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 a 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 infection can, rarely, lead to pneumonia, and 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; moderate to severe croup; and impending respiratory failure because of severe croup? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2008 (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 43 systematic reviews, RCTs, or observational 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: antibiotics, corticosteroids, dexamethasone (intramuscular, oral, single-dose oral, route of administration), heliox, humidification, intermittent positive pressure breathing, L-adrenaline, nebulised adrenaline (epinephrine), nebulised budesonide, nebulised short-acting beta$_2$ agonists, oral decongestants, oral prednisolone, oxygen, and sedatives.

QUESTIONS

INTERVENTIONS

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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 a 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 infection can, rarely, lead to respiratory failure and arrest.

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

  Although humidification and oral decongestants are often used in children with mild to moderate croup, there is no evidence to support their use in clinical practice.

  There is consensus that antibiotics do not improve symptoms in croup of any severity, as croup is usually viral in origin.

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

  Oxygen is standard treatment in children with respiratory distress. 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.

  Nebulised adrenaline (epinephrine) has a short-term effect on symptoms of croup, but we don't know whether adding intermittent positive-pressure breathing to nebulised adrenaline further improves symptoms.

  We don't know whether heliox (helium–oxygen mixture), humidification, short-acting nebulised beta$_2$ agonists, or oral decongestants are beneficial in children with moderate to severe croup, or with impending respiratory failure.

- In children with impending respiratory failure caused by severe croup, nebulised adrenaline (epinephrine) is considered likely to be beneficial. Oxygen is standard treatment.

  Nasogastric prednisolone reduces the need for, or duration of, intubation, but sedatives and antibiotics are unlikely to be beneficial.

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:** In this review, we have included children up to the age of 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. For this review, we have elected to use definitions derived by a committee consisting of a range of specialists and sub-specialists 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 39), [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

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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 of 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 (at least 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, 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%–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 39]); 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** of treatment. For the question concerning children with impending respiratory failure because of severe croup: **rate and duration of airway intubation**; **symptom severity**; adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal June 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2008, Embase 1980 to June 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 2 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs, RCTs, and observational studies (cohort studies, case studies, and case reports) in any language. There was no minimum length of follow-up required to include studies. We did not exclude studies on the basis of loss to follow-up. We did not exclude RCTs described as "open", "open label", or not blinded. Studies on corticosteroids were required to have at least 20 participants, but for all other interventions we included studies

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of any size. 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 RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 40). 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 in children with mild croup?

OPTION DEXAMETHASONE (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- A single oral dose of dexamethasone improves symptoms in children with mild croup, compared with placebo.
- We found no clinically important results from RCTs or observational studies comparing the effects of oral dexamethasone versus other corticosteroids, or comparing single-dose dexamethasone with multiple doses, in children with mild croup.

Benefits and harms

Oral dexamethasone versus placebo:

We found no systematic review, but found two RCTs. [28] [29]

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 39) at presentation of 2 or less	**Proportion of children with mild croup , first 24 hours after treatment** with oral dexamethasone 0.6 mg/kg (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

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

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).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional medical attention for ongoing croup symptoms					
[28] RCT	100 children aged 4–10 years, presenting with mild croup not requiring hospital admission, and without stridor and chest wall indrawing at rest	**Proportion of children seeking additional medical attention for ongoing croup symptoms , within 7–10 days** 0/50 (0%) with oral dexamethasone 0.15 mg/kg (single dose) 8/50 (16%) with placebo	ARR 16% 95% CI 6% to 26% NNT 6 95% CI 4 to 17	○○○	oral dexamethasone
[29] RCT	720 children with onset of mild croup in the previous 72 hours with Westley croup score (see table 1, p 39) at presentation of 2 or less	**Proportion of children seeking additional medical attention for ongoing croup symptoms , within 7 days** 26/354 (7%) with oral dexamethasone 0.6 mg/kg (single dose) 54/354 (15%) with placebo	OR 0.41 95% CI 0.26 to 0.71 NNT 13 95% CI 8 to 30 ARR 8.0% 95% CI 3.3% to 12.5%	●●○	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 hours with Westley croup score (see table 1, p 39) at presentation of 2 or less	**Adverse events** 32 with oral dexamethasone 0.6 mg/kg (single dose) 32 with placebo Denominator not reported	Significance not assessed		

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

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).

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Comment: We found one RCT in which children were broadly described as having "mild" croup. [30] 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 DECONGESTANTS (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- Although oral decongestants are often used in children with mild to moderate croup, there is no evidence to support their use in clinical practice.
- We found no direct information from RCTs or observational studies about oral decongestants in children with mild croup.

Benefits and harms

Oral decongestants versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality on oral decongestants in children with mild croup.

Further information on studies

Comment: **Clinical guide:**
Although there is little evidence regarding the use of oral decongestants in children with croup, surveys of practice patterns in Canada showed that, in some communities, a large proportion of children with croup are treated with oral decongestants. [31]

OPTION HUMIDIFICATION

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 or observational studies about the effects of humidification in children with mild croup.

Benefits and harms

Humidification versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating the effects of humidification in children with mild croup.

Further information on studies

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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.

OPTION ANTIBIOTICS

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- There is consensus that antibiotics do not improve symptoms in croup of any severity, as croup is usually viral in origin.
- We found no direct information from RCTs or observational studies about the effects of antibiotics in children with mild croup.

Benefits and harms

Antibiotics versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating antibiotics in children with mild croup (see comment).

Further information on studies

Comment: **Clinical guide:**
The routine use of antibiotics in children with croup is not recommended because most cases of croup are of viral origin. [33] [34] [35] [36] [37] Surveys of practice patterns in Germany, Spain, and Canada showed that, in some communities, 30%–80% of children with croup are treated with antibiotics. [31] [38] [39]

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 40 .
- In children with moderate to severe croup, nebulised budesonide reduces symptoms 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 2003, 6 RCTs). [40]] 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 score 2 or greater after breathing humidified oxygen for 15 minutes). [6]

Symptom severity

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

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[40] Systematic review	287 children 5 RCTs in this analysis Most studies were in children admitted to hospital for croup	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1, p 39]) , 6 hours** with nebulised budesonide with placebo Absolute results not reported	WMD –1.37 95% CI –2.00 to –0.68	○○○	nebulised budesonide
[40] Systematic review	127 children 2 RCTs in this analysis Most studies were in children admitted to hospital for croup	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1]) , 12 hours** with nebulised budesonide with placebo Absolute results not reported	WMD –1.34 95% CI –2.03 to –0.66	○○○	nebulised budesonide
[40] Systematic review	67 children Data from 1 RCT Most studies were in children admitted to hospital for croup	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1]) , 24 hours** with nebulised budesonide with placebo Absolute results not reported	WMD –2.03 95% CI –3.30 to –0.76	○○○	nebulised budesonide

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 readmissions 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					
[40] 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	●●○	nebulised budesonide

Adverse effects

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

Nebulised budesonide versus oral dexamethasone:

See option on dexamethasone (oral) versus nebulised budesonide, p 12 .

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

Nebulised budesonide versus budesonide (nebulised) plus oral dexamethasone:
See option on dexamethasone (oral) plus budesonide (nebulised), p 18 .

Further information on studies

Comment: **None.**

OPTION DEXAMETHASONE (INTRAMUSCULAR OR ORAL) VERSUS PLACEBO

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 2003). [40]

Symptom severity

Intramuscular or oral dexamethasone compared with placebo Oral or intramuscular dexamethasone seems no more effective at reducing symptom severity at 6 hours, but may be more effective at 12 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					
[40] Systematic review	186 children 4 RCTs in this analysis	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1, p 39]) , 6 hours** with dexamethasone (intramuscular or oral) with placebo Absolute results not reported	WMD –0.50 95% CI –2.44 to +1.45 Significant statistical heterogeneity among RCTs (P <0.0001). See further information on studies	⟷	Not significant
[40] Systematic review	67 children 2 RCTs in this analysis	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1]) , 12 hours** with dexamethasone (intramuscular or oral) with placebo Absolute results not reported	WMD –2.27 95% CI –2.86 to –1.68	○○○	dexamethasone (intramuscular or oral)

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] Systematic review	26 children Data from 1 RCT	**Difference between groups in change in croup score from baseline (assessed using Westley croup score [see table 1]) , 24 hours** with dexamethasone (intramuscular or oral) with placebo Absolute results not reported	WMD –2.00 95% CI –2.83 to –1.17	○○○	dexamethasone (intramuscular or oral)

Need for additional medical attention / admission to hospital

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

Adverse effects

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

Further information on studies

[40] Three of the five RCTs (148 children) included in the meta-analysis were in children described as having moderate croup, while the other 2 RCTs (67 children) were in children admitted to hospital for croup, although the severity of croup in these children was not clearly described.

Comment: None.

OPTION DEXAMETHASONE (INTRAMUSCULAR) VERSUS BUDESONIDE (NEBULISED)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 2003), [40] which identified two RCTs. [41] [42]

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).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in croup score					
[41] RCT	144 children with moderately severe croup In review [40]	**Mean change in croup score from baseline (assessed using Westley croup score [see table 1, p 39]) , 5 hours** –2.9 with intramuscular dexamethasone 0.6 mg/kg –2.0 with nebulised budesonide 4 mg	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
[42] RCT	59 children aged 3 months to 6 years hospitalised for croup In review [40] Full RCT published in Danish, with abstract in English	**Improvement in Westley croup score , 6 hours** with intramuscular dexamethasone 0.6 mg/kg with nebulised budesonide 1 mg Absolute results not reported	P = 0.001 Information about how blinding was carried out was not available in the abstract	○○○	intramuscular dexamethasone
[42] RCT	59 children aged 3 months to 6 years hospitalised for croup In review [40] Full RCT published in Danish, with abstract in English	**Improvement in Westley croup score , 12 hours** with intramuscular dexamethasone 0.6 mg/kg with nebulised budesonide 1 mg Absolute results not reported	P = 0.0004 Information about how blinding was carried out was not available in the abstract	○○○	intramuscular dexamethasone

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 (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission					
[41] RCT	144 children with moderately severe croup In review [40]	**Hospital admission rate** 11/47 (23%) with intramuscular dexamethasone 0.6 mg/kg 18/48 (38%) with nebulised budesonide 4 mg	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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	144 children with moderately severe croup In review [40]	**Adverse effects** with intramuscular dexamethasone 0.6 mg/kg with nebulised budesonide 4 mg The RCT reported that no children in any of the treatment groups experienced an adverse effect			

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Further information on studies

[41] 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. [41] 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 40 .
- 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 2003), [40] which identified two RCTs. [43] [44]

Symptom severity

Oral dexamethasone compared with nebulised budesonide Oral dexamethasone and nebulised budesonide are 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40] The third arm evaluated oral dexamethasone 0.6 mg/kg plus nebulised budesonide 2 mg	**Mean change in croup score from baseline , within 4 hours** –2.4 with oral dexamethasone 0.6 mg/kg –2.3 with nebulised budesonide 2 mg	Mean treatment difference (clinically important = 1): –0.12 95% CI –0.53 to +0.29	⟷	Not significant

No data from the following reference on this outcome. [44]

Need for additional medical attention / admission to hospital

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

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission rate					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40] The third arm evaluated oral dexamethasone 0.6 mg/kg plus nebulised budesonide 2 mg	**Proportion of children admitted to hospital , 1 week** 1/68 (1%) with oral dexamethasone 0.6 mg/kg 0/65 (0%) with nebulised budesonide 2 mg	RR 2.87 95% CI 0.12 to 69.20	⟷	Not significant
[44] RCT **3-armed trial**	80 children aged 5 months to 13 years evaluated in an emergency department with croup, with Westley croup score 3 or greater (range not reported) In review [40] The third arm evaluated placebo	**Proportion of children admitted to hospital , 24 hours** 2/23 (9%) with oral dexamethasone 0.6 mg/kg 5/27 (19%) with nebulised budesonide 2 mg	ARR +10% 95% CI –9% to +28%	⟷	Not significant

Adverse effects

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

Further information on studies

Comment: **Intramuscular 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 40 .
- 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 two RCTs. [45] [46]

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Symptom severity

No data from the following reference on this outcome. [45] [46]

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 (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-presentations for further medical care					
[45] RCT	133 children aged 3 months or older with Taussig croup score 1–4 (see table 1, p 39)	**Proportion of children with unscheduled re-presentations for medical care for croup , 7–10 days** 5/68 (7%) with oral dexamethasone 0.15 mg/kg 19/65 (29%) with oral prednisolone 1 mg/kg	significance not assessed		
[46] RCT **3-armed trial**	99 children aged 6 months to 6 years with Westley Croup Score greater than 2 (see table 1, p 39)	**Proportion of children re-presenting for additional medical attention for croup , 1 week** 4/30 (13%) with oral dexamethasone 0.15 mg/kg 3/27 (11%) with oral dexamethasone 0.6 mg/kg 5/29 (17%) with oral prednisolone 1 mg/kg	P = 0.86 for difference among the three groups Significance of each dexamethasone group alone versus prednisolone alone not reported	⟷	Not significant
Hospital admission rates					
[46] RCT **3-armed trial**	99 children aged 6 months to 6 years with Westley Croup Score greater than 2	**Proportion of children admitted to hospital during the initial emergency department attendance** 2/33 (6%) with oral dexamethasone 0.15 mg/kg 1/30 (3%) with oral dexamethasone 0.6 mg/kg 4/34 (12%) with oral prednisolone 1 mg/kg	P = 0.498 for difference among the three groups Significance of each dexamethasone group alone versus prednisolone alone not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [46] [45]

Further information on studies

Comment: None.

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OPTION DEXAMETHASONE (INTRAMUSCULAR) VERSUS DEXAMETHASONE (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 2003, 2 RCTs). [40]

Symptom severity

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

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 readmission rates					
[40] RCT	372 children presenting to the emergency department with moderate croup, Westley score of 2 or greater (see table 1, p 39) 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 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. [40]

Further information on studies

[40] One of the RCTs (95 children) identified by the review included children with Westley 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 40 .

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

Benefits and harms

Higher-dose dexamethasone versus lower-dose dexamethasone:

We found one systematic review (search date 2003) [40] and two subsequent RCTs. [46] [47] The systematic review [40] identified one RCT. [48]

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					
[40] Systematic review	120 children aged 6 months to 14 years with stridor and chest wall retractions at rest and croup score 3 or greater (see table 1, p 39) Data from 1 RCT	**Change in croup score from baseline , 6 hours** with single oral dexamethasone dose of 0.3 mg/kg with single oral dexamethasone dose of 0.6 mg/kg Absolute results not reported Croup was measured on a score of 0-6 points: stidor 0-3, retraction 0-3, where 0=none, 1= only on exertion, crying, 2= at rest, 3=severe (biphasic)	WMD +0.29 95% CI –0.40 to +0.98	⟷	Not significant
[40] Systematic review	120 children aged 6 months to 14 years with stridor and chest wall retractions at rest and croup score 3 or greater Data from 1 RCT	**Change in croup score from baseline , 6 hours** with single oral dexamethasone dose of 0.15 mg/kg with single oral dexamethasone dose of 0.3 mg/kg Absolute results not reported Croup was measured on a score of 0-6 points: stidor 0-3, retraction 0-3, where 0=none, 1= only on exertion, crying, 2= at rest, 3=severe (biphasic)	WMD +0.23 95% CI –0.46 to +0.92	⟷	Not significant

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

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					
[40] Systematic review	120 children aged 6 months to 14 years with stridor and chest wall retractions at rest and croup score 3 or greater (see table 1, p 39) 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	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] Systematic review	120 children aged 6 months to 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	⟷	Not significant
[46] RCT **3-armed trial**	99 children aged 6 months to 6 years with Westley Croup Score greater than 2 (see table 1, p 39)	**Proportion of children re-presenting for additional medical attention for croup , 1 week** 4/30 (13%) with oral dexamethasone 0.15 mg/kg 3/27 (11%) with oral dexamethasone 0.6 mg/kg 5/29 (17%) with oral prednisolone 1 mg/kg	P = 0.86 for difference among the three groups Significance of each dexamethasone group alone versus prednisolone alone not reported	⟷	Not significant
Hospital admission rates					
[46] RCT **3-armed trial**	99 children aged 6 months to 6 years with Westley Croup Score greater than 2 (see table 1, p 39)	**Proportion of children admitted to hospital during the initial emergency department attendance** 2/33 (6%) with oral dexamethasone 0.15 mg/kg 1/30 (3%) with oral dexamethasone 0.6 mg/kg 4/34 (12%) with oral prednisolone 1 mg/kg	P = 0.498 for difference among the three groups Significance of each dexamethasone group alone versus prednisolone alone not reported	⟷	Not significant
[47] RCT	72 children aged 6 months to 13 years with Westley Croup Score of 3–6	**Proportion of children admitted to hospital after the initial clinic visit** 14/36 (39%) with single oral dexamethasone dose of 0.15 mg/kg 15/36 (42%) with single oral dexamethasone dose of 0.6 mg/kg	P = 0.36	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [40] [46] [47]

Further information on studies

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). [49] 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

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given, the greater the difference in the proportion of children reported to be improved between the corticosteroid and placebo groups. [49]

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

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 2003), [40] which identified one RCT (see option on dexamethasone [oral] versus budesonide [nebulised], p 12). [43]

Symptom severity

Oral dexamethasone plus nebulised budesonide compared with nebulised budesonide alone Oral dexamethasone plus nebulised budesonide is no more effective than nebulised budesonide alone at reducing symptom severity at 4 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40] The third arm assessed the effects of oral dexamethasone alone	**Mean change in croup score from baseline , 4 hours** –2.3 with nebulised budesonide alone –2.4 with dexamethasone plus budesonide	Mean treatment difference (clinically important = 1) +0.14 95% CI –0.27 to +0.55	⟷	Not significant

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 at 1 week 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40]	**Proportion of children admitted to hospital , 1 week** 1/68 (1%) with oral dexamethasone 0/65 (0%) with nebulised budesonide 0/64 (0%) with nebulised budesonide plus dexamethasone	P = 1.00 for difference among the three groups Significance of each drug alone versus combination treatment not reported	⟷	Not significant

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40]	**Adverse effects** with oral dexamethasone with nebulised budesonide with nebulised budesonide plus dexamethasone 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 2003), [40] which identified one RCT (see option on dexamethasone [oral] versus budesonide [nebulised], p 12), [43] and one subsequent RCT. [50]

Symptom severity

Oral dexamethasone plus nebulised budesonide compared with oral dexamethasone alone Oral dexamethasone plus nebulised budesonide is no more effective than oral dexamethasone alone at reducing symptom severity at 4 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40] The third arm assessed the effects of nebulised budesonide alone	**Mean change in croup score from baseline , 4 hours** –2.4 with oral dexamethasone –2.4 with dexamethasone plus budesonide	Mean treatment difference (clinically important = 1) +0.02 95% CI –0.39 to +0.43	⟷	Not significant

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

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 at 1 week 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40]	**Proportion of children admitted to hospital , 1 week** 1/68 (1%) with oral dexamethasone 0/65 (0%) with nebulised budesonide 0/64 (0%) with nebulised budesonide plus dexamethasone	P = 1.00 for difference among the three groups Significance of each drug alone *v* combination treatment not reported	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of hospital stay					
[50] RCT	72 children aged at least 3 months with stridor and chest wall retractions at rest admitted to hospital	**Duration of hospital stay** with oral dexamethasone 0.15 mg/kg with nebulised budesonide 2 mg plus dexamethasone 0.15 mg/kg 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					
[43] RCT **3-armed trial**	198 children aged 3 months to 5 years with Westley croup score 2–7 (see table 1, p 39) In review [40]	**Adverse effects (any)** with oral dexamethasone with nebulised budesonide with nebulised budesonide plus dexamethasone The RCT reported on adverse effects in 4 children (see further information on studies)			

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

Further information on studies

[43] 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 OXYGEN

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- Oxygen is standard treatment in children with respiratory distress.
- We found no direct information from RCTs or observational studies about the effects of oxygen in children with moderate to severe croup. There is widespread consensus that oxygen is beneficial in children with severe respiratory distress.

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Benefits and harms

Oxygen versus no oxygen treatment:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating the effects of oxygen in children with moderate to severe croup. An RCT comparing oxygen versus no oxygen in children with severe croup would be considered unethical. We found one prospective cohort study, which showed that children with croup can have hypoxia, even in the absence of severe upper airway obstruction, apparently because of intrapulmonary shunting. [51] This study did not attempt to find out if administration of oxygen decreases respiratory effort.

Oxygen versus heliox (helium–oxygen mixture):

See option on heliox (helium–oxygen mixture), p 28 .

Further information on studies

Comment: **Clinical guide:**
There is compelling logic for giving oxygen in children with severe respiratory distress, and no evidence of harm. There is widespread consensus that oxygen is beneficial in children with severe respiratory distress.

OPTION ADRENALINE (EPINEPHRINE), NEBULISED

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- In children with moderate to severe croup, nebulised adrenaline (epinephrine) reduces symptoms compared with placebo.
- Nebulised adrenaline given as three doses within 1 hour has been associated with MI.

Benefits and harms

Nebulised adrenaline (epinephrine) versus placebo or no treatment:

We found no systematic review but found three small RCTs. [5] [52] [53] The RCTs reported no adverse effects, and in particular observed no increase in heart rate or respiratory rate with adrenaline (see adverse effects for details from one SR, search date 2004). [54]

Symptom severity

Nebulised adrenaline (epinephrine) compared with placebo or no treatment Nebulised adrenaline (epinephrine) is more effective in the short term at reducing symptom severity at 10–30 minutes 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					
[52] RCT	54 children aged 4 months to 11 years with combined Taussig croup score/Westley croup score (see table 1, p 39) of 2–9 (possible range 0–15)	**Change from baseline croup score (baseline score same for both groups mean 4.7) , at 30 minutes** –2.7 with nebulised racemic adrenaline (2.25%, 0.5 mL/kg by nebuliser) –1.1 with placebo	P = 0.003	○○○	nebulised racemic adrenaline

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[5] RCT	20 children aged 4 months to 12 years admitted to an intensive care high-humidity mist room with a Westley croup score of 3–6	**Mean croup score , at 10 minutes** 1.7 with nebulised racemic adrenaline (2.25%, 0.5 mL/kg by nebuliser) 3.7 with placebo Nebulised adrenaline given by intermittent positive pressure breathing	P <0.01	○○○	nebulised racemic adrenaline
[5] RCT	20 children aged 4 months to 12 years admitted to an intensive care high-humidity mist room with a Westley croup score of 3–6	**Mean croup score , at 30 minutes** 1.7 with nebulised racemic adrenaline (2.25%, 0.5 mL/kg by nebuliser) 3.1 with placebo Nebulised adrenaline given by intermittent positive pressure breathing	P <0.01	○○○	nebulised racemic adrenaline
[5] RCT	20 children aged 4 months to 12 years admitted to an intensive care high-humidity mist room with a Westley croup score of 3–6	**Mean croup score , at 120 minutes** 3.3 with nebulised racemic adrenaline (2.25%, 0.5 mL/kg by nebuliser) 3.8 with placebo Nebulised adrenaline given by intermittent positive pressure breathing	Reported as not significant P value not reported	⟷	Not significant
[53] RCT	13 children aged 5 months to 11 years, admitted to hospital with croup, with a Taussig croup score of 5–12	**Mean croup score , at 10 minutes** with nebulised racemic adrenaline (2.25%, dose weight-adjusted) with no treatment Absolute results not reported Nebulised adrenaline given by intermittent positive pressure breathing	P = 0.011	○○○	nebulised racemic adrenaline

Need for additional medical attention / admission to hospital

No data from the following reference on this outcome. [5] [52] [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[54] Systematic review	238 children with either croup or bronchiolitis 7 RCTs in this analysis	**Increase in heart rate** with 3 mL or greater of adrenaline with baseline In children treated with 3 mL or greater of adrenaline (1:1000			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	2 RCTs identified by the review assessed croup and 5 RCTs focused on bronchiolitis	[1 mg/mL]), 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			
[55]	Previously healthy 11-year old child with severe croup treated with three nebulised doses of racemic adrenaline (2.25%, 0.5 mL) 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 an MI based on a persistently abnormal ECG, elevated creatinine phosphokinase-myocardial band levels, and an abnormal nuclear stress test			

Adrenaline, nebulised versus heliox (helium–oxygen mixture):

We found no systematic review but found one small RCT. [56]

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					
[56] RCT	29 children aged 6 months to 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 39) Children had already been treated with humidified oxygen and intramuscular dexamethasone 0.6 mg/kg	**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. [56]

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Adverse effects

No data from the following reference on this outcome. [56]

Further information on studies

[56] **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 (2.25%, 0.5 mL), 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. [56]

[5] [52] [53] [54] **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] [52] [53]

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 ventricular tachycardia and MI 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 40 .
- We don't know whether L-adrenaline or racemic adrenaline is more effective at reducing symptom severity in children with moderate to severe croup.

Benefits and harms

L-adrenaline versus racemic adrenaline (epinephrine):

We found no systematic review but found one small RCT. [57] 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					
[57] RCT	31 children aged 6 months to 6 years evaluated in an emergency department with croup; modified Downes and Raphaely croup score 6 or greater, possible	**Mean croup scores , 30 minutes** with L-adrenaline (1:1000, 5 mL) with racemic adrenaline (2.25%, 5 mL) Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	range 0–10 (see table 1, p 39)				
[57] RCT	31 children aged 6 months to 6 years evaluated in an emergency department with croup; modified Downes and Raphaely croup score 6 or greater, possible range 0–10	**Mean croup scores , 60 minutes** with L-adrenaline (1:1000, 5 mL) with racemic adrenaline (2.25%, 5 mL) Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant

Need for additional medical attention / admission to hospital

No data from the following reference on this outcome. [57]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[55]	Previously healthy 11-year old child with severe croup treated with three nebulised doses of racemic adrenaline (2.25%, 0.5 mL) 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. [57]

Further information on studies

[57] The RCT gave no information on adverse effects; in particular, it observed no increase in heart rate or respiratory rate with adrenaline.

Comment: None.

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OPTION ADRENALINE (EPINEPHRINE) (NEBULISED) PLUS INTERMITTENT POSITIVE PRESSURE BREATHING VERSUS NEBULISED ADRENALINE ALONE

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- Nebulised adrenaline (epinephrine) has a short-term effect on symptoms of croup, but we don't know whether adding intermittent positive-pressure breathing (IPPB) to nebulised adrenaline further improves symptoms.

Benefits and harms

Nebulisation alone versus nebulisation plus intermittent positive pressure breathing (IPPB):

We found no systematic review but found one small, weak RCT. [58] The RCT gave no comparative data on adverse effects, but observed no increase in heart rate or respiratory rate with adrenaline.

Symptom severity

Nebulised adrenaline plus intermittent positive pressure breathing (IPPB) compared with nebulised adrenaline alone

Nebulised adrenaline plus IPPB may be no more effective than nebulised adrenaline alone 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					
[58] RCT **Crossover design**	14 children aged 4 months to 5 years admitted to hospital with croup with minimum inspiratory stridor at rest	**Mean croup scores , 30 mins** 2.4 with adrenaline (epinephrine) (2.25%, 0.25 mL) delivered by nebulisation alone 3.1 with adrenaline delivered by nebulisation plus intermittent positive pressure breathing (IPPB) (15–17 cm pressure) The washout period between treatments was 2 hours Mean baseline croup scores: 5.7 with adrenaline delivered by nebulisation alone *v* 6.7 with nebulised adrenaline plus IPPB	Reported as not significant P value not reported	⟷	Not significant
[58] RCT **Crossover design**	14 children aged 4 months to 5 years admitted to hospital with croup with minimum inspiratory stridor at rest	**Mean croup scores , 60 mins** 2.8 with adrenaline (epinephrine) (2.25%, 0.25 mL) delivered by nebulisation alone 3.2 with adrenaline delivered by nebulisation plus IPPB (15–17 cm pressure) The washout period between treatments was 2 hours Mean baseline croup scores: 5.7 with adrenaline delivered by nebulisation alone *v* 6.7 with nebulised adrenaline plus IPPB	Reported as not significant P value not reported	⟷	Not significant
[58] RCT **Crossover design**	14 children aged 4 months to 5 years admitted to hospital with croup with minimum inspiratory stridor at rest	**Mean croup scores , 90 mins** 4.0 with adrenaline (epinephrine) (2.25%, 0.25 mL) delivered by nebulisation alone 5.1 with adrenaline delivered by nebulisation plus IPPB (15–17 cm pressure) The washout period between treatments was 2 hours Mean baseline croup scores: 5.7 with adrenaline delivered by nebulisation alone *v* 6.7 with nebulised adrenaline plus IPPB	Reported as not significant P value not reported	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[58] RCT **Crossover design**	14 children aged 4 months to 5 years admitted to hospital with croup with minimum inspiratory stridor at rest	**Mean croup scores , 120 mins** 5.9 with adrenaline (epinephrine) (2.25%, 0.25 mL) delivered by nebulisation alone 5.5 with adrenaline delivered by nebulisation plus IPPB (15–17 cm pressure) The washout period between treatments was 2 hours Mean baseline croup scores: 5.7 with adrenaline delivered by nebulisation alone *v* 6.7 with nebulised adrenaline plus IPPB	Reported as not significant P value not reported	⟷	Not significant

Need for additional medical attention / admission to hospital

No data from the following reference on this outcome. [58]

Adverse effects

No data from the following reference on this outcome. [58]

Further information on studies

[58] The RCT found that both methods of adrenaline delivery significantly reduced croup score from baseline at 30 and 60 minutes (P <0.01) but not at 90 or 120 minutes.

Comment: **Clinical guide:**
Despite the relative lack of evidence showing the effectiveness of nebulised adrenaline without IPPB, adrenaline is no longer routinely given by nebulisation with IPPB.

OPTION BETA2 AGONISTS, SHORT-ACTING (NEBULISED)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- We don't know whether short-acting nebulised beta$_2$ agonists are beneficial in children with moderate to severe croup as we found no studies.

Benefits and harms

Nebulised short-acting beta2 agonists versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating the effects of nebulised short-acting beta$_2$ agonists in children with moderate to severe croup.

Further information on studies

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Comment: **Clinical guide:**
Although there is neither empirical evidence showing benefit nor a clear theoretical reason for using nebulised short-acting beta$_2$ agonists, [33] [34] [35] [36] surveys of practice patterns show that, in some communities, a significant proportion of children with croup are treated with nebulised short-acting beta$_2$ agonists. [31] [39] [59]

OPTION DECONGESTANTS (ORAL)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- We don't know whether oral decongestants are beneficial in children with moderate to severe croup.

Benefits and harms

Oral decongestants versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality on oral decongestants in children with moderate to severe croup.

Further information on studies

Comment: **Clinical guide:**
Although there is little evidence of benefit from oral decongestants, surveys of practice patterns show that in some communities a significant proportion of children with croup are treated with oral decongestants. [31]

OPTION HELIOX (HELIUM–OXYGEN MIXTURE)

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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 RCT comparing heliox (helium 70%–oxygen 30%) versus oxygen 30% alone. [60]

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					
[60] RCT	15 children aged 6 months to 4 years evaluated in an emergency department with croup, modified Westley croup score (see table 1, p 39) about 1–5, possible range 0–16	**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

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Need for additional medical attention / admission to hospital

No data from the following reference on this outcome. [60]

Adverse effects

No data from the following reference on this outcome. [60]

Heliox (helium–oxygen mixture) versus nebulised adrenaline (epinephrine):
See option on nebulised adrenaline (epinephrine), p 21 .

Further information on studies

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 ANTIBIOTICS

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- We found no direct information from RCTs or observational studies about the effects of antibiotics in children with moderate to severe croup. There is consensus that antibiotics do not shorten the clinical course of a disease that is predominantly viral in origin. However, this does not apply if bacterial tracheitis is suspected.

Benefits and harms

Antibiotics versus placebo or other interventions:
We found no systematic review, RCTs, or observational studies of sufficient quality on antibiotics in children with moderate to severe croup.

Further information on studies

[61] [62] We found two case reports of children initially diagnosed with croup who were treated with both dexamethasone and antibiotics for several days. One child was later diagnosed as having herpetic tracheitis, and the other as having candida laryngotracheitis.

Comment: **Clinical guide:**
The routine use of antibiotics in children with croup is widely assumed to be of no benefit because most cases of croup are of viral origin. [33] [34] [35] [36] An exception to this rule occurs in children who have more severe distress with signs and symptoms consistent with bacterial tracheitis. Although bacterial tracheitis should be a consideration in only a small percentage of children, surveys

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of practice patterns show that in some communities 30%–80% of children with croup are treated with antibiotics. [31] [38] [39]

OPTION HUMIDIFICATION

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- 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) [63] and one additional RCT. [64]

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					
[63] 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
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater (see table 1, p 39) The third arm assessed low humidity (40%)	**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	Mean predicted change +0.19 95% CI –0.87 to +0.49	⟷	Not significant
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater The third arm assessed low humidity (40%)	**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	Mean predicted change +0.14 95% CI –0.54 to +0.89	⟷	Not significant
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater The third arm assessed high humidity (100%)	**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	Mean predicted change +0.03 95% CI –0.72 to +0.66	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater The third arm assessed high humidity (100%)	**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	Mean predicted change +0.05 95% CI –0.63 to +0.74	⟷	Not significant
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater The third arm assessed humidity delivered by blow-by technique (effectively the humidity of room air)	**Change in mean Westley croup score from baseline , 30 mins** with low humidity (40%) with high humidity (100%) Absolute results not reported	Mean predicted change +0.16 95% CI –0.86 to +0.53	⟷	Not significant
[64] RCT **3-armed trial**	140 children aged 3 months to 10 years evaluated in an emergency department with croup, modified Westley croup score 2 or greater The third arm assessed humidity delivered by blow-by technique (effectively the humidity of room air)	**Change in mean Westley croup score from baseline , 60 mins** with low humidity (40%) with high humidity (100%) Absolute results not reported	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. [63] [64]

Adverse effects

No data from the following reference on this outcome. [63] [64]

Further information on studies

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Comment:

Adverse effects:
We found a small case series of children with croup who suffered scalds from hot humidified air. [65] 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. [66]

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

QUESTION What are the effects of treatments in children with impending respiratory failure because of severe croup?

OPTION ADRENALINE (EPINEPHRINE), NEBULISED IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- In children with impending respiratory failure caused by severe croup, nebulised adrenaline (epinephrine) is considered likely to be beneficial.

Benefits and harms

Nebulised adrenaline (epinephrine) versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies evaluating the effects of adrenaline (epinephrine) in children with impending respiratory failure due to severe croup. Such an RCT would be considered unethical. There is consensus that adrenaline is beneficial in children with impending respiratory failure due to severe croup (see comment). We found two cohort studies in children treated with adrenaline for acute upper airway obstruction (see comments).

Further information on studies

Comment:

The first cohort study (17 children aged 8 months to 5 years admitted to a paediatric intensive care unit with severe croup) assessed and monitored the severity of airway obstruction using the Westley croup score (see table 1, p 39) and continuous transcutaneous carbon dioxide pressure monitoring. [67] It found that, in children with acute upper airway obstruction, nebulised L-adrenaline (1:1000, 0.2 mL/kg) significantly improved mean croup score and reduced carbon dioxide levels (mean Westley croup score: 12.4 before treatment *v* 5.3 after L-adrenaline treatment; P less than or equal to 0.001; mean transcutaneous carbon dioxide pressure monitoring: 51.0 mmHg before treatment *v* 42.8 mmHg after L-adrenaline treatment; P less than or equal to 0.001). [67] The cohort study found no significant increase in heart rate or respiratory rate in children treated with racemic adrenaline. Six children eventually needed intubation. [67]

The second cohort study (17 children aged 1 month to 4 years admitted to a paediatric intensive care unit with croup) assessed the severity of airway obstruction using a respiratory inductance plethysmograph to measure thoracoabdominal asynchrony (paradoxical breathing), which was expressed as a phase angle ranging from 0° to 180°. [68] It found that, in children with acute upper airway obstruction, nebulised racemic adrenaline (0.03 mL/kg, concentration not reported) significantly reduced mean phase angles (mean phase angles: 83.6° before treatment *v* 38.3° after adrenaline treatment; P = 0.001). This cohort study also reported a high association between the phase angle and the degree of stridor. [68] The cohort study found no significant increase in heart rate or respiratory rate in children treated with racemic adrenaline. [68] One child was intubated. [68]

Clinical guide:
In children with severe impending respiratory failure, nebulised adrenaline causes rapid improvement, which can forestall the need for intubation. Although the effect of adrenaline is relatively transient, it provides a "window of opportunity" for corticosteroid treatment to take effect.

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OPTION CORTICOSTEROIDS IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- Nasogastric prednisolone reduces the need for, or duration of, intubation.

Benefits and harms

Corticosteroids versus placebo:

We found one systematic review (search date 1987) [49] and one subsequent RCT. [69]

Need for intubation

Corticosteroids compared with placebo Corticosteroids (oral, intramuscular or subcutaneous) are more effective than placebo at reducing the need for intubation, the duration of intubation, and the need for re-intubation in children with severe croup (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of endotracheal intubation					
[49] Systematic review	1126 children 9 RCTs in this analysis	**Rate of endotracheal intubation** 1/575 (0.2%) with corticosteroid 7/551 (1.3%) with placebo The review included studies using different types of corticosteroid and route of administration (dexamethasone [intramuscular, subcutaneous, or oral]; methylprednisolone [intramuscular]; prednisolone [oral]), and the authors converted all corticosteroids to cortisone dose equivalents for a 12.5 kg child (doses used ranged from 4.2–267 mg or about 0.05–0.66 mg/kg dexamethasone)	ARR 1.1% 95% CI 0.1% to 2.1%	○○○	corticosteroid
Duration of intubation					
[69] RCT	70 children	**Median duration of intubation** 98 hours with prednisolone 138 hours with placebo Prednisolone was given 1 mg/kg by nasogastric tube every 12 hours until 24 hours after extubation	Reported as significant difference between groups Two of the children randomised to placebo were later diagnosed as having bacterial tracheitis and were excluded from analysis	○○○	prednisolone
Need for re-intubation					
[69] RCT	70 children	**Need for re-intubation** 2/38 (5%) with prednisolone 11/32 (34%) with placebo Prednisolone was given 1 mg/kg by nasogastric tube every 12 hours until 24 hours after extubation	ARR 29% 95% CI 11% to 47% NNT 3 95% CI 2 to 8 Two of the children randomised to placebo were later diagnosed as having bacterial tracheitis and were excluded from analysis	○○○	prednisolone

Symptom severity

No data from the following reference on this outcome. [49] [69]

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Adverse effects

No data from the following reference on this outcome. [49] [69]

Further information on studies

Comment: None.

OPTION OXYGEN IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- In children with impending respiratory failure caused by severe croup, oxygen is standard treatment.

Benefits and harms

Oxygen versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating the effects of oxygen in children with impending respiratory failure due to severe croup. An RCT comparing oxygen versus no oxygen in children with severe croup would be considered unethical. There is consensus that oxygen is beneficial in children with severe respiratory distress.

Further information on studies

Comment: There are unlikely to be any important complications resulting from administration of oxygen to children with severe respiratory distress.

Clinical guide:
Children with impending respiratory failure are typically hypoxic, and administration of oxygen helps to prevent hypoxic cell injury. There is compelling logic for giving oxygen to children with severe respiratory distress, and no evidence of harm.

OPTION HELIOX (HELIUM–OXYGEN MIXTURE) IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- We don't know whether heliox (helium–oxygen mixture) is beneficial in children with impending respiratory failure due to severe croup as we found no studies.

Benefits and harms

Heliox versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality evaluating the effects of heliox (helium–oxygen mixture) in children with impending respiratory failure due to severe croup.

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Further information on studies

Comment: **Clinical guide:**
The theoretical advantage of heliox is that oxygen combined with helium is less dense than either room air or 100% oxygen. Lower density allows laminar, rather than turbulent, gas flow in a narrow airway. Because laminar flow is more efficient, children with a narrow airway can be better ventilated, potentially preventing respiratory failure.

OPTION ANTIBIOTICS IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- We found no direct information from RCTs or observational studies about the effects of antibiotics in children with impending respiratory failure due to severe croup. There is strong consensus that antibiotics do not shorten the clinical course of a disease that is predominantly viral in origin. This does not apply if bacterial tracheitis is suspected.

Benefits and harms

Antibiotics versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies of sufficient quality on antibiotics in children with impending respiratory failure due to severe croup.

Further information on studies

Comment: **Clinical guide:**
The routine use of antibiotics in children with croup is widely assumed to be of no benefit because most cases of croup are of viral origin. [33] [34] [35] [36] An exception occurs in those children who have more severe distress with signs and symptoms consistent with bacterial tracheitis. Although bacterial tracheitis should be a consideration in only a small percentage of children, surveys of practice patterns show that in some communities 30%–80% of children with croup are treated with antibiotics. [31] [38] [39]

OPTION SEDATIVES IN CHILDREN WITH IMPENDING RESPIRATORY FAILURE DUE TO SEVERE CROUP

- For GRADE evaluation of interventions for Croup, see table, p 40 .
- Sedatives are unlikely to be beneficial; they may decrease respiratory effort without improving ventilation.

Benefits and harms

Sedatives versus placebo or other interventions:

We found no systematic review, RCTs, or observational studies evaluating the effects of sedatives in children with impending respiratory failure due to severe croup.

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Further information on studies

Comment: We found one prospective cohort study (17 children aged 8 months to 5 years with croup, severe to impending respiratory failure, mean Westley croup score 12 [see table 1, p 39]) in which children with impending respiratory failure were continuously monitored using clinical scores and transcutaneous carbon dioxide measurements. [67] The cohort study showed that children treated with chloral hydrate 30–40 mg/kg over 4–6 hours had significantly improved croup scores, but found no corresponding decrease in transcutaneous carbon dioxide measurements (mean change from baseline in croup scores: 11.2 before chloral hydrate *v* 6.5 after chloral hydrate; P <0.001; mean transcutaneous carbon dioxide level: 46.5 mmHg before chloral hydrate *v* 47.3 mmHg after chloral hydrate; reported as not significant, P value not reported). This cohort study also showed that nebulised adrenaline (epinephrine) 1:1000 (2 mL/10 kg) significantly improved both the croup scores and transcutaneous carbon dioxide (both P <0.001). [67] We found no analytical studies evaluating the effects of other sedatives in children with impending respiratory failure in severe croup. Although sedative treatment is no longer accepted as standard treatment for children with croup, [33] [34] [35] [36] and there is no empirical evidence showing benefit, sedatives are still occasionally used in hospitalised children to treat more severe croup. [67] [70]

GLOSSARY

Intermittent positive pressure breathing A type of physiotherapy which involves assisted breathing with a pressure cycled ventilator triggered into inspiration by the user and allowing passive expiration. The user begins to inhale through the machine, which senses the breath and augments it by delivering gas to the user. When a preset pressure is reached, the machine stops delivering gas and allows the user to breathe out. In most devices, the inspiratory sensitivity, flow rate, and pressure can be varied to suit the user's needs, but some devices adjust the sensitivity and flow automatically. The aim is to increase lung volume, which is thought to cause a reduction in airways resistance and an improvement in ventilation. [71]

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

Dexamethasone (oral), higher dose versus lower dose in children with moderate to severe croup One RCT added comparing dexamethasone 0.6 mg/kg versus dexamethasone 0.15 mg/kg versus prednisolone, all given orally. [46] It found no significant difference among the groups in hospital admission or in the need for further medical attention. Condition re-structured: separated from Dexamethasone (im) *v* dexamethasone (oral). Categorisation unchanged (Unknown effectiveness).

Dexamethasone (oral) versus prednisolone (oral) in children with moderate to severe croup One RCT added comparing prednisolone versus dexamethasone 0.6 mg/kg versus dexamethasone 0.15 mg/kg, all given orally. [46] It found no significant difference among the groups in hospital admission or in the need for further medical attention. Categorisation changed (Unknown effectiveness).

Adrenaline (epinephrine), nebulised in children with impending respiratory failure due to severe croup No new evidence. RCTs in children with impending respiratory failure are unlikely to take place as they would be considered unethical. Most clinicians believe nebulised adrenaline to be effective, so categorisation changed to Likely to be beneficial by consensus.

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Dexamethasone (oral) plus budesonide (nebulised) versus either drug alone in children with moderate to severe croup No new RCTs added; evidence re-evaluated. One systematic review and one subsequent RCT found no significant difference in croup severity scores at 4 hours, or the proportion of children admitted to hospital, between combined treatment with dexamethasone and budesonide, and either treatment alone; thus, combining interventions confers no additional benefit. [40] [50] Categorisation for combination changed (Unlikely to be beneficial).

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TABLE 1 **Clinical scores for assessing severity of croup.**

Croup scoring systems
Downes and Raphaely croup score [72]
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 [56]
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)

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GRADE **Evaluation of interventions for Croup.**

Important outcomes	Need for additional medical attention / admission to hospital, Need for intubation, Symptom severity								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments in children with mild croup?									
1 (720) [29]	Symptom severity	Oral dexamethasone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (820) [28] [29]	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) [40]	Symptom severity	Nebulised budesonide versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of children with mild croup
4 (228) [40]	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) [40]	Symptom severity	Intramuscular or oral dexamethasone versus placebo	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results at different end points
2 (154) [41] [42]	Symptom severity	Intramuscular dexamethasone versus nebulised budesonide	4	–2	0	0	0	Low	Quality points deducted for sparse data and for flaws with blinding
1 (95) [41]	Need for additional medical attention / admission to hospital	Intramuscular dexamethasone versus nebulised budesonide	4	–2	0	0	0	Low	Quality points deducted for sparse data and for flaws with blinding
1 (198) [43]	Symptom severity	Oral dexamethasone versus nebulised budesonide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (278) [43] [44]	Need for additional medical attention / admission to hospital	Oral dexamethasone versus nebulised budesonide	4	0	0	0	0	High	
2 (232) [45] [46]	Need for additional medical attention / admission to hospital	Oral dexamethasone versus oral prednisolone	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results (including not carrying out a between-group assessment in one RCT). Consistency point deducted for conflicting results
2 (372) [40]	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
1 (120) [40]	Symptom severity	Higher-dose dexamethasone versus lower-dose dexamethasone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (168) [40] [46] [47]	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)

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Important outcomes	Need for additional medical attention / admission to hospital, Need for intubation, Symptom severity								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (198) [43]	Symptom severity	Oral dexamethasone plus nebulised budesonide versus nebulised budesonide alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (198) [43]	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 (1 event in total)
1 (198) [43]	Symptom severity	Oral dexamethasone plus nebulised budesonide versus oral dexamethasone alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (270) [43] [50]	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 small number of events (1 event in total in 1 RCT)
3 (87) [5] [52] [53]	Symptom severity	Nebulised adrenaline (epinephrine) versus placebo or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (29) [56]	Symptom severity	Adrenaline, nebulised 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 (31) [57]	Symptom severity	L-adrenaline versus racemic adrenaline (epinephrine)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (14) [58]	Symptom severity	Nebulisation alone versus nebulisation plus intermittent positive pressure breathing (IPPB)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (15) [60]	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) [63] [64]	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
What are the effects of treatments in children with impending respiratory failure because of severe croup?									
10 (1196) [49] [69]	Need for intubation	Corticosteroids versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of different doses and routes of corticosteroids

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.

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