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Pre-School wheezing treatment

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Introduction

A wheeze is a continuous, musical, high-pitched, expiratory sound, heard on chest auscultation as a result of airways narrowing and subsequent airflow limitation [1].

Parents hardly are able to report correctly a child's wheezing, since often they can't distinguish it from a heavy breathing or a whistling and sometimes consider it as the same as cough. This is the reason why both GINA guidelines and in the ERS task force report state that a clinician or a health professional should assess a wheezing diagnosis [1,2].

Despite its clear definition, however, a high agreement between paediatricians in the recognition of wheezing on chest auscultation is far to be achieved [3].

Type of Wheezing

Pre-school wheeze is very common and it has been estimated that a half of infants below six years of age has had at least one wheezing episode, mostly associated with a viral upper respiratory tract infection [4].High viral load in RSV bronchiolitis [5] and exposure to tobacco smoke [6] are reported as risk factors for recurrence of wheezing episodes below six years of age.

However, wheezing in this age group is a highly heterogeneous condition, and differential diagnosis should be always taken into account since not all that wheeze is asthma.

The natural history of pre-school wheezing has been cleverly described in 1995 by Martinez et al. in the Tucson study [4]. They found that among children with pre-school wheeze, a few will continue to have symptoms and can develop asthma, other will stop wheezing by the age of 6 years.

Two type of classification have been proposed by 2008 ERS report: one based on the temporal pattern (episodic versus multiple-trigger), the other based on the duration of symptom (transient versus persistent versus late onset wheeze) [1].

Episodic wheeze is associated with a viral respiratory tract infection and it is defined by the European Respiratory Society

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(ERS) as "wheeze in discrete episodes, with the child being well between episodes" [1].

Multiple trigger wheezing occurs when symptoms are present also between discrete episodes and/or triggers other than viral infections can rouse wheeze (such as crying, laugher or exercise).

The second classification, based on symptoms' duration, is used in epidemiological studies and can only be applied retrospectively. When symptoms occur after the age of three years and last after six years of age it is classified as late-onset wheezing. Transient and persistent wheezing appear before the age of three, but the former disappears at age of six, the latter continues to wheeze beyond six years [1].

The temporal definition of acute viral wheeze and multiple trigger wheeze is now considered too strict, since the clinical expression of preschool wheeze can change over time, and it enables physicians to predict the long term outcome, which is more related to frequency and severity of clinical presentation [7].

Acute episode treatment

An acute exacerbation of wheezing in children under five years is an acute worsening of symptoms that requires additional medication and physician attendance. Symptoms may include shortness of breath, wheeze and increasing cough during night or exercise. Caregivers should be able to recognise an exacerbation and start a proper intervention as soon as possible [2]. Both GINA and NICE guidelines [2,8] recommends urgent medical referral in children with severe distress (especially if below 1 year of age) or unresponsive to inhaled bronchodilator.

Inhaled Short Acting B2-Agonists (SABAs) are the first choice drugs for acute wheeze. The metered-dose inhalers by spacers have proved to be at least as effective as the nebulised delivery [9] and they were associated with lower economic costs [10]. Alternative ways of administration should be considered with caution since oral administration is limited by systemic side-effects and intravenous SABAs are indicated as second line treatment in severely ill children [11].

Addition of inhaled anti cholinergic drugs to SABAs for acute wheeze improve clinical outcome after 24 hours, without effect on length of hospital stay in children under 24 months of age [12]. The use of systemic corticosteroids (including oral prednisolone, intravenous methyl prednisone and intravenous hydrocortisone) in children hospitalised for severe acute wheeze proved to reduce days of hospitalization and improve clinical score [13].

Regarding the use of Inhaled Corticosteroid (ICS), a double-blind placebo-control trial demonstrated that inhaled budesonide as add-on therapy for the acute treatment halved the rate of hospitalization in moderate-severe preschool wheeze [14].

Pre-emptive therapy

Pre-school wheeze economic impact has been estimated around 53 million pound in United Kingdom in 2015 [15], mostly due to general practitioner visits for mild symptoms, that's why a primary preventive therapy could be effective in costs reduction.

Regarding who the pre-emptive therapy should be prescribed, GINA Guidelines recognise two different scenarios: the first one includes children with a very likely diagnosis of asthma with poor symptom control and frequent exacerbations (three or more episodes/ season) and the second one includes children with less likely diagnosis of asthma but who requires inhaled SABAs treatment quite often (every 6-8 weeks) [2]. The updated ERS paper on management of preschool wheeze suggests prescribing a controller treatment in children with multiple trigger wheeze and in those with episodic viral wheeze who presented frequent and/or severe clinical manifestation [7].

Any pre-emptive therapy should be considered as a treatment trial, with a regular review during scheduled follow-up [2,7].

When looking at which is the best pre-emptive treatment, a recent systematic review and meta-analysis reported a lower number of exacerbation in children treated with daily ICS compared with placebo (RR 0.56) and with montelukast (RR 0.59) [16]. The same paper reported also a significant reduction in exacerbation of pre-emptive high-dose intermittent ICS compared with placebo (RR 0.65).

Systemic side effect of ICS has been extensively studied and a recent met analysis of 25 trials including more than 8000 children found a mean decrease of 0.48 cm/year in linear growth velocity during the first year of treatment with low-medium doses of ICS [17]. High dose ICS can also cause low bone mineral density [18] and adrenal suppression [19]. For these reasons the lower effective dose of ICS should be prescribed to preschool children with the aim to control wheeze exacerbation [17] and a step-up approach should be considered only after an assessment of a good parents' compliance to treatment [2].

Daily use of montelukast as pre-emptive therapy of recurrent wheezing is not supported by the results of a recent meta-analysis included more than 3900 patients, since no differences in the number of wheezing episodes was reported by the pooled analysis between the drug and placebo [20] and also a recent Cochrane review found montelukast unable to reduce the use of oral corticosteroids for viral-induced wheeze [21,22], however the use of leukotriene receptor antagonist as add-on therapy in not well control children is supported by GINA and NICE guidelines [2,8].

The rationale for the use azithromycin as pre-empitve treatment in pre-school wheeze is based on two different possible mechanisms: the first bring into play the role of bacteria in virus induced wheeze [23], the second relies on immune-modulatory and antiviral effects of macrolides [24]. However, contrasting data are available in literature. Two recent double-blind, placebo-controlled trials demonstrated opposite results: the first showed that it was able to reduce the exacerbation duration of 63.3% [25], the second found no differences compared to placebo in reducing the length of symptom nor the subsequent number of exacerbations [21].

Future research

Further research should aim to understand the pathogenetic mechanisms underlying preschool wheeze, to achieve better biomarkers to predict response to treatment, to develop better ways to assess symptoms and their impact on child's activity [5].

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