ClinicalEvidence

Croup

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ABSTRACT

INTRODUCTION: Croup is characterised by the abrupt onset, most commonly at night, of a barking cough, inspiratory stridor, hoarseness, and respiratory distress due to upper airway obstruction. It leads to signs of upper airway obstruction, and must be differentiated from acute epiglottitis, bacterial tracheitis, or an inhaled foreign body. Croup affects about 3% of children per year, usually between the ages of 6 months and 3 years, and 75% of infections are caused by parainfluenza virus. Symptoms usually resolve within 48 hours, but severe upper airway obstruction can, rarely, lead to respiratory failure and arrest. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments in children with mild croup and moderate to severe croup? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 19 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids (dexamethasone, intramuscular and oral), nebulised budesonide, oral prednisolone, heliox, humidification, and nebulised adrenaline (racemate and L-adrenaline [ephinephrine]).

QUESTIONS

INTERVENTIONS

Footnote

*Based on consensus.

Key points

- Croup leads to signs of upper airway obstruction, and must be differentiated from acute epiglottitis, bacterial tracheitis, or an inhaled foreign body.

  Croup affects about 3% of children per year, usually between the ages of 6 months and 3 years, and 75% of infections are caused by parainfluenza virus.

  Symptoms usually resolve within 48 hours, but severe upper airway obstruction can, rarely, lead to respiratory failure and arrest.

  Oxygen is standard treatment in children with respiratory distress.

- A single oral dose of dexamethasone improves symptoms in children with mild croup, compared with placebo.

  Although humidification is often used in children with mild to moderate croup, we found no RCT evidence to support its use in clinical practice.

- In children with moderate to severe croup, intramuscular or oral dexamethasone, nebulised adrenaline (epinephrine), and nebulised budesonide reduce symptoms compared with placebo.

  Oral dexamethasone is as effective as nebulised budesonide at reducing symptoms, and is less distressing for the child.

  A dexamethasone dose of 0.15 mg/kg may be as effective as a dose of 0.6 mg/kg. Adding nebulised budesonide to oral dexamethasone does not seem to improve efficacy compared with either drug alone.

  We don't know whether heliox (helium-oxygen mixture) or humidification are beneficial in children with moderate to severe croup.

DEFINITION Croup is characterised by the abrupt onset, most commonly at night, of a barking cough, inspiratory stridor, hoarseness, and respiratory distress due to upper airway obstruction. Croup symptoms are often preceded by symptoms like those of upper respiratory tract infection. The most important diagnoses to differentiate from croup include bacterial tracheitis, epiglottitis, and the inhalation of a foreign body. Some investigators distinguish subtypes of croup. [1] [2] [3] Those most commonly distinguished are acute laryngotracheitis and spasmodic croup. Children with acute laryngotracheitis have an antecedent upper respiratory tract infection, are usually febrile, and are thought to have more persistent symptoms. Children with spasmodic croup do not have an antecedent upper respiratory tract infection, are afebrile, have recurrent croup, and are thought to have more transient symptoms. However, there is little empirical evidence that spasmodic croup responds differently from acute laryngotracheitis. **Population:** We have included children aged up to 12 years with croup; no attempt has been made to exclude spasmodic croup. We could not find definitions of clinical severity that are either widely accepted or rigorously derived. We have elected to use definitions derived by a committee consisting of a range of specialists and subspecialists during the development of a clinical practice guideline from Alberta Medical Association (Canada). [4] The definitions of severity have been correlated with the Westley Croup Score (see table 1, p 29), [5] as it is the most widely used clinical score, and its validity and reliability have been well demonstrated. [6] [7] However, RCTs included in the review use a variety of croup scores. **Mild croup:** occasional barking cough; no stridor at rest; and no-to-mild suprasternal, intercostal indrawing (retractions of the skin of the chest wall), or both corresponding to a Westley Croup Score of 0–2. **Moderate croup:** frequent barking cough, easily audible stridor at rest, and suprasternal and sternal wall retraction at rest, but no or little distress or agitation, corresponding to a Westley Croup Score of 3–5. **Severe croup:** frequent barking cough, prominent inspiratory and, occasionally, expiratory stridor, marked sternal wall retractions, decreased air entry on auscultation, and significant distress and agitation, corresponding to a Westley Croup Score of 6–11. **Impending respiratory failure:** barking cough (often not prominent), audible stridor at rest (can occasionally be hard to hear), sternal wall retractions (may not be marked), usually lethargic or decreased level of consciousness, and often dusky complexion without supplemental oxygen, corresponding to a Westley Croup Score greater than 11. During severe respiratory distress, a young child's compliant chest wall 'caves in' during inspiration, causing unsynchronised chest and abdominal wall expansion (paradoxical breathing). By this classification scheme, about 85% of children attending general emergency departments with croup symptoms have mild croup, and less than 1% have severe croup (unpublished prospective data obtained from 21 Alberta general emergency departments).

INCIDENCE/ PREVALENCE Croup has an average annual incidence of 3% and accounts for 5% of emergency admissions to hospital in children aged under 6 years in North America (unpublished population-based data from Calgary Health Region, Alberta, Canada, 1996–2000). [8] One retrospective Belgian study found that 16% of children aged 5–8 years had suffered from croup at least once and 5% had experienced recurrent croup (>3 episodes). [9] We are not aware of epidemiological studies establishing the incidence of croup in other parts of the world.

AETIOLOGY/ RISK FACTORS One long-term prospective cohort study suggested that croup occurred most commonly in children aged between 6 months and 3 years, but can also occur in children as young as 3 months and as old as 12–15 years. [8] Case-report data suggest that it is extremely rare in adults. [8] Infections occur predominantly in late autumn, but can occur during any season. [8] Croup is caused by a variety of viral agents and, occasionally, by *Mycoplasma pneumoniae*. [8] Parainfluenza accounts for 75% of all cases, with the most common type being parainfluenza type 1. Prospective cohort studies suggest that the remaining cases are mainly respiratory syncytial virus, metapneumovirus, influenza A and B, adenovirus, coronavirus, and mycoplasma. [8] [10] [11] [12] [13] Viral invasion of the laryngeal mucosa leads to inflammation, hyperaemia, and oedema. [1] This leads to narrowing of the subglottic region. Children compensate for this narrowing by breathing more quickly and deeply. In children with more severe illness, as the narrowing progresses, their increased effort at breathing becomes counter-productive, airflow through the upper airway becomes turbulent (stridor), their compliant chest wall begins to cave in during inspiration, resulting in paradoxical breathing,

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and consequently the child becomes fatigued. With these events, if untreated, the child becomes hypoxic and hypercapnoeic, which eventually results in respiratory failure and arrest. [14] [15]

PROGNOSIS	Croup symptoms resolve in most children within 48 hours. [16] However, a small percentage of children with croup have symptoms that persist for up to a week. [16] Rates of hospital admission vary significantly between communities but, on average, less than 5% of all children with croup are admitted to hospital. [17] [18] [19] [20] Of those admitted to hospital, only 1% to 3% are intubated. [21] [22] [23] [24] Mortality is low; in one 10-year study, less than 0.5% of intubated children died. [22] Uncommon complications of croup include pneumonia, pulmonary oedema, and bacterial tracheitis. [25] [26] [27]
AIMS OF INTERVENTION	To minimise the duration and severity of disease episodes, with minimal adverse effects.
OUTCOMES	**Symptom severity**: change in clinical severity over time (as measured by a range of clinical scores, e.g., the Westley Croup Score [see table 1, p 29]); change in upper airway obstruction (as measured by several pathophysiological measurement tools). **Need for additional medical attention/admission to hospital**: rate of return to healthcare practitioner after an episode; rate and duration of hospital admission. **Adverse effects**.
METHODS	*Clinical Evidence* search and appraisal November 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2013, Embase 1980 to November 2013, and The Cochrane Database of Systematic Reviews 2013, issue 10 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language. We did not exclude studies on the basis of blinding (i.e., RCTs described as 'open', 'open label', or not blinded were included). There was no required minimum length of follow-up or loss to follow-up. Studies on corticosteroids (dexamethasone, budesonide, prednisolone) were required to have at least 20 participants, but for all other interventions we included studies of any size. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 30). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION	What are the effects of treatments (dexamethasone or humidification) in children with mild croup?

OPTION	DEXAMETHASONE (ORAL SINGLE DOSE)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- A single oral dose of dexamethasone improves symptoms in children with mild croup, compared with placebo.

- We found no clinically important results from RCTs comparing the effects of oral dexamethasone versus other corticosteroids, or comparing single-dose dexamethasone with multiple doses, in children with mild croup.

Oral dexamethasone versus placebo:

We found one systematic review (search date 2010), [28] which included three RCTs comparing oral dexamethasone with placebo.

Symptom severity

Oral dexamethasone compared with placebo A single dose of oral dexamethasone is more effective than placebo at reducing symptom severity in the first 24 hours in children with mild croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[29] RCT	720 children with onset of mild croup in the previous 72 hours with Westley Croup Score (see table 1, p 29) at presentation of 2 or less In review [28]	**Proportion of children with mild croup , first 24 hours after treatment** with oral dexamethasone (single dose) with placebo Mild croup assessed using the Telephone Outpatient Score for Clinical Status, score range 0–3, with a higher score indicating greater symptom severity	OR for a high score 0.31 95% CI 0.15 to 0.67 See Further information on studies for details of results at 72 hours	●●○	oral dexamethasone

Need for additional medical attention/admission to hospital

Oral dexamethasone compared with placebo A single dose of oral dexamethasone is more effective than placebo at reducing the need for additional medical attention in children with mild croup (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional medical attention for ongoing croup symptoms					
[28] Systematic review	100 children (4–10 years) presenting with mild croup not requiring hospital admission, and without stridor and chest wall indrawing at rest Data from 1 RCT	**Proportion of children seeking additional medical attention for ongoing croup symptoms , within 7–10 days** 0/48 (0%) with oral dexamethasone (single dose) 8/48 (17%) with placebo	RR 0.06 95% CI 0.00 to 0.99 P value not reported	○○○	oral dexamethasone
[28] Systematic review	720 children with onset of mild croup in the previous 72 hours with Westley Croup Score (see table 1, p 29) at presentation of 2 or less Data from 1 RCT	**Proportion of children seeking additional medical attention for ongoing croup symptoms , within 7 days** 26/352 (7%) with oral dexamethasone (single dose) 54/352 (15%) with placebo	RR 0.49 95% CI 0.31 to 0.77 P value not reported	●●○	oral dexamethasone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	720 children with onset of mild croup in the previous 72	**Adverse events** 32 with oral dexamethasone 0.6 mg/kg (single dose)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	hours with Westley Croup Score (see table 1, p 29) at presentation of 2 or less In review [28]	32 with placebo Denominator not reported			

No data from the following reference on this outcome. [30]

Single versus multiple doses of oral dexamethasone:
We found no systematic review or RCTs.

Corticosteroids other than dexamethasone:
We found no systematic review or RCTs.

Further information on studies

[29] **Oral dexamethasone versus placebo:** The RCT reported that, by 72 hours after treatment, differences between the dexamethasone and placebo groups in symptom severity were diminished, with complete symptom resolution in more than 75% of children in both groups (no further data reported).

Comment: We found one RCT in which children were broadly described as having 'mild' croup. [31] However, we have excluded it from this review because it included children with stridor at rest and chest wall indrawing, who would qualify as having 'moderate' croup, according to the definitions used for this review.

Clinical guide:
Children with mild croup have been shown to have short-lived symptoms usually lasting no more than 48 hours without treatment. Treatment with a single oral dose of dexamethasone, however, seems to provide several small but important benefits, such as reducing the proportion of children who return to care, the duration of croup symptoms, and the amount of sleep lost by the child and their parents.

OPTION   HUMIDIFICATION

• For GRADE evaluation of interventions for Croup, see table, p 30 .

• Although humidification is often used in children with mild to moderate croup, there is no evidence to support its use in clinical practice and current consensus suggests that it is ineffective.

• We found no direct information from RCTs about the effects of humidification in children with mild croup.

Benefits and harms

Humidification versus placebo or no treatment:
We found no systematic review or RCTs of sufficient quality evaluating the effects of humidification in children with mild croup.

Comment: **Clinical guide:**
Although humidification has been widely used as a treatment for croup since the 1800s, [32] current consensus suggests that it is not effective at reducing symptoms.

QUESTION	What are the effects of treatments in children with moderate to severe croup?

OPTION	BUDESONIDE (NEBULISED)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- In children with moderate to severe croup, nebulised budesonide reduces symptoms compared with placebo.

- In children with moderate to severe croup, nebulised budesonide reduces the proportion of children requiring return hospital visits and re-admissions compared with placebo.

- Oral dexamethasone is as effective as nebulised budesonide at reducing symptoms, and is less distressing for the child.

- Adding nebulised budesonide to oral dexamethasone does not seem to improve efficacy compared with either drug alone.

Benefits and harms

Nebulised budesonide versus placebo:

We found one systematic review (search date 2010), [28] which included six RCTs. Although most of the studies included in the review were in children admitted to hospital for croup, it included one RCT (54 children) that included children with mild to moderate croup (hoarseness, inspiratory stridor, and barking cough; also, Westley Croup Score 2 or greater after breathing humidified oxygen for 15 minutes). [6]

Symptom severity

Nebulised budesonide compared with placebo Nebulised budesonide seems more effective than placebo at reducing symptom severity over 6 to 24 hours in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	287 children 5 RCTs in this analysis Most studies were in children admitted to hospital for croup	**Mean between-group change in croup score from baseline (assessed using Westley Croup Score [see table 1, p 29]) , 6 hours** with nebulised budesonide (166 children) with placebo (121 children) Absolute results not reported	WMD –1.37 95% CI –2.06 to –0.68 P = 0.00011 Heterogeneity: I^2 = 55%, P = 0.07 See Further information on studies	○○○	nebulised budesonide
[28] Systematic review	127 children 2 RCTs in this analysis Both studies were in children admitted to hospital for croup	**Mean between-group change in croup score from baseline (assessed using Westley Croup Score [see table 1]) , 12 hours** with nebulised budesonide (71 children) with placebo (56 children) Absolute results not reported	WMD –1.34 95% CI –2.03 to –0.65 P = 0.00015	○○○	nebulised budesonide
[28] Systematic review	67 children Data from 1 RCT Study in children admitted to hospital for croup	**Mean between-group change in croup score from baseline (assessed using Westley Croup Score [see table 1]) , 24 hours** –4.14 with nebulised budesonide (35 children)	WMD –2.03 95% CI –3.30 to –0.76 P = 0.0017	○○○	nebulised budesonide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–2.11 with placebo (32 children)			

Need for additional medical attention/admission to hospital

Nebulised budesonide compared with placebo Nebulised budesonide seems more effective than placebo at reducing the proportion of children requiring return hospital visits and re-admissions in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Return hospital visits and re-admissions					
[28] Systematic review	228 children 4 RCTs in this analysis Most studies were in children admitted to hospital for croup	**Return hospital visits and re-admissions** 22/131 (17%) with nebulised budesonide 33/97 (34%) with placebo	RR 0.39 95% CI 0.17 to 0.92 P = 0.032	●●○	nebulised budes-onide

Adverse effects

No data from the following reference on this outcome. [28]

Nebulised budesonide versus oral dexamethasone:
See option on Dexamethasone (oral) versus nebulised budesonide, p 10 .

Nebulised budesonide versus intramuscular dexamethasone:
See option on Dexamethasone (intramuscular) versus nebulised budesonide, p 9 .

Nebulised budesonide versus budesonide (nebulised) plus oral dexamethasone:
See option on Dexamethasone (oral) plus budesonide (nebulised), p 16 .

Further information on studies

[28] Three of the five RCTs (161 children) included in the meta-analysis were in children admitted to hospital for croup, while the other two RCTs (126 children) were in children presenting to the emergency department. One RCT included children with mild-to-moderate croup. Three RCTs gave single-dose nebulised budesonide, the other two RCTs allowed repeat doses. The systematic review also reported an analysis of scoring systems other than Westley Croup Scores. In general these other scores showed a smaller treatment effect. However, most of these scores were not validated and may not be sensitive to important changes in patients' clinical status and so we have not reported these in detail here.

Comment: None.

OPTION	DEXAMETHASONE (INTRAMUSCULAR OR ORAL) VERSUS PLACEBO

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- In children with moderate to severe croup, intramuscular or oral dexamethasone reduces symptoms compared with placebo.

Benefits and harms

Intramuscular or oral dexamethasone versus placebo:
We found one systematic review (search date 2010). [28]

Symptom severity

Intramuscular or oral dexamethasone compared with placebo Oral or intramuscular dexamethasone seems to be more effective at reducing symptom severity at 6, 12, and 24 hours in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	148 children (3 months–12 years) with moderate croup 3 RCTs in this analysis	**Mean between-group change from baseline in Westley Croup Score , 6 hours** with dexamethasone (intramuscular, oral, or nebulised) (87 children) with placebo (61 children) Absolute results not reported	WMD −1.27 95% CI −1.67 to −0.87 P <0.00001	○○○	dexamethasone (oral, intramuscular, or nebulised)
[28] Systematic review	67 children 2 RCTs in this analysis	**Mean between-group change from baseline in Westley Croup Score , 12 hours** with dexamethasone (intramuscular or oral) (39 children) with placebo (28 children) Absolute results not reported	WMD −2.27 95% CI −2.86 to −1.68 P <0.00001	○○○	dexamethasone (intramuscular or oral)
[28] Systematic review	26 children Data from 1 RCT	**Mean between-group change from baseline in Westley Croup Score , 24 hours** −3.5 with dexamethasone (intramuscular) (13 children) −1.5 with placebo (13 children) Absolute results not reported	WMD −2.00 95% CI −2.83 to −1.17 P <0.00001	○○○	dexamethasone (intramuscular)

Need for additional medical attention/admission to hospital

No data from the following reference on this outcome. [28]

Adverse effects

No data from the following reference on this outcome. [28]

Further information on studies

[28] Three of the five RCTs (148 children) included in the meta-analysis were in children described as having moderate croup, while the other two RCTs (67 children) were in children admitted to hospital for croup, although the severity of croup in these children was not clearly described. The systematic review also reported an analysis of scoring systems other than Westley Croup Scores. In general, these other scores showed a smaller treatment effect. However, most of these scores were not validated and may not be sensitive to important changes in patients' clinical status and so we have not reported these in detail here.

Comment: None.

OPTION	DEXAMETHASONE (INTRAMUSCULAR) VERSUS BUDESONIDE (NEBULISED)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- Intramuscular dexamethasone may be more effective than nebulised budesonide at reducing symptoms in children with moderate to severe croup.

Benefits and harms

Intramuscular dexamethasone versus nebulised budesonide:
We found one systematic review (search date 2010), [28] which identified three RCTs. [33] [34] [35]

Symptom severity
Intramuscular dexamethasone compared with nebulised budesonide Intramuscular dexamethasone may be more effective than nebulised budesonide at reducing symptoms in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[33] RCT	144 children with moderately severe croup In review [28]	**Mean change in croup score from baseline (assessed using Westley Croup Score [see table 1, p 29]) , 5 hours** −2.9 with intramuscular dexamethasone −2.0 with nebulised budesonide	Estimated treatment difference −0.9 95% CI −1.5 to −0.3 P = 0.003 Potential methodological issue with blinding; see Further information on studies	◯◯◯	intramuscular dexamethasone
[28] Systematic review	34 children (3 months–6 years) hospitalised with croup Data from 1 RCT	**Mean between-group change from baseline in croup score , 12 hours** −3.91 with dexamethasone (intramuscular) (19 children) −3.07 with nebulised budesonide (15 children) Similar significant results found at 6 hours	SMD −0.92 95% CI −1.63 to −0.20 P = 0.012	◯◯◯	dexamethasone (intramuscular)

Need for additional medical attention/admission to hospital
Intramuscular dexamethasone compared with nebulised budesonide We don't know how intramuscular dexamethasone and nebulised budesonide compare at reducing the need for admission to hospital (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission					
[33] RCT	144 children with moderately severe croup In review [28]	**Hospital admission rate** 11/47 (23%) with intramuscular dexamethasone 18/48 (38%) with nebulised budesonide	OR 0.5 95% CI 0.2 to 1.2 P = 0.18 Potential methodological issue with blinding; see Further information on studies	⟷	Not significant
[28] Systematic review	50 children (at least 6 months old) presenting with croup (Westley Croup Score 2 or greater) in the emergency department Data from 1 RCT	**Return visits and/or (re-)admissions** 0/31 (0%) with dexamethasone (intramuscular) 0/19 (0%) with nebulised budesonide	RD 0 95% CI –0.08 to +0.08	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] RCT	144 children with moderately severe croup In review [28]	**Adverse effects** with intramuscular dexamethasone with nebulised budesonide	The RCT reported that no children in any of the treatment groups experienced an adverse effect		

Further information on studies

[33]   In this RCT, children randomised to receive budesonide did not receive a placebo intramuscular injection but had an elastic bandage placed on their thigh to aid in masking. Therefore, it is possible that masking may not have been maintained, potentially biasing the results of the study.

Comment: **Intramuscular dexamethasone versus nebulised budesonide:**
The first RCT conducted *a priori* analyses to evaluate the relationship between subtypes of croup (spasmodic croup, acute laryngotracheitis, or a mixed presentation) and treatment effect. [33] It found that the type of croup did not qualitatively alter the differences between treatment groups for either hospital admission rates, the number of additional treatments, or the change in the Westley Croup Score (quantitative data not reported).

OPTION	DEXAMETHASONE (ORAL) VERSUS BUDESONIDE (NEBULISED)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- Oral dexamethasone is as effective as nebulised budesonide at reducing symptoms, and is less distressing for the child.

Benefits and harms

Oral dexamethasone versus nebulised budesonide:
We found one systematic review (search date 2010), [28] which identified two RCTs. [36] [37]

Symptom severity

Oral dexamethasone compared with nebulised budesonide Oral dexamethasone and nebulised budesonide seem equally effective at reducing symptom severity in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[36] RCT **3-armed trial**	198 children (3 months–5 years) with Westley Croup Score 2–7 (see table 1, p 29) In review [28]	**Mean change in croup score from baseline , within 6 hours** –2.4 with oral dexamethasone (69 children) –2.3 with nebulised budesonide (65 children) The third arm evaluated oral dexamethasone plus nebulised budesonide	SMD –0.09 95% CI –0.43 to +0.25 P = 0.59	⟷	Not significant

No data from the following reference on this outcome. [37]

Need for additional medical attention/admission to hospital

Oral dexamethasone compared with nebulised budesonide Oral dexamethasone and nebulised budesonide seem equally effective at reducing the need for admission to hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission rate					
[36] RCT **3-armed trial**	198 children (3 months–5 years) with Westley Croup Score 2–7 (see table 1, p 29) In review [28]	**Proportion of children admitted to hospital , 1 week** 1/68 (1%) with oral dexamethasone 0/65 (0%) with nebulised budesonide The third arm evaluated oral dexamethasone plus nebulised budesonide	RD +0.01 95% CI –0.03 to +0.05	⟷	Not significant
[37] RCT **3-armed trial**	80 children (5 months–13 years) evaluated in an emergency department with croup, with Westley Croup Score 3 or greater (range not reported) In review [28]	**Proportion of children admitted to hospital , 24 hours** 2/23 (9%) with oral dexamethasone 5/27 (19%) with nebulised budesonide The third arm evaluated placebo	ARR +10% 95% CI –9% to +28%	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [28]

Comment:	**Oral dexamethasone versus nebulised budesonide:**

While the results of two RCTs suggest that oral dexamethasone and nebulised budesonide may be equivalent, there are several practical reasons for preferentially using oral dexamethasone. Important clinical considerations include the stress involved for the child (nebulisation usually causes prolonged agitation and crying, which worsens the child's respiratory distress) and the time required to deliver the drugs (on average, oral administration takes 1–2 minutes, whereas nebulisation requires 15 minutes).

OPTION	DEXAMETHASONE (ORAL) VERSUS PREDNISOLONE (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- We don't know whether oral dexamethasone is more effective than oral prednisolone at reducing symptom severity in children with moderate to severe croup.

- We don't know whether oral dexamethasone or oral prednisolone is more effective at reducing the need for further medical attention.

Benefits and harms

Oral dexamethasone versus oral prednisolone:
We found one systematic review (search date 2010), [28] and one subsequent RCT. [38]

Symptom severity
Oral dexamethasone compared with oral prednisolone We don't know whether oral dexamethasone is more effective than oral prednisolone at reducing symptom severity in children with moderate to severe croup (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	99 children (6 months–6 years) with moderate croup (Westley Croup Score 2 or greater) in an out-patient setting Data from 1 RCT	**Mean between-group change from baseline Westley Croup Score , 6 hours** –2.16 with oral dexamethasone (65 children) –2.35 with oral prednisolone (34 children)	WMD 0.19 95% CI –0.17 to +0.55 P = 0.30	⟷	Not significant
[38] RCT	87 children (1–8 years) with mild (42%) or moderate (58%) croup presenting in primary care	**Mean croup score (assessed using Telephone Out Patient score; 0 = no symptoms, 3 = barky cough and stridor at rest) , day 1 post-treatment commencement** 0.9 with oral dexamethasone (single dose) followed by 2 days of placebo 1.0 with oral prednisolone for 3 days Similar non-significant results found for day 2, 3, and 4	P = 0.42	⟷	Not significant

Need for additional medical attention/admission to hospital
Oral dexamethasone compared with oral prednisolone We don't know how oral dexamethasone and oral prednisolone compare at reducing the need for further medical attention (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital return visits and/or (re-)admission rates					
[28] Systematic review	219 children (3 months–12 years) with moderate croup in an outpatient setting 2 RCTs in this analysis	**Return visits and/or (re-)admissions** 12/125 (10%) with oral dexamethasone 28/94 (30%) with oral prednisolone	RR 0.32 95% CI 0.17 to 0.60 P = 0.00045		Oral dexamethasone
[38] RCT	87 children (1–8 years) with mild (42%) or moderate (58%) croup presenting in primary care	**Hospital admission , day 11** 1/46 (2%) with oral dexamethasone (single dose) followed by 2 days of placebo 0/41 (0%) with oral prednisolone for 3 days	P = 0.0	⟷	Not significant
[38] RCT	87 children (1–8 years) with mild (42%) or moderate (58%) croup presenting in primary care	**Office or clinic visit , day 11** 0/46 (0%) with oral dexamethasone (single dose) followed by 2 days of placebo 3/41 (7%) with oral prednisolone for 3 days	P = 0.1	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [39] [40]

Comment: None.

OPTION	DEXAMETHASONE (INTRAMUSCULAR) VERSUS DEXAMETHASONE (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- Intramuscular and oral dexamethasone seem to be equally effective at reducing symptom severity.

- We don't know whether intramuscular or oral dexamethasone is more effective at reducing the need for additional medical attention.

Benefits and harms

Intramuscular versus oral dexamethasone:
We found one systematic review (search date 2010), [28] which included two RCTs.

Symptom severity
Intramuscular dexamethasone compared with oral dexamethasone Intramuscular dexamethasone and oral dexamethasone seem to be equally effective at reducing symptom severity in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	277 children (3 months–12 years) with moderate croup presenting to an emergency department Data from 1 RCT	**Mean between-group change from baseline in croup score , at discharge** 0.38 with oral dexamethasone (138 children) 0.42 with intramuscular dexamethasone (139 children)	WMD 0 95% CI 0 to 0 Potential methodological issue with blinding and population; see Further information on studies	⟷	Not significant

No data from the following reference on this outcome. [28]

Need for additional medical attention/admission to hospital

Intramuscular dexamethasone compared with oral dexamethasone We don't know how intramuscular dexamethasone and oral dexamethasone compare at reducing the need for additional medical attention (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Return hospital visits and re-admission rates					
[28] RCT	372 children presenting to the emergency department with moderate croup, Westley Croup Score of 2 or greater (see table 1, p 29) 2 RCTs in this analysis	**Proportion of children needing a return visit or re-admission to hospital** 45/184 (24%) with oral dexamethasone 57/188 (30%) with intramuscular dexamethasone	RR 0.80 95% CI 0.58 to 1.12 P = 0.20 Potential methodological issue with blinding and population; see Further information on studies	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [28]

Further information on studies

[28] One of the RCTs (95 children) identified by the review included children with Westley Croup Scores of 2 or greater, and may, therefore, have included some children with mild-to-moderate croup. In both RCTs, those children randomised to receive oral dexamethasone did not receive a placebo intramuscular injection, but had a syringe hub pressed against their thigh. It is possible, therefore, that blinding may not have been maintained, potentially biasing the results of the study.

Comment: None.

OPTION	DEXAMETHASONE (ORAL): HIGHER DOSE VERSUS LOWER DOSE

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- A dexamethasone dose of 0.15 mg/kg may be as effective as a dose of 0.6 mg/kg.

- In children with moderate to severe croup, we don't know whether higher or lower dose dexamethasone differ in effectiveness at reducing return visits or hospital admissions.

Benefits and harms

Higher-dose dexamethasone versus lower-dose dexamethasone:

We found one systematic review (search date 2010), [28] which included three RCTs [39] [41] [42] comparing higher-dose with lower-dose dexamethasone.

Symptom severity

Higher-dose dexamethasone compared with lower-dose dexamethasone Higher-dose (0.6 mg/kg) and lower-dose (0.3 mg/kg and 0.15 mg/kg) dexamethasone seem equally effective at improving symptom scores at 6 hours (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	60 children (6 months–13 years) with moderate croup (Westley Croup Score 3 or greater) in an out-patient setting Data from 1 RCT	**Mean between-group change from baseline in croup score , 6 hours** −2.23 with oral dexamethasone 0.6mg/kg (31 children) −2.52 with oral dexamethasone 0.3mg/kg (29 children)	SMD 0.21 95% CI −0.30 to +0.72 P = 0.42	⟷	Not significant
[28] Systematic review	129 children (3 months–9 years) with moderate croup (Westley Croup Score 2 or greater) in an out-patient setting 2 RCTs in this analysis	**Mean between-group change from baseline in croup score , 6 hours** with oral dexamethasone 0.6mg/kg (63 children) with oral dexamethasone 0.15mg/kg (66 children)	SMD −0.02 95% CI −0.37 to +0.32 P = 0.90	⟷	Not significant

Need for additional medical attention/admission to hospital

Higher-dose dexamethasone compared with lower-dose dexamethasone We don't know whether higher- and lower-dose dexamethasone differ in effectiveness at reducing return visits or hospital admissions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Return visit or re-admission to hospital					
[28] Systematic review	60 children (6 months–14 years) with stridor and chest wall retractions at rest and croup score 3 or greater (see table 1, p 29) Data from 1 RCT	**Proportion of children requiring return visit or re-admission to hospital , by 7–10 days** 2/31 (6%) with single oral dexamethasone dose of 0.6 mg/kg 1/29 (3%) with single oral dexamethasone dose of 0.3 mg/kg	RR 1.87 95% CI 0.18 to 19.55 P = 0.60	⟷	Not significant
[28] Systematic review	60 children (6 months–14 years) with stridor and chest wall retractions at rest and croup score 3 or greater Data from 1 RCT	**Proportion of children requiring return visit or re-admission to hospital , by 7–10 days** 1/31 (3%) with single oral dexamethasone dose of 0.3 mg/kg 0/29 (0%) with single oral dexamethasone dose of 0.15 mg/kg	RR 2.81 95% CI 0.12 to 66.40 P = 0.52	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] Systematic review	130 children (3 months–9 years) with moderate croup (Westley Croup Score 2 or greater) in an outpatient setting 2 RCTs in this analysis	**Return visits and/or (re-)admissions** 18/63 (29%) with oral dexamethasone 0.6 mg/kg 18/67 (27%) with oral dexamethasone 0.15 mg/kg	RR 1.04 95% CI 0.62 to 1.75 P = 0.88	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [28]

Comment: We found one additional systematic review of randomised and non-randomised studies (search date 1987, 10 trials, 1286 children), which evaluated different types of corticosteroids. The authors converted all corticosteroids to cortisone dose equivalents for a 12.5 kg child (doses used ranged from 4.2–267 mg cortisone or around 0.05–0.66 mg/kg dexamethasone). [43] The cortisone dose equivalent was plotted relative to the difference in the proportion of children improved between the corticosteroid and placebo groups. The review found that the higher the dose of corticosteroid given, the greater the difference in the proportion of children reported to be improved between the corticosteroid and placebo groups. [43]

OPTION	DEXAMETHASONE (ORAL) PLUS BUDESONIDE (NEBULISED) VERSUS EITHER DRUG ALONE

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- Adding nebulised budesonide to oral dexamethasone does not seem to improve efficacy compared with either drug alone.

Benefits and harms

Oral dexamethasone plus nebulised budesonide versus nebulised budesonide alone:

We found one systematic review (search date 2010), [28] which identified one RCT (see option on dexamethasone [oral] versus budesonide [nebulised], p 10). [36]

Symptom severity

Oral dexamethasone plus nebulised budesonide compared with nebulised budesonide alone Oral dexamethasone plus nebulised budesonide seems no more effective than nebulised budesonide alone at reducing symptom severity at 6 hours in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	129 children presenting with croup (Westley Croup Score 2 or greater) in the emergency department	**Mean between-group change from baseline in croup score , 6 hours** –2.3 with nebulised budesonide alone (65 children)	SMD +0.19 95% CI –0.15 to +0.54 P = 0.27	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	–2.5 with nebulised budesonide plus oral dexamethasone (64 children) The third arm assessed the effects of oral dexamethasone alone			

Need for additional medical attention/admission to hospital

Oral dexamethasone plus nebulised budesonide compared with nebulised budesonide alone We don't know whether oral dexamethasone plus nebulised budesonide is more effective than either drug alone at reducing hospital admission rates in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission rate					
[28] Systematic review	129 children presenting with croup (Westley Croup Score 2 or greater) in the emergency department	**Return visits and/or (re-)admissions** 0/65 (0%) with nebulised budesonide 0/64 (0%) with nebulised budesonide plus oral dexamethasone	Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT **3-armed trial**	198 children (3 months–5 years) with Westley Croup Score 2–7 (see table 1, p 29) In review [28]	**Adverse effects** with oral dexamethasone with nebulised budesonide with nebulised budesonide plus dexamethasone Absolute values not reported	The RCT reported on adverse effects in 4 children (see Further information on studies)		

Oral dexamethasone plus nebulised budesonide versus oral dexamethasone alone:

We found one systematic review (search date 2010), [28] which identified three RCTs.

Symptom severity

Oral dexamethasone plus nebulised budesonide compared with oral dexamethasone alone Oral dexamethasone plus nebulised budesonide seems no more effective than oral dexamethasone alone at reducing symptom severity at 6 hours in children with moderate to severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[28] Systematic review	254 children presenting with croup (Westley Croup Score 2 or greater) 3 RCTs in this analysis	**Mean between-group change from baseline in croup score , 6 hours** with oral dexamethasone (130 children)	SMD +0.08 95% CI –0.48 to +0.64 P = 0.78 Heterogeneity: I^2 = 78%, P = 0.01	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with oral dexamethasone plus nebulised budesonide (124 children) Absolute results not reported	See Further information on studies		

Need for additional medical attention/admission to hospital

Oral dexamethasone plus nebulised budesonide compared with oral dexamethasone alone We don't know whether oral dexamethasone plus nebulised budesonide is more effective than either drug alone at reducing hospital admission rates or duration in hospital stay in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission rate					
[28] Systematic review	252 children presenting with croup (Westley Croup Score 2 or greater) 3 RCTs in this analysis	**Return visits and/or (re-)admissions** 12/128 (10%) with oral dexamethasone 9/124 (8%) with oral dexamethasone plus nebulised budesonide	RR 0.87 95% CI 0.41 to 1.85 P = 0.72	⟷	Not significant
Duration of hospital stay					
[44] RCT	72 children aged at least 3 months with stridor and chest wall retractions at rest admitted to hospital In review [28]	**Duration of hospital stay** with oral dexamethasone with nebulised budesonide plus dexamethasone Absolute results reported graphically	RR 1.3 95% CI 0.82 to 2.1	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT **3-armed trial**	198 children (3 months–5 years) with Westley Croup Score 2–7 (see table 1, p 29) In review [28]	**Adverse effects (any)** with oral dexamethasone with nebulised budesonide with nebulised budesonide plus dexamethasone Absolute results not reported	The RCT reported on adverse effects in 4 children (see Further information on studies)		

Further information on studies

[28]   Two of the three RCTs were in children presenting to the emergency department and gave higher dose oral dexamethasone plus nebulised budesonide (single dose). The other RCT was in children admitted to hospital and used lower dose oral dexamethasone plus nebulised budesonide. A subgroup analysis for inpatient versus outpatient treatment explained some, but not all, of the heterogeneity.

[36]   The RCT reported that one child developed oral thrush after treatment with budesonide; one child developed hives with dexamethasone; another child was reported to show violent behaviour after treatment with oral dexamethasone; and one child was reported to be more hyperactive than usual after treatment with both oral dexamethasone and nebulised budesonide.

Comment: **Clinical guide:**
Co-administration of nebulised budesonide with oral dexamethasone does not seem to provide an additional benefit over administration of oral dexamethasone alone.

OPTION	ADRENALINE (EPINEPHRINE), NEBULISED

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- In children with moderate to severe croup, nebulised adrenaline (epinephrine) reduces symptoms compared with placebo at 30 minutes and 6 hours, but not at 2 hours.

- Nebulised adrenaline, given as three doses within 1 hour, has been associated with myocardial infarction.

Benefits and harms

Nebulised adrenaline (epinephrine) versus placebo or no treatment:

We found one systematic review (search date 2013), [45] which included six RCTs comparing nebulised adrenaline (epinephrine) with placebo or no treatment.

Symptom severity

Nebulised adrenaline (epinephrine) compared with placebo or no treatment Nebulised adrenaline (epinephrine) may be more effective than placebo at reducing symptom severity in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[45] Systematic review	94 children with croup in an inpatient or outpatient setting 3 RCTs in this analysis	**Mean between-group change from baseline croup score , 30 minutes** with nebulised racemic adrenaline (45 children) with placebo (49 children)	SMD −0.94 95% CI −1.37 to −0.51 P = 0.000018	○○○	nebulised racemic adrenaline
[45] Systematic review	37 children with moderate croup in an inpatient setting Data from 1 RCT	**Mean between-group change from baseline croup score , 6 hours** 2 with nebulised racemic adrenaline (16 children) 2.5 with placebo (21 children) Nebulised adrenaline given by intermittent positive pressure breathing	SMD −1.06 95% CI −1.76 to −0.36 P = 0.0029	○○○	nebulised racemic adrenaline
[45] Systematic review	20 children with moderate croup in an inpatient setting Data from 1 RCT	**Mean between-group change from baseline croup score , 2 hours** −0.6 with nebulised racemic adrenaline (10 children) −0.3 with placebo (10 children) Nebulised adrenaline given by intermittent positive pressure breathing	SMD −0.15 95% CI −1.03 to +0.73	⟷	Not significant

Need for additional medical attention/admission to hospital

Nebulised adrenaline (epinephrine) compared with placebo or no treatment We don't know whether nebulised adrenaline (epinephrine) is more effective at reducing the length of hospital stay in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Length of stay					
[45] Systematic review	37 children with moderate croup in an inpatient setting Data from 1 RCT	**Mean length of stay (hours)** 59 with nebulised racemic adrenaline (16 children) 91 with placebo (21 children)	MD –32.00 95% CI –59.14 to –4.86	○○○	epinephrine
[45] Systematic review	54 children with moderate croup in an outpatient setting Data from 1 RCT	**Mean length of stay (hours)** 11.5 with nebulised racemic adrenaline (25 children) 13.3 with placebo (29 children)	MD –1.80 95% CI –4.07 to +0.47	←→	Not significant

No data from the following reference on this outcome. [5]   [46]   [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] Systematic review	238 children with either croup or bronchiolitis 7 RCTs in this analysis 2 RCTs identified by the review assessed croup and 5 RCTs focused on bronchiolitis	**Increase in heart rate** with adrenaline with baseline In children treated with adrenaline, the mean increase in heart rate varied between 7 beats a minute and 21 beats a minute up to 60 minutes after treatment See Further information on studies			
[49]	1 previously healthy 11-year old child with severe croup treated with 3 nebulised doses of racemic adrenaline within 60 minutes Case report	**Ventricular tachycardia** with 3 doses of nebulised adrenaline within 60 mins with baseline During administration of the third dose, the child developed ventricular tachycardia, treatment was discontinued, and normal sinus rhythm returned The child was later shown to have normal cardiac anatomy, and clear evidence of a myocardial infarction based on a persistently abnormal ECG, elevated creatinine phosphokinase-myocardial band levels, and an abnormal nuclear stress test			

Nebulised adrenaline (epinephrine) versus heliox (helium-oxygen mixture):
We found no systematic review but found one small RCT. [50]

Symptom severity

Nebulised adrenaline (epinephrine) compared with heliox We don't know whether nebulised adrenaline plus oxygen is more effective than nebulised saline plus heliox at improving symptom severity over 4 hours in children with moderate to severe croup (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[50] RCT	29 children (6 months–3 years) evaluated in a paediatric emergency department and intensive care unit with moderate to severe croup (modified Taussig Croup Score 5–9, possible range 0–14; see table 1, p 29) Children had already been treated with humidified oxygen and intramuscular dexamethasone	**Mean change in croup scores , 4 hours** with nebulised racemic adrenaline with heliox Absolute results reported graphically Children were treated with either one or two normal saline nebulisations followed by the delivery of heliox, or one or two racemic adrenaline nebulisations followed by oxygen (see Further information on studies)	P = 0.13 After 30 minutes the mean croup scores for children treated with heliox were consistently lower than the mean croup scores for children treated with adrenaline	⟷	Not significant

Need for additional medical attention/admission to hospital

No data from the following reference on this outcome. [50]

Adverse effects

No data from the following reference on this outcome. [50]

Further information on studies

[50] **Adrenaline, nebulised versus heliox (helium-oxygen mixture)** Children were treated with either one or two normal saline nebulisations, followed by the delivery of heliox (helium 70%–oxygen 30%) for 3 hours, or one or two racemic adrenaline nebulisations, followed by the delivery of 100% oxygen for 3 hours, both delivered through a tightly fitting mask. The second nebulisation was ordered at the discretion of the attending physician, based on whether the child had continued respiratory distress. [50]

[5] [46] [47] [48] **Adrenaline (epinephrine), nebulised versus placebo or no treatment — adverse effects:** In one of the RCTs (21 children with acute bronchiolitis) included in the review, pallor was reported in 47% of children treated with adrenaline compared with 14% treated with placebo (significance of difference between groups not reported). The RCTs reported no adverse effects, and in particular observed no increase in heart rate or respiratory rate with adrenaline. [5] [46] [47]

Comment: **Clinical guide:**
Although nebulised adrenaline is widely used to treat children with moderate to severe respiratory distress, some clinicians have questioned whether it provides additional benefit when given with corticosteroids. While the child treated with repeated adrenaline treatments who developed ventric-

ular tachycardia and myocardial infarction is a concern, it is important not to place too much weight on this one case report. Nebulised adrenaline has been given to children with severe croup for several decades in many hospitals around the world without any other similar published adverse reports.

| OPTION | L-ADRENALINE (EPINEPHRINE) VERSUS RACEMIC ADRENALINE |

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- In children with moderate to severe croup, L-adrenaline may be more effective at reducing symptom severity at 2 hours, but not at 30 minutes; however, evidence is very limited.

- We don't know whether L-adrenaline is more effective than racemic adrenaline at reducing the proportion of children with moderate to severe croup who need to be intubated.

| Benefits and harms |

L-adrenaline versus racemic adrenaline (epinephrine):
We found one systematic review (search date 2013), [45] which included one RCT. [51] The RCT gave no comparative data on adverse effects, but observed no increase in heart rate or respiratory rate with adrenaline.

Symptom severity
L-adrenaline compared with racemic adrenaline We don't know how L-adrenaline and racemic adrenaline compare for at reducing symptom severity in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[45] Systematic review	28 children with moderate croup (excluding spasmodic croup) in an inpatient setting Data from 1 RCT	**Mean between-group change from baseline croup score , 30 minutes** −2.28 with nebulised racemic adrenaline (14 children) −2.84 with nebulised L-adrenaline (14 children) See Further information on studies	SMD 0.33 95% CI −0.42 to +1.08	⟷	Not significant
[45] Systematic review	28 children with moderate croup (excluding spasmodic croup) in an inpatient setting Data from 1 RCT	**Mean between-group change from baseline croup score , 2 hours** −0.65 with nebulised racemic adrenaline (14 children) −2.2 with nebulised L-adrenaline (14 children) See Further information on studies	SMD 0.87 95% CI 0.09 to 1.65	◌◌◌	L-adrenaline

Need for additional medical attention/admission to hospital
L-adrenaline compared with racemic adrenaline We don't know whether L-adrenaline is more effective than racemic adrenaline at reducing the proportion of children with moderate to severe croup who need to be intubated (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Intubation					
[45] Systematic review	30 children with moderate croup (excluding spasmodic croup) in an inpatient setting Data from 1 RCT	**Proportion of children receiving intubation** 3/16 (19%) with nebulised racemic adrenaline 0/14 (0%) with nebulised L-adrenaline	RD 0.19 95% CI −0.03 to +0.40	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	31 children with moderate croup (excluding spasmodic croup) in an inpatient setting Data from 1 RCT	**Cardiovascular side effects (not further defined)** with nebulised racemic adrenaline (16 children) with nebulised L-adrenaline (15 children)	Reported as not significant	⟷	Not significant
[49]	1 previously healthy 11-year old child with severe croup treated with 3 nebulised doses of racemic adrenaline within 60 minutes Case report	**Adverse effects** with 3 doses of adrenaline within 60 min with baseline During administration of the third dose, the child developed ventricular tachycardia, treatment was discontinued, and normal sinus rhythm returned The child was later shown to have normal cardiac anatomy, and clear evidence of an MI based on a persistently abnormal ECG, elevated creatinine phosphokinase-myocardial band levels, and an abnormal nuclear stress test			

No data from the following reference on this outcome. [51]

Further information on studies

[51] The RCT defined the croup score as a scale of 10 points: inspiratory breath sounds 0 to 2 points, stridor 0 to 2 points, cough 0 to 2 points, retractions/nasal flaring 0 to 2 points, cyanosis 0 to 2 points. The RCT gave no information on adverse effects; in particular, it observed no increase in heart rate or respiratory rate with adrenaline.

Comment: None.

OPTION	HELIOX (HELIUM-OXYGEN MIXTURE)

*   For GRADE evaluation of interventions for Croup, see table, p 30 .

*   We don't know whether heliox (helium-oxygen mixture) is beneficial in children with moderate to severe croup.

Benefits and harms

Heliox (helium-oxygen mixture) versus oxygen alone:

We found one systematic review (search date 2008), [52] which included one RCT comparing heliox (helium 70%–oxygen 30%) versus oxygen 30% alone. [53]

Symptom severity

Heliox (helium-oxygen mixture) compared with oxygen alone We don't know how heliox and oxygen alone compare at reducing symptom severity in children with moderate to severe croup (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[53] RCT	15 children (6 months–4 years) evaluated in an emergency department with croup, modified Westley Croup Score (see table 1, p 29) about 1–5, possible range 0–16 In review [52]	**Mean change from baseline in modified Westley Croup Score , 20 minutes** –2.25 with heliox –1.42 with oxygen 30% alone Both treatments were delivered by humidification for 20 minutes	P = 0.32 RCT was too small to detect a clinically important difference	⟷	Not significant

Need for additional medical attention/admission to hospital

No data from the following reference on this outcome. [53]

Adverse effects

No data from the following reference on this outcome. [53]

Heliox (helium-oxygen mixture) versus nebulised adrenaline (epinephrine):
See option on nebulised adrenaline (epinephrine), p 19 .

Comment: **Heliox (helium-oxygen mixture) versus oxygen alone:**
Potential adverse effects include hypoxia secondary to inadequate oxygen concentrations in the heliox mix, and hypothermia secondary to prolonged administration of heliox.

OPTION	HUMIDIFICATION

- For GRADE evaluation of interventions for Croup, see table, p 30 .

- We don't know whether humidification is beneficial in children with moderate to severe croup.

- Hot humidified air has been associated with scalds.

Benefits and harms

Humidified air versus non-humidified or low humidified air:
We found one systematic review (search date 2006), [54] and one additional RCT. [55]

Symptom severity

Humidified air compared with non-humidified or low-humidity air Humidified air is no more effective than non-humidified or low-humidity air at reducing symptom severity in children with moderate to severe croup at 30–60 minutes (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup scores					
[54] Systematic review	135 children 3 RCTs in this analysis	**Difference in change from baseline in croup score , 20–60 minutes** with humidified air with placebo Absolute results not reported	Weighted SMD –0.14 95% CI –0.75 to +0.47	⟷	Not significant
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater (see table 1, p 29)	**Change in mean Westley Croup Score from baseline , 30 mins** with humidity delivered by blow-by technique (effectively the humidity of room air) with high humidity (100%) Absolute results not reported The third arm assessed low humidity (40%)	Mean predicted change +0.19 95% CI –0.87 to +0.49	⟷	Not significant
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater	**Change in mean Westley Croup Score from baseline , 60 mins** with humidity delivered by blow-by technique (effectively the humidity of room air) with high humidity (100%) Absolute results not reported The third arm assessed low humidity (40%)	Mean predicted change +0.14 95% CI –0.54 to +0.89	⟷	Not significant
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater	**Change in mean Westley Croup Score from baseline , 30 mins** with humidity delivered by blow-by technique (effectively the humidity of room air) with low humidity (40%) Absolute results not reported The third arm assessed high humidity (100%)	Mean predicted change +0.03 95% CI –0.72 to +0.66	⟷	Not significant
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater	**Change in mean Westley Croup Score from baseline , 60 mins** with humidity delivered by blow-by technique (effectively the humidity of room air) with low humidity (40%) Absolute results not reported The third arm assessed high humidity (100%)	Mean predicted change +0.05 95% CI –0.63 to +0.74	⟷	Not significant
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater	**Change in mean Westley Croup Score from baseline , 30 mins** with low humidity (40%) with high humidity (100%) Absolute results not reported The third arm assessed humidity delivered by blow-by technique	Mean predicted change +0.16 95% CI –0.86 to +0.53	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		(effectively the humidity of room air)			
[55] RCT **3-armed trial**	140 children (3 months–10 years) evaluated in an emergency department with croup, modified Westley Croup Score 2 or greater	**Change in mean Westley Croup Score from baseline , 60 mins** with low humidity (40%) with high humidity (100%) Absolute results not reported The third arm assessed humidity delivered by blow-by technique (effectively the humidity of room air)	Mean predicted change +0.09 95% CI –0.61 to +0.77	⟷	Not significant

Need for additional medical attention/admission to hospital

No data from the following reference on this outcome. [54] [55]

Adverse effects

No data from the following reference on this outcome. [54] [55]

Comment: **Adverse effects:**
We found a small case series of children with croup who suffered scalds from hot humidified air. [56] We found no reports of bronchospasm or hyponatraemia associated with humidification, or of complications resulting from exposure to contaminated humidifiers, although there have been reports of both bacterial and fungal contamination of humidifiers. [57]

Clinical guide:
Although humidification has been widely used for croup since the 1800s, current evidence does not support its use in clinical practice.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Paradoxical breathing (thoracoabdominal asynchrony) A form of breathing that occurs in young children with severe respiratory distress. Typically, in well people the abdomen and chest expand and contract in a synchronised fashion with respiration. Children compensate for narrowing of their upper airway by increasing their work of breathing, which increases intrapleural pressure and the rate of airflow through the upper airway. With greater increases in pleural pressure, during inspiration, a young child's compliant chest wall begins to collapse as the abdomen protrudes, owing to diaphragmatic contraction. This thoracoabdominal asynchrony is commonly referred to as paradoxical breathing. The severity of paradoxical breathing can be measured using a respiratory inductance plethysmograph, which measures the phase angle. A decrease in phase angle equates to a reduction in the severity of paradoxical breathing.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Budesonide (nebulised) One systematic review updated. [28] Categorisation unchanged (beneficial).

Dexamethasone (intramuscular or oral) versus placebo One systematic review updated. [28] Categorisation unchanged (beneficial).

Dexamethasone (intramuscular) versus budesonide (nebulised) One systematic review updated. [28] Categorisation unchanged (likely to be beneficial).

Dexamethasone (intramuscular) versus dexamethasone (oral) One systematic review updated. [28] Categorisation unchanged (unknown effectiveness).

Dexamethasone (oral single dose) for children with mild croup One systematic review updated. [28] Categorisation unchanged (beneficial).

Dexamethasone (oral) plus budesonide (nebulised) versus either drug alone One systematic review updated. [28] Categorisation unchanged (unlikely to be beneficial).

Dexamethasone (oral) versus budesonide (nebulised) One systematic review updated. [28] Categorisation unchanged (likely to be beneficial).

Dexamethasone (oral) versus prednisolone (oral) One systematic review updated. [28] One RCT added. [38] Categorisation unchanged (unknown effectiveness).

Dexamethasone (oral): higher dose versus lower dose One systematic review updated. [28] Categorisation unchanged (unknown effectiveness).

Heliox (helium-oxygen mixture) One systematic review added. [52] Categorisation unchanged (unknown effectiveness).

L -adrenaline (epinephirine) versus racemic adrenaline One systematic review added. [45] Categorisation unchanged (unknown effectiveness).

Adrenaline (epinephrine), nebulised One systematic review added. [45] Categorisation changed from beneficial to likely to be beneficial.

Humidification for children with mild croup Treatment re-evaluated. Categorisation changed from unknown effectiveness to unlikely to be beneficial by consensus.

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Competing interests: DJ is the author of references cited in this review.

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TABLE 1	Clinical scores for assessing severity of croup.

Croup scoring systems

Downes and Raphaely Croup Score [58]

Total score ranging from 0–10 points. Five component items make up the score:

• inspiratory breath sounds (0 = normal, 1 = harsh with rhonchi, 2 = delayed)

• stridor (0 = normal, 1 = inspiratory, 2 = inspiratory and expiratory)

• cough (0 = none, 1 = hoarse cry, 2 = bark)

• retractions/nasal flaring (0 = normal, 1 = suprasternal/present, 2 = suprasternal and intercostal/present)

• cyanosis (0 = none, 1 = in room air, 2 = in FIO_2 0.4)

Taussig Croup Score [50]

Total score ranging from 0–14 points. Five component items make up the score:

• colour (0 = normal, 1 = dusky, 2 = cyanotic in air, 3 = cyanotic in 30–40% oxygen)

• air entry (0 = normal, 1 = mildly diminished, 2 = moderately diminished, 3 = substantially diminished)

• retractions (0 = none, 1 = mild, 2 = moderate, 3 = severe)

• level of consciousness (0 = normal, 1 = restlessness, 2 = lethargy [depression])

• stridor (0 = none, 1 = mild, 2 = moderate, 3 = severe [or no stridor in the presence of other signs of severe obstruction])

Westley Croup Score [5]

Total score ranging from 0–17 points. Five component items make up the score:

• stridor (0 = none, 1 = with agitation only, 2 = at rest)

• retractions (0 = none, 1 = mild, 2 = moderate, 3 = severe)

• cyanosis (0 = none, 4 = cyanosis with agitation, 5 = cyanosis at rest)

• level of consciousness (0 = normal [including asleep], 5 = disorientated)

• air entry (0 = normal, 1 = decreased, , 2 = markedly decreased)

GRADE	Evaluation of interventions for Croup.

Important outcomes		Need for additional medical attention/admission to hospital , Symptom severity							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments (dexamethasone or humidification) in children with mild croup?									
1 (720) [28]	Symptom severity	Oral dexamethasone versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (820) [28]	Need for additional medical attention/admission to hospital	Oral dexamethasone versus placebo	4	0	0	0	0	High	
What are the effects of treatments in children with moderate to severe croup?									
6 (287) [28]	Symptom severity	Nebulised budesonide versus placebo	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of children with mild croup
4 (228) [28]	Need for additional medical attention/admission to hospital	Nebulised budesonide versus placebo	4	0	0	−2	+1	Moderate	Directness points deducted for inclusion of children with mild croup and composite outcome (visits and admissions); effect size point added for RR <0.5
5 (215) [28]	Symptom severity	Intramuscular or oral dexamethasone versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (178) [33] [34]	Symptom severity	Intramuscular dexamethasone versus nebulised budesonide	4	−2	0	0	0	Low	Quality points deducted for sparse data and for flaws with blinding
2 (194) [33] [35]	Need for additional medical attention/admission to hospital	Intramuscular dexamethasone versus nebulised budesonide	4	−3	0	0	0	Very low	Quality points deducted for sparse data, for flaws with blinding, and use of co-intervention
1 (134) [36]	Symptom severity	Oral dexamethasone versus nebulised budesonide	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
2 (183) [36] [37]	Need for additional medical attention/admission to hospital	Oral dexamethasone versus nebulised budesonide	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
2 (186) [28] [38]	Symptom severity	Oral dexamethasone versus oral prednisolone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for inclusion of children with mild croup
3 (306) [28] [38]	Need for additional medical attention/admission to hospital	Oral dexamethasone versus oral prednisolone	4	−1	−1	−1	0	Very low	Quality point deducted for incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for inclusion of children with mild croup
1 (277) [28]	Symptom severity	Intramuscular versus oral dexamethasone	4	−1	0	0	0	Moderate	Quality point deducted for flaws with blinding

			Need for additional medical attention/admission to hospital , Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (372) [28]	Need for additional medical attention/admission to hospital	Intramuscular versus oral dexamethasone	4	−1	0	−1	0	Low	Quality point deducted for flaws with blinding; directness point deducted for inclusion of children with mild croup
3 (189) [28]	Symptom severity	Higher-dose dexamethasone versus lower-dose dexamethasone	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
3 (190) [28]	Need for additional medical attention/admission to hospital	Higher-dose dexamethasone versus lower-dose dexamethasone	4	−1	0	−1	0	Low	Quality point deducted for sparse data; directness point deducted for composite outcome (return visit or hospital admission)
1 (129) [28]	Symptom severity	Oral dexamethasone plus nebulised budesonide versus nebulised budesonide alone	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (129) [28]	Need for additional medical attention/admission to hospital	Oral dexamethasone plus nebulised budesonide versus nebulised budesonide alone	4	−1	0	−1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of events (0 events in total)
3 (254) [28]	Symptom severity	Oral dexamethasone plus nebulised budesonide versus oral dexamethasone alone	4	0	−1	0	0	Moderate	Consistency point deducted for significant heterogeneity between trials
3 (252) [28]	Need for additional medical attention/admission to hospital	Oral dexamethasone plus nebulised budesonide versus oral dexamethasone alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for composite outcome (return visit or hospital admission)
4 (at least 131) [45]	Symptom severity	Nebulised adrenaline (epinephrine) versus placebo or no treatment	4	−1	−1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for conflicting results
2 (91) [45]	Need for additional medical attention/admission to hospital	Nebulised adrenaline (epinephrine) versus placebo or no treatment	4	−1	−1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for conflicting results
1 (29) [50]	Symptom severity	Nebulised adrenaline (epinephrine) versus heliox (helium-oxygen mixture)	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; consistency point deducted for conflicting results at different time points
1 (28) [45]	Symptom severity	L-adrenaline versus racemic adrenaline (epinephrine)	4	−1	−1	0	0	Low	Quality points deducted for sparse data; consistency point deducted for conflicting results
1 (30) [45]	Need for additional medical attention/admission to hospital	L-adrenaline versus racemic adrenaline (epinephrine)	4	−1	0	−1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of events (3 events in total in 1 RCT)
1 (15) [53]	Symptom severity	Heliox (helium-oxygen mixture) versus oxygen alone	4	−2	0	0	0	Low	Quality points deducted for sparse data and short follow-up
4 (275) [54] [55]	Symptom severity	Humidified air versus non-humidified or low humidified air	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important out-comes	Need for additional medical attention/admission to hospital , Symptom severity								
Studies (Partici-pants)	Outcome	Comparison	Type of evi-dence	Quality	Consis-tency	Direct-ness	Effect size	GRADE	Comment

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.