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Overview of Reviews

The Cochrane Library and the Treatment of Bronchiolitis in Children: An Overview of Reviews

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Background: Bronchiolitis describes a viral inflammation of the bronchioles in the lower respiratory tract that is typically caused by infection with respiratory syncytial virus (RSV). Bronchiolitis is characterized by high morbidity and affects approximately one in three infants. Children are currently treated with a variety of therapies that may be ineffective or even harmful; potential therapies include antibiotics, bronchodilators, chest physiotherapy, epinephrine, extrathoracic pressure, glucocorticoids, heliox, hypertonic saline, immunoglobulin, inhaled corticosteroids and oxygen therapy.

Objectives: This updated overview of reviews aims to synthesize evidence from the *Cochrane Database of Systematic Reviews* (CDSR) on the effectiveness and safety of 11 pharmacologic and non-pharmacologic treatments to improve bronchiolitis symptoms in outpatient, inpatient and intensive care populations.

Methods: The CDSR was searched using the term 'bronchiolitis' restricted to the title, abstract or keywords for all systematic reviews examining pharmacologic or non-pharmacologic interventions for the treatment of bronchiolitis in infants and children. Data were extracted, complied into tables, and synthesized using qualitative and quantitative methods.

Main Results: For outpatients with bronchiolitis (defined as the first episode of wheezing in children under two), nebulized epinephrine decreased hospitalization rate on day one by 33% (RR: 0.67; 95% CI: 0.50, 0.89; 4 trials; 920 participants). With the addition of glucocorticoids, there was a reduction of similar magnitude for hospitalization rate within seven days (RR: 0.65; 95% CI: 0.44, 0.95; 1 trial; 400 participants). For inpatients, nebulized epinephrine versus bronchodilator and 3% hypertonic saline versus 0.9% saline each decreased length of stay: epinephrine decreased length of stay by seven hours (MD: −0.28; 95% CI: −0.46, −0.09; 4 trials; 261 participants), and 3% hypertonic saline decreased length of stay by 28 hours (MD: −1.16; 95% CI: −1.55, −0.77; 4 trials; 282 participants).

Outpatients treated with epinephrine or epinephrine and glucocorticoid combined both had significantly lower clinical scores at 60 minutes (SMD: −0.45; 95% CI: −0.66, −0.23; 4 trials; 900 participants, and SMD: −0.34; 95% CI: −0.54, −0.14; 1 trial; 399 participants). For inpatients, epinephrine versus bronchodilator led to a significantly lower clinical score at both 60 minutes (SMD: −0.79; 95% CI: −1.45, −0.13; 4 trials; 248 participants; I^2: 79%) and 120 minutes (SMD: −0.52; 95% CI: −0.86, −0.18; 1 trial; 140 participants). Inpatients treated with chest physiotherapy or 3% hypertonic saline both had significantly lower clinical scores at 1–3 days (SMD: −0.55; 95% CI: −0.98, −0.12; 1 trial; 87 participants, and SMD: −0.84; 95% CI: −1.39, −0.30; 3 trials; 183 participants).

Authors' Conclusions: For outpatients with bronchiolitis, nebulized epinephrine can be effective in avoiding hospitalization. Systemic glucocorticoids such as dexamethasone cannot be recommended as a routine therapy given the current level of evidence and potential for adverse events. For inpatients, regular nebulized hypertonic saline (3%) driven using oxygen may reduce the length of hospital stay. Chest physiotherapy, nebulized epinephrine and systemic and inhaled glucocorticoids cannot be recommended for inpatients given the weak level of evidence. For the sickest of patients in the intensive care unit, intravenous immunoglobulin, helium-oxygen mixtures (heliox) and extrathoracic pressure cannot be recommended due to lack of available evidence and/or methodological flaws of reviews.

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Editors' Note: *Overviews of reviews, compiling evidence from multiple Cochrane reviews into one accessible and usable document, are a regular feature of this journal. Our aim for each overview is to focus on the treatment question, 'which treatment should I*

use for this condition?', and to highlight the Cochrane reviews and their results in doing so. It is our hope that the overview will serve as a 'friendly front end' to the Cochrane Library, allowing the reader a quick overview (and an exhaustive list) of Cochrane reviews relevant to the clinical decision at hand.

Plain Language Summary

Bronchiolitis is a viral infection that causes a bad 'cold' which affects the chest and causes swelling and congestion of the smallest air passages in the lungs. About one in three babies will get bronchiolitis before they are one year of age. Babies that get bronchiolitis breathe fast and appear out of breath, and very small babies can even stop breathing for a few seconds. When babies have trouble breathing, they feed poorly and may need to go to the hospital. Very small babies who are born early usually get sicker than healthy babies. Bronchiolitis is most common in late winter and early spring, around the same time that older children usually get colds. Most babies feel better after two weeks, but for some babies it takes upto one month. If your baby is in the emergency department he or she could receive medication called epinephrine (also called adrenaline) inhaled as a mist through a mask. If this does not work then your baby may be admitted to the hospital where he or she could receive a different medication (hypertonic saline) also given as a mist through a mask. Only those babies who are very ill would be transferred to the hospital's intensive care unit.

Background

Description of the condition

Acute viral bronchiolitis is the most common acute infection of the lower respiratory tract during the first year of life (1–3). Its clinical picture includes rhinorrhoea and low-grade fever, which progress in a few days to cough and respiratory distress, often accompanied by feeding and sleeping disturbances (4,5). Respiratory findings include tachypnoea, chest wall retractions, and wheeze and/or crackles, and apnoea may also occur in neonates and young infants (2,6–9). The hallmark pathological changes are acute inflammation of the bronchiolar airways, with oedema, necrosis and mucous plugging causing airflow obstruction (4). A majority of bronchiolitis infections are caused by respiratory syncytial virus (RSV), usually during seasonal epidemics (10,11). Other causative viral agents include adenovirus, bocavirus, rhinovirus and human metapneumovirus (10,12), with viral co-infections occurring in 6–30% of infants (5,13,14). There is some variability in how physicians define bronchiolitis, mostly due to poor agreement on early childhood wheezing phenotypes and differences in disease definitions worldwide (15).

Bronchiolitis causes considerable morbidity and financial burden. Population-based studies in developed countries show an incidence rate of approximately 33% within the first year of life, but in developing countries the impact of RSV disease (the major causative agent of bronchiolitis) may be greater (5,16). The majority of mild cases are cared for in the community and result in decreased quality of life, loss of parental work time and visits to the emergency department (17,18). Approximately 20% of emergency department visits result in hospital admission, which has risen in North America and Europe in recent years (3,11,19,20). About 3% of hospitalized patients have symptoms severe enough to require admission to the intensive care unit (21,22).

Bronchiolitis severity is directly related to the size and weight of the infant, with clinical determinants of severe course including prematurity, young age and low birth weight (2,23). Other risk factors include chronic lung, heart or neurological disease, as well as immunodeficiency and certain ethnicities (22,24–27). The roles of other pre- and post-natal factors such as genetic markers, socioeconomic factors, environmental exposures and type of viral agent are currently unclear but seem to increase the risk of developing the disease (9,28–32). While bronchiolitis usually resolves within one or two weeks, 20% of patients experience 'postbronchiolitic syndrome', which is characterized by more than four weeks of recurrent wheeze and chronic dry cough (33–35). Research has not yet clarified the link, if any, between bronchiolitis and asthma, but has shown that bronchiolitis is a risk factor for recurrent wheezing in preschool and school-aged children (32,36–38).

Description of the interventions

The current treatment of bronchiolitis is controversial. A large number of interventions are commonly used and there is substantial variation in the management of bronchiolitis throughout the world, which suggests that the ideal treatment has not yet been identified (19,39–43). This overview examines evidence for 11 interventions for the treatment of bronchiolitis in infants, including antibiotics, bronchodilators, chest physiotherapy, epinephrine (adrenaline), extrathoracic pressure, glucocorticoids, heliox, hypertonic saline, immunoglobulin, inhaled corticosteroids and oxygen therapy (44–52). These treatments have been tested in different settings characterized by varying levels of disease severity (i.e. outpatient, inpatient and intensive care settings) with the aim of improving short and long-term outcomes.

How the interventions might work

Similarities between the clinical findings of bronchiolitis and acute asthma led to the wide use of *glucocorticoids* (i.e. *inhaled corticosteroids*), *bronchodilators* and *epinephrine*, as these interventions were thought

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to have equivalent benefits in both asthma and bronchiolitis. *Glucocorticoids* are potent anti-inflammatory agents that target the airway inflammation putatively seen in bronchiolitis and post-bronchiolitic recurrent wheeze (53,54). Inhaled and systemic glucocorticoids have been used in both outpatient and inpatient settings to improve short and long-term outcomes. *Bronchodilators* such as salbutamol (albuterol) and ipratropium bromide act acutely on beta-adrenergic and cholinergic receptors in bronchial smooth muscle to dilate airways, improve airflow and expectoration and reduce bronchospasm (45). *Epinephrine* (adrenaline) may confer an extra advantage by stimulating alpha-adrenergic receptors, which are thought to reduce capillary leakage and mucosal oedema (54).

Other inhaled therapies have addressed different pathological features of bronchiolitis. *Hypertonic saline* was initially used in the treatment of cystic fibrosis and has been tested in bronchiolitis inpatients and outpatients. It has the potential to hydrate airway surface liquid, improve impaired mucociliary clearance, increase water absorption from the mucosa and reduce airway wall oedema (50). *Heliox* is a helium-oxygen gas mixture that is mostly used in acute respiratory disorders in intensive care settings. Helium acts as a low-density 'carrier' gas, resulting in lower resistance to oxygen flow, increased gas exchange and decreased work of breathing (55).

A number of additional therapies have also been tested in the treatment of bronchiolitis. *Antibiotics* might be useful in treating the small subset of infants with secondary bacterial infections or co-infections (44,56), while RSV *immunoglobulin* is a specific therapy mainly used for RSV prophylaxis in high-risk patients (55). Supplemental *oxygen therapy* is essential for hypoxemic respiratory insufficiency, and different modalities (i.e. nasal prongs, nasopharyngeal catheters) have been tested using clinically appropriate variable oxygen saturation thresholds (52). Different types of *chest physiotherapy* aim to enhance clearance of bronchial secretions and relieve airway obstruction (46), and in severe cases, *extrathoracic pressure* is used to improve pulmonary compliance and gas exchange in an attempt to prevent invasive mechanical ventilation (48).

Why it is important to do this overview

Despite the large number of interventions commonly used to treat bronchiolitis, best practice guidelines from 2006–2008 recommend supportive care as the mainstay of bronchiolitis management (9,57,58). However, these guidelines are potentially outdated due to the emergence of new evidence in the past several years. New trials have been conducted, including recently published data from the two largest multicentre trials in this field (59,60). Furthermore, several new systematic reviews have been published (44,47–50,52) and existing reviews have been updated (46,61–63). We aim to present the current body of evidence from the *Cochrane Database of Systematic Reviews* (CDSR) so that clinicians working in outpatient, inpatient and intensive care settings have the most up-to-date evidence on effective treatments for acute childhood bronchiolitis.

Objectives

This is an updated overview of reviews that was first published in 2006 (64). This updated overview aims to synthesize current evidence from the CDSR on the efficacy and safety of pharmacologic and non-pharmacologic treatments to improve bronchiolitis symptoms in outpatient, inpatient and intensive care populations.

Methods

Criteria for considering reviews for inclusion

Reviews were included providing they were published in the CDSR and examined pharmacologic or non-pharmacologic interventions for the treatment of bronchiolitis in children.

Search methods for identification of reviews

The search strategy was similar to the one published in the previous version of this overview (64). Issue 8, 2010, of the CDSR was searched using the term 'bronchiolitis' restricted to the title, abstract or keywords. This resulted in 15 reviews and two protocols. We then consulted with the Cochrane Acute Respiratory Infections Group to ensure that we did not miss any relevant reviews.

Outcome measures

A priori outcomes with pre-specified time points were selected for outpatient, inpatient, and intensive care unit (ICU) populations. When available, data on adverse events was also recorded.

Outpatient outcomes

- Hospitalization rate on day one, within seven days and at any other time points
- Length of stay in emergency department
- Clinical severity score at 60 and 120 minutes

Inpatient outcomes

- Length of stay
- Re-admissions
- Clinical severity score at 60 minutes, 120 minutes, 1–3 days and 3–10 days

ICU outcomes

- Length of stay

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- Need for non-invasive or invasive ventilation
- Length of non-invasive or invasive ventilation

Data collection and analysis

For this overview, one reviewer (MF) extracted the following information from each of the included reviews: inclusion criteria (including population, intervention, comparisons, and outcomes), characteristics of included reviews and numeric results. A second reviewer (LB) extracted methodological quality assessments and independently verified accuracy of numeric results. Review Manager 5 was used for all statistical analyses (65), and random effects modelling was used for all outcome measures in order to provide the most conservative effect estimate.

All dichotomous data was summarized using relative risks (RR) with 95% confidence intervals (CI). RR describes the probability of the event in the treatment group compared to the probability of the event in the control group, and is interpreted as statistically significant if the 95% CI does not cross one. To measure the treatment effect for dichotomous outcomes that reached statistical significance, 'number needed to treat for additional benefit' (NNTB) was calculated. For all comparisons, including those based on a single trial, NNTB was calculated from the trials' baseline risk (the risk of the event occurring for those not receiving treatment) (66).

Continuous data was summarized using either standardized mean differences (SMD) or mean differences (MD), both with 95% CIs. SMD was used to calculate clinical severity scores because a variety of clinical scales were used across studies, and expressing the effects as standardized values allowed results from the different scales to be combined. MD was calculated for all other outcomes because the same scale (i.e. days) was used to measure these outcomes. Effect sizes expressed using standardized mean differences were described as small (<0.40), moderate (0.40–0.70) or large (>0.70) based on decision rules outlined in the Cochrane Handbook (66). SMD and MD results were interpreted as statistically significant if the 95% CI did not cross zero.

For all pooled effect estimates, the accompanying I^2 values were reported and represent the degree of statistical heterogeneity between the trials. An I^2 value close to 0% indicates minimal or no heterogeneity of trials, whereas an I^2 of 50% or greater represents substantial heterogeneity (66). I^2 values of 50% or greater were included in the results text along with the effect sizes.

Results of all outcomes have been assessed for strength of evidence using the GRADE methodology (Grading of Recommendations Assessment, Development, and Evaluation), which examines the following four domains: risk of bias, directness, consistency and precision (67,68). For consistency and precision, we defined two a priori thresholds of clinical relevance based on expert opinion and GRADE guidelines: RR reduction of more than 25% for hospital admissions, and reduction in length of stay of more than 0.5 days (69). Overall strength of evidence was graded as high, moderate, low or insufficient based on the likelihood of further research changing our confidence in the estimate of effect, and evidence was only considered insufficient when it was unavailable or did not permit estimation of an effect size. Two reviewers (LB, RF) independently graded each outcome, and disagreements were resolved through consensus. GRADE assessments for all outcomes are presented in the results tables.

Results

Description of included reviews

Out of 15 potential reviews and two protocols, one review on ribavirin (70) and another on surfactant therapy (71) had been withdrawn from the *Cochrane Library* for being out of date and therefore could not be used in this overview. One review on vitamin A (72) was excluded as it examined bronchiolitis prevention instead of treatment, and one review on anticholinergic drugs (73) was excluded as it examined childhood wheeze and excluded children with bronchiolitis. Also, two protocols on nebulized deoxyribonuclease (74) and steam or humidified oxygen inhalation (75) were excluded as they were not yet published in full form. Therefore, 11 reviews (containing 8,556 participants) were included in this overview (44–52,76,77). Each review examined a different intervention: antibiotics (AB), bronchodilators (Broncho), chest physiotherapy (Physio), epinephrine (Epi), extrathoracic pressure (ETP), glucocorticoids (Gluco), heliox (Heliox), hypertonic saline (HTS), immunoglobulin (IG), inhaled corticosteroids (ICS) and oxygen therapy (O2). Table 1 presents the study characteristics of the included reviews.

All included reviews were published between 2008–2010 and were last assessed as up-to-date between 2006–2010. Based on contact with review authors, we found that four of the 11 reviews were in the process of being updated (Broncho, Epi, Gluco, HTS). These four manuscripts (61–63,78) were obtained from the review authors and were used in place of the original reviews in order to incorporate the most recent data into this overview.

Trials

The number of trials included in each review ranged from one (AB, ETP) to 22 (Broncho). Two reviews included one trial each (AB, ETP), six reviews included three to five trials (Heliox, HTS, ICS, IG, O2, Physio), and three reviews included 17 or more trials (Broncho, Epi, Gluco). The number of participants in each review ranged from 33 (ETP) to 2,596 (Gluco).

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Table I. Characteristics of included reviews

Review title Authors Last assessed as up-to-date	Number of studies Sample size (range)	Population	Definition of bronchiolitis	Intervention	Comparison	Outcomes for which data are reported
Antibiotics for bronchiolitis in children Spurling GKP, Fonseka K, Doust J, Del Mar C November 2006	1 52	Inpatient Children <2 years	Bronchiolitis: respiratory distress preceded by coryzal symptoms with or without fever	Antibiotics (oral, intravenous, intramuscular or inhaled)	Placebo control	Primary: pulmonary markers, respiratory distress, wheeze, crepitations and fever Secondary: hospital admissions, adverse events and radiological findings
Bronchodilators for bronchiolitis (in press) Gadomski AM, Bhasale AL March 2010	29 1912 (16–186)	Inpatient, outpatient and ICU Children <2 years	Bronchiolitis: acute LRTI with wheezing	Bronchodilator therapy (nebulized, oral or subcutaneous)	Placebo control	Primary: oxygen saturation Secondary: clinical score, admission to hospital, duration of hospital stay and time to resolution of illness
Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old Perrotta C, Ortiz Z, Roqué i Figuls M October 2006	3 172 (32–90)	Inpatient Children <2 years	Acute bronchiolitis	Any type of chest physiotherapy (postural drainage, chest percussion, vibration, chest shaking, directed coughing or forced exhalation)	Standard care (excluding chest physiotherapy) or other drainage or breathing techniques	Primary: change in the severity status of bronchiolitis Secondary: duration of oxygen supplementation and length of hospital stay
Epinephrine for bronchiolitis (in press) Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, Patel H, Klassen TP, Fernandes RM November 2009	17 2010 (27–800)	Inpatient and outpatient Children <2 years	Bronchiolitis: first episode of wheezing (with or without cough, tachypnea and increased respiratory effort) associated with clinical evidence of viral infection	Epinephrine	Placebo or any other bronchodilator	Primary: length of stay (inpatient) and rate of admission (outpatient) Secondary: change in clinical score, oxygen saturation, respiratory rate, heart rate and adverse events

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Table I. (*Continued*)

Review title Authors Last assessed as up-to-date	Number of studies Sample size (range)	Population	Definition of bronchiolitis	Intervention	Comparison	Outcomes for which data are reported
Continuous negative extrathoracic pressure or continuous positive airway pressure for acute hypoxemic respiratory failure in children Shah PS, Ohlsson A, Shah JP October 2007	1 33	ICU Children between 1 month and 18 years	AHRF: alveolar arterial oxygenation gradient >100 and arterial oxygen tension in presence of respiratory symptoms (or PaO2 <10 kPa with FiO2 more than 0.5, with bilateral diffuse infiltrates on chest x-ray in the absence of cardiogenic causes)	CNEP with or without assisted PPV or Ni-CPAP without assisted PPV	Standard care (including PPV with endotracheal intubation)	Improvement in oxygenation, failure (death or use of any additional form of assisted ventilation) and duration of oxygen therapy
Glucocorticoids for acute viral bronchiolitis in infants and young children (in press) Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, Johnson DW, Klassen TP, Hartling L November 2009	17 2596 (32–800)	Inpatient and outpatient Children ≤2 years	Acute viral bronchiolitis: a first episode of acute wheezing, respiratory distress, and clinical evidence of a viral infection (cough, coryza, or fever). Children with a history of wheezing or respiratory distress, or with a formal diagnosis of asthma, were excluded	Short-term systemic or inhaled glucocorticoids with or without co-interventions	Placebo or any other intervention	Primary: length of stay (inpatient) and rate of admission by days one and seven (outpatient) Secondary: clinical severity scores, oxygen saturation, respiratory rate, heart rate, hospital re-admissions (inpatient), return healthcare visits, length of stay (outpatient) and short and long-term adverse events
Heliox inhalation therapy for bronchiolitis in infants Liet J-M, Ducruet T, Vineet G, Cambonie G June 2009	5 97 (12–39)	ICU Children <2 years	Acute bronchiolitis: signs of respiratory distress secondary to RSV infection and/or patients with respiratory distress and symptoms that occur within RSV epidemic periods and are not due to other medical conditions	Inhaled heliox	Placebo control (oxygen or air)	Primary: in-hospital mortality, need for mechanical ventilation, rate of endotracheal intubation, length of ICU stay and adverse events Secondary: gas exchange and clinical respiratory scores within first hour after starting heliox treatment

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Table I. (*Continued*)

Review title Authors Last assessed as up-to-date	Number of studies Sample size (range)	Population	Definition of bronchiolitis	Intervention	Comparison	Outcomes for which data are reported
Nebulized hypertonic saline solution for acute bronchiolitis in infants (in press) Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP June 2010	7 581 (44–186)	Inpatient and outpatient Children <2 years	Acute bronchiolitis: first episode of acute wheezing associated with clinical evidence of a viral infection (cough, coryza or fever). Children with recurrent wheezing were excluded	Nebulized hypertonic saline solution alone or with bronchodilator	No intervention, nebulized 0.9% saline or nebulized 0.9% saline plus bronchodilator	Primary: length of hospital stay and rate of hospitalization (outpatient) Secondary: clinical severity scores
Immunoglobulin treatment for respiratory syncytial virus infection Fuller HL, Del Mar C January 2006	4 311 (35–107)	ICU Children <3 years	Laboratory documented RSV infection: bronchiolitis, pneumonia or other LRTI	Immunoglobulin	Placebo control	Primary: length of hospitalization and need for mechanical ventilation Secondary: adverse effects
Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing Blom DJM, Marieke E, Bont L, van Woensel JBM, Van Aalderen WMC October 2006	5 374 (40–161)	Inpatient Children <2 years	Acute bronchiolitis: the first period of cough, tachypnoea, chest recessions, hyperinflation, and crepitations with or without wheezing. Children with a history of wheezing were excluded	Inhaled corticosteroids	Placebo control	Primary: incidence of physician-diagnosed wheezing episodes Secondary: hospital re-admissions for bronchial obstructions and use of bronchodilator during follow up

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Table I. (*Continued*)

Review title Authors Last assessed as up-to-date	Number of studies Sample size (range)	Population	Definition of bronchiolitis	Intervention	Comparison	Outcomes for which data are reported
Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age Rojas-Reyes MX, Rugeles CG, Charry-Anzola LP March 2008	4 418 (80–121)	Inpatient Children between 3 months and 15 years	Severe LRTI: cough with or without fever, signs of respiratory distress, pneumonia, or bronchiolitis (first wheezing episode in children <3 years, with or without radiological diagnosis of pneumonia/bronchiolitis, with or without low blood oxygen saturation). Children with other respiratory disorders or underlying diseases were excluded	Oxygen administration using a facemask, head box or hood, nasopharyngeal catheter, nasal catheter, nasal prongs or nasal cannula, or nasal CPAP	No oxygen therapy or oxygen administration using a facemask, head box or hood, nasopharyngeal catheter, nasal catheter, nasal prongs or nasal cannula, or nasal CPAP	Primary: clinical failure, improvement of respiratory signs during first 24h and/or improvement in oxygen saturation, ability to relieve hypoxaemia and frequency of complications Secondary: adverse events

AHRF: acute hypoxemic respiratory failure; CNEP: continuous negative extrathoracic pressure ventilation; ICU: intensive care unit; LRTI: lower respiratory tract infection; Ni-CPAP: non-invasive continuous positive airway pressure ventilation; PICU: pediatric intensive care unit; PPV: positive pressure ventilation; RSV: respiratory syncytial virus.

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Participants

Age ranges and clinical definitions of bronchiolitis varied slightly between reviews. Eight reviews (AB, Broncho, Epi, Gluco, Heliox, HTS, ICS, Physio) included children less than two years old with 'bronchiolitis' or 'acute bronchiolitis' and one review (IG) included children less than three years old with a laboratory documented RSV infection (i.e. bronchiolitis, pneumonia or other lower respiratory tract infection). The last two reviews included a wider range of ages and illnesses: children aged one month to 18 years with acute hypoxemic respiratory failure (ETP) and children aged three months to 15 years with lower respiratory tract infections (O2). Four reviews restricted inclusion criteria to children experiencing their first episode of wheezing (Epi, Gluco, HTS, ICS).

Of the 11 included reviews, three included both outpatients and inpatients (Epi, Gluco, HTS), four looked at inpatients only (AB, ICS, O2, Physio), three looked at ICU patients only (ETP, Heliox, IG) and one included outpatients, inpatients and ICU patients (Broncho). In total, the four outpatient reviews consisted of 32 trials, the eight inpatient reviews consisted of 49 trials and the four ICU reviews consisted of 11 trials. The majority of participants for outpatient trials were enrolled from emergency departments, with some recruitment from ambulatory clinics.

Interventions

Seven reviews compared an active treatment to placebo (AB, Broncho, Epi, Gluco, Heliox, ICS, IG), two reviews compared an active treatment to standard care (ETP, Physio) and five reviews compared an active treatment to another active treatment (Epi, Gluco, HTS, O2, Physio). Some reviews included more than one type of comparison (Epi, Gluco, Physio).

Outcome measures

Ten reviews specified primary outcomes (AB, Broncho, Epi, Gluco, Heliox, HTS, ICS, IG, O2, Physio), with the most frequently reported primary outcomes being outpatient rate of admission (Epi, Gluco, HTS) and inpatient length of stay (Epi, Gluco, Heliox, HTS, IG). Other common primary outcomes were adverse events (Broncho, O2), oxygen saturation (Broncho, O2), need for mechanical ventilation (Heliox, IG), pulmonary markers (AB, O2) and wheeze (AB, ICS). Timing of measurements for all primary outcomes varied across reviews.

Search methods

All 11 reviews searched the CENTRAL, EMBASE and MEDLINE databases, and all but one review (HTS) hand-searched reference lists. Eight reviews contacted experts and/or authors (AB, Broncho, Epi, ETP, Gluco, Heliox, ICS, IG), six reviews searched the LILACS database (Epi, Gluco, Heliox, HTS, O2, Physio) and five reviews searched for published abstracts (AB, Broncho, ETP, ICS, Physio).

Data analysis

Eight reviews conducted at least one meta-analysis. Two of the remaining reviews (AB, ETP) could not meta-analyze results as there was only one included trial in each review. The final review (Physio) did not contain a meta-analysis, but based on outcomes listed in the review it appeared there was data within the three included trials that would contribute to two a priori outcomes (length of stay and clinical score). The overview authors thus extracted the relevant data from the trials, and for two of the trials standard deviations were not reported and had to be imputed from ranges (79).

Methodological quality of included reviews

Various instruments were used to evaluate the methodological quality of studies within each review, with four reviews using more than one type of instrument (Epi, Gluco, ICS, IG). Two reviews (ICS, IG) used the five-point Jadad scale to assess trial quality based on randomization technique, double-blinding procedure and documentation of losses to follow-up and withdrawals (80). The average Jadad scores for trials included in the two reviews were 3.6 and 4, respectively.

Five of the reviews (ETP, ICS, IG, O2, Physio) assessed the quality of allocation concealment to treatment groups (81). Altogether, these five reviews assessed allocation concealment as adequate in 29% of trials and unclear in 71%.

Another five reviews (Broncho, Epi, Gluco, Heliox, HTS) used the Cochrane Risk of Bias tool to assess trial quality based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias (i.e. study design or stopping early) (66). Based on the Risk of Bias criteria, 42% of trials in the five reviews were assessed as low risk of bias, 24% as unclear and 34% as high risk of bias.

One review (AB) assessed methodological quality using a published method based on an 11-point scale consisting of blinding, treatment assignment, control of selection bias and outcome assessment (82). The single study included in this review was assigned six of 11 points and was judged to be of high quality.

Lastly, two of the reviews (Epi, Gluco) used GRADE methodology to assess the strength of evidence for the trials' primary outcomes (67,68). All GRADE assessments for all included reviews can be found in Tables 2, 3 and 4.

Effect of interventions

Outpatients

Table 2 presents outpatient data for hospitalization rate, length of stay and clinical severity score.

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Table II. Outpatient outcomes

Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2	Quality of evidence (GRADE)
Hospitalization rate on day 1	Glucocorticoid *vs* placebo	1730 (8)	RR: 0.92 (0.78, 1.08)	0%	High
	Epinephrine *vs* placebo	**920 (4)**	**RR: 0.67 (0.50, 0.89)[a]**	**0%**	**Moderate**
	Epinephrine and glucocorticoid *vs* placebo	401 (1)	RR: 0.64 (0.40, 1.04)	—	Low
	Epinephrine *vs* bronchodilator	295 (6)	RR: 0.65 (0.38, 1.13)	48%	Moderate
	Glucocorticoid *vs* epinephrine	444 (2)	RR: 1.12 (0.66, 1.88)	2%	Moderate
Hospitalization rate within 7 days	Glucocorticoid *vs* placebo	1498 (5)	RR: 0.86 (0.70, 1.06)	31%	Moderate
	Epinephrine *vs* placebo	800 (1)	RR: 0.78 (0.59, 1.05)	21%	Low
	Epinephrine and glucocorticoid *vs* placebo	**400 (1)**	**RR: 0.65 (0.44, 0.95)[b]**	—	**Low**
	Epinephrine *vs* bronchodilator	63 (1)	RR: 1.03 (0.66, 1.60)	—	Low
	Glucocorticoid *vs* epinephrine	399 (1)	RR: 1.08 (0.77, 1.52)	—	Moderate
Hospitalization rate: unspecified	Bronchodilator *vs* placebo	650 (10)	RR: 0.87 (0.63, 1.19)	0%	Moderate
	3% hypertonic saline *vs* 0.9% saline	262 (3)	RR: 0.63 (0.34, 1.17)	0%	Low
Length of stay for those hospitalised	Glucocorticoid *vs* placebo	225 (3)	MD: 0.10 (−0.81, 1.01)	13%	Moderate
	Epinephrine *vs* bronchodilator	42 (1)	MD: 0.46 (−0.27, 1.20)	—	Low
Clinical score at 60 minutes	Glucocorticoid *vs* placebo	1006 (4)	SMD: −0.04 (−0.16, 0.09)	0%	High
	Epinephrine *vs* placebo	**900 (4)**	**SMD: −0.45 (−0.66, −0.23)[a]**	**40%**	**High**
	Epinephrine and glucocorticoid *vs* placebo	**399 (1)**	**SMD: −0.34 (−0.54, −0.14)[b]**	—	**Moderate**
	Epinephrine *vs* bronchodilator	248 (6)	SMD: −0.11 (−0.36, 0.14)	0%	Moderate
	Glucocorticoid and bronchodilator *vs* placebo	30 (1)	SMD: −0.30 (−1.02, 0.42)	—	Low
	Glucocorticoid *vs* epinephrine	**442 (2)**	**SMD: 0.31 (0.12, 0.50)[a]**	**0%**	**High**
Clinical score at 120 minutes	Glucocorticoid *vs* placebo	214 (3)	SMD: −0.17 (−0.55, 0.21)	43%	Moderate
	Glucocorticoid and bronchodilator *vs* placebo	30 (1)	SMD: −0.22 (−0.94, 0.50)	—	Low
	Epinephrine *vs* placebo	**30 (1)**	**SMD: −0.83 (−1.58, −0.08)[a]**	—	**Low**
	Epinephrine *vs* bronchodilator	207 (4)	SMD: −0.09 (−0.37, 0.18)	0%	Moderate
	Glucocorticoid *vs* epinephrine	45 (1)	SMD: 0.35 (−0.27, 0.98)	—	High

[a] Significantly favours epinephrine; [b] Significantly favours epinephrine and glucocorticoid.

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MD: mean difference; RR: risk ratio; SMD: standardized mean difference.

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Data was available for eight outpatient comparisons, and relevant results for each outcome are presented below.

Hospitalization rate: Results were significant for hospitalization rates on day one and within seven days. Compared with placebo, treatment with nebulized epinephrine significantly decreased hospitalization rate on day one by 33% (RR: 0.67; 95% CI: 0.50, 0.89; 4 trials; 920 participants) and treatment with epinephrine and glucocorticoid combined significantly decreased hospitalization rate within seven days by 35% (RR: 0.65; 95% CI: 0.44, 0.95; 1 trial; 400 participants). The number needed to treat to prevent one additional hospital admission was 16 on day one and 11 by day seven.

Length of stay: Only two comparisons measured outpatient length of stay in the emergency department, and neither was significant.

Clinical severity score: For outpatients with bronchiolitis, clinical score was measured at 60 minutes and 120 minutes. Compared to placebo, both epinephrine and epinephrine and glucocorticoid combined led to statistically significant small or moderate decreases in clinical severity scores at 60 minutes (SMD: −0.45; 95% CI: −0.66, −0.23; 4 trials; 900 participants, and SMD: −0.34; 95% CI: −0.54, −0.14; 1 trial; 399 participants). At 120 minutes, epinephrine versus placebo led to a large, significant decrease in clinical severity (SMD: −0.83; 95% CI: −1.58, −0.08; 1 trial; 30 participants).

Inpatients

Table 3 presents inpatient data for length of stay, re-admissions and clinical severity scores. Data was available for seven inpatient comparisons, and all relevant outcomes are described below.

Length of stay: Nebulized epinephrine significantly decreased inpatient length of stay by almost seven hours when compared to bronchodilator (MD: −0.28 days; 95% CI: −0.46, −0.09; 4 trials; 261 participants), but not when compared to placebo. Also, 3% hypertonic saline versus 0.9% saline significantly decreased length of stay by more than one full day (MD: −1.16 days; 95% CI: −1.55, −0.77; 4 trials; 282 participants).

Re-admissions: Three treatments were compared to placebo, and none were found to decrease hospital re-admissions during follow-up periods ranging from two days to one year.

Clinical severity score: Clinical score was measured at 60 minutes, 120 minutes, 1–3 days and 3–10 days. Treatment with epinephrine versus bronchodilator led to a statistically significant, moderate reduction in clinical severity at both 60 minutes (SMD: −0.79; 95% CI: −1.45, −0.13; 4 trials; 248 participants) and 120 minutes (SMD: −0.52; 95% CI: −0.86, −0.18; 1 trial; 140 participants). No data was provided beyond these time-points, and comparisons with placebo were not significant. Note that there is evidence of significant ($p = 0.0002$) and substantial ($I^2 = 79\%$) high heterogeneity for clinical score at 60 minutes.

Clinical severity score at 1–3 days showed a significant, moderate decrease when children were treated with chest physiotherapy versus standard care (SMD: −0.55; 95% CI: −0.98, −0.12; 1 trial; 87 participants), but this difference was not significant at 3–10 days. 3% hypertonic saline versus 0.9% saline also led to a large, significant decrease in clinical severity at 1–3 days but not 3–10 days (SMD: −0.84; 95% CI: −1.39, −0.30; 3 trials; 183 participants).

ICU patients

Table 4 presents ICU data for length of stay and need for invasive or non-invasive ventilation. Data was available for three interventions, and relevant outcomes are presented below.

Length of stay: A comparison of immunoglobulin versus placebo found that immunoglobulin treatment significantly decreased the number of days spent in the ICU by almost one day (MD: −0.85 days; 95% CI: −1.56, −0.14; 2 trials; 163 participants). The only other comparison (heliox versus air or oxygen inhalation) was not significant.

Need for ventilation: Neither heliox nor extrathoracic pressure significantly decreased the need for invasive and/or non-invasive ventilation in ICU patients.

Adverse events

Table 5 presents all available adverse events data divided by outpatients, inpatients and ICU patients. Adverse events data was reported in six reviews examining bronchodilators, epinephrine, glucocorticoids, immunoglobulin, inhaled corticosteroids and oxygen therapy. For outpatients, no general or intervention-specific adverse events were significantly different between groups. For inpatients, only one adverse event was significant: when comparing oxygen delivery methods, use of nasal prongs versus nasopharyngeal catheters decreased nasal obstruction due to severe mucous production by 81% (RR: 0.19; 95% CI: 0.09, 0.43; 3 trials; 338 participants). Lastly, for ICU patients, likelihood of experiencing a drug-associated adverse event was almost two times higher when receiving immunoglobulin versus placebo (RR: 1.96; 95% CI: 1.06, 3.64; 1 trial; 33 participants).

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Table III. Inpatient outcomes

Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2	Quality of evidence (GRADE)
Length of stay	Glucocorticoid *vs* placebo	633 (8)	MD: −0.18 (−0.39, 0.04)	16%	High
	Bronchodilator *vs* placebo	349 (6)	MD: 0.06 (−0.27, 0.39)	0%	Moderate
	Epinephrine *vs* placebo	292 (2)	MD: −0.35 (−0.87, 0.17)	0%	Moderate
	Epinephrine *vs* bronchodilator	**261 (4)**	**MD: −0.28 (−0.46, −0.09)[a]**	**0%**	**Moderate**
	3% hypertonic saline *vs* 0.9% saline	**282 (4)**	**MD: −1.16 (−1.55, −0.77)[b]**	**0%**	**Moderate**
	Chest physiotherapy *vs* standard care or other drainage/breathing technique	172 (3)	MD: 0.07 (−0.58, 0.73)	0%	Low
Re-admissions between 2 days and 4 months	Glucocorticoid *vs* placebo	359 (3)	RR: 1.04 (0.12, 8.72)	66%	Low
	Inhaled corticosteroid *vs* placebo	309 (4)	RR: 1.15 (0.60, 2.22)	45%	Moderate
	Epinephrine *vs* placebo	192 (2)	RR: 0.29 (0.05, 1.86)	0%	Low
Re-admissions between 3 months and 1 year	Inhaled corticosteroid *vs* placebo	358 (5)	RR: 1.05 (0.63, 1.75)	29%	Moderate
Clinical score at 60 minutes	**Epinephrine *vs* bronchodilator**	**248 (4)**	**SMD: −0.79 (−1.45, −0.13)[a]**	**79%**	**Low**
	Epinephrine *vs* placebo	232 (2)	SMD: −0.04 (−0.49, 0.40)	46%	Moderate
Clinical score at 120 minutes	**Epinephrine *vs* bronchodilator**	**140 (1)**	**SMD: −0.52 (−0.86, −0.18)[a]**	—	**Low**
Clinical score at 1–3 days	Glucocorticoid *vs* placebo	113 (4)	SMD: −0.74 (−1.48, 0.01)	70%	Low
	3% hypertonic saline *vs* 0.9% saline	**183 (3)**	**SMD: −0.84 (−1.39, −0.30)[b]**	**66%**	**Low**
	Chest physiotherapy *vs* standard care or other drainage/breathing technique	**87 (1)**	**SMD: −0.55 (−0.98, −0.12)[c]**	—	**Low**
Clinical score at 3–10 days	Chest physiotherapy *vs* standard care or other drainage/breathing technique	91 (2)	SMD: −0.14 (−0.81, 0.53)	59%	Low
	3% hypertonic saline *vs* 0.9% saline	156 (3)	SMD: −1.08 (−2.47, 0.31)	93%	Moderate

[a] Significantly favours epinephrine; [b] Significantly favours 3% hypertonic saline; [c] Significantly favours chest physiotherapy.
CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MD: mean difference; RR: risk ratio; SMD: standardized mean difference.

Table IV. ICU outcomes

Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2	Quality of evidence (GRADE)
Length of ICU stay	**Immunoglobulin *vs* placebo**	**163 (2)**	**MD: −0.85 (−1.56, −0.14)[a]**	**11%**	**Low**
	Heliox inhalation *vs* air or oxygen inhalation	58 (2)	MD: −0.15 (−0.92, 0.61)	0%	Low
Need for non-invasive or invasive ventilation	Immunoglobulin *vs* placebo	163 (2)	RR: 0.76 (0.42, 1.37)	0%	Low
	Heliox inhalation *vs* air or oxygen inhalation	58 (2)	RR: 1.11 (0.36, 3.40)	0%	Low
	Continuous negative extrathoracic pressure *vs* standard care	33 (1)	RR: 0.40 (0.02, 9.06)	—	Low

[a] Significantly favours immunoglobulin.
CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; ICU: intensive care unit; MD: mean difference; RR: risk ratio.

Table V. Adverse events for outpatient, inpatient and ICU populations

Population	Comparison	Adverse event	Number of subjects (studies)	Measure of effect (95% CI)	I^2
Outpatient	Glucocorticoid *vs* placebo	Vomiting	1469 (3)	RR: 1.07 (0.60, 1.91)	0%
		Hypertension	1400 (2)	RR: 1.00 (0.06, 15.93)	N/A*
		Bleeding	1001 (2)	RR: 0.97 (0.59, 1.58)	N/A*
		Pallor/flushing	869 (2)	RR: 1.00 (0.65, 1.53)	N/A*
		Tremor	869 (2)	RR: 1.50 (0.54, 4.18)	N/A*
		Pneumonia	600 (1)	RR: 0.48 (0.04, 5.30)	—
	Epinephrine and glucocorticoid *vs* placebo	Vomiting	401 (1)	RR: 0.67 (0.11, 3.97)	—
		Bleeding	401 (1)	RR: 1.07 (0.56, 2.05)	—
		Tremor	401 (1)	RR: 2.01 (0.37, 10.85)	—
		Pallor/flushing	401 (1)	RR: 1.44 (0.79, 2.65)	—
	Glucocorticoid *vs* epinephrine	Pallor/flushing	399 (1)	RR: 0.68 (0.36, 1.27)	—
		Vomiting	399 (1)	RR: 1.24 (0.34, 4.56)	—
		Bleeding	399 (1)	RR: 0.85 (0.40, 1,80)	—
		Tremor	399 (1)	RR: 1.24 (0.34, 4.56)	—
		Hypertension	399 (1)	RR: 0.99 (0.06, 15.80)	—
	Bronchodilator *vs* placebo	Flushing	76 (2)	RR: 5.41 (0.65, 44.77)	0%
		Tachycardia and prolonged cough	66 (1)	RR: 4.71 (0.23, 94.58)	—
		Hyperactivity	39 (1)	RR: 6.05 (0.33, 109.75)	—
Inpatient	Oxygen therapy (nose prongs) *vs* oxygen therapy (nasopharyngeal catheter)	**Nasal obstruction due to severe mucous production**	**338 (3)**	**RR: 0.19 (0.09, 0.43)[a]**	**0%**
		Apnoea	338 (3)	RR: 0.64 (0.35, 1.15)	0%
		Nose ulceration or bleeding	338 (3)	RR: 0.40 (0.16, 1.01)	0%
		Fighting/discomfort in first 24 hours	239 (2)	RR: 0.73 (0.32, 1.63)	28%
		Abdominal distension	238 (2)	RR: 0.30 (0.01, 7.26)	N/A*
	Bronchodilator *vs* placebo	Tremor	71 (2)	RR: 2.06 (0.23, 18.54)	0%
		Tachycardia and prolonged cough	66 (1)	RR: 4.71 (0.23, 94.58)	—
	Glucocorticoid *vs* placebo	Pneumonia	251 (2)	RR: 0.42 (0.06, 3.10)	0%
		Bleeding	179 (1)	RR: 1.98 (0.18, 21.42)	—
	Inhaled corticosteroid *vs* placebo	Oral candidiasis	48 (1)	RR: 5.00 (0.25, 98.96)	—
ICU	Immunoglobulin *vs* placebo	**Overall adverse events**	**33 (1)**	**RR: 1.96 (1.06, 3.64)[b]**	—

[a] Significantly favours oxygen therapy (nose prongs); [b] Significantly favours placebo; * I^2 not estimable.
CI: confidence interval; ICU: intensive care unit; N/A: not applicable; RR: risk ratio.

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Discussion

This overview presents the most current Cochrane evidence regarding the efficacy and safety of interventions for acute viral bronchiolitis in different treatment settings. Treatment of bronchiolitis is a controversial topic in pediatrics, and current best practice guidelines recommend supportive measures as the mainstay of management (9,57,58). In both ambulatory and hospital settings, this includes adequate oxygenation combined with attention to nasal obstruction, fluid intake and nutrition. However, there are many additional therapies that clinicians try in an effort to reduce the tremendous number of hospital admissions, and this may explain the wide variation in bronchiolitis treatment, despite the absence of clear evidence for many therapeutic approaches. Recent evidence presented in this overview provides some clarity as to the current most effective interventions for outpatients, inpatients, and ICU patients. This evidence must be weighed against possible harms, and its interpretation must be viewed in light of the methodological limitations of research within the field.

Summary of main results

Outpatients

There is moderate quality evidence that inhaled epinephrine substantially improves short-term outcomes for outpatients presenting with bronchiolitis, when bronchiolitis is defined as the first episode of wheezing in children under two years of age. Epinephrine substantially reduces hospital admissions within the first day of treatment, and these findings are supported by positive results from other clinical outcomes, especially an improvement in clinical score within the first one and two hours of treatment. Most direct comparisons between epinephrine and other active interventions (bronchodilators and glucocorticoids) were not significant, and compared to placebo, neither bronchodilators nor glucocorticoids improved short-term outcomes. In this overview, we did not include outpatient measures of clinical severity at 24, 48 or 72 hours, as these time-points are often too delayed to be clinically relevant in an outpatient setting. However, it is worth noting that for outpatients with bronchiolitis, 3% hypertonic saline leads to large, statistically significant reductions in clinical severity at all three of the indicated time-points (78).

Results suggest that combining inhaled epinephrine with the systemic glucocorticoid dexamethasone (as opposed to stand-alone therapy with either drug alone) may be effective in improving the longer-term outcome of outpatient admissions within seven days. However, this finding should be interpreted with caution as this conclusion was based on a small number of events from a single trial, therefore resulting in low strength of evidence.

These positive results should be balanced against data on harms. There are safety concerns when considering the widespread use of epinephrine, and especially glucocorticoids, in young children with viral wheezing. High-dose glucocorticoids (i.e. dexamethasone), such as the dosages used in the glucocorticoid and epinephrine reviews (0.6–1.0 mg/kg), are potentially dangerous, and the effects of glucocorticoids and/or epinephrine on children with comorbid illnesses are currently unknown (83,84). The results from the randomized control trials (RCTs) included in this overview do not suggest any serious short-term adverse effects of epinephrine administered either with or without glucocorticoids, and data from RCTs and observational studies on a related illness – croup – also suggest a favorable short-term safety profile for both epinephrine and dexamethasone (85,86). However, it should be noted that no studies had long-term follow-ups assessing the harms of glucocorticoids, and many of the studies would have been unable to detect important differences in adverse events due to limited power. Furthermore, RCTs do not adequately address all drug safety concerns (87).

In summary, epinephrine is the most effective treatment for outpatients presenting with bronchiolitis, and appears to be superior to both bronchodilators and glucocorticoids. The benefits and risks of adding glucocorticoids to epinephrine for longer-term benefits needs to be further clarified, along with whether results from combination therapies are generalizable to lower doses of glucocorticoids and glucocorticoids other than dexamethasone. The above findings likely apply to outpatients presenting to the emergency department with moderate to severe bronchiolitis.

Inpatients

Hypertonic saline was the only inpatient treatment that resulted in a clinically meaningful reduction in length of stay, supported by improvements in the clinical severity score at one to three days (moderate strength of evidence). Adverse events were rare in trials of hypertonic saline, which is consistent with the favorable safety profile shown in infants with cystic fibrosis (88).

While chest physiotherapy also improved clinical severity score at one to three days, evidence was weak and the magnitude of improvement small. No other interventions for short-term outcomes were found to be superior to placebo, including epinephrine, glucocorticoids and bronchodilators. Therefore, the direct comparisons showing the superiority of epinephrine to other bronchodilators are of questionable relevance. For long-term outcomes, inhaled corticosteroids did not show any significant reduction in post-bronchiolitis symptoms and related re-admissions within the first year after the acute episode.

The differences in the effectiveness of epinephrine with or without glucocorticoids for outpatient and inpatient populations may be due to many factors. For example, inpatients might have been non-responsive

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to initial, short-term outpatient interventions in the emergency department (i.e. inhaled therapies) due to increased illness severity and duration of symptoms, thus making them less likely to respond to the same therapies in an inpatient setting.

ICU patients

Only immunoglobulin was found to improve ICU patient outcomes by reducing length of stay; however, evidence was hampered by the limited number of studies and methodological limitations of the systematic review. No other interventions, including heliox therapy and extrathoracic pressure, improved length of stay or need for ventilation. Although treatment with surfactant was not included there is previous evidence indicating its usefulness in this overview in ICU settings (64,71).

Limitations

The limitations of this overview are partially due to the difficulties inherent to the field of bronchiolitis research. There is no standard definition of bronchiolitis, as definitions and classification of clinical and epidemiological findings vary worldwide (15). Therefore, the definitions of bronchiolitis used by the included reviews varied based on age, clinical findings and viral etiology. It is also possible that bronchiolitis is a first manifestation of heterogeneous wheezing phenotypes that appear later on in childhood and that respond differently to treatment (84). Most studies included in this overview were restricted to healthy infants, which makes it difficult to apply these findings to children with chronic conditions or prematurity, even though it is these children who are at increased risk of developing bronchiolitis and experiencing adverse effects (22,27,89).

Another limitation is the heterogeneity in primary outcomes and the way these outcomes are measured. The absence of standardized and validated patient-important outcomes and outcome scales has been a serious threat to bronchiolitis trial validity (90). For example, admissions and length of stay are often influenced by factors aside from treatment (i.e. volume of patients per day), and clinical severity scales are limited by their inconsistency and unknown clinical relevance (90).

In this overview, we included side-by-side comparisons of all relevant data from separate meta-analyses, but were unable to numerically quantify the benefits of one treatment versus another. Currently, new developments in statistics allow for the simultaneous analysis of all treatments versus each other in networks that make it possible to rank order the effectiveness of each treatment (91), and integration of evidence using these network meta-analysis techniques is currently being performed elsewhere in bronchiolitis research (92). However, even without these new statistical procedures, we were able to analyze the available data and reach statistically sound conclusions to recommend the most effective treatments for outpatients and inpatients with acute bronchiolitis.

Authors' Conclusions

Implications for practice

Outpatients

For patients initially presenting to a health care setting (usually an emergency department or ambulatory clinic) with wheezing as the major manifestation of bronchiolitis, nebulized epinephrine (either L-epinephrine or racemic epinephrine) may be tried in an effort to avoid hospitalization. Observation facilities need to be available for two to three hours after treatment to monitor changes in symptoms. Given the rapidly changing nature of this acute illness, rapid follow-up should be available should deterioration occur. If there is clinical improvement such as decreased wheezing, decreased indrawing and better feeding, then discharge back home is possible.

Glucocorticoids and bronchodilators (other than epinephrine) cannot be recommended as a routine therapy given the current level of evidence and potential for adverse events.

Inpatients

For patients admitted to hospital with acute bronchiolitis, nebulized hypertonic saline (3%) driven using oxygen may be given to improve respiratory distress from accumulated secretions in the upper and lower airways. The ideal dose frequency is currently unclear, but most studies administer the treatment three to six times daily. This treatment is likely to be most beneficial during the first three days of admission.

Routine chest physiotherapy cannot be recommended given the weak evidence for this maneuver. Similarly, nebulized epinephrine cannot be recommended for regular use, although there may be some benefit in improving short-term clinical severity, which may be useful in an acutely deteriorating infant. Systemic and inhaled glucocorticoids have not been shown to reduce re-admissions and should not be used for this purpose.

ICU patients

For the sickest patients who are transferred to intensive care units, intravenous immunoglobulin reduced length of stay in one review, but is not recommended due to high risk of adverse events and low methodological quality of the review. Due to sparse and low quality data, there is insufficient evidence to support the use of heliox or extrathoracic pressure; however, data on extrathoracic pressure look promising and more studies are needed.

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Implications for research

In outpatient settings, further research is necessary to examine the effectiveness of epinephrine compared to placebo and salbutamol, as well as treatment with epinephrine and glucocorticoid combined. These interventions also need to assess the benefits and risks for different subsets of patients. Furthermore, 3% hypertonic saline also needs to be tested in outpatient settings using clinically relevant time-points.

For both outpatient and inpatient populations, studies should examine the potential of using epinephrine/glucocorticoid combinations along with hypertonic saline to provide additional clinical benefit. Research should also focus on the frequency, concentration and mode of administration of hypertonic saline that confers the greatest clinical benefit, as well as the mechanism of action of nebulized hypertonic saline in patients with viral bronchiolitis. For inpatients with bronchiolitis, further studies assessing the benefits of chest physiotherapy need to be conducted.

For very ill patients in intensive care, further research should examine the benefits of promising therapies such immunoglobulin and surfactant, with attention paid to standardized ventilation protocols. Further studies on immunoglobulin could assess effects of using different titres of neutralizing or monoclonal antibodies. More evidence is also required around the effectiveness of non-invasive ventilation strategies.

Lastly, there is also a need to develop a validated and reliable scoring system that is sensitive to important clinical changes in patients with bronchiolitis.

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Contributions of Authors

All authors contributed to this overview. MF and LB extracted all data and wrote the Methods and Results sections. MF, LB, RF and MS wrote the Background section, and RF and MS wrote the Discussion and Authors' Conclusions sections. LB is the primary author of this report. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of Interest

RF and LB are each authors of two included reviews. No other declarations of interest are noted.

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