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Pharmacotherapy of acute stenosing laryngotracheitis. Which drugs are evidence-based?

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Acute stenosing laryngotracheitis is the most common cause of upper respiratory tract obstruction in children aged from 6 months to 6 years old and is a rapidly developing syndrome, which includes barking cough, hoarseness and stridor. The disease can be associated with development of respiratory failure and asphyxia, so its rational pharmacotherapy should be well known to pediatricians and emergency physicians. This review describes the drugs, effectiveness of which has been confirmed by credible evidence.

Keywords: *Acute stenosing laryngotracheitis: its symptoms, course, complications and treatment.*

Acute stenosing laryngotracheitis (ASLT) is the most common cause of upper airway obstruction in children aged 6 months - 6 years old which is a rapidly developing syndrome, including a barking cough, hoarseness, stridor and respiratory failure; preceded by rhinitis and increased temperature [1-3]. Most cases of the disease are associated with SARS caused by Para influenza or influenza viruses [3, 4]. Fortunately, most registered children have mild symptoms, which resolve on their own within 48 h [3, 4]. Moderate and severe courses are not frequently observed, but severe obstruction may lead to a respiratory failure and asphyxia [1-4]. For parents, symptoms seem intimidating, which is why ASLT is one of the most common causes of emergency care. Since this condition is potentially life-threatening, its rational pharmacotherapy should be well known by pediatricians and emergency physicians. However, our literature often recommends medications that do not contain chemical description with effectiveness approval or offering use of drugs whose effectiveness is at least questionable. For example, it is recommended to use "interferon inducers," antiviral drugs, mucolytic agents, vitamins, and antibiotics. This review is devoted to rational pharmacotherapy of ASLT, having the necessary evidenced background.

Systemic corticosteroids

Systemic corticosteroids have been an ASLT therapy foundation for ages [3]. Systemic corticosteroids reduce the time spent in intensive care; they also reduce the length of stay, frequency of repeated visits for medical care and intubation [3, 5]. Studies have shown the high efficiency of prednisolone, dexamethasone, taken orally and parentally [3, 5]. Available data does not allow making an unambiguous conclusion about the advantages of one system over the other or any of the routes of administration [3, 5]. It was shown that after a single oral administration of prednisolone at a dose of 1.0 mg / kg and of dexamethasone in doses of 0.15, 0.3 and 0.6 mg / kg comparable clinical efficiency has been achieved [3, 5]. Thus, there is no

need to use excessively high doses (domestic literature recommends prednisone doses of 10 mg / kg). Meta-analysis of several randomized trials proved direct correlation between effectiveness of one systemic corticosteroids dose, which ranged from 0.05 to 0.66 mg / kg of dexamethasone [6]. Consequently, unreasonably low doses should not be administered (0.05 mg / kg in this example). Despite the fact that the effectiveness of single and multiple dose systemic corticosteroids were not compared, the re-appointment of these drugs is generally impractical, since a single application is sufficient in most cases evidenced by numerous studies [3, 5]. Many of the existing guidelines recommend the use of dexamethasone, which is based on a longer duration of action compared with alternative means [3, 4, and 7]. Since there are not enough publications allowing to determine the optimal dose, the recommended dose of dexamethasone is 0.6 mg / kg, which is reasonable due to high efficiency, the relative safety and low cost [3, 4, 7]. It should be noted that the use of systemic corticosteroids is appropriate for any severity of ASLT, including its light form [3, 5].

Inhaled corticosteroids

Inhaled corticosteroids are widely used for bronchial asthma treatment in children. Despite the obvious theoretical assumptions (such as high local anti-inflammation and anti-activity and possibly quick effect due to a rapid direct delivery to the site of inflammation), the research on inhaled corticosteroids effectiveness began only in the early 90s of the XX century [8]. The first double-blind study described the results of placebo-controlled suspension of budesonide (Pulmicort, a suspension for nebulizer) effectiveness with moderate / severe manifestations of ASLT in children aged from 3 months to 4.9 years and the severity of symptoms for more than 5 points (modified Wesley croup scale *) [8]. It was found that after 2 hours of inhalation of 2 mg of budesonide, suspension of symptoms decreased by about 2 times (from 8 to 4.5 points), while index remained unchanged in the placebo group [8]. Similar findings were described by Godden and colleagues, whose results are worth reflecting, because observation was carried out over a longer period, up to 28 h after hospitalization [9]. In the subgroup of patients with moderate / severe ASLT significant improvement in the clinical picture was observed after 2 h and then it has been maintained (Fig. 1) [9]. The use of inhaled corticosteroids was accompanied by a shorter time of hospitalization (33%) [9]. These data are particularly significant, because recovering patients were discharged from the hospital, and those remaining under hospital supervision had a more severe condition. Despite this, the positive trend continued, indicating a high clinical efficacy of budesonide suspension.

* The score on Westley croup severity (Westley index) is defined as the sum of severity scores on individual symptoms; index varies from 0 (no symptoms) to 17 (maximal manifestation) points. There are several versions of it; the original scale takes into account the following symptoms: stridor (0-2 points), chest wall retraction (0-3), air entry (0-2 points), cyanosis when breathing room air (0 - 5 points), consciousness (0-5 points) [10]. Positive results of the inhaled corticosteroid are also described in patients with mild / moderately symptomatic ASLT. It was shown that appointment of a suspension of budesonide for patients with Westley index from 2 to 7 points led to a rapid (within the first 4 hours) and clinically significant improvement (from 4 to 1 point) [11]. Satisfactory response to therapy was observed after 4 hours in 70% of patients treated with inhaled corticosteroid, and only in 37% of the placebo group patients [11].

The results of these studies provided the impetus for further study of the efficacy of budesonide suspension for ASLT. The main objective was to compare the results of therapy with inhaled and systemic corticosteroids.

A comparison of budesonide suspension (2 mg inhaled), dexamethasone (0.6 mg / kg orally), and combinations of these drugs in children aged from 3 months to 5 years old with mild / moderate ASLT clinical course (2 points on a scale Wesley) showed that all the proposed options for treatment had the same efficiency (Fig. 2) [12]. About 80% of children in all three groups were

discharged within 4 hours after the call for help [12]. Most likely, it is impractical to combine two different ways of corticosteroid administration [3]. However, for a population of patients with more severe clinical course (3 points on a scale of Wesley), results indicated that such approach (a combination of systemic and inhaled corticosteroids) provides a faster clinical response [13]. It was shown that, being given an additional appointment of budesonide suspension (2 mg) along with dexamethasone treatment (0.6 mg / kg orally) 84% of patients had clinically significant improvement after 4 h, versus only 56% of treated with dexamethasone solely [13].

It is important to mention, that there is no published evidence of clinical efficacy of inhaled hydrocortisone, prednisolone, or any other systemically used corticosteroid. In comparison with systemic corticosteroids inhaled corticosteroids have only a small local activity. If it taken through inhalation (via nebulizer), a significant proportion of the nominal dose is swallowed, and given a high bioavailability of ingested fraction (60% for hydrocortisone and 100% for prednisolone and methylprednisolone) the effect will be realized only through the system action, not a local one. Thus, the choice of hydrocortisone, prednisolone and other similar means for inhalation use is not appropriate. In addition to budesonide the possibility of fluticasone propionate at a dose of 2 mg along with dosing of the aerosol inhaler with placebo was also studied but the no difference between them was established [14].

The only inhaled corticosteroid with proven efficacy in ASLT belongs to a suspension of budesonide (more than 20 randomized trials) [1, 3-5]. Due to a large research base, supported by the results of the Cochrane systematic review in 2011 [5], constrictive laryngotracheitis was also included into the indication list for use of Pulmicort (budesonide suspension for inhalation therapy), so it certainly enhances the pharmacotherapy of this disease.

Nebulized epinephrine therapy

Epinephrine has been used for ASLT treatment for a long time, and its effectiveness has been confirmed by many clinical studies [2-4]. Inhalation of epinephrine by nebulizer is followed by fast - within 10-30 minutes – improvements of symptoms, which remains for only 1-2 hours [3, 4]. It is important to mention that adrenaline inhalations by nebulizer have at least the same efficacy of intermittent delivery as the one by positive pressure [3]. In most studies there was investigated usage of racemic (synthetic) epinephrine, while the randomized controlled studies have shown that L-adrenaline (used in our country) has the same efficiency [3]. In a comparative valuation of adrenaline and budesonide suspension for moderate ASLT, it was discovered that use of both drugs leads to the same improvement of symptoms after 1-2 h [15]. However, it should be noted that usage of adrenaline and corticosteroids (systemic or inhaled) is not alternative to each other [3, 4, and 7]. Epinephrine should be considered as a fast and short-term way to improve larynx patency; corticosteroids with effect developing within 1-2 h (according to placebo controlled Research) have a longer duration of action. Despite the fact that ASLT can disappear on its own, the use of adrenaline solely may require repeated inhalation of the drug [3, 15]. In this article, the abovementioned results show that additional inhalation of epinephrine was required for 3% of patients treated with budesonide suspension, and for 10% of patients who initially injected epinephrine inhalation [15]. One should also remember about possibility of developing the return syndrome after discontinuation of adrenaline treatment. Appropriateness of intaking systemic and inhaled corticosteroids with epinephrine was not only obvious, but it was also demonstrated in Duman and colleagues' study [16]. It was found that nebulized epinephrine therapy along with suspension of budesonide (inhaled) or dexamethasone (intramuscularly) leads to the better symptoms dynamics, and to the smaller need for additional inhaled epinephrine if compared with dexamethasone monotherapy [16].

Severe course of ASLT and increasing respiratory distress require immediate use of epinephrine by nebulizer [3, 4, and 7]. At the same time oxygen, but not the air, is the preferred carrier. The standard dose for inhalation therapy is 4 ml of 0.1% solution (undiluted) [3, 4, and 7]. We do not recommend repeated inhalation of epinephrine for 1 h. Usually adrenaline is well tolerated, but its use may cause a slight tachycardia and pallor [3].

Conclusion

Despite the fact there is no wide choice of ASLT drugs, these drugs are well-studied; they are effective and relatively safe. General principles for selection of pharmacotherapy ASLT, listed in the table with the severity classification, were used in research.

For deciding on the appointment of a particular drug and its application mode, it is necessary to take into consideration the clinical picture and the emotional state of the patient. It is important that the route of administration would not create additional anxiety for the child, which might lead to increased obstruction [1, 4, and 7]. If the clinical picture requires the use of adrenaline by nebulizer, a suspension of budesonide is preferable, because drugs can be mixed thus eliminating additional stress for the child. In case of vomiting inhaled budesonide is desirable as a less painful and distressing for the patient, compared with intramuscular or intravenous injection. If the choice is made in favor of parenteral administration, than intravenous administration is advisable, as this approach may be necessary for intake of other drugs, if child's condition may require so. And finally, it should be noted that ASLT may recur, while repeated introductions of systemic corticosteroids are unsafe.

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TABLE: General principles for selection of pharmacotherapy of acute stenosing laryngotracheitis. Adapted to changes in I. Syed et al., 2009; S. Rajapaksa, M. Starr, 2010; D. Johnson, 2009 [2, 3, 6]

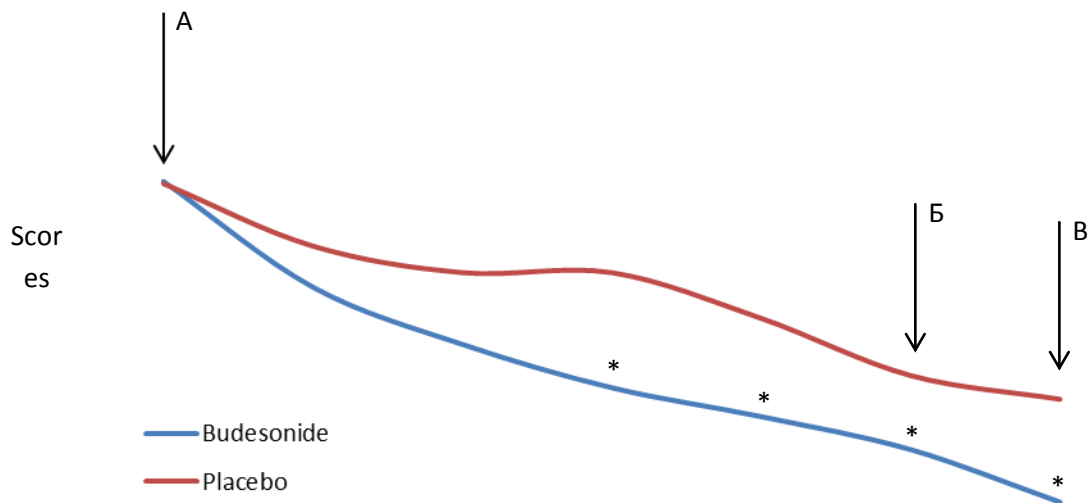
Assessment of acute stenosing laryngotracheitis severity			
Severity is determined by the most evident sign			
Easy	Moderate	Severe	Life threatening
Rare barking cough	Rare barking cough		
The absence of stridor at rest	Audible stridor	Severe stridor	
There are no indrawings of compliant sites of the chest at rest	There are indrawings of compliant sites of the chest at rest		
Auxiliary muscles don't participate in the act of breathing	Auxiliary muscles participate in the act of breathing marginally	Significant part of the auxiliary muscles participate in the act of breathing	Maximal participation of the auxiliary muscles in the act of breathing
-	The child is restless and looks tired	The child is excited and looks exhausted	The apathetic child is with confusion and drowsiness
Normal Heart Rate	Increased Heart Rate	Significantly increased heart rate	Significantly increased heart rate or decreased heart rate
A child can speak and eat	Ability to eat and talk a little bit limited	Increased respiratory rate; a child can not eat or talk due to shortness of breath	«Silent lung»
-	-	Severe pallor, a low tone of skeletal muscles	Cyanosis
Principles of therapy			
		Hospitalization	
		Oxygen	
		Epinephrine inhalation by using a nebulizer 4 ml of 0.1% Do not dilute If possible to use oxygen as the carrier gas	
The suspension of budesonide by nebulizer 2 mg or dexamethasone 0.6 mg / kg orally or prednisolone 1.0 mg / kg orally	The suspension of budesonide by nebulizer of 2 mg or dexamethasone 0.6 mg / kg orally or dexamethasone 0.6 mg / kg intramuscularly or intravenously		Dexamethasone 0.6 mg / kg intravenously
Re-assessment every 1-2 hours			
Discharge (if the patient was hospitalized) in case of improvement and absence of stridor at rest in 4 hours			-

For lack of effectiveness re-appointment of corticosteroids (inhaled or systemic) is appointed every 12 hours for the next 24	-
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Notice: HR - heart rate, respiratory rate - the frequency of respiratory movements

Fig. A. The dynamics of the modified index of Westley with moderate-severe (4 - 17 points) acute stenosing laryngotracheitis in children aged from 7 months to 9 years taking budesonide suspension at a dose of 2 mg and placebo for 8 months

1



Notice: A - budesonide suspension at a dose of 2 mg or placebo, B - budesonide suspension at a dose of 1 mg or placebo; V - suspension of budesonide at a dose of 1 mg or placebo; * - $p < 0.05$

Fig. 2: The dynamics of the Westley index(A) and time spent in the emergency department(B) at light and moderate (from 2 points) acute stenosing laryngotracheitis in children aged from 3 months to 5 years during treatment with budesonide suspension at a dose of 2 mg, dexamethasone at a dose of 0.6 mg / kg, and a combination of these drugs

