Nebulized hypertonic saline solution for acute bronchiolitis in children (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
To assess the effects of nebulized hypertonic saline solution in children with acute bronchiolitis.

BACKGROUND

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants (Klassen 1997a). Most cases are viral in origin, with the leading cause being the respiratory syncytial virus. Other less common pathogens include parainfluenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and *Mycoplasma pneumoniae (M. pneumoniae)* (Garcia-Garcia 2006; Henderson 1979; Jacques 2006; Rose 1987; Shay 2001). Approximately 10% of infants are affected by acute bronchiolitis in the first year of life (Panitch 1993; Rakshi 1997) and 1 to 3% are hospitalized with it (Shay 1999). Rates of hospitalization with bronchiolitis have increased over the past decade in USA and Canada (Njoo 2001; Shay 1999).

There is peribronchial infiltrate of inflammatory cells, mucosal and submucosal edema, necrosis and desquamation of ciliated epithelial cells, proliferation of non-ciliated cubial cells and excess mucus secretion (Panitch 1993; Wohl 1978). The combination of airway wall swelling, sloughing of necrotic debris, increased mucus production and impaired secretion clearance leads to small airway obstruction, gas trapping, atelectasis and impaired gas exchange.

Diagnosis is usually based on clinical grounds. In spite of differences in definition of bronchiolitis in different countries, generally acute bronchiolitis refers to the first episode of acute wheezing in children less than two years of age, starting as a viral upper respiratory infection (coryza, cough or fever) (Panitch 1993). These criteria for diagnosis of acute bronchiolitis have also been widely used in clinical trials (Bertrand 2001; Klassen 1997b; Schuh 1992; Wainwright 2003; Zhang 2003). The causative pathogen may be identified by direct fluorescent antibody test, enzyme immunoassay techniques or culture of the nasopharyngeal aspirate.

The standard treatment for acute bronchiolitis is supportive, and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant (Panitch 2003; Wohl 2003). There is a lack of convincing evidence for any other therapy. As airway edema and mucus plugging are the predominant pathological features in acute bronchiolitis, any therapeutic modality which can reduce these pathological changes and improve the clearance of airway secretions may be expected to be of benefit.

Epinephrine has a theoretical effect on acute bronchiolitis because it has an alpha adrenergic property which leads to vasoconstriction and reduction of airway edema (Wohl 1978). However, one recent Cochrane review showed that nebulized epinephrine for acute bronchiolitis results in a modest short-term improvement in outpatients, but not among inpatients (Hartling 2006). Inhaled recombinant deoxyribonuclease (rhDNase), a mucolytic agent, has also been tested in hospitalized infants with acute bronchiolitis (Nasr 2001). This drug is thought to exert its major effect by enhancing airway secretion clearance. However, no significant effect was observed on clinical severity scores and on the length of hospital stay. Another widely used approach is chest physiotherapy which is thought to assist infants in enhancing the clearance of secretions and reducing ventilatory effort. However, the current evidence concluded that chest physiotherapy, using vibration and percussion techniques, does not reduce the length of hospital stay,

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oxygen requirements or improve the clinical severity score in infants with acute bronchiolitis (Perrotta 2006).

Hypertonic saline solution has been shown to increase mucociliary clearance in normal subjects, in asthma, in bronchiectasis, in cystic fibrosis, and in sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2006). Hypertonic saline has recently been trialed in patients with acute bronchiolitis (Amirav 2005; Mandelberg 2003; Sarrell 2002). The postulated mechanism of benefit is as follows: 1) hypertonic saline 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 (Ziment 1978); 2) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating secretions and improving mucus rheology (Robinson 1997); 3) hypertonic saline stimulates cilial beat via the release of prostaglandin E2 (Assouline 1977). Moreover, hypertonic saline solution also increases water absorption from the mucosa and submucosa. Hypertonic saline solution can also theoretically reduce edema of the airway wall in children with acute bronchiolitis (Mandelberg 2003; Sarrell 2002). These theoretical benefits provide the rationale for the treatment of acute bronchiolitis with nebulized hypertonic saline solution. The hypothesis of this review is that nebulized hypertonic saline solution is beneficial in the management of acute bronchiolitis as assessed by clinically relevant outcomes, both in inpatients and outpatients. The establishment of a therapeutic role for hypertonic saline solution in acute bronchiolitis has relevant clinical implications. This modality may provide a cheap and effective therapy for children with acute bronchiolitis.

OBJECTIVES

To assess the effects of nebulized hypertonic saline solution in children with acute bronchiolitis.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Controlled clinical trials, both random allocation and quasi-random allocation (where there is alternate allocation to treatment and control groups) will be included in this review. Studies which include patients who have had recurrent wheezing or patients who were intubated and ventilated, or studies which assessed pulmonary function alone will be excluded.

Types of participants

Children up to 24 months of age with acute bronchiolitis. Acute bronchiolitis will be defined as the first episode of acute wheezing associated with clinical evidence of a viral infection (cough, coryza, or fever). Confirmation of viral etiology will not be not necessary for study inclusion. Studies of inpatients or outpatients will be included.

Patients with recurrent wheezing will be excluded.

Types of intervention

- Nebulized hypertonic saline plus bronchodilator versus placebo (nebulized 0.9% saline)
- Nebulized hypertonic saline plus bronchodilator versus no intervention
- Nebulized hypertonic saline plus bronchodilator versus placebo plus same bronchodilator

Hypertonic saline will be defined as a concentration of saline greater than or equal to 3%.

Types of outcome measures

Primary outcome measures

- Rate of hospitalization (outpatients) or length of hospital stay (inpatients) or time to be ready for discharge (inpatients)

Secondary outcome measures

- Clinical severity scores
- Rate of re-admission to hospital
- Hemoglobin saturation (oximetry)
- Respiratory rate
- Heart rate
- Time for the resolution of symptoms/signs
- Duration of in-hospital oxygen supplementation
- Results of pulmonary function tests
- Radiological findings
- Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting and acute urinary retention)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* latest issue), MEDLINE (1951 to present), EMBASE (1974 to present) and LILACS.

The following search terms will be combined with the highly sensitive search strategy as recommended by the Cochrane Collaboration (Dickersin 1994) to search MEDLINE. These terms will be adapted to search CENTRAL, EMBASE and LILACS as required.

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(exp Bronchiolitis/ OR bronchiolit* OR exp Respiratory Syncytial Viruses/ OR exp Respiratory Syncytial Virus Infections/ OR respiratory syncytial vir* OR RSV OR exp Parainfluenza Virus 1, Human/ OR exp Parainfluenza Virus 2, Human/ OR exp Parainfluenza Virus 3, Human/ OR exp Respirovirus Infections/ OR exp Adenoviridae Infections/ OR exp Influenza, Human/ OR parainfluenza OR adenovirus* OR influenza OR exp Metapneumovirus OR MPV)
AND
(exp Saline Solution, Hypertonic/ OR hypertonic saline OR exp Sodium Chloride/ OR saline)
AND
(exp "Nebulizers and Vaporizers"/ OR nebulis* OR nebuliz* OR exp Administration, Inhalation/ OR inhal* OR exp Aerosols/ OR aerosol$*)

We will search reference lists of the retrieved articles from electronic searches. We will contact authors of published trials, other experts in the field, pharmaceutical companies and manufacturers for information on unpublished trials. There will be no language, publication year, or publication status restrictions on searching. We will perform a search for existing meta-analyses and non-Cochrane systematic reviews and scan their reference lists for additional trials. There will be no language restrictions.

METHODS OF THE REVIEW

Study selection
Two review authors will independently assess the titles and abstracts of all studies identified by the searches. Articles that do not meet the inclusion criteria will be excluded. The full articles will be obtained when they appear to meet the inclusion criteria or there are insufficient data in the title and abstract to make a clear decision. Details of the studies and the reasons for their exclusion will be noted. Any disagreement between the review authors regarding study inclusion will be resolved by discussion.

Assessment of methodological quality
The methodological quality of all included trials will be assessed independently by two review authors using a 5-point scoring system proposed by Jadad (Jadad 1996). This method evaluates the reported quality of randomization, blinding, and description of withdrawals and dropouts. Inter-rater agreement will be assessed using the kappa statistic, with any disagreement resolved by discussion.
Quality of allocation concealment will also be ranked independently by two review authors using the following Cochrane approach.

- Grade A: adequate concealment.
- Grade B: uncertain.
- Grade C: clearly inadequate concealment.

Data extraction
Study details from the included trials will be extracted by one review author using a standardized data extraction form, and checked by another review author. Any disagreement will be resolved by discussion. Missing information will be sought from trial authors wherever possible. The extracted data will be entered into Review Manager 4.2. We will extract the following data.

- Study characteristics: publication status, year, country of study and setting.
- Methods: method of allocation, blinding of participants and assessment of outcome, exclusion of participants after randomization, proportion of follow up losses and intention-to-treat analysis.
- Participants: sample size, age, sex, and inclusion and exclusion criteria.
- Intervention: concentration of saline, volume of saline, interval of administration, treatment duration and co-interventions.
- Control: placebo or nil.
- Outcomes: primary and secondary outcomes as described previously.

Data analysis
Data analysis will be on an intention-to-treat basis. The Cochrane Collaboration statistical guidelines and plan for assessment of heterogeneity will be followed. Pooling of data will be performed if the data extracted from the included trials are comparable and of sufficient quality. Relative risks (RRs) or odds ratios (ORs) and 95% confidence intervals (CI) will be calculated for all dichotomous data. The number needed to treat (NNT) and the number needed to harm (NNH) will be calculated if possible from the pooled RR or OR, applied to appropriate levels of baseline risk. For continuous data, standardized mean differences (SMDs) and 95% CI will be used for clinical scores in order to standardize across clinical scores. Other outcomes will be analyzed as mean differences (MDs) and 95% CIs. Fixed-effect and random-effects models will be used to combine the data as appropriate.

If there are a sufficient number of included trials, we plan to conduct sensitivity analyses to assess the impact of the following potentially important factors on the overall outcomes.

- Study quality.
- Differences in the concentration of nebulized saline.
- Differences between inpatients and outpatients.
- Analysis using random- and fixed-effect model.
- Analysis by " intention-to-treat" and "treatment received".

We will use funnel plots to examine any indication of publication bias.

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POTENTIAL CONFLICT OF INTEREST

None.

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COVER SHEET

Title	Nebulized hypertonic saline solution for acute bronchiolitis in children
Authors	Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen T
Contribution of author(s)	Linjie Zhang (LZ) conceived the idea and wrote the draft protocol. Raul Mendoza-Sassi (RMS), (Claire Wainwright (CW) and Terry Klassen (TK) provided input for writing the protocol.

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	LZ and RMS will be responsible for study selection, quality assessment, data collection and data analysis. RMS will write the following parts of the review: methods of the review, description of studies and the methodological quality of included studies. LZ, CW and TK will write the remaining parts of the review. The final draft of the review will be approved by all authors.
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