REVIEW

Italian Pediatric Respiratory Society (SIMRI) position paper on treatment of croup in childhood: an expert group statement approved by SIMRI **Advocacy Council and Executive Committee**

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Supplementary Table 1 can be found at: https://www.pediatric-respiratory-journal.com/

ABSTRACT

Croup, also known as acute laryngotracheobronchitis, is common in the first years of life and is mainly caused by respiratory viral infections leading to laryngeal edema with subsequent onset of hoarseness, barking cough and stridor. Although most of the cases are classified as mild, some patients may show severe respiratory distress requiring up to intensive care. Moreover, even mild and moderate cases result in a high rate of pediatric emergency departments visits since croup symptoms, often occurring at night, can be frightening for caregivers. Treatment of pediatric croup is based on corticosteroids administration, with the addition of inhaled epinephrine in severe cases. However, croup management is still highly heterogeneous worldwide due to the paucity of dedicated randomized controlled trials. This statement outlines the most recent evidence supporting the use of corticosteroids and epinephrine in the treatment of croup in childhood and reports the recommendations for optimal treatment from the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili - SIMRI).

IMPACT STATEMENT

Systemic corticosteroids represent the first-line treatment for managing croup in childhood, with the addition of inhaled epinephrine in severe cases. However, management of this condition is heterogeneous worldwide due to the lack of evidence-based guidelines and paucity of dedicated randomized clinical trials. This statement outlines the evidence supporting the use of corticosteroids and epinephrine in the treatment of croup in childhood and reports the recommendations of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili - SIMRI) in treating this condition. The statement will have a significant role in improving croup treatment at least at a national level.

INTRODUCTION

Croup, also known as acute laryngotracheobronchitis, is a prevalent respiratory condition in young children. It is a frequent cause for pediatric healthcare visits, accounting for approximately 15% of all respiratory-related healthcare visits in this age group. Croup typically leads to obstructions in the upper airways, character-

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KEY WORDS

Children; inhaled corticosteroids; larynx; laryngotracheobronchitis; respiratory infections.

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ized by distinctive symptoms including hoarseness, a barking cough, stridor and/or noisy breathing. Children may also experience difficulty with inhalation and varying degrees of respiratory distress that can worsen rapidly (1). While usually self-limiting, croup places a significant burden on healthcare resources due to frequent doctor visits, emergency room use, and occasional hospitalization in a small proportion of cases. This condition predominantly occurs during the fall and winter months, affecting boys more often than girls (ratio of 1.5:1). Although most common between six months and three years of age, with peak incidence at two years, croup can affect children up to 6 years old, and even younger infants in rare cases (2). In children <2 years the majority of cases (around 85%) are classified as mild, potentially to be managed at home by educating parents or through greater access to primary care (3). Less than 5% of children with croup require hospitalization, and only 1-3% need intubation. The prognosis is generally favorable, with a mortality rate of less than 0.5%, even in intubated patients (4). Recurrent croup, defined as more than two episodes per year, should be viewed as a potential indicator of an underlying airway abnormality. This could be structural, as seen in children with a history of intubation or prematurity, or inflammatory, as in cases with a history suggestive of asthma or gastroesophageal reflux. Such cases warrant further investigation to identify the underlying cause (5, 6).

Before the 20th century, the term "croup" was mainly used to refer to diphtheria, while viral infections are currently the most common cause, identified in up to 80% of patients, and triggering inflammation and swelling in the subglottic region and laryngeal mucosa, leading to respiratory difficulties and stridor. Parainfluenza viruses are implicated in 75% of cases, with human parainfluenza virus 1 being the most frequent. Other viral causes include influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, and enterovirus (7). Nowadays, croup is rarely caused by bacteria such as Mycoplasma pneumoniae and Corynebacterium diphtheriae (8). Notably, croup can be caused also by SARS-CoV-2 (9, 10). Viral croup usually presents with 12-72 hours of lowgrade fever and a runny nose. The progressive narrowing of the larynx results in stridor, hoarseness and a barking cough, often accompanied by an increased respiratory rate and chest retractions. Symptoms may worsen with emotional distress, are often more pronounced at night (11) and typically resolve spontaneously within 48 hours to one week. Diagnosis is primarily based on clinical findings so that diagnostic testing is usually unnecessary. A blood count can help differentiate viral croup from bacterial causes of stridor (like epiglottitis, peritonsillar abscess, or retropharyngeal abscess), with lymphocytosis suggesting a viral etiology. Viral cultures and rapid antigen tests may be considered if initial treatment fails. Imaging is not routinely recommended, since only in 50% of cases croup exhibits the "steeple sign" on X-rays, indicative of glottic and subglottic narrowing (12, 13). Computed tomography of the neck may be reserved for cases with suspected abscess, tumor, or foreign body aspiration. Laryngoscopy can be considered to confirm the diagnosis in atypical presentations (2, 14). As a matter of fact, other conditions can cause acute and recurrent stridor in children, so that differential diagnosis is of particular importance in such cases (6, 15, 16). Differentiating croup from epiglottitis is critical, as the treatment and prognosis for these conditions differ significantly due to the potential for rapid deterioration in epiglottitis. Although epiglottitis can also present with cough, fever, and difficulty breathing, it is more likely to manifest initially with a sore throat (17). Management of croup is based on its severity. A number of different scores have been used to classify the severity of disease in patients with croup. The most commonly used scoring system is the Westley Croup Score (WCS) which is based on the assessment of the following clinical signs: level of consciousness, cyanosis, stridor, air entry, and retractions. The sum of the partial scores related to each clinical sign allows us to classify croup into mild, moderate, and severe according to a total score of ≤2, 3 to 7 and 8 to 11, respectively. A condition of impending respiratory failure is identified when the total score is ≥12 (**Table 1**) (18, 19). Another croup scoring system is the Taussig Croup Score which relies on five components such as cyanosis, air entry, retractions, level of consciousness, and stridor, for a maximum of 15 points. A higher score represents a more abnormal clinical examination (20) (Table 1).

METHODOLOGY

This position paper was developed by a panel of experts identified by SIMRI Executive Committee during the

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Table 1. Most commonly used clinical scores to classify the severity of croup. **1a**. Westley Croup Score (WCS): A total score of ≤2 indicates mild, 3-7 moderate, 8-11 severe croup, ≥12 impending respiratory failure (18, 19).

	SCORE				
ITEM	0			5	
LEVEL OF CONSCIOUSNESS	Normal (including sleep) □			Disoriented	
	0		4	5	
CYANOSIS	None		Cyanosis	Cyanosis at rest	
			with agitation \Box		
	0	1	2		
STRIDOR	None	When Agitated □	At rest		
	0	1	2		
AIR ENTRY	Normal	Decreased □	Markedly decreased □		
	0	1	2	3	
RETRACTIONS	None □	Mild □	Moderate □	Severe	

1b. Taussig Croup Score. A higher score (up to a maximum of 15 points) indicates a more abnormal clinical examination (20).

ITEM	0	1	2	3
SKIN COLOUR	Normal	Dusky	Cyanotic in room air	Cyanotic on 30% oxygen
		Ц		Ш
AIR ENTRY	Normal	Mildly decreased	Moderately decreased	Substantially decreased
RETRACTIONS	None □	Mild □	Moderate □	Severe
CONSCIOUSNESS	Normal	Restless	Lethargy (depressed)	Obtunded
STRIDOR	None	Mild	Moderate	Severe or absent in the presence of severe obstruction

XXVIIIth SIMRI national congress held in Turin in October 2024: the panel includes pediatric pulmonologists and researchers with proved experience in the field and in active clinical practice, who were asked to propose and produce position statements on cornerstone subjects in Pediatric Pulmonology, to improve the management of the most common respiratory conditions in our country. Considering the lack of national guidelines and the heterogeneous data available on management of croup in Italy, the panel proposed to develop a position paper on

this condition. Following approval by SIMRI Executive committee, a conference call was held in November 2024 to disclosure potential conflicts of interest, assign tasks and settle the timing of the project. Moreover, four main subjects regarding croup were identified, which include: role of 1) systemic corticosteroids, 2) inhaled corticosteroids, 3) inhaled epinephrine, 4) outdoor cold air/room temperature exposure and Heliox. At least two panelists performed a systematic literature review in December 2024 for each item, including all relevant publications in

English from PubMed, EMBASE, Cochrane Database of Systematic Reviews, Web of Science, and in January 2025 a list of recommendations was provided and collegially discussed. In February 2025 the first draft of the position statement was submitted to SIMRI Executive Committee and SIMRI Advocacy Committee: after appropriate review, the final version of the statement was completed in March 2025 and received formal approval before submission.

TREATMENT OF CROUP

Role of systemic corticosteroids

Efficacy of corticosteroids compared to placebo

Since their introduction in the clinical practice in the 90s to treat croup, corticosteroids (CS) have rapidly become the cornerstone of the management of this condition (21), which should be guided by illness severity. The use of CS is supported by their anti-inflammatory properties, which decrease capillary dilation and permeability, reducing the swelling of the laryngeal mucosal, improving the respiratory effort and facilitating air entry into the airways (5). However, data is limited, with a few Randomized Controlled Trials (RCT) evaluating different therapeutic approaches to croup in childhood. Dexamethasone is the most studied systemic steroid for the treatment of croup, being a long-acting steroid requiring less frequent dosing (onset of action in 30-60 minutes, peaking after 6-12 hours and lasting up to 36-72 hours), with a 25 times greater potency than short-acting products. The traditional dosage for croup management is 0.6 mg/kg. It can be administered via parental, oral or nebulized routes, with the oral one preferred due to its ease of use and patient tolerance (22). The most recent Cochrane systematic review on glucocorticoids for the treatment of croup in children confirms their mainstay role for reducing symptoms of croup at two hours, shortening hospital stays, and reducing the rate of return visits or (re)admissions. Across various levels of croup severity, various delivery methods of glucocorticoids (intramuscular, intravenous, oral, or inhaled) proved to be effective (23). The review included 45 RCTs conducted between 1964 and 2021 and involving 5888 pediatric inpatients and outpatients diagnosed with croup (23), showing that the administration of any CS was followed by 1) a greater reduction in croup score at 2, 6, and 12 hours after treatment; 2) a decreased rate of return visits or hospital (re)admissions; and 3) shorter hospital stays when compared to placebo. However, there was no reported difference between CS and placebo in the use of additional treatment such as antibiotics, epinephrine, supplementary steroids, or tracheal intubation (23).

Dexamethasone vs other corticosteroids

When considering different systemic CS, betamethasone shows a similar profile as dexamethasone in terms of onset of action, half-life and anti-inflammatory properties. Nevertheless, only a single RCT has compared dexamethasone to betamethasone, showing that dexamethasone resulted in a greater reduction in croup score after two (SMD-0.62, 95% CI -1.17 to -0.06; P = 0.03; 1 RCT, 52 children; low-certainty evidence) and six hours (SMD -0.67, 95% CI -1.23 to -0.11; P = 0.02; 1 RCT, 52 children; low-certainty evidence), while no difference in the rate of re-examinations between groups was found (24). In this study, patients were randomized to receive either a high dose of intramuscular dexamethasone (26 patients, 0.6 mg/kg) or oral betamethasone (26 patients, 0.4 mg/kg) and those treated with dexamethasone exhibited a higher risk of requiring epinephrine (24). However, this result may have been influenced by a higher mean croup score at baseline in the dexamethasone group, despite random assignment. As for prednisone and prednisolone, these are considered as viable options in several studies, despite their palatability: data from the four available studies comparing oral dexamethasone to prednisolone show no superior efficacy for dexamethasone in reducing WCS at 2 and 6-hour post-treatment (25-27). Nevertheless, dexamethasone reduced return visits and hospital (re) admissions for croup when used in Emergency Departments (ED) or hospital settings, while no significant difference has been observed between dexamethasone and prednisolone regarding the use of additional epinephrine, or length of in the ED and hospital stay (25-28). Dexamethasone is associated with a lower need for supplemental CS compared to prednisolone (22, 25) (Suppl tab. 1).

Dexamethasone dosage and administration route

Comparison between oral and intramuscular administration route of dexamethasone at the same dosage (0.6 mg/kg) reveals no difference in the rate of return visits or admissions to the hospital, or the need for addi-

tional treatments such as epinephrine, antibiotics, supplementary steroids, or intubation (22, 29, 30). Focusing on the dosage, 0.6 mg/kg of dexamethasone reduces croup severity at 24 hours, if compared to the dosage of 0.15 mg/kg, but no significant changes in severity of WCS are observed between these doses at 2, 6, and 12 hours. In addition, no difference between dexamethasone doses is recorded in terms of return visits or (re) admissions, ED or hospital length of stay, or requirement for additional treatments (epinephrine, additional steroids, or tracheal intubation) (25, 27, 30-33). Based on the above analysis, dexamethasone, at any dosage (both 0.6 mg/kg and 0.15 mg/kg) and administered via any route (both oral and intramuscular), appears to be effective in the treatment of viral croup. However, given the comparable efficacy across doses and to minimize potential side effects, a lower dose of 0.15 mg/kg of dexamethasone may be considered as an alternative to the standard 0.6 mg/kg dose (22, 33), but more studies are needed to support this strategy. Notably, no significant adverse events have been reported in patients treated properly with systemic CS, confirming their safety profile, and supporting their prescription in croup (22) (Suppl tab. 1).

Role of inhaled corticosteroids

Inhaled CS have long and effectively been used in croup management, since high doses of inhaled CS may have a faster anti-edema effect than systemic CS, estimated in minutes more than hours, which is due to their "membrane" or "non-genomic" effect: CS bind an endocellular receptor determining an increase in smooth muscle tone of the laryngeal and bronchial vessels, with consequent vasoconstriction and reduction of local oedema (the so-called bleaching effect) (34). Such an effect is particularly pronounced for budesonide, which is therefore the most studied and used nebulized CS to treat croup in childhood, at least in Italy (35, 36). When nebulized, budesonide shows onset of action in 30-60 minutes, peaking after 1-2 hours, and a single dose of 2 mg has been shown to be effective in all grades of severity, with a marked reduction of symptoms in the first 24 hours (22). Nebulization should always be the preferred route for inhalation therapy in croup, since it allows that most of the drug settle in the upper airways, while pressurized metered dose inhalers are not recommended

since most of their molecules reach the lower airways (34, 37, 38). In the recent Cochrane review on the role of CS in pediatric croup, only 4 RCT comparing inhaled budesonide and systemic dexamethasone have been included in the meta-analysis, despite their heterogeneity: all the studies showed efficacy of budesonide over placebo at all levels of severity (patients with WCS ≥3, with one study excluding patents with score >6), but dexamethasone was slightly superior to budesonide in improving symptoms scores at 6 and 12 hours and reducing the risk of additional treatment with epinephrine, while there was no significant difference in return visits or readmission rates as well as length in hospital/ ED stay (22) (Suppl tab. 1). Notably, two of these studies compared inhaled budesonide (1 or 4 mg) to intramuscular dexamethasone (0.6 mg/kg) (39, 40) while the other two compared inhaled budesonide (2 mg) with oral dexamethasone (0.6 mg/kg) (41, 42). Taken together, these data suggest that nebulized budesonide can be administered as an alternative for children who do not tolerate oral drugs or considering availability, cost and ease of administration of other oral CS, and as an alternative to intramuscular dexamethasone too. As for the use of budesonide as a combination therapy with dexamethasone, only two RCT have been performed, showing conflicting results, with one reporting no benefit in adding 2 mg inhaled budesonide to a single oral dose of 0,15 mg/kg dexamethasone (43) and the other reporting clinically significant faster response when added to a single oral dose of 0,6 mg/kg dexamethasone (44). Treatment with budesonide was found to be safe, with only one case of oral thrush in the budesonide group in the study by Klassen et al. (42). Studies are too scarce to determine which is the best dose for budesonide, but in most of the studies evaluating such molecule 2 mg was the chosen dosage. As for other CS, we found 2 RCT on beclomethasone dipropionate and fluticasone propionate respectively. In the first one, the administration of 200 mcg via metered dose inhaler and spacer was found as effective as a single dose of 0.6 mg/kg intramuscular dexamethasone to treat mild to moderate croup (45), while in the second one, 2000 mcg of fluticasone propionate administered with metered dose inhaler and spacer showed no therapeutical effect in a small group of children hospitalized with moderate croup (46).

Role of nebulized epinephrine

Nebulized epinephrine (also known as adrenaline) has become a standard treatment for moderate to severe croup, since it decreases mucosal oedema through vasoconstriction by stimulating α-adrenergic receptors in subglottic mucous membranes (2). The clinical effect starts at 30 min, is sustained for at least 1 h, but disappears after 2 h. Both racemic epinephrine (that is composed of equal ratio of L-epinephrine and D-epinephrine) and L-epinephrine have been studied in croup. In 2013 a Cochrane systematic review evaluated the efficacy and safety of nebulized epinephrine versus placebo in children with croup (47). The review evaluated six studies including 183 participants with moderate to severe croup. Nebulized epinephrine (racemic epinephrine in five studies, L□epinephrine in one study) was associated with higher croup score improvement at 30 minutes, but not two- and six-hours post-treatment and significantly shorter hospital stay than placebo. In one small study (28 participants, average age of 11 months) comparing racemic and L-epinephrine (0.5 ml of 2.25% and 5 ml of 1:1000 dilution, respectively), no difference in croup score was found after 30 minutes, while after two hours, L-epinephrine showed significant score reduction (48) (Suppl tab. 1). Eghbali et al. in 2016 demonstrated that nebulized L-epinephrine (0.5 mg/kg/dose, maximum dose: 5 ml) in addiction to a single dose of intramuscular dexamethasone (0.6 mg/kg, maximum dose: 8 mg) reduced mild and moderate symptoms of croup more effectively over time without cardiac side effects (49). Epinephrine should be administered in addition to glucocorticoids in children with moderate to severe croup at a dose of 0.25-0.5 mL/kg (1:1000) plus 3 ml saline via nebulizer. However, evidence on the optimal dosage is limited. Children who received epinephrine should be observed for at least 2 hours (even if the optimal duration of the observation has not been established yet) to evaluate symptoms relapse as the effect of epinephrine wanes (50). The risk of a rebound was disavowed because studies demonstrated that no children was clinically worse hours after epinephrine administration and the relapsed symptoms were less marked in children who received also CS (51). Repeated doses are associated with a low increase in heart rate for up to 60 min after treatment. Pallor was also noted in some trials. Epinephrine can be repeated every 2 hr in case of severe upper airway obstruction, but the patient should be continuously electrocardiographic monitored (2). Ventricular tachycardia with a small myocardial infarct in a child with an anatomically normal heart with normal coronary circulation who required multiple doses of nebulized racemic epinephrine to treat severe croup has been reported anecdotically (52). The only relative contraindication for nebulized epinephrine is ventricular outflow tract obstruction (53).

Role of outdoor cold air/room temperature exposure and Heliox

Exposure to cold air and Heliox have been studied to treat croup, but these treatments are not universally applicable or as robustly effective as CS. An open-label, single-center RCT recently evaluated the therapeutic effects of exposure to cold outdoor air for 30 minutes in 118 children (aged 3 months to 10 years) with croup symptoms with WCS >2, suggesting that brief exposure to cold air (temperature below 10°C), can alleviate the severity of croup symptoms of moderate intensity. In this study the effectiveness of such treatment was comparable to the administration of a single 0.6 mg/kg dose oral dexamethasone, particularly when considering the improvement or resolution of symptoms 60 minutes after treatment (54). Heliox is a biologically inert, colourless, odourless, and non- combustible gas mixture of helium and oxygen (at 70:30 or 80:20 ratio), with lower density than air (helium is in place of nitrogen) or oxygen. Heliox should decrease airflow turbulence due to its reduced density but has a limitation due to the low fractional concentration of oxygen which should be considered in case of hypoxia. A Cochrane review on Heliox for croup in children included 3 RCT (91 children aged 6 months - 4 years) conducted in ED and concluded that it may not be more effective than 30% humidified oxygen for children with mild croup but may be beneficial in the short term for children with moderate croup treated with dexamethasone. In the study by Weber et al (55), the effect of Heliox was found to be similar to 100% oxygen given with one or two doses of epinephrine (1:1000, 0.5 mL/kg, max 5 mL). Adverse events were not reported, but it is unclear if these were monitored in the included studies. Further Heliox versus standard treatment RCT are certainly needed to understand the role of Heliox in moderate-severe croup (19).

TREATMENT OF CROUP IN REAL LIFE: WHAT DOES SIMRI SUGGEST?

Treatment of croup is highly heterogeneous at a world level, due to the paucity of studies supporting the preferred CS molecule, route of administration, and dosage. To our knowledge, no guidelines are available so far, but only clinical practice algorithms. In Italy, a recent online survey administered to a sample of primary care and hospital-based pediatricians (326 and 323 participated, respectively) showed extensive use of inhaled CS (mostly budesonide) for mild and moderate croup as well as of nebulized epinephrine for mild cases. As for systemic CS, the most prescribed was oral betamethasone, both in ED and as a short course home therapy. The Authors found also a relatively poor application of the WCS to assess disease severity, especially among primary care physicians (35). The same research group conducted an observational, retrospective cohort study by reviewing the medical records of more than 650 patients discharged with a diagnosis of croup from two Italian pediatric ED (82%, 16% and 1.9% had mild, moderate or severe crop respectively), confirming that inhaled CS were prescribed in more than 54% of cases (budesonide was the only inhaled CS prescribed), while oral CS were given to 35.8% patients (betamethasone in more than 90% of cases; in 75.7% of cases at 0.1 mg/kg). Almost all patients received a prescription for home therapy for a few days (mostly inhaled budesonide, often associated with oral betamethasone). However, no difference was found in terms of hospitalization rates, return visits rates and length of hospital stay among the different treatment groups (36). Even if croup is usually mild and responds to both inhaled and oral CS in most cases, a more unified approach and adequate management should be sought, especially in our country, since it has been estimated that the high rate of home therapy prescription costs our national health system ten times more than providing the single-shot CS administration in the ED (36). Taking all this into consideration and the available evidence, we suggest implementing the use of CS in the ED and outpatient services in case of mild or moderate croup (Table 2). Oral dexamethasone should be preferred at the dose of 0.6 mg/kg, until further studies prove that lower dosages could be equally effective. When dexamethasone is not available or difficult to administer, oral betamethasone or prednisolone could be considered as a second option on a case-bycase basis, but it is difficult to state at what dosage so far. Other alternatives to the single oral dose of CS are 2 mg of nebulized budesonide or intramuscular administration of dexamethasone (0.6 mg/kg). Combination therapy with budesonide and dexamethasone may be beneficial but data are too limited to suggest such treatment, which should be avoided so far. Nebulized epinephrine should be administered in severe cases in association with CS. Heliox and cold air may be useful in croup treatment.

SIMRI advocates for improved management of croup, including in mild cases, emphasizing the importance of enhancing prescription practices to ensure greater

Table 2. SIMRI recommendations for the treatment of croup in children.

CRITICAL POINTS BASED ON EVIDENCE FROM THE LITERATURE

Croup should be diagnosed clinically and its severity assessed through scoring systems.

The preferred single dose of oral CS should be of dexamethasone (0.6 mg/kg; 0.15 may be effective) *.

As for alternative treatments, nebulized budesonide (2 mg) or intramuscular administration of CS (dexamethasone, 0.6 mg/kg) are feasible

Other systemic CS could be used when dexamethasone is not available or not easy to administer.

Nebulized epinephrine (0.25-0.5 mL/kg (1:1000), max 5 mg) must be administered in combination with systemic CS in severe cases.

Cold air exposure is beneficial; Heliox, where available, could be useful to treat pediatric croup.

WHAT NOT TO DO IN CLINICAL PRACTICE

Combination therapy of inhaled and systemic CS.

Home therapy (limited exception on a case-by-case basis).

^{*}In Italy, tablets and drop formulations are available.

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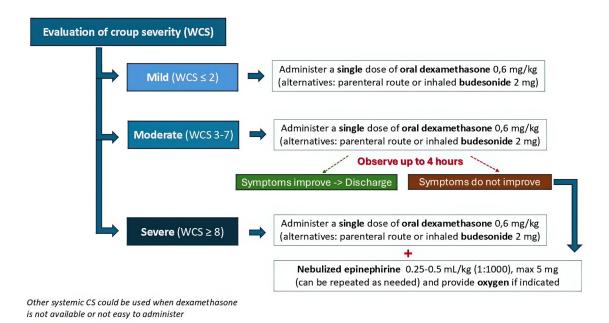


Figure 1. Algorithm for initial management of croup in the ED or primary care.

safety, appropriateness, and to reduce the economic impact of prescribing errors. SIMRI encourages adherence to current guidelines and recommendations, both in primary care and emergency department settings and remains committed to supporting this effort by offering ongoing residential and online training programs. We also strongly advocate for the need for more RCT on a large number of patients.

CONCLUSIONS

Despite being a very common condition among young children, croup continues to be heterogeneously treated worldwide. Treatment of pediatric croup should be based on a single dose of systemic corticosteroid, with inhaled budesonide as an alternative, with the addition of inhaled epinephrine in severe cases (**Figure 1**). SIMRI advocates for the need of dedicated pediatric RCT in order to evaluate whether other approaches may be feasible.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have no conflict of interests relevant to this article to disclose.

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Author contributions

MEDC and SLG conceptualized the study; MEDC, GFen, GFer, RN, FP and SLG drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. The members of SIMRI Advocacy Council and Executive Committee contributed to drafting the paper based on their expertise on the subject. All authors discussed and approved the final recommendations. All authors read, critically reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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