

# Understanding mild asthma/episodic asthma in children

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## Abstract

Asthma may be intermittent or persistent and persistent asthma may be mild, moderate, or severe. Many factors influence asthma severity, both from day-to-day and from month-to-month. In individual patients, asthma severity may fluctuate because of many extrinsic (allergens, viral infections) and intrinsic (behavioural) factors. This article discusses the pathogenesis of episodic asthma and wheezing outlines a treatment approach for episodic asthma.

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### Introduction

Asthma is a chronic disease of airway inflammation that affects all age groups.<sup>1</sup> Despite national and international treatment guidelines and the availability of very good controller medications, asthma morbidity remains significant.<sup>2</sup> This translates into a considerable socio-economic burden. Asthma may be intermittent or persistent and persistent asthma may be mild, moderate, or severe. Many factors influence asthma severity, both from day-to-day and from month-to-month. In individual patients, asthma severity may fluctuate because of many extrinsic (allergens, viral infections) and intrinsic (behavioural) factors.

Most of the information on the pathogenesis of asthma is based on studies obtained through bronchial biopsies and bronchoalveolar lavage in adults and young adults.<sup>3</sup> For obvious reasons airway endoscopy is limited in infancy and early childhood. Although it remains true that an asthma-like inflammation, with increased inflammatory cells and thickening of the lung basement membrane, is present even in infancy, clinical and epidemiologic studies suggest that asthma manifestations in preschool children often differ significantly from those in older children.<sup>3</sup> The vast majority of infants and young children have episodic (or intermittent) asthma, and the exacerbations, generally called "wheezing episodes", occur more frequently in winter, usually related to acute viral infections.<sup>3</sup>

### Clinical manifestation

#### Understanding wheezing

Since wheezing is a symptom, not a diagnosis, wheezing disorders are not equal to childhood asthma. Wheezing in

the youngest children is often episodic, associated with upper respiratory infection. Early wheezing disorders, particularly in the first 2-3 years of life, should be considered as different to later childhood asthma.<sup>4</sup> It is difficult to distinguish an initial episode of asthma triggered by a viral respiratory infection from acute viral bronchiolitis. Most of the infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life. This means that most wheezy young children do not benefit from standard asthma treatments such as nebulised  $\beta_2$ -agonists. Martinez and colleagues classified wheezing into three distinct categories based on outcome. *Transient early wheezing* was wheezing in the first three years of life but then stopping, *late-onset wheezing* was no wheezing during the first three years of life, but onset during the fourth year, and *persistent wheezing* was wheezing continuing from early onset beyond five years of life.<sup>5</sup> These epidemiological studies have shown that in the main wheeze in young children is often not due to asthma while a wheezy older child may well have asthma.

Transient (limited to a few months or years) wheezing in infancy is more likely to be a function of small airways, and wheezing in the first year of life does not persist as asthma in two-thirds of those afflicted. RSV infection can predispose to recurrent wheeze. Certainly it has been shown that RSV bronchiolitis severe enough to cause hospitalisation is a risk factor for allergic asthma in early adolescence.

There is strong epidemiological evidence that approximately 2/3 of all children who wheeze because of viral in-

fections in early life (and are not atopic) have a transient condition that tends to disappear during early school years. All respiratory viruses may be implicated in the wheezing episodes, the commonest being respiratory syncytial virus (RSV) and, with a lower frequency, adenovirus and parainfluenza viruses during the first 3 years of life, and rhinoviruses after that age.<sup>3</sup> Infants and preschool children have on average 6-8 "colds" per year,<sup>6</sup> but the illness tends to be limited to the upper respiratory tract alone in a considerable proportion of individuals, without causing symptomatic involvement of the lower respiratory tract. The variety of factors determining the different outcomes are only partially known, but complex interactions between the intrinsic pathogenicity of the virus and host factors, including the socio-economic conditions of the family, are central to define the type of manifestations and the severity of the process.

A typical presentation of asthma in infancy is wheezing but since not all wheezing in this age group is asthma, care should be taken with a differential diagnosis. Recurrent wheezing in infancy may be asthma or not. The latter category is more likely but again the disease has important quality of life issues and may be quite severe, hence a trial of anti-asthma therapy is usually indicated. No infant or child should be treated with regular courses of antibiotics for chronic chest symptoms without being evaluated for asthma.

### Management

#### Anti-inflammatory therapy

In a study of episodic wheezing preschoolers (all 21 children had a history of significant episodic wheezing

(>2 episodes per year), and used only as-needed beta-agonist treatment.<sup>7</sup> Bronchoalveolar lavage (BAL) was obtained using bronchoscopic lavage (study group) and non-bronchoscopic lavage (control group). Differential cell counts of BAL and flow cytometry were performed to identify T-lymphocyte phenotypes, and intracellular cytokine profiles. No significant differences in BAL differential cell counts were noted, and in both groups, the majority of T-cells were CD3+ CD8+, with a median CD4:CD8 ratio of 0.6. There was no significant difference in T-cell expression of the activation markers HLA-DR and CD25 (IL-2 receptor), or in PMA-induced production of the intracellular TH2 cytokines IFN-gamma, IL-2, IL-4, IL-5, and IL-10. The results of this study suggest that significant T-cell-driven airway inflammation is absent in mild or non-atopic, asymptomatic children of this age group who have episodic wheeze. Their findings support asthma management guidelines that do not recommend long-term treatment of this group of patients with an anti-inflammatory.

Episodic wheeze triggered by viral colds is common in children aged between 1 and 5 years (preschool viral wheeze). Most affected children are asymptomatic by age 6 years. Persistence of wheeze is associated with above-average systemic eosinophil priming. Use of parental-initiated oral prednisolone is recommended at the first sign of preschool viral wheeze. However, evidence for this treatment strategy is conflicting. Most studies find no clear benefit of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years even in those with eosinophilia.<sup>8</sup>

Inhaled corticosteroids (ICSs) are safe and well tolerated, and are the preferred long-term treatment for controlling persistent asthma of all severities in adults and children. However their place in episodic asthma is not clear and some studies suggest no benefit.<sup>9</sup>

Where persistent asthma occurs the therapy is in no question. A persistent use of an anti-inflammatory drug (such as an ICS) is important. Attached to this, patients require education and advice. In a cross-sectional descriptive study conducted at the Royal Children's Hospital and Sunshine Hospital, Melbourne 51% of parents do not feel they have enough information about asthma triggers, more than 60% of children with persistent or frequent episodic asthma are not using regular preventive medication, 48% do not have a written action plan, 39% have

not had their asthma reviewed in the last 6 months, and 38% of parents do not feel that they have enough information about their child's asthma.<sup>10</sup> Areas where current practice was close to best practice: 83% of doctors had talked to parents about what causes or 'triggers' their child's asthma, less than 1% of children are using puffers without a spacer, 83% of parents who had an action plan used it for the current visit to the emergency department. Clearly large gaps still exist between current management and best practice in real life.

### Leukotriene receptor antagonists


Leukotriene receptor antagonists are orally available anti-inflammatory drugs and are safe and efficacious in children from 2 years and older.<sup>11</sup> There improved compliance and safety make these agents seem attractive as alternatives for ICS in young children with mild persistent asthma. They also provide an alternative to long-acting  $\beta_2$ -agonists as add on therapy. A 12-week, multicentre, randomized, placebo-controlled, double-blind, parallel-group study was conducted to evaluate the clinical safety and efficacy of oral montelukast in 689 children 2 to 5 years of age with chronic asthma.<sup>11</sup> Montelukast significantly improved each of the components of the composite symptom score over 12 weeks of treatment. For example reduction in activity limitation scores were 40% versus 22% ( $p < 0.001$ ). During the 12 weeks of double-blind treatment, significantly fewer patients receiving montelukast, than those receiving placebo, required corticosteroid rescue to maintain asthma control. In addition there were no important adverse experiences and the tolerability profile of montelukast was similar to that of placebo.

The 2-5 year age group is a difficult one for asthma. The disease is truly inflammatory and therapy needs to address this inflammation and yet most therapies (certainly the inhaled corticosteroids) are not registered for use in this age group. In addition children are reluctant to use spacer devices with face masks and compliance with therapy is poor, making exacerbations more common and pushing up the cost of asthma in this age group.<sup>12</sup> It is also an age group in which diagnostic tests for asthma are absent and symptoms drive diagnosis. Symptoms are often misleading (such as wheeze) or poorly recognized (chronic cough) as features of asthma.


Viral respiratory tract infections are the most common trigger of asthma exacerbations in the paediatric population

and in addition respond poorly to conventional inhaled anti-inflammatory therapy. The 'PREVIA' Study<sup>13</sup> was designed to investigate the role of montelukast in the prevention rate of asthma exacerbations in children aged 2 to 5 years with a history of episodic symptoms. Montelukast reduced the rate of asthma exacerbations by 32% ( $p < 0.001$ ), and the rate of oral corticosteroid courses ( $p = 0.024$ ) compared to placebo. The incidence of adverse experiences was similar to placebo. The Pre-Empt study attempted to address the use of Montelukast in episodes of asthma/wheeze with some success. This strategy of intermittent use is now under investigation as it holds promise of a specific therapy for a scenario where continuous therapy is both difficult and often ineffective.

### Conclusion

Whatever therapy is ultimately picked for managing asthma in the young child it is important to meet the 'Goals of treatment' as set out in the asthma guidelines. Episodic asthmatic young children may respond to specific therapy at the time of an exacerbation. However, persistent asthma symptoms require regular anti-inflammatory therapy. 

See CPD Questionnaire, page 39

 This article has been peer reviewed

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