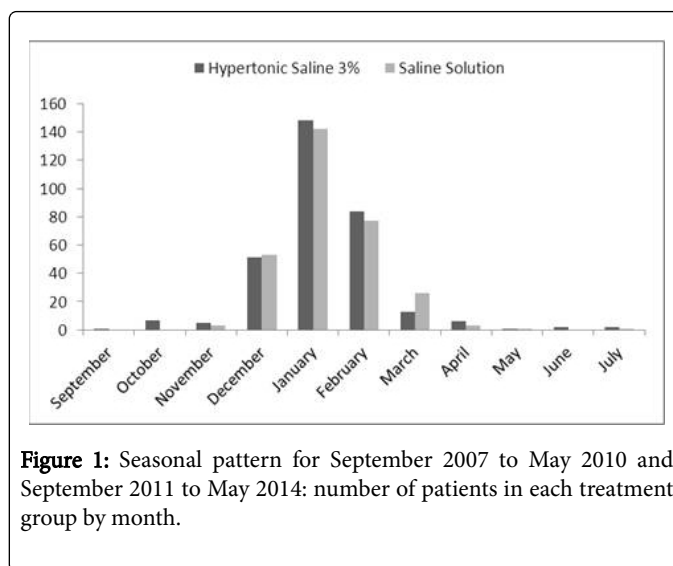
A total of 626 patients with acute moderate bronchiolitis were included in the study; 306 (48.9%) had been treated with nebulized saline (NS group) and 320 (51.1%) with nebulized 3% hypertonic saline (HS group). We found no differences between groups in disease severity as measured by the WDF score at admission (group 0:5 (2-9) vs group 1:5 (1-10),  $p=0.127$ , proportion of positive RSV tests (195 (63.9%) vs 207 (64.7%),  $p=0.603$ ), or in the number of patients with risk factors for serious disease (49 (16%) vs 39 (12.2%),  $p=0.169$ ). Pre-admission use of salbutamol, was significantly higher in NS group ( $p<0.004$ ) but there was no difference in the pre-admission use of corticosteroids or antibiotics ( $p=0.366$  and  $p=0.347$ , respectively) (Table 2). The number of patients admitted per epidemic year was similar in both groups (Figure 1), and there is not difference in the mean age between groups ( $p=0.113$ ).

Bronchodilators employed in NS group (nebulized in 0.9% saline), were salbutamol in 99 cases (32.4%) and epinephrine in 205 (67%). HS group received salbutamol in 24 (7.5%), epinephrine in 181 (56.7%) and no bronchodilator in 35.9% of cases.

Variable	NS Group	HS Group	p
Patients (n)	306	320	
Mean age (months)	2.1 (0.3-24.28)	2.0 (0.16-15.34)	0.113
Male sex (n and %)	186 (60.8%)	175 (54.7%)	0.123
Presence of risk factors for serious disease (n and %)	49 (16%)	39 (12.2%)	0.169
WDF score on admission (Score and range)	5 (2-9)	5 (1-10)	0.127
Positive RSV test (n and %)	195 (63.9%)	207 (64.7%)	0.169
Patients receiving Salbutamol prior to admission (n and %)	120 (43%)	101 (31.6%)	0.004
Patients receiving Corticosteroids prior to admission (n and %)	56 (20.1%)	74 (23.1%)	0.366
Patients receiving Antibiotics prior to admission (n and %)	21 (7.5%)	18 (5.6%)	0.347

WDF=Wood-Downes clinical scoring system scale modified by Ferres, RSV=Respiratory Syncytial Virus.

**Table 2:** Baseline demographic, clinical, and therapeutic characteristics of infants with acute bronchiolitis treated with normal saline (NS group) or 3% Hypertonic saline (HS group).



**Figure 1:** Seasonal pattern for September 2007 to May 2010 and September 2011 to May 2014: number of patients in each treatment group by month.

## Primary and secondary outcomes

Admission rates to the PICU were 53 out of 306 (17.3%) in NS group and 41 out of 320 (12.8%) in HS group ( $p=0.115$ ). Median of length of intensive care stay was one day shorter in the group receiving 3% HS, though this difference did not reach statistical significance (6 (1-26) vs 5 days (1-30),  $p=0.402$ ). Mechanical ventilation was required in 18 (34%) of the 53 children admitted to the PICU in NS group and in 9 (22.5%) of the 41 children admitted in HS group ( $p=0.228$ ). Mechanical ventilation was required for 6.5 (3-18) days in NS group compared with 7 (4-10) days in HS group, but again, this difference was not significant (0.717). PICU admission rates remained similar in both groups also, after age-stratified analysis (Table 3).

Of the 626 patients analyzed overall, 538 (85.9%) had no risk factors for serious disease, 68 (10.9%) had been born preterm, 11(1.8%) had congenital cardiopathy, 1 (0.2%) had an immunodeficiency disorder, and 6 (1%) had a neuromuscular disorder. The distribution of these conditions was similar in both groups (49 (16%) vs 39 (12.2%);  $p=0.169$ ). In total, 30 (34%) of the 86 patients with risk factors were admitted to the PICU. The rate of high risk patients needing PICU was 20 (40.8%) in NS group versus 10 (25.6%) in HS group, this difference however, was not significant ( $p=0.136$ ). As expected, the overall PICU admission rate for patients without risk factors was significantly lower than for patients with risk factors: 64 (11.9%) vs 30 (34%);  $p<0.0005$ ). Within these patients without risk factors, treatment option did not make a difference either in PICU admission rates; 33 (12.8%) were from NS group and 31 (11%) from HS group). Nine (30%) of the patients with risk factors required mechanical ventilation.

Age (months)	Admission to Intensive Care Unit		
	Group 0 n (%)	Group 1 n (%)	p
<1	12 (3.9%)	15 (4.6%)	0.796
1-3	24 (7.8%)	19 (5.9%)	0.272
3-6	12 (3.9%)	5 (1.5%)	0.098
>6	5 (1.6%)	2 (0.6%)	0.523

**Table 3:** Admission rate to pediatric intensive care unit (ICU) by age.

Length of hospital stay was significantly reduced in HS group (5 (1-73) vs 4 (0-46) days;  $p < 0.0001$ ). During their stay, 56 (20.1%) of the infants in NS group and 74 (23.1%) of those in HS group received corticosteroids at some point ( $p = 0.366$ ). The corresponding rates for antibiotic treatment were 21 (7.5%) and 18 (5.6%) respectively ( $p = 0.347$ ).

## Discussion

In our study, the admission rates to the PICU of infants with acute bronchiolitis were similar in infants treated with nebulized 3% hypertonic saline and normal saline ( $p = 0.876$ ). In accordance with other authors, shorter hospital stays [16] were observed in infants treated with 3% hypertonic saline. Hypertonic saline receiving infants admitted to the PICU stayed in this unit for one day less than infants admitted while receiving physiological saline, but this one day difference was not statistically significant, probably due to the small overall number of patients needing PICU. Nor did we find any significant differences between groups in the need for mechanical ventilation ( $p = 0.228$ ), or duration of ventilation ( $p = 0.717$ ), so these factors are unlikely the reason for the one day shorter PICU stay of the 3%HS receiving group. We observed no differences between the groups for admission to the PICU, even after stratification by age.

Similarly, two recent series have failed to find differences in PICU admission rates in patients receiving 3% hypertonic saline versus those receiving physiological saline. However, this comparison was not the primary aim of any of these studies. Both of them, report an overall length of hospital stay similar to our series, but in contrast with our results, none of these two find a shorter length of stay in the group receiving 3% Hypertonic saline [20,21].

Although several factors have been associated with an increased risk of severe disease, most infants with acute bronchiolitis admitted to the PICU are reported to be previously healthy and not considered of high risk [22,23]. The rate of patients with high risk factors admitted to the intensive care unit in our sample was 6.5% in the group receiving physiological saline and 3.1% in the group with 3% hypertonic saline, similar to that described in other series. Thus, in this sub-group of patients with risk factors, receiving 3% hypertonic saline reduces by half the requirement of PICU admission. This difference did not reach statistical significance (probably due to the small overall number of such patients admitted to the PICU), however, it may well be clinically relevant.

Length of hospital stay was significantly shorter in the 3% hypertonic saline group, which is consistent with previous reports [16,21-26]. The use of corticosteroids and antibiotics during hospitalization was similar in both groups, so these are unlikely to account for such difference.

Numerous studies have shown considerable variations in how acute bronchiolitis is managed [27-29]. The fact that many patients progress adequately regardless of the treatment received, probably explains why drugs without a proven clinical benefit are still used, with many professionals being guided more by personal or institutional preferences, rather than by an objective assessment of disease severity [27-29]. We observed a higher use of inhaled salbutamol prior to admission in the NS group and the same use of oral corticosteroids during admission although these treatments are not supported by current evidence.

The main limitation of our study is the use of a historical control group. Although we think that this limitation may not affect the results because the two periods analyzed were relatively close in time, and bronchiolitis treatment plans by primary care physicians don't appear to have changed so much. Nevertheless, we believe our findings are clinically relevant, since it was in the second group, in which the pre-admission use of salbutamol was significantly lower, in whom we observed a shorter mean hospital stay. Our findings add weight to the growing evidence that nebulized 3% hypertonic saline solution has beneficial effects in infants with acute bronchiolitis with a median stay above 3 days.

## Conclusions

We observed no difference nor in PICU admission, either in PICU stay in patients with a moderate acute bronchiolitis treated with 3% hypertonic saline compared with those treated with normal saline. In the subgroup of patients with a history of risk factors for serious disease, there was a not statically significant reduction in admissions to intensive care in patients receiving nebulized 3% hypertonic saline. Larger series are needed to determine whether or not nebulized 3% hypertonic saline significantly reduces PICU admission in patients with risk factors. In accordance with reports in the literature, patients treated with 3% hypertonic saline in our series, had significantly shorter hospital stays compared with those treated with normal saline.

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## Conflicts of Interest and Source of Funding

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