Croup in children

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Croup develops in more than 80 000 Canadian children each year, making it the second most common cause of respiratory distress in the first decade of life.[1,2] It affects boys more than girls (1.4:1) and young children between 6 months and 3 years of age more commonly than younger infants, older children and adolescents.[2] Croup is frequently preceded by 24–72 hours of nonspecific cough, rhinorrhea, coryza and fever, with abrupt onset of barky cough, hoarse voice and, often, inspiratory stridor during the night. Croup is caused by a viral infection of the respiratory tract that causes edema and inflammation of the upper airway, and laryngeal mucosa resulting in narrowing in the subglottic region of the airway.[3] Human parainfluenza virus (types 1 and 3) is the most common pathogen,[4] but other causative viruses include influenza A and B viruses, respiratory syncytial virus, rhinovirus, coronavirus, human metapneumovirus and adenovirus.[2,5,6] Predictable seasonal patterns occur; the peak incidence of croup typically appears in late fall.[2] Annual patterns are also found, with about 50% more cases occurring in odd-numbered years,[4] correlating with prevalence of parainfluenza viruses in the community.

Croup symptoms are most often worse at night and can fluctuate rapidly depending on whether the child is calm or agitated.[7] Typically, symptoms are short-lived, with about 60% of children having resolution of the barky cough by 48 hours and less than 2% having symptoms persisting for longer than 5 nights.[7] Based on a review of utilization data from pediatric and general emergency departments in Alberta, at least two-thirds of children with croup have mild symptoms on presentation (personal observation). Population-based data indicate that 1%–5% of children with croup are admitted to hospital,[8–10] and, of those admitted, less than 3% receive intubation.[11–14] Death appears to be rare; based on a combination of data from several reports, we estimate death occurs in no more than 1 in 30 000 cases.[11–16]

This review will address the diagnosis and management of croup in children, specifically focusing on clinical assessment of disease severity to guide management decisions. The recommendations in this review are based primarily on robust systematic reviews and randomized controlled trials, as well as the clinical practice guideline for croup that was developed by the Toward Optimized Practice Program.17 Box 117–20 outlines the evidence used in this review.

Box 1: Evidence used in this review

We searched The Cochrane Library, MEDLINE and Embase databases from 1966 to Jan. 31, 2013, for relevant literature on the topic of croup, and for each clinical question used in this review. We sought high-quality evidence, particularly randomized clinical trials and systematic reviews of randomized clinical trials. Abstracts of articles identified in the searches were reviewed by both authors and selected for inclusion using validated criteria based on the work of Jadad and colleagues,[18,19] and Sackett and colleagues.[20] When no robust systematic reviews or large randomized clinical trials were identified, we included smaller randomized clinical trials, with consideration and discussion of studies' limitations. We also used the clinical practice guideline for the diagnosis and management of croup that was developed by the Toward Optimized Practice Program.[17]

When should croup be suspected?

In the child with classic signs and symptoms (i.e., abrupt onset of barky cough, hoarse voice, inspiratory stridor and, often, fever), the diagnosis of croup is straightforward and can be done reliably and safely by use of the history and physical examination alone. Although far less than 1% of children with acute-onset stridor have another diagnosis, clinicians should consider an alternate

Key points

- Caused by a viral upper respiratory infection, croup is the second most common cause of respiratory distress in children.
- Croup is characterized by the abrupt onset of barky cough, inspiratory stridor, hoarseness and respiratory distress.
- Oral corticosteroids reduce the severity and duration of respiratory distress, the need for hospital admission, airway intubations and repeat health care visits.
- For children with severe respiratory distress, nebulized epinephrine yields rapid but temporary relief.
- Most children, including many with severe respiratory distress at presentation, can be safely discharged home after treatment and a few hours of observation.

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cause if children do not respond to standard therapy or appear extremely unwell (Box 2).[3]

Bacterial tracheitis is an acute, potentially life-threatening illness that can present with sudden onset of stridor and respiratory distress resulting from the presence of thick membranous secretions within the trachea, and can be very challenging to distinguish from croup.[21] It often follows a viral-like respiratory illness from which a child appears to be recovering but then becomes acutely worse.[3] In a child who has an extremely unwell appearance and fever, and who shows little to no improvement after administration of nebulized epinephrine, bacterial tracheitis should be considered.[21] Treatment should include careful attention to the airway and preparation for possible endotracheal intubation, because thick secretions within the tracheal lumen can precipitate sudden airway obstruction.[21] The most frequently isolated bacterial pathogen is *Staphylococcus aureus*, but others have also been found, including streptococci (*Streptococcus pneumoniae* and group A streptococcus), *Moraxella catarrhalis*, *Haemophilus influenzae* and anaerobic bacteria.[3,21] Thus, initiation of broad-spectrum intravenous antibiotics is recommended.

Epiglottitis is now uncommonly seen since the implementation of vaccination programs targeting type B *Haemophilus influenzae,* but it should be considered in children who present with atypical croup symptoms.[22] Epiglottitis presents with an abrupt onset of dysphagia, drooling, anxiety and fever, but the barky cough typical of croup is absent. The child prefers to sit in an upright posture to maintain the airway in an optimal "sniffing" position.[3] A child with epiglottitis is at risk for progression to complete airway obstruction. Therefore, constant monitoring by physicians with the skill and experience to secure the child's airway is required, along with rapid initiation of broad-spectrum intravenous antibiotics.[21] Management in an intensive care setting is needed to monitor the child's airway until antibiotic treatment takes effect.[21]

Box 2: Differential diagnosis of stridor[3]

Common

- Croup

Less common

- Bacterial tracheitis
- Epiglottitis

Rare

- Upper-airway abscess
  - Peritonsillar
  - Retropharyngeal
- Foreign-body aspiration or ingestion
  - Tracheal
  - Esophageal
- Allergic reaction causing upper-airway edema
- Angioedema
- Laryngeal diphtheria

Other rare causes of stridor should be considered, depending on the presentation. Tracheal or esophageal foreign body can present with sudden onset of stridor, especially if there is a history of ingestion or choking on a foreign body.[3] Unlike in croup, prodromal viral symptoms or fever are usually absent unless the foreign body has been retained and secondary bacterial infection has occurred. Hoarse voice and barky cough are not typically observed. Other infectious causes, including retropharyngeal or peritonsillar abscess, can also present with stridor and dyspnea, torticollis, dysphagia, drooling, neck pain or stiffness, and cervical lymphadenopathy;[21] however, the barky cough characteristic of croup is not present. Allergic reactions or acute angioedema can occur at any age with the rapid onset of upper airway obstruction and stridor, along with other signs of allergy including urticarial skin rash.[3] Underlying causes of airway obstruction can worsen during a viral infection, and stridor can become more prominent, mimicking croup. Some examples are laryngomalacia, congenital subglottic stenosis, and vocal cord paresis or paralysis. However, in most cases, the child would have a prior history of at least mild stridor when not acutely sick.

What investigations, if any, are needed?

As noted previously, the diagnosis of croup is reliably determined by history and physical examination in most cases. In the child presenting with typical symptoms and absence of features suggestive of an alternate diagnosis, diagnostic studies are not helpful. Ancillary testing should be reserved for the rare atypical presentation.

According to the guideline developed by the Toward Optimized Practice Program, viral cultures and rapid antigen tests are not needed to confirm diagnosis or to direct therapy.[17] Radiographic studies are rarely indicated and should be considered only in a child with atypical symptoms in whom the diagnosis is unclear or who is not responding as expected to treatment.[17] If frontal radiography of the neck is performed, one may see narrowing of the subglottic space, often termed the steeple sign. However, the absence of this sign does not rule out croup. Radiographic studies should be used cautiously, if at all, in patients considered to have bacterial tracheitis or epiglottitis, because these studies can agitate children and trigger acute airway

obstruction.[17] If radiography is performed, the child must be monitored closely by personnel with skills and experience in the management of difficult airways.[21] Characteristic radiographic features include the following: for epiglottitis, an abnormally thickened epiglottis and arytenoepiglottic folds; for retropharyngeal abscess, bulging soft tissue of the posterior pharyngeal wall;[23] and for bacterial tracheitis, an irregular tracheal mucosa, or strands projecting into or across the tracheal lumen.[23] Although radiographs can be used to support an alternate diagnosis, a normal-appearing film does not necessarily rule out alternate diagnoses.

How is disease severity assessed?

Clinical assessment is used to assess disease severity in croup. Methods to objectively assess severity of respiratory distress in children have been proposed and examined, but are not practically applicable in the acute care setting.[24–27] Clinical trials have adopted a variety of clinical scores as outcome measures, but these scores have shown a lack of reliability when used by a wide range of clinicians.[28] However, elements of the clinical features in these scoring tools are useful in estimating severity of croup (Box 3).[17]

The severity of a child's symptoms at presentation can reliably guide management. Although there are no universally accepted standards for assessing disease severity, clinical scoring systems used for research all involve common signs. These include severity of chest wall indrawing, presence of stridor at rest or only with agitation, stridor only with inspiration or with both inspiration and expiration, cyanosis and lethargy.[25,29,30] In practice, most clinicians characterize respiratory distress as mild, moderate, severe or impending respiratory failure. One potential classification scheme using these categories was developed by expert consensus for the Toward Optimized Practice guideline and is shown in Box 3.[17] In this scheme, the absence of stridor at rest is the key feature that distinguishes mild from moderate respiratory distress, the absence of sustained agitation mainly distinguishes moderate from severe distress, and the absence of lethargy or cyanosis on room air mainly distinguishes severe distress from impending respiratory failure.[17]

How should croup be treated?

Care must be taken to keep the child comfortable and to avoid frightening the child, which can precipitate agitation and worsen symptoms.[17] This can best be accomplished by seating the child on the lap of the parent or caregiver. There is general consensus that if the child is in respiratory distress, then oxygen should be administered.[17,30] The most practical method of oxygen administration is via plastic tubing held by the parent to within a few centimetres of the child's nose and mouth (blow-by oxygen). Although this has not been formally studied, our practical bedside experience supports the use of blow-by oxygen in this clinical situation for improving oxygen saturation. Though traditionally used for decades in the acute care setting, humidified air (mist) has now been definitively shown to be ineffective in croup and should not be given.[31]

Pharmacotherapy

A simple treatment algorithm from the Toward Optimized Practice guideline based on assessment of severity of respiratory distress can be used to guide management of croup in children (Figure 1).[17] The algorithm outlines indications for using the 2 standard treatments, corticosteroids and nebulized epinephrine, which have been shown to be beneficial.

Corticosteroids

There is clear evidence that corticosteroids benefit children with symptoms of croup that range from mild to severe.[32–34] In a meta-analysis of data from 10 clinical trials that included children with severe croup who required intensive care, corticosteroid treatment decreased endotracheal intubation by fivefold (odds ratio [OR] 0.21, 95% confidence interval [CI] 0.05 to 0.84).[33] A randomized clinical trial found that, in children admitted to hospital, corticosteroid treatment reduced length of hospital

Box 3: Level of severity of croup and clinical features[17]

Mild
- Barky cough: occasional
- Stridor: none to limited at rest
- Indrawing (suprasternal and/or intercostal): none to mild

Moderate
- Barky cough: frequent
- Stridor: easily audible at rest
- Indrawing (suprasternal and/or intercostal): visible at rest
- Distress or agitation: none to limited

Severe
- Barky cough: frequent
- Stridor: prominent inspiratory and occasionally expiratory
- Indrawing (suprasternal and/or intercostal): marked or severe
- Distress or agitation: substantial
- Lethargy may be present

Impending respiratory failure
- Barky cough: often not prominent because of fatigue
- Stridor: audible at rest, but may be quiet or hard to hear
- Indrawing: may not be marked
- Lethargy or decreased level of consciousness
- Dusky or cyanotic without supplemental oxygen

stay by one-third compared with placebo (duration of hospital stay: 12 h for dexamethasone and 13 h for budesonide v. 20 h for placebo, $p < 0.03$).[35] In children who presented to emergency departments with moderate to severe croup included in a randomized clinical trial, corticosteroid treatment reduced admission rates by half compared with placebo (35% v. 67%, $p < 0.001$).[36] A randomized placebo-controlled trial included 720 children with mild croup seen in an emer-

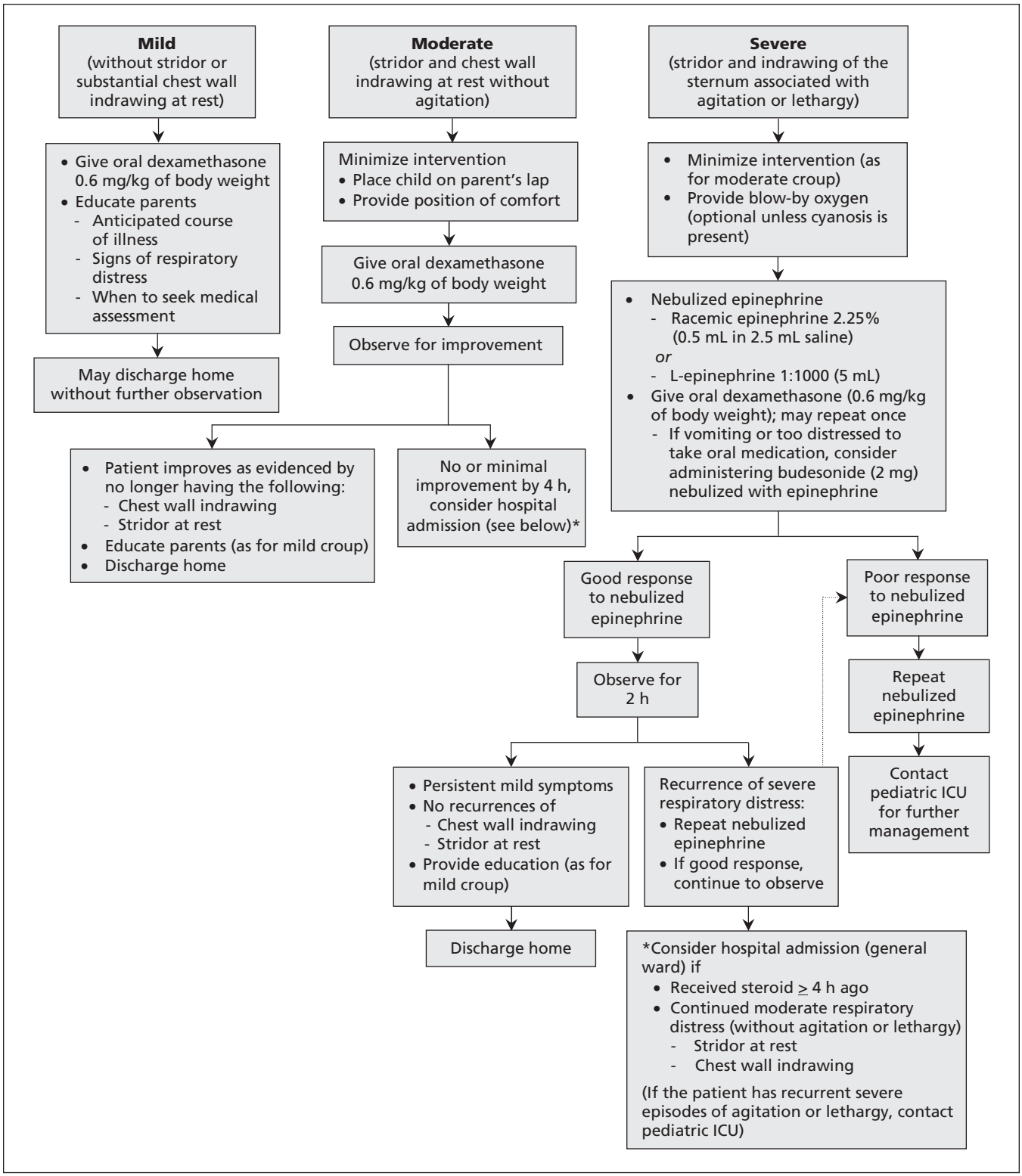

Figure 1: Algorithm for the outpatient management of croup in children, by level of severity. ICU = intensive care unit. Adapted, with permission, from the Toward Optimized Practice Program.[17]

gency department and showed that corticosteroid treatment reduced return medical visits by half (7% v. 15%, $p < 0.001$), resulted in less stress and loss of sleep by parents, and reduced overall health care costs.[37] Whereas corticosteroids appear to start reducing respiratory distress within an hour of oral administration,[38,39] the drug effect continues to increase for at least 10 hours after administration.[36] The reduction in the rate of use of health services, such as hospital admissions, is not significant until 3–6 hours after administration of corticosteroids, which supports an observation period of that length before the decision is made whether to admit a child to hospital.[36]

Published trials have used several different types of corticosteroid and modes of administration. Two randomized controlled trials compared the 2 most commonly used oral corticosteroids, dexamethasone and prednisolone. In the first study, a single oral dose of dexamethasone was found to be superior to prednisolone in reducing the rate of return to medical care (reduction of 22%, 95% CI 8% to 35%).[40] The other study compared oral dexamethasone with oral prednisolone and found no difference in change in clinical croup score at 4 hours ($p = 0.479$) or in rate of return for medical care.[41]

The standard dose of dexamethasone is 0.6 mg/kg, but doses as low as 0.15 mg/kg have been studied in 4 randomized trials. None of these trials showed significant differences between low-dose (0.15 mg/kg) and standard-dose (0.6 mg/kg) dexamethasone, though their samples were small and none were designed as noninferiority studies.[38,41–43] In contrast, a meta-analysis of 6 studies on children admitted to hospital with croup found that higher doses of corticosteroid were associated with a higher proportion of children showing clinical improvement.[33] This type of analysis, given the wide range of study designs, may yield misleading results. Consequently, definitive recommendations regarding dosing are not appropriate, and, for the moment, clinicians can reasonably defend using either low-dose (0.15 mg/kg) or standard-dose (0.6 mg/kg) dexamethasone.

The route of administration of corticosteroid (oral, nebulized or intramuscular injection) has received extensive study. Three randomized clinical trials comparing nebulized budesonide with either oral or intramuscular dexamethasone did not find a difference in duration of hospital stay (13 h for budesonide v. 12 h for intramuscular dexamethasone, nonsignificant),[35] rate of admission to hospital (35% for budesonide v. 17% for intramuscular dexamethasone, $p = 0.18$)[36] or clinical croup score at 4 hours ($p = 0.70$).[44] Three randomized clinical trials have shown that intramuscular dexamethasone does not provide benefit over oral corticosteroid in either change in clinical croup score at 4 hours ($p = 0.18$),[45] resolution of croup symptoms at 24 hours (2% for intramuscular v. 8% for oral administration, nonsignificant)[46] or rate of return to medical care (32% for intramuscular v. 25% for oral administration, $p = 0.198$).[47] The kinetics of oral dosing also show a rapid peak in serum levels occurring within 1 hour.[48] However, nebulized administration could be considered in the rare case of a patient with sustained vomiting.

No published studies have compared the effectiveness of single-dose to multiple-dose corticosteroids. In a randomized trial that included children with mild croup treated with a single oral dose of dexamethasone, the symptoms of children in the placebo group had largely resolved within 48 hours after enrolment.[37] Hence, it is unlikely that treatment of mild croup with additional doses would provide substantial benefit. Children with longer-lasting symptoms who are admitted to hospital may achieve benefit from further doses; however, this question has yet to be addressed by formal study.

Nebulized epinephrine

Although comparatively few randomized trials have examined the benefit of nebulized epinephrine in children with croup,[29,34,49,50] their results are sufficiently consistent and compelling to support its routine use to provide rapid, short-term relief of severe respiratory distress.[51] These trials have shown onset of effect within 10 minutes and waning of effect between 1 and 2 hours.[29,49,50] Whereas the few published trials have not shown any consistent benefit beyond short-term improvement in clinical score,[51] data from an early historical cohort study showed a decreased number of intubations and deaths in children with croup following introduction of treatment with epinephrine.[52] Evidence for the safety of using epinephrine in outpatients comes from 5 prospective cohort studies that included a total of 253 children who received epinephrine and dexamethasone.[36,53–56] The studies found that 12 (5%) children returned for care within 48–72 hours after discharge, 6 (2%) were subsequently admitted to hospital and none had any other adverse event.[36,53–56] A Cochrane review that included data from 8 randomized clinical trials found that treatment with nebulized epinephrine was associated with important clinical improvement in croup score 30 minutes following administration (standardized mean difference –1.56, 95% CI –2.23 to –0.89).[51] In children admitted to hospital with croup, length of stay was shorter in the group that received nebulized epinephrine as compared with placebo (mean difference –32 h, 95% CI –59.1 to –4.9).[51]

Studies of nebulized epinephrine treatment of croup have used both racemic and L-epinephrine. One small trial found that L-epinephrine (5.0 mL,

0.1% [1:1000]) was as effective and safe as racemic epinephrine (0.5 mL, 2.25%).[57] The Cochrane review compared racemic and L-epinephrine and found no difference in croup score at 30 minutes (standardized mean difference 0.33, 95% CI –0.42 to 1.08), but at 2 hours, L-epinephrine showed a small but significant reduction in croup score compared with racemic epinephrine (standardized mean difference 0.87, 95% CI 0.09 to 1.65).[51] L-epinephrine is now widely used in place of racemic epinephrine, as the latter is no longer commercially available in Canada.

Other pharmacotherapies

North American studies of practice variation suggest frequent use of several other pharmaceutical agents including salbutamol and antibiotics to treat croup in children.[58] Although no randomized trials have been published assessing the effectiveness of these agents, their use, based on theoretical considerations, should not provide benefit. Salbutamol, a selective β_2 agonist, is unlikely to reverse the narrowing of the upper airway because it does not contain smooth muscle, and antibiotics are unlikely to shorten the duration of symptoms because croup is caused by a viral infection.[30]

Heliox is used in some North American centres, although there is insufficient evidence to support its general use. Heliox, a mixture of low-density helium (in place of nitrogen) with oxygen, is thought to decrease airflow turbulence through a narrowed airway, thereby decreasing the work of breathing. However, a Cochrane systematic review of clinical trial data did not show a clinically or statistically significant benefit in children with moderate or severe croup.[59]

When is it safe for a child to be discharged home?

The Toward Optimized Practice guideline suggests that children with no stridor or chest wall indrawing at rest may be safely discharged home, whereas children with persistent stridor and chest wall indrawing more than 4 hours after treatment with corticosteroids should be admitted to hospital (Figure 1).[17] The guideline also suggests that sociodemographic or conditional factors such as parents' dependence on public transport, living a long distance from medical care and inclement weather should be considered.[17]

Little rigorous evidence has been published to guide the development of standards for when it is safe to discharge children home or when it is necessary to admit them to hospital. A prospective observational study, conducted before either corticosteroids or epinephrine were routinely used in outpatients, included 527 children with croup who were seen in an emergency department.[60] The study found that children with sternal and chest wall indrawing at initial presentation had a substantially higher risk for longer hospital stays and intubation compared with children without indrawing.[60]

Controversies in treatment and gaps in knowledge

After decades of controversy and rigorous study, corticosteroid treatment has been established as the treatment of choice for children with croup of all levels of severity. However, areas requiring further study are the most effective corticosteroid dose range and whether there is benefit from repeated doses of corticosteroid in the treatment of more severe croup. Although there is comparatively less literature on epinephrine treatment, there is sufficiently strong evidence to support its use for the temporary relief of upper airway obstruction in more severe cases of croup. On the other hand, although mist therapy was firmly entrenched in the arsenal of outpatient croup treatment for many years, it has now been shown to be ineffective and consequently is rarely used in the acute care setting.

Conclusion

Treatment of all children with croup with corticosteroids and those with severe respiratory distress with nebulized epinephrine can substantially decrease intubations, hospital admissions and return visits for medical care, thereby decreasing health care costs while improving children's outcomes and lessening the burden of the disease on children's families.

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