Phenotype-directed treatment and outcome prediction of preschool wheezing: possible and useful?

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Approximately one in three children has at least one episode of wheeze before their third birthday. At population level, almost two thirds of wheezy preschoolers cease to wheeze by age 4-6 years, whilst the remaining children develop chronic persistent asthma. These different longitudinal patterns of wheeze over time are known as the transient and persistent wheeze phenotypes, respectively, and population studies have shown significant differences in the risk factors associated with these phenotypes.[1, 2] Although these findings have improved our understanding of the natural history and the multifaceted pathophysiology of preschool wheezing disorders, the lack of evidence based guidelines on the diagnosis and management of preschool wheezing disorders was a major limitation in providing these patients with effective care. In 2008, a European Respiratory Society (ERS) Task Force published a report on the classification, diagnosis and management of preschool wheezing.[1] This report proposed to classify preschool wheezers into two phenotypes, based on the temporal pattern of symptoms: episodic viral wheeze (EVW, characterized by discrete episodes of wheezing associated with upper respiratory tract infections [URTIs], with symptom-free intervals between episodes) and multiple trigger wheeze (MTW, characterized by wheeze associated with URTIs *and* with other triggers) because it was felt at that time that this distinction was important in determining the choice of daily controller therapy. One of the main findings of this task force report, however, was that the evidence on which recommendations could be based was limited; the task force predicted that these recommendations would be likely to change as new evidence became available.[1] In 2014, the ERS published an update of the Task Force report on preschool wheezing disorders, based on a review of the evidence published between 2008 and 2014.[3]

In the revised guidelines, it has now been recognized that the distinction between EVW and MTW is unclear in many cases.[3] Children commonly cross over between phenotypes over time.[4] In addition, it is the frequency and severity of episodes that usually determines the need for daily controller therapy, not the pattern over time.[5] In contrast to popular belief, EVW of sufficient severity to warrant referral to and treatment by a hospital based paediatrician, commonly persists over time, and develops into chronic persistent asthma in the majority of cases.[6] Given the multifactorial nature of wheeze in preschool children, with important influences of genetic, viral, bacterial, allergic, and irritant environmental factors, it is unlikely that a clear-cut distinction into two mutually exclusive phenotypes will be possible. The 2014 update of the ERS Task Force report therefore concludes that the distinction between the EVW and MTW phenotypes is of limited usefulness.[3]

In a systematic review of randomized clinical trials, inhaled corticosteroids were shown to be effective in all groups of preschool children with wheeze, irrespective of their clinical phenotype.[7] In most children in this review, however, the clinical phenotype was not reported. The overall effect of inhaled corticosteroids in this age group appears to be smaller than that in school-aged children and

adolescents with asthma, suggesting that there are subgroups of preschool wheezy children who fail to respond to inhaled corticosteroids. Unfortunately, no robust and reliable predictors of inhaled corticosteroid responsiveness have been identified in preschool children to date. In head-to-head comparisons, inhaled corticosteroids have been shown to be more effective than montelukast in controlling wheeze in preschool children.[8] Taken together, the literature now suggests that inhaled corticosteroids are the preferred and most effective daily controller therapy in preschool children with recurrent troublesome wheeze.[9] A recent observational study showed that adherence to daily inhaled corticosteroid treatment over one year in 2-6 year old children with recurrent wheeze followed up by hospital-based paediatrician was the only significant determinant of asthma control in these patients, in a dose-dependent fashion.[10]

Parents and physicians share the desire to be able to predict the outcome of preschool wheezing at school age ("will my child have asthma when s/he grows up?"). In population based studies, more than half of the preschool children with wheeze cease to wheeze by age 6.[1,2] Statistically significant associations between certain clinical characteristics and the risk of persistent wheeze beyond the age of 6 have been found, and this has led to the development of scoring systems predicting the outcome of preschool wheezing after the age of 6 years.[11] The predictive value of these scoring systems, however, is poor. The likelihood ratios of asthma predictive indices are too poor to be used as reliable predictors of outcome in an outpatient setting, or to base decisions on regarding the start of withdrawal of daily controller therapy. [11] Therefore, the use of asthma prediction instruments in preschool wheezers is not recommended.

Preschool children with recurrent wheeze should be assessed by their frequency and severity of episodes and interval symptoms, because this determines the need for daily controller therapy. Irespective of whether the temporal pattern of wheeze reflects EVW or MTW, inhaled corticosteroids appear to be the most effective form of daily controller therapy in preschool children with recurrent troublesome wheeze, although the effect is smaller than in school-aged children and adolescents with asthma. Ensuring good adherence to daily controller therapy through patient-centered care and shared decision making is essential in controlling troublesome wheeze in preschool children.

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