

# Phenotype specific treatment of obstructive airways disease in infancy and childhood: new recommendations of the Swiss Paediatric Pulmonology Group

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## Summary

In 2003 and 2004 the Swiss Paediatric Pulmonology Group (SAPP) revised the recommendations for the management of obstructive airways disease in infancy and childhood (Paediatrica 2004;15:13–28) and published recommendations for the management of acute bronchiolitis in infancy (Paediatrica 2003;14:18–21).

The concept underlying these new guidelines is the fact that childhood wheezing illness encompasses a range of disorders or phenotypes with a similar clinical manifestation (wheeze, cough and breathlessness) but varying pathology, aetiology, prognosis and response to treatment. Based on the available scientific evidence, phenotype-specific and age-dependent management of wheezing ill-

ness is advocated in the revised guidelines. Major changes compared to earlier recommendations include a stepwise approach to management depending on age, phenotype and severity of disease and use of  $\beta_2$ -agonists purely on an on-demand basis. Comparison of these recommendations with epidemiological data on current treatment practice of obstructive airways disease in Swiss children suggests that many children with bronchiolitis and mild viral wheeze might be overtreated while management of children with severe persistent symptoms could be improved.

*Key words: asthma; bronchiolitis; treatment; guidelines; epidemiology; management; child; infant*

## Introduction

In 2003 and 2004, the Swiss Paediatric Pulmonology Group (Schweizerische Arbeitsgemeinschaft für Paediatrische Pneumologie, SAPP) published evidence-based recommendations on the management of acute bronchiolitis in infancy [1], and revised the guidelines on the management of obstructive airways disorders (including asthma) in infancy and childhood [2, 3]. These new guidelines, based on strong evidence for the coexistence of different asthma phenotypes, differ significantly

from earlier recommendations of the SAPP [4] in that they strongly advocate phenotype-specific management [5].

This article summarises the special issues of obstructive airways disorders in childhood that led to the revision of the guidelines, outlines the main changes in the new guidelines compared to previous recommendations and summarises the current epidemiologic data on the management of these disorders in Swiss children.

## Special issues of obstructive airways diseases in childhood

### Phenotypes

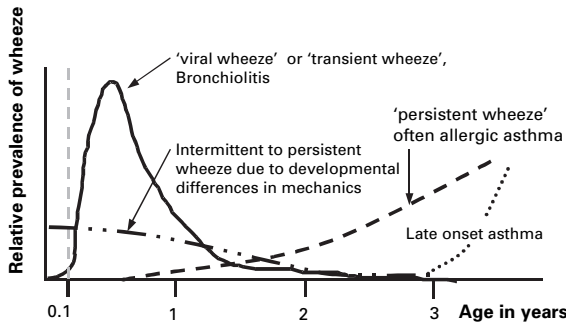
There is now an international consensus that the relatively homogeneous symptomatology of reversible obstructive airways disease in childhood, characterised by symptoms of wheeze, cough and breathlessness, comprises several distinctive disorders, usually called phenotypes [6–9].

These phenotypes include classic atopic asthma, viral wheeze or obstructive bronchitis, recurrent wheeze due to disturbed airway development and non-atopic late onset asthma. The relative prevalence of these phenotypes varies with the age of the child (figure 1).

Clinically very important in preschool chil-

**Figure 1**

Hypothetic diagram, illustrating the relative frequency of different phenotypes of wheeze at different ages. Total prevalence of wheeze at a certain age would be the sum of all curves at that point (from [3], modified from Wilson [33]).



dren is the distinction between classic atopic asthma and “viral wheeze” or “early transient wheeze” [7]. Children suffering from atopic asthma have persistent symptoms induced by a number of triggers, including exercise, contact with allergens and infections. In contrast, children with viral wheeze typically have only episodic symptoms associated with viral infections and remain asymptomatic in the interval. Acute bronchiolitis associated with RSV infection is a distinctive subtype of viral wheeze, with a typical clinical presentation due to predominant involvement of peripheral airways. Therefore, these infants present with hyperinflation and fine crackles by auscultation rather than with wheezing.

The distinctions between viral wheeze and atopic asthma also include differences in epidemiological risk factors, bronchial hyperreactivity, endobronchial inflammation and immunological findings [7]. Even more importantly, response to treatment differs between phenotypes, in that there is no current evidence to favour use of low dose inhaled corticosteroids in the prevention and management of episodic mild viral induced wheeze [10]. Also an effect of high dose inhaled steroids or oral prednisolone during acute attacks has not clearly been demonstrated [11]. Even the evidence for a clinical benefit of bronchodilators on episodic wheeze in children aged less than two years is conflicting, with paradoxical effects in some patients

[12]. Therefore, the effect of bronchodilators should actually be observed in every child before this treatment is prescribed.

**Long-term prognosis**

Long-term prognosis has been investigated in several cohort studies, where large population-based samples of children with wheeze were followed-up [9, 13–16, 34]. One of these, the Tucson Children’s Respiratory Study, showed that 50% of 6-year olds had wheezed at some time in their life, but most of them only transiently. In fact, 80% of those wheezing during their first year of life, 60% of those wheezing in the second year and 30 to 40% of those wheezing in the third year did not continue to wheeze after the age of three. These children with transient symptoms did not display markers of atopic diathesis. In contrast, children with atopic asthma were much more likely to have persistent disease.

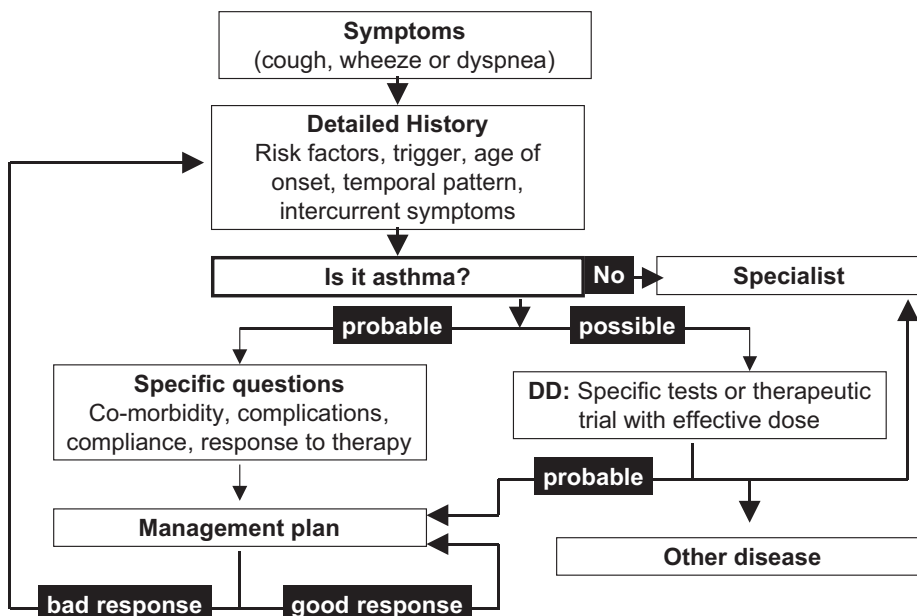
Besides the phenotype, the number of wheezing episodes during the past 12 months is an important predictor of long-term prognosis. This was shown in Melbourne, where 484 children with wheeze were recruited at age 7 and followed-up at regular intervals until age 42. All follow-ups showed consistently that children with frequent symptoms were more likely to have reduced lung function and persistent symptoms during adolescence and adulthood compared to those with fewer episodes [14–16].

**Distinction between phenotypes**

The best way of discriminating phenotypes in children has yet to be found. Attempts to classify children have either focussed on the time course of the disease (transient wheeze, persistent wheeze, late onset wheeze) [9] or on its aetiology (viral episodic wheeze, persistent wheeze induced by multiple triggers, wheeze due to developmental differences in lung mechanics) [6, 7]. Furthermore,

**Figure 2**

Diagnosis of asthma syndrome in children (from [3], modified from [18]).



the disorders, being all relatively common, are not mutually exclusive so that one child can display features of more than one phenotype. A clinical index to define risk of persistent asthma in toddlers with recurrent wheeze has been proposed by authors from Tucson [17] and is integrated in the Swiss guidelines. However, this model will need to be

cross-validated and refined using data from other cohorts. As some uncertainty about the underlying disease and/or phenotype is likely to remain in many young children, it is advisable to reassess the children at regular intervals, re-evaluating the diagnosis if management is ineffective (figure 2) [3, 18].

## What has changed in the new guidelines?

### Acute viral bronchiolitis in infancy

Management recommendations for acute viral bronchiolitis in infancy are new for Switzerland. They are based on current evidence summarised in several Cochrane reviews [10–12, 19–24]. In summary, there is no scientific evidence that any pharmacological agent –  $\beta_2$ -mimetics, anticholinergics, adrenalin, oral or inhaled steroids, antibiotics, ribavirin or aminophylline – changes the natural course of disease in the majority of infants with RSV bronchiolitis. Management recommendations for in- and out-patients in the Swiss guidelines recommend therefore primarily good supportive care and emphasise the following:

- minimal handling
- fluid management
- oxygen therapy and respiratory support as needed
- inhaled bronchodilators and possibly steroids to be considered only in children with pre-existing bronchial hyperresponsiveness
- chest X-rays, white blood count and C reactive protein are rarely helpful for initial decisions on management and for differentiation from bacterial pneumonia

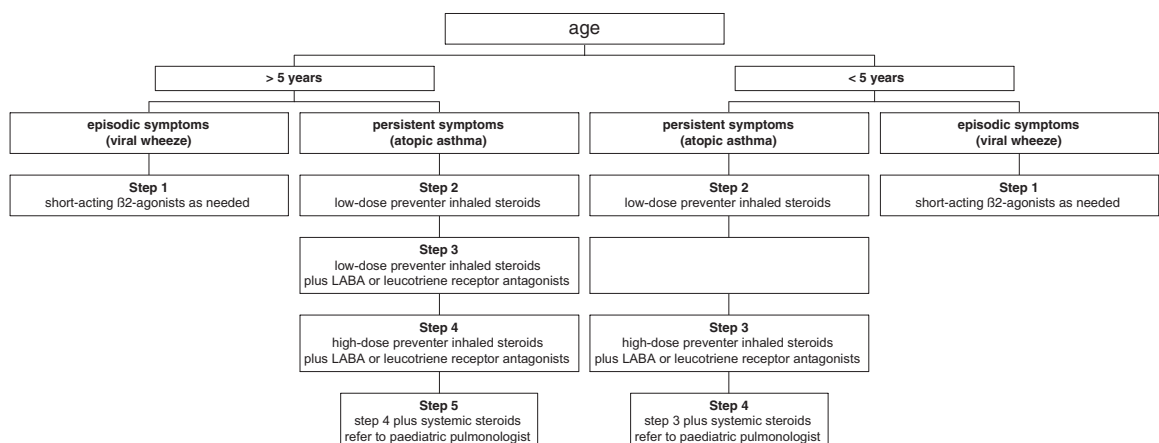
### Asthma and other obstructive airways disease

The new guidelines attempt to be strictly evidence-based, in accordance with international guidelines on asthma management in children [18, 25, 26] and advocate an age- and phenotype-specific approach to management [5]. Figure 3 summarises the treatment recommendations, as a function of age, phenotype and disease severity. The main changes compared to previous recommendations of the SAPP include the following:

- Treatment recommendations differ between children aged less than five years and children aged five years and older. This is justified by the varying prevalence of asthma phenotypes in different age groups and by the scarcity of data available for some drugs in pre-school children.
- Management recommendations depend on the phenotype and on frequency and severity of symptoms and are presented as a stepwise approach, like in other guidelines [18, 25, 26].
- For children with infrequent wheezing episodes triggered by viral infections,  $\beta_2$ -agonists are recommended as needed, without addition of inhaled corticosteroids.
- More generally, use of  $\beta_2$ -agonists is always recommended on an on-demand basis. That means that even children with moderate asthma should use anti-inflammatory drugs only (without short-acting bronchodilators) for daily treatment, as long as their disease is stable and their symptoms are well controlled.
- Due to lack of evidence, doubling the dose of inhaled steroids during acute attacks is no longer recommended, whereas a short course of oral steroids at the beginning of a severe episode should be considered.
- For the first time, recommendations for treating acute asthma attacks including status asthmaticus are also published. For administration of  $\beta_2$ -agonists in the acute episode, aerosols with spacers are as effective as nebulisers if sufficiently high and equivalent doses are given.

**Figure 3**

Schematic diagram summarising the new Swiss treatment recommendations, by age, phenotype and disease severity.



## Where can the guidelines be obtained?

The new recommendations for treatment of bronchiolitis and other obstructive airways disorders in children have been published in *Paediatrica* [1, 3]. French and German versions of the recom-

mendations, as well as asthma management plans and parents information sheets in both languages can be downloaded from the Internet (table 1).

**Table 1**

Internet sites with recommendations of the Swiss Paediatric Pulmonology Group (SAPP) on the management of bronchiolitis, asthma and other obstructive airways disease in childhood.

<b>Bronchiolitis:</b>
Guidelines for physicians:
In French: <a href="http://www.sapp.ch/arzt/files/bronchiolitis-fr.pdf">http://www.sapp.ch/arzt/files/bronchiolitis-fr.pdf</a>
In German: <a href="http://www.sapp.ch/arzt/files/bronchiolitis-ge.pdf">http://www.sapp.ch/arzt/files/bronchiolitis-ge.pdf</a>
Information sheets for parents:
In French: <a href="http://www.sapp.ch/arzt/files/bronchiolitis_elterinformationf.doc">http://www.sapp.ch/arzt/files/bronchiolitis_elterinformationf.doc</a>
In German: <a href="http://www.sapp.ch/arzt/files/bronchiolitis_elterinformationd.doc">http://www.sapp.ch/arzt/files/bronchiolitis_elterinformationd.doc</a>
Asthma and other obstructive airways disease:
<b>Guidelines for physicians:</b>
In French: <a href="http://www.sapp.ch/arzt/files/asthmaGUIDEF.pdf">http://www.sapp.ch/arzt/files/asthmaGUIDEF.pdf</a>
In German: <a href="http://www.sapp.ch/arzt/files/asthmaGUIDED.pdf">http://www.sapp.ch/arzt/files/asthmaGUIDED.pdf</a>
Asthma management plans for patients:
In French: <a href="http://www.sapp.ch/arzt/files/asthmaGUIDEBEHF.pdf">http://www.sapp.ch/arzt/files/asthmaGUIDEBEHF.pdf</a>
In German: <a href="http://www.sapp.ch/arzt/files/asthmaGUIDEBEHD.pdf">http://www.sapp.ch/arzt/files/asthmaGUIDEBEHD.pdf</a>

## Epidemiological data on current treatment practice in Switzerland

### Bronchiolitis

In 2001, a postal questionnaire was sent to all paediatricians registered with the Swiss Society of Paediatrics, aiming to assess their current practice for treating acute bronchiolitis in children [27]. The standardised questions had been used in other studies [28]. With a response rate of 58%, the results reflect treatment practice in the majority of Swiss Paediatricians. Despite lack of evidence of benefit of pharmaceutical agents in the management of acute bronchiolitis, 99% of paediatricians used bronchodilators in the out-patient or in-patient management, either routinely (up to 62%) or occasionally (37%). Steroids were used by 41% in the out-patient and by 57% in the in-patient management, and antibiotics were prescribed by 38% of paediatricians for out-patients. Paediatric respiratory physicians were less likely to use bronchodilators, corticosteroids and antibiotics compared to general paediatricians. However, specialists also tended to overtreat children in most cases, considering the lack of scientific evidence for any benefit of these drugs on the natural course of the disease.

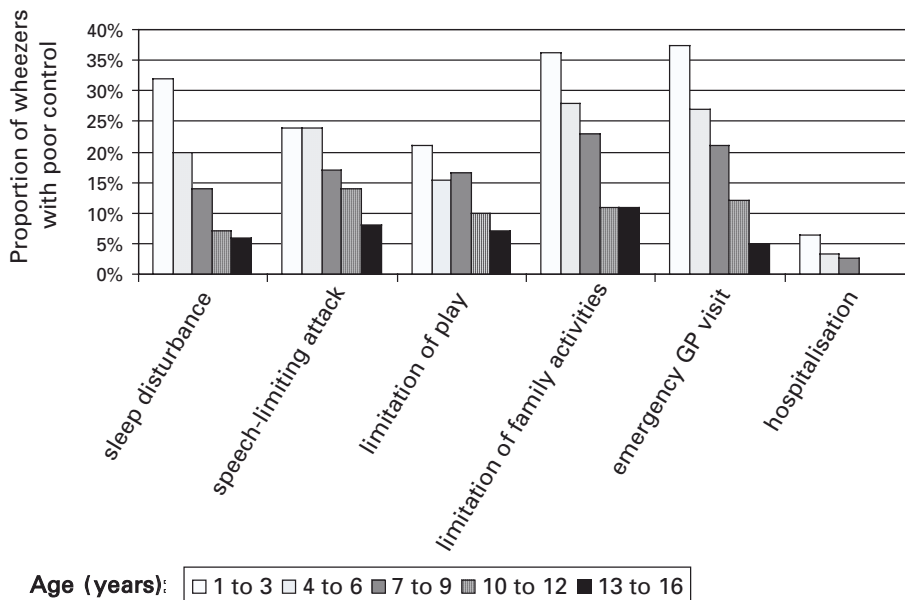
These results from Switzerland are comparable to reported management of acute bronchiolitis in Europe and Canada. In contrast, only a minority of physicians in Australia, where national guidelines had been published in 1993 [29], reported to use bronchodilators and steroids in the management of bronchiolitis [28].

### Asthma and other wheezing disorders

Recent data on management of asthma are derived from a survey of the Swiss association of parents with asthmatic and allergic children (SEAAK) in 1998 [30]. With a response rate of 85%, data from 572 Swiss-German children with wheeze were analysed in this study. The majority (95%) of these children were followed up by a doctor, often by a specialist (42%), and were receiving  $\beta_2$ -agonists (82%) and inhaled steroids (68%). In accordance with previous Swiss guidelines (but in disagreement with the new ones) most patients, including viral wheezers, received a combined treatment of bronchodilators and inhaled steroids. In contrast, for children with frequent and severe symptoms, intensity and duration of treatment were not adjusted sufficiently to asthma severity. Therefore, asthma control was unsatisfactory in nearly 50% of the children with disturbed sleep, restricted activities and school absences. Stratification by age showed that asthma control was significantly poorer in younger children: good control was achieved by 66% of children aged 13–16 years, but only by 56%, 44% and 38% of those aged 10–12, 7–9 and 4–6 years respectively (fig. 4). In many children with unsatisfactory asthma control, the full potential of treatment modalities, as proposed in guidelines with a stepwise approach, was not fully exploited (figure 5) [18, 25, 26]. On the other hand, some of these children might suffer from phenotypes which respond poorly to conventional asthma treatment such as preventive therapy with inhaled steroids (e.g. viral wheeze). In this population, parents played an important role in the management

**Figure 4**

Proportion of current wheezers with poor symptom control by age group (in the Swiss association of parents with asthmatic and allergic children, 1998 (n = 572). All age trends are clinically and statistically highly significant (p <0.001) [30].

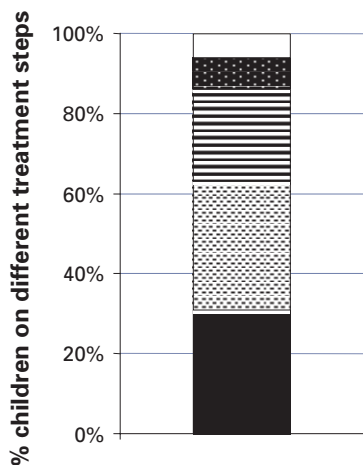


**Figure 5**

Pharmacological treatment in children with unsatisfactory asthma control (n = 279) in the Swiss association of parents with asthmatic and allergic children, 1998 [30].

Abbreviations: SABA = short-acting β<sub>2</sub>-agonists; LABA long-acting β<sub>2</sub>-agonists

- none
- SABA as needed
- ▨ episodic steroids
- ▤ preventive low dose inhaled steroids
- preventive high dose inhaled steroids/LABA



of their children's disease. 28% of the parents reported that they used less treatment than prescribed, usually in fear of side effects. Asthma management knowledge was also insufficient in many parents; only 45% could clearly distinguish mode of action and indications of bronchodilators and inhaled steroids. However, even in children whose asthma control was, compared to guidelines, unsatisfactory or poor, most parents were satisfied with the results of the treatment.

These data may not be representative for Switzerland, as they come from a parents' association whose voluntary nature suggests a more than average degree of motivation. It is therefore likely that symptom control and asthma treatment in the community are poorer than this study suggests. In fact, a population-based survey of a random sample of 4353 schoolchildren performed in 1991 in the canton of St. Gallen showed that only 31% of boys and 15% of girls with current wheeze reported any bronchodilator treatment in the past 12 months [31]. Unfortunately more recent data from random population samples in Switzerland are not available.

In summary, these epidemiological data suggest that bronchiolitis and mild viral wheeze might be overtreated in Switzerland, with a large proportion

of children receiving pharmaceutical agents in spite of a lack of scientific evidence. In contrast, management of children with severe chronic asthma often seems to be insufficient, with a failure to step up treatment adequately. It remains to be assessed whether the implementation of the new guidelines will have an impact on treatment practice in Switzerland.

Longitudinal studies showed that up to 50% of six year old children had wheezed at some time in their life. Most of these children had only transient symptoms, suffering from viral-induced bronchiolitis or bronchitis. This is a phenotype that responds only poorly, if at all, to preventive treatment with inhaled corticosteroids. The approach taken in the new recommendations is therefore likely to reduce health care costs for asthma, because treatment with inhaled steroids and other expensive drugs is discouraged in the large number of mild viral wheezers where it is unlikely to have any benefit. In contrast, stepping up treatment is recommended in the small group of severe asthmatics where it has been shown to be cost-effective through prevention of acute exacerbations and hospitalisations [32].

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