Early Halt of a Randomized Controlled Study with 3% Hypertonic Saline in Acute Bronchiolitis

Ania Carsin^a Emilie Sauvaget^b Violaine Bresson^a Karine Retornaz^b
Maria Cabrera^c Elisabeth Jouve^d Romain Truillet^d Emmanuelle Bosdure^a
Jean-Christophe Dubus^{a, b, e}

^aPediatric Pulmonology and Pediatrics, University Hospital of La Timone-Enfants, Aix-Marseille University,

^bPediatrics, North University Hospital, Aix-Marseille University, Marseille, ^cINSERM, Study Centre for Respiratory Diseases, UMR 1100, François Rabelais University, Tours, ^dClinical Investigation Centre, University Hospital of La Timone, Aix-Marseille University, and ^eAix-Marseille University, CNRS, IRD, INSERM, URMITE, IHU – Méditerranée Infection, Marseille, France

Keywords

Acute bronchiolitis · Hypertonic saline · Infant · Nebulizer

Abstract

Background: Albeit not recommended because of contradictory results, nebulized 3% hypertonic saline is widely used for treating acute viral bronchiolitis. Whether clinical differences may be attributed to the type of nebulizer used has never been studied. **Objectives:** By modifying the amount of salt deposited into the airways, the nebulizer characteristics might influence clinical response. **Methods:** A prospective, randomized, controlled trial included infants hospitalized in a French university hospital for a first episode of bronchiolitis. Each child received 6 nebulizations of 3% hypertonic saline during 48 h delivered with 1 of the 3 following nebulizers: 2 jet nebulizers delivering large or small particles, with a low aerosol output, and 1 mesh nebulizer delivering small particles, with a high aerosol output. The

primary endpoint was the difference in the Wang score at 48 h. **Results:** Only 61 children of 168 were recruited before stopping this study because of severe adverse events ($n = 4$) or parental requests for discontinuation due to discomfort to their child during nebulization ($n = 2$). One minor adverse event was noted in 91.8% ($n = 56/61$) of children. A high aerosol output induced 75% of the severe adverse events; it was significantly associated with the nebulization-induced cough between 24 and 48 h ($p = 0.036$). Decreases in Wang scores were not significantly different between the groups at 48 h, 9 recoveries out of 10 being obtained with small particles. **Conclusion:** No beneficial effects and possibly severe adverse events are observed with 3% hypertonic saline in the treatment of bronchiolitis.

© 2017 S. Karger AG, Basel

Trial registration: EU Clinical Trial Register (EudraCT, No. 2010-A01237-32) and Clinical Trials Register (ClinicalTrials.gov, No. NCT 01295398).

Introduction

Acute viral bronchiolitis affects millions of infants worldwide each year. As of yet, there is no curative treatment. Only a few symptomatic treatments, including oxygen, hydration, and nasal suction, are commonly accepted treatments [1, 2]. The use of nasal instillation with isotonic saline is still debated, and chest physiotherapy is currently not recommended [1, 2], contrary to our 16 years old French guidelines [3].

Recently, nebulized hypertonic saline (HS) has been used to treat acute bronchiolitis due to its potential osmotic effect and mucus clearance facilitation. The pooled result of the main clinical studies on this subject is not convincing, either for out-patients [4–11] or for in-patients [12–25]. The most recent meta-analyses revealed a negative effect of the 3% HS [26, 27], and the latest consensus statements [1, 2] do not recommend its use. Despite this, others continue to support the suggestion that 3% HS reduces the rates of hospitalization and the duration of admissions [28]. From an inhalotherapist's point of view, the effect of HS is linked to the amount of salt deposited into the airways [29]. The more the salt is locally present, the greater the osmotic effect would be. In a hypothesis such as this, the nebulizer used for the delivery of the 3% HS in extremely young infants with acute viral bronchiolitis turns out to be extremely important. The characteristics of the nebulizer are not mentioned or not well described in the majority of those studies (12 among 21) [4, 5, 7, 9–11, 15–20, 25]. The aim of our study was to compare the clinical effect and tolerance of delivery of 3% HS by different nebulizers in infants hospitalized for a viral acute bronchiolitis.

Materials and Methods

Study Design

This is a prospective, randomized, open label study enrolling infants treated with 3% HS for acute bronchiolitis and carried out in the 2 general pediatric units of the University Hospital of Marseille from October 2012 to April 2014.

Patients

We recruited children aged <18 months hospitalized for a first episode of acute viral bronchiolitis. Bronchiolitis was defined as a viral upper respiratory tract prodrome followed by the apparition of cough, tachypnea, wheezing, rales, and increased respiratory effort manifested as grunting, nasal flaring, and intercostal and/or subcostal retractions [1]. Patients were included if the clinical score of Wang (based on the respiratory rate, the auscultation, the muscular retraction, and the general status) was >4 points on a scale with a maximum of 12 points [30]. Infants with apnea, with

respiratory distress requiring transfer to a pediatric intensive care unit, with a notion of prematurity (<34 gestational weeks) and a corrected age of <3 months, with an underlying disease (neuromuscular disease, immunodeficiency, bronchopulmonary dysplasia, and asthma), with a corticoid or bronchodilator treatment within the 6 previous hours, or with a parental refusal for study participation were excluded. The demographic data and the history of the acute bronchiolitis before the hospitalization, such as the number of days of symptoms or the delivered treatments, were noted. We evaluated the clinical score of Wang at baseline and 24 and 48 h after initiating 3% HS. Tolerance during the nebulization delivery was assessed by trained nurses and/or pediatricians who noted occurrences of immediate respiratory distress, hypoxemia, cough, bronchospasm, tears, agitation, bradycardia, or tachycardia. In addition, we noted the need of oxygen or nutritional support (intravenous fluids or nasogastric tube feeding) at baseline and at 24 and 48 h. The identified virus, the chest X-ray results (chest X-rays were performed before the nebulization, and the radiologist was blinded to the intervention), and parental perception of the nebulizer were noted. Of note, the 2 general pediatric units used the same management protocol for the treatment of viral acute bronchiolitis according to our national French recommendations which propose multiple nasal 0.9% saline instillations, chest physiotherapy (which was performed in this study twice daily, after a nebulization), and chest X-ray for hospitalized infants [3].

Nebulizers

The infants were allocated to a randomization stratified by center (1:1:1 allocation, random block sizes of 6 per center) to 1 of the 3 following nebulizers: a jet nebulizer Pari LC Sprint (Pari GmbH, Germany), a jet nebulizer Pari LC Sprint Baby (Pari GmbH), and a new prototype mesh nebulizer Babynimbus (Telemaq, France). The nebulizers were previously characterized by diffractometry (Malvern 3000 laser, MA, USA; mean of 6 sets). They were different in terms of mass median aerodynamic diameter (MMAD) and aerosol output: Pari LC Sprint: MMAD $4.1 \pm 0.1 \mu\text{m}$, aerosol output $0.2 \pm 0.09 \text{ mL/min}$; Pari LC Sprint Baby: MMAD $2.7 \pm 0.4 \mu\text{m}$, aerosol output $0.1 \pm 0.08 \text{ mL/min}$; and Babynimbus: MMAD $2.8 \pm 0.2 \mu\text{m}$, aerosol output $0.5 \pm 0.1 \text{ mL/min}$. All children received 1 nebulization every 8 h of 3% HS (4 mL MucoClear 3% unidose, Pari GmbH, Germany) for 48 h (total of 6 nebulizations) with 1 of the 3 nebulizers. All of the nebulizers in the study were equipped with a facemask. The gas vector was always the air.

Statement of Ethics

The study was approved by the Ethical Committee Sud Méditerranée I (Marseille, France) and registered in the EU Clinical Trial Register (EudraCT, No. 2010-A01237-32) and Clinical Trials Register (ClinicalTrials.gov, No. NCT 01295398). A written informed consent was obtained from both parents.

Analysis

Comparing efficacy among nebulizers on a clinical score was the primary outcome. As in some studies the Wang score was as low as 2.2–2.8 after 2 days of treatment [4, 16], we postulated that a 0.5 point difference in the Wang score at 48 h proved the superiority of one nebulizer compared to another one. To demonstrate this difference, with a standard deviation of 0.5, a power of

Fig. 1. Flow chart of the study enrolling children aged <18 months, hospitalized for an acute viral bronchiolitis, and treated with 3% hypertonic saline delivered with 3 different nebulizers.

80% and an α risk of 5%, 51 patients per group were necessary (Tukey-Kramer method). As we considered a follow-up loss of 10% of the patients, 56 infants per group (total of 168) were required. The main secondary endpoints were the number of severe and minor secondary effects (severe adverse events defined by an acute respiratory distress during or immediately after the nebulization or a SpO_2 decrease >10%, and minor adverse events defined by the occurrence of cough, bronchospasm, tears, agitation, minor hypoxemia, and cardiac rate modification), the rate of recoveries (defined as a Wang score below 2 points), the number of children requiring oxygen and/or feeding support, and the parental perception of the nebulizer. No control group was deemed necessary for this study, as we wanted to compare the different nebulizers.

Continuous variables (Wang score and differences in Wang score) were compared with analysis of variance (ANOVA), 2 means or medians were compared with a t test or a Mann-Whitney test, and noncontinuous variables (population data, recoveries, adverse events, parental perception, and ease of use) were compared with a χ^2 test or a Fisher test. A p value <0.05 was considered as statistically significant.

Results

We were unable to include the required number of children for this study. Because of the occurrence of 3 immediately consecutive severe adverse events, we decided to stop the study although only 61 children had been included (Fig. 1). Their characteristics were similar in all the nebulizers groups (Table 1), with a median age of 2.5 (1.5–4.0) months and a median delay of 4.0 (5.0–2.0) days between the beginning of the disease and the first 3% HS nebulization.

We observed 4 discontinuations (6.5%) linked to severe adverse events (Table 2). Two withdrawals were linked to an acute transitory respiratory distress occurring within 5 min after the nebulization and responsible for transfers to a pediatric intensive care unit ($n = 1$ with the Babynimbus and $n = 1$ with Pari LC Sprint). Two discontinuations were due to a severe transitory hypoxemia during nebulization with the Babynimbus. Moreover, 91.8% of the patients ($n = 56/61$) suffered from minor ad-

Table 1. Characteristics of 61 hospitalized infants treated with nebulized 3% hypertonic saline with 3 different nebulizers for acute bronchiolitis

	All children (n = 61)	LC Sprint ^a (n = 20)	LC Sprint Baby ^b (n = 21)	Babynimbus ^c (n = 20)	p value
Baseline data	(n = 61)	(n = 20)	(n = 21)	(n = 20)	
Median age, months	2.5 (1.5–4.0)	2.5 (1.5–4.0)	2.5 (2.0–5.5)	2.5 (1.5–4.0)	0.67 ^f
Number of boys	38/61 (62.3)	11/20 (55.0)	12/21 (57.1)	15/20 (75.0)	0.36 ^f
Median BMI	16.5 (15.0–17.2)	16.7 (15.1–18.1)	15.5 (14.7–16.8)	16.5 (15.5–17.5)	0.34 ^f
Parental smoking	21/61 (34.4)	8/20 (40.0)	4/21 (40.0)	9/20 (45.0)	0.18 ^f
Positive RSV	48/55 (87.2)	16/17 (94.1)	17/20 (85.0)	15/18 (83.3)	0.68 ^f
Abnormal chest X-ray ^d	26/56 (46.4)	4/19 (21.1)	11/20 (55.0)	11/17 (64.7)	0.02 ^f
Median initial Wang score	9.0 (8.0–10.0)	9.0 (7.5–11.0)	10.0 (8.0–10.0)	9.0 (7.5–10.0)	0.77 ^g
Oxygen	49/61 (80.3)	14/20 (70.0)	17/21 (81.0)	18/20 (90.0)	0.29 ^h
Nutritional support	29/61 (47.5)	10/20 (50.0)	9/21 (42.8)	10/20 (50.0)	0.89 ^f
24-h data	(n = 57)	(n = 18)	(n = 21)	(n = 18)	
Δ Wang score at 24 h ^e	−2.9±2.7	−3.2±2.4	−3.2±2.8	−2.2±2.9	0.41 ^g
Oxygen	41/57 (70.7)	12/18 (66.6)	15/21 (71.4)	14/18 (77.8)	0.76 ^f
Nutritional support	24/57 (42.1)	9/18 (50.0)	8/21 (38.1)	7 (38.9)	0.26 ^h
48-h data	(n = 51)	(n = 18)	(n = 17)	(n = 16)	
Δ Wang score at 48 h ^e	−4.2±3.2	−3.9±2.9	−4.6±2.4	−4.3±3.8	0.76 ^g
Oxygen	32/51 (62.7)	14 (77.8)	10 (58.8)	8 (50.0)	0.23 ^f
Nutritional support	18/51 (35.3)	6/18 (33.3)	5/17 (29.4)	7/16 (43.7)	0.10 ^h
Recoveries	10/61 (16.4)	1/20 (5.0)	5/21 (23.8)	4/20 (20.0)	0.26 ^h

Values are median (range), *n*/total *n* (%), or mean ± standard deviation. BMI, body mass index (in kg/m²); RSV, respiratory syncytial virus. ^a LC Sprint delivers large particles with a low aerosol output. ^b LC Sprint Baby delivers small particles with a low aerosol output. ^c Babynimbus delivers small particles with a high aerosol output. ^d Abnormal chest X-ray means condensation or retraction. ^e Difference in Wang score from the initial measure. ^f χ^2 test. ^g ANOVA test. ^h Fisher test.

verse events: transitory tachycardia or bradycardia (*n* = 2), transitory mild desaturation (*n* = 20), excessive coughing during nebulization (*n* = 42), bronchospasm (*n* = 1), and behavioral modifications (agitation or tears, *n* = 50). To note, cough during inhalation was more frequent between 24 and 48 h with the Babynimbus than with the Pari LC Sprint Baby (75 vs. 27.8% of cases, *p* = 0.036). Two additional treatment discontinuations were due to parental requests because of the discomfort to their child during nebulization (*n* = 1 with the Pari LC Sprint and *n* = 1 with the Pari LC Sprint Baby). In total, 9.8% of the children stopped the trial because of adverse events or parental requests. Nevertheless, whichever nebulizer was used, 44% of the parents judged HS nebulizations very efficient. The Babynimbus was considered the nebulizer the least easy to use (*p* = 0.0005).

Of note, the decrease in the Wang score was similar in the 3 groups of nebulizers (Table 1). The rate of recoveries was similar in each group, 9 of 10 occurring with nebulizers delivering the smallest particles. At the end of the

trial, 62.7% of the children (*n* = 32/51) still required oxygen and 35.3% (*n* = 18/51) a nutritional support.

Discussion

The aim of our study was to compare 3 different nebulizers for delivering 3% HS to infants hospitalized for a first episode of viral acute bronchiolitis. Due to a high rate of severe adverse events and severe patient discomfort leading us to discontinue the trial, we have been unable to prove that differences in nebulizers may play a role in the clinical outcome of hospitalized infants with acute bronchiolitis treated with 3% HS.

The authors acknowledge some limitations of this study. Our trial is not structured for specifically identifying adverse events with nebulized 3% HS in bronchiolitis. There is no control group, which would have allowed us to be completely certain of the nebulizations' responsibility in the occurrence of the adverse events rather than that

Table 2. Adverse events reported in 61 hospitalized infants treated with nebulized 3% hypertonic saline delivered for 48 h with 3 different nebulizers for acute viral bronchiolitis (1 or more events may be reported for the same infant during the 48 h of treatment)

	LC Sprint ^a (<i>n</i> = 20)	LC Sprint Baby ^b (<i>n</i> = 21)	Babynimbus ^c (<i>n</i> = 20)	<i>p</i> value
Severe adverse events	1 infant (5.0%)	0 infants	3 infants (15.0%)	0.31 ^d
PICU transfer (<i>n</i> = 2 infants)	1 event	0 events	1 event	1 ^d
Severe hypoxemia (<i>n</i> = 2 infants)	0 events	0 events	2 events	1 ^d
Minor adverse events	17 infants (85.0%)	20 infants (95.2%)	19 infants (95.5%)	0.52 ^d
Tachycardia/bradycardia (<i>n</i> = 2 infants)	0 events	0 events	2 events	1 ^d
Mild hypoxemia (<i>n</i> = 20 infants)	9 events	6 events	5 events	0.42 ^e
Cough with treatment (<i>n</i> = 42 infants)	22 events	18 events	28 events	0.29 ^e
Bronchospasm (<i>n</i> = 1 infant)	0 events	1 event	0 events	1 ^d
Agitation (<i>n</i> = 23 infants)	12 events	24 events	19 events	0.39 ^e
Tears (<i>n</i> = 27 infants)	21 events	24 events	23 events	0.85 ^e
Patients ceasing the trial	2 infants (10.0%)	1 infant (4.8%)	3 infants (15.0%)	0.51 ^d

PICU, pediatric intensive care unit. ^a LC Sprint delivers large particles with a low aerosol output. ^b LC Sprint Baby delivers small particles with a low aerosol output. ^c Babynimbus delivers small particles with a high aerosol output. ^d Fisher test. ^e χ^2 test.

of the unpredictable evolution of a moderate to severe bronchiolitis (defined by the Wang score we have obtained [30]) in very young infants. On the other hand, our study design permitted to observe that the reported adverse events occurred during or within the few minutes following nebulization, highlighting the potential link between treatment and adverse event occurrence. Our patients have also been treated with chest physiotherapy, which may favor respiratory distress or discomfort [1, 2], but, as performed long after the nebulization, chest physiotherapy is likely not responsible for the adverse events we observed.

In the previous studies looking, like ours, for a clinical effect, only few adverse events were reported, with nebulizations of 3% HS considered as safe and very well tolerated in in-patients with acute bronchiolitis [12–25]. Only 2 studies described a high rate of adverse events. In 1 retrospective study [17], only 4 mild adverse effects and 1 episode of bronchospasm were noted on 377 delivered doses of 3% HS, but when this number is related to the number of treated infants (*n* = 68), this concerns about 7% of the population. In another recent prospective study [24] where only 80% of the population corresponded to our criteria of bronchiolitis, a clinical worsening (defined as transfer to the pediatric intensive care unit or bronchospasm within 30 min of a nebulization) was observed in 9% of the infants treated with 3% HS. We have also observed many minor adverse events; some of them, such as tears, agitation, and/or coughing during inhalation, may

additionally compromise the theoretical efficacy of the 3% HS by limiting the penetration of the aerosol into the respiratory tree and then by negatively affecting its bronchial deposition.

There are a number of reasons that might explain the high report of adverse events with 3% HS in our population. One can first hypothesize that we have enrolled a more severely affected population than others. A Wang score as high as 9 was only reported in 2 other studies but with no declared adverse events in one study [18] and absolutely no reported data on tolerance in the other [19]. A large majority of our children required oxygen, which was also described in 2 other studies with 100% [21] and 43% [22] of the children being dependent on oxygen. However, nearly half of our population had a lung parenchymal abnormality on chest X-ray that may have compromised the respiratory deposition and potentially increased the risk of diminished tolerance. This rate was only 5% in one previous study [15], data being unavailable in all the other clinical studies, as chest X-ray is currently not recommended routinely in acute bronchiolitis. Secondly, the nebulization effect itself could be questioned. Although 2 studies showed a Wang score decrease 30 min after the beginning of a nebulization with 3% HS and bronchodilators [4, 12], recent data show that a normal saline nebulization induces comparable clinical worsening events as a 3% HS nebulization [24]. Collecting data before and after a nebulization with only 3% HS would be helpful to support this hypothesis.

Thirdly, the nebulizer and gas vector used could be accountable. In the previously reported clinical studies [4–25], the device was not specified in 11 cases, the MMAD in 12 cases, the aerosol output rate in 16 cases, and the gas vector in 16 cases. Because some studies [12, 16, 17, 21, 25] have used, like ours, nebulizations with air and have reported no side effects, the influence of the gas vector on the 3% HS tolerance is inconclusive. In our study, a higher proportion of adverse events were noted with the mesh nebulizer, maybe because of its high aerosol output rate that may favor cough and respiratory trouble. Therefore, in the one other study [12] using such a high output rate (0.5 mL/min), no side effects were reported. With 9 recoveries obtained among 10 patients, the smallest particles may be of interest. Theoretically, a nebulizer combining the delivery of small particles with a low aerosol output might be beneficial to the infants, but the multicenter SABRE study [21] using the Pari LC Sprint Baby shows negative results with 3% HS.

Conclusion

Currently, 3% HS is not recommended for treating acute viral bronchiolitis. 3% HS nebulizations cause minor and severe adverse events as seen in our study. The association between adverse events and the potential role of nebulization, medication and nebulizer utilized, and bronchiolitis phenotype [31] needs further exploration.

Acknowledgements

We would like to thank all the families who participated in the study and all the nurses who cared for the patients. We also thank Mrs. Marion Robbins who has corrected the English version of the manuscript.

Funding Sources

This study was part of a project sponsored by the French National Agency for Research (ANR).

References

- Ralston SL, Lieberthal AS, Meissner HC, et al: Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474–e1502.
- NICE (National Institute for Health and Care Excellence): Bronchiolitis: diagnosis and management of bronchiolitis in children. Clinical Guideline NG9:301p. <https://www.nice.org.uk/guidance/ng9/evidence.pdf> (accessed June 2017).
- Stagnara J, Balagny E, Cossatier B, et al: Management of bronchiolitis in the infant. Recommendations. Long text (in French). *Arch Pediatr* 2001;8(suppl 1):11S–23S.
- Sarrell EM, Tal G, Witzling M, et al: Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. *Chest* 2002;122:2015–2020.
- Grewal S, Ali S, McConnell DW, et al: A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Arch Pediatr Adolesc Med* 2009;163:1007–1012.
- Anil AB, Anil M, Saglam AB, et al: High volume normal saline alone is as effective as nebulised salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. *Pediatr Pulmonol* 2010;45:41–47.
- Kuzik BA, Flavin MP, Kent S, et al: Effect of inhaled hypertonic saline on hospital admission rate in children with viral bronchiolitis: a randomized trial. *CJEM* 2010;12:477–484.
- Ipek IO, Yalcin EU, Sezer RG, Bozaykut A: The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. *Pulm Pharmacol Ther* 2011;24:633–637.
- Florin TA, Shaw KN, Kittick M, et al: Nebulized hypertonic saline for bronchiolitis in emergency department: a randomized clinical trial. *JAMA Pediatr* 2014;168:664–670.
- Jacobs JD, Foster M, Wan J, Pershad J: 7% hypertonic saline in acute bronchiolitis: a randomized controlled trial. *Pediatrics* 2014;133:e8–e13.
- Khanal A, Sharma A, Basnet S, et al: Nebulised hypertonic saline (3%) among children with mild to moderately severe bronchiolitis – a double blind randomized controlled trial. *BMC Pediatrics* 2015;15:115.
- Mandelberg A, Tal G, Witzling M, et al: Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest* 2003;123:481–487.
- Tal G, Cesar K, Oron A, et al: Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. *Isr Med Assoc J* 2006;8:169–173.
- Kuzik BA, Al Qadhi SA, Kent S, et al: Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr* 2007;151:266–270.
- Al-Ansari K, Sakran M, Davidson BL, et al: Nebulized hypertonic 5, 3, and 0.9% saline for treating acute bronchiolitis in infants. *J Pediatr* 2010;157:630–634.
- Luo Z, Liu E, Luo J, et al: Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatr Int* 2010;52:199–202.
- Ralston S, Hill V, Martinez M: Nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis. *Pediatrics* 2010;126:520–525.
- Luo Z, Fu Z, Liu E, et al: Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis. *Clin Microbiol Infect* 2011;17:1829–1833.
- Miraglia Del Giudice M, Saitta F, Leonardi S, et al: Effectiveness of nebulized hypertonic saline and epinephrine in hospitalized infants with bronchiolitis. *Int J Immunopathol Pharmacol* 2012;25:485–491.
- Sharma BS, Gupta MK, Rafik SP: Hypertonic (3%) saline versus 0.93% saline nebulization for acute viral bronchiolitis: a randomized controlled trial. *Indian Pediatr* 2013;50:743–747.

- 21 Everard ML, Hind D, Ugonna K, et al: SABRE: a multicentre randomized control trial of nebulised hypertonic saline in infants hospitalized with acute bronchiolitis. *Thorax* 2014;69:1105–1112.
- 22 Teunissen J, Hochs AH, Vaessen-Verberne A, et al: The effect of 3 and 6% hypertonic saline in viral bronchiolitis: a randomised controlled trial. *Eur Respir J* 2014;44:913–921.
- 23 Tinsa F, Abdelkafi S, Bel Haj I, et al: A randomized, controlled trial of nebulized 5% hypertonic saline and mixed 5% hypertonic saline with epinephrine in bronchiolitis. *Tunis Med* 2014;92:674–677.
- 24 Silver AH, Esteban-Cruciani N, Azzarone G, et al: 3% hypertonic saline versus normal saline in inpatient bronchiolitis: a randomized controlled trial. *Pediatrics* 2015;136:1036–1043.
- 25 Gupta HV, Gupta VV, Kaur G, et al: Effectiveness of 3% hypertonic saline nebulization in acute bronchiolitis among Indian children: a quasi-experimental study. *Perspect Clin Res* 2016;7:88–93.
- 26 Maguire C, Cantrill H, Hind D, et al: Hypertonic saline (HS) for acute bronchiolitis: systematic review and meta-analysis. *BMC Pulm Med* 2015;15:148.
- 27 Brooks CG, Harrison WN, Ralston SL: Association between hypertonic saline and hospital length of stay in acute viral bronchiolitis: a reanalysis of 2 meta-analyses. *JAMA Pediatr* 2016;170:577–584.
- 28 Zhang L, Mendossa-Sassi RA, Klassen TP, Wainwright C: Nebulized hypertonic saline for acute bronchiolitis: a systematic review. *Pediatrics* 2015;136:687–701.
- 29 Mandelberg A, Amirav I: Hypertonic saline or high volume normal saline for viral bronchiolitis: mechanisms and rationale. *Pediatr Pulmonol* 2010;45:36–40.
- 30 Wang EE, Milner RA, Navas L, Maj H: Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis* 1992; 145:106–109.
- 31 Dumas O, Mansbach JM, Jartti T, et al: A clustering approach to identify severe bronchiolitis profiles in children. *Thorax* 2016;71:712–718.