



**HAL**  
open science

## GLOBAL STRATEGY FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER

Soren Pedersen, Suzanne Hurd, Robert Lemanske, Allan Becker, Heather Zar,  
Peter Sly, Manuel Soto-Quiroz, Gary Wong, Eric Bateman

► **To cite this version:**

Soren Pedersen, Suzanne Hurd, Robert Lemanske, Allan Becker, Heather Zar, et al.. GLOBAL STRATEGY FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER. *Pediatric Pulmonology*, 2010, 46 (1), pp.1. 10.1002/ppul.21321 . hal-00599822

**HAL Id: hal-00599822**

**<https://hal.science/hal-00599822>**

Submitted on 11 Jun 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**GLOBAL STRATEGY FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER**

Journal:	<i>Pediatric Pulmonology</i>
Manuscript ID:	PPUL-10-0175
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	29-May-2010
Complete List of Authors:	Pedersen, Soren; University of Southern Denmark Hurd, Suzanne; 2Global Initiative for Asthma Lemanske, Robert; Univ of Wisconsin Becker, Allan; University of Manitoba, Pediatrics and Child Health Zar, Heather; University of Cape Town Sly, Peter; Telethon Institute for Child Health Research Soto-Quiroz, Manuel; National Children's Hospital Wong, Gary; Childrens Hospital Bateman, Eric; University of Cape Town
Keywords:	Asthma guidelines, Children, Chronic disease



## GLOBAL STRATEGY FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER

Soren Erik Pedersen<sup>1</sup>, Suzanne S. Hurd<sup>2</sup>, Robert F. Lemanske, Jr.<sup>3</sup>, Allan Becker<sup>4</sup>, Heather J. Zar<sup>5</sup>, Peter D. Sly<sup>6</sup>, Manuel Soto-Quiroz<sup>7</sup>, Gary Wong<sup>8</sup>, Eric D. Bateman<sup>9</sup>

<sup>1</sup>Kolding Hospital, Kolding, Denmark; <sup>2</sup>Global Initiative for Asthma, Vancouver, Washington, USA; <sup>3</sup>Madison, WI, USA; <sup>4</sup>Winnipeg, Manitoba, Canada; <sup>5</sup>University of Cape Town, Cape Town, South Africa; <sup>6</sup>Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, Western Australia, Australia; <sup>7</sup>National Children's Hospital San José, Costa Rica; <sup>8</sup>Hong Kong ROC; <sup>9</sup>University of Cape Town, Cape Town, South Africa;

**Abstract:** Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits, and hospitalizations<sup>1</sup>. During the past two decades, many scientific advances have improved our understanding of asthma and our ability to manage and control it effectively. However, in children 5 years and younger, the clinical symptoms of asthma are variable and non-specific. Furthermore, neither airflow limitation nor airway inflammation, the main pathologic hallmarks of the condition, can be assessed routinely in this age group. For this reason, to aid in the diagnosis of asthma in young children, a symptoms-only descriptive approach that includes the definition of various wheezing phenotypes has been recommended<sup>2</sup>.

In 1993, the Global Initiative for Asthma (GINA) was implemented to develop a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma while at the same time assuring a mechanism to incorporate the results of scientific investigations into asthma care. Since then, GINA has developed and regularly revised a *Global Strategy for Asthma Management and Prevention*. Publications based on the *Global Strategy for Asthma Management and Prevention* have been translated into many different languages to promote international collaboration and dissemination of information.

In this report, *Global Strategy for Asthma Management and Prevention in Children 5 Years and Younger*, an effort has been made to present the special challenges that must be taken into account in managing asthma in children during the first 5 years of life, including difficulties with diagnosis, the efficacy and safety of drugs and drug delivery systems, and the lack of data on new therapies. Approaches to these issues will vary among populations in the world based on

1  
2  
3 socioeconomic conditions, genetic diversity, cultural beliefs, and differences in health care  
4 access and delivery. Patients in this age group are often managed by pediatricians and general  
5 practitioners routinely faced with a wide variety of issues related to childhood diseases.  
6  
7  
8  
9

10 KEY Words: Asthma, guidelines, human, children, chronic disease  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

**CONTENTS**

## Introduction

## Methodology

## Risk Factors Associated With Development Of Asthma

## Aeroallergens

## Maternal Dietary Avoidance During Pregnancy and/or Lactation

## Polluants

## Microbes and Their Products

## Psychosocial Factors

## Other Risk Factors

## Summary

## Diagnosis

## Symptoms

## Clinical History

## Tests for Diagnosis and Monitoring

## Differential Diagnosis

TABLE 1: Differential Diagnosis of Asthma in Children 5 Years and Younger

## Wheezing Phenotypes

## Management And Pharmacologic Treatment

## Asthma Education

## Asthma Control

Table 2. Levels of Asthma Control in Children 5 Years and Younger

## Pharmacotherapy

Table 3: Choosing an Inhaler Device for Children with Asthma

## Treatment Strategy

Table 4. Low Daily Doses of Inhaled Glucocorticosteroids for Children 5 Years and Younger

Table 5. Asthma Management Approach Based on Control for Children 5 Years and Younger

## Acute Exacerbations

Table 6. Initial Assessment of Acute Asthma in Children 5 Years and Younger

Table 7. Indications for Immediate Referral to Hospital (if *any* of the following are present)

Table 8: Initial Management of Acute Asthma in Children 5 Years and Younger

## Summary: Key Messages

## References

## INTRODUCTION

Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease as measured by school absences, emergency department visits, and hospitalizations<sup>1</sup>. Asthma typically begins in early childhood, with an earlier onset in males than females<sup>3-5</sup>. Atopy is present in the majority of children with asthma over the age of 3, and allergen-specific sensitization is one of the most important risk factors for the development of asthma<sup>6</sup>. However, no intervention has yet been shown to prevent the development of asthma or to modify the long-term natural course of the disease.

Asthma is defined as a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing<sup>7</sup>. However, in children 5 years and younger, the clinical symptoms of asthma are variable and non-specific. Furthermore, neither airflow limitation nor airway inflammation, the main pathologic hallmarks of the condition, can be assessed routinely in this age group. For this reason, to aid in the diagnosis of asthma in young children, a symptoms-only descriptive approach that includes the definition of various wheezing phenotypes has been recommended<sup>2</sup>.

For all patients with a confirmed diagnosis of asthma, the goal of treatment is to achieve control of the clinical manifestations of the disease, and maintain this control for prolonged periods, with appropriate regard to the safety and cost of the treatment required to achieve this goal. Control of asthma can be achieved in a majority of children 5 years and younger with a pharmacologic intervention strategy developed in partnership between the family/caregiver and the health care practitioner. As in older children and adults, inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years and younger.

## Methodology

Recommendations are made based on the best evidence currently available, and are intended to serve as an initial reference point with the recognition that some recommendations may need to

1  
2  
3 be modified to adapt to the population characteristics and health care resources present in  
4 different clinical practice settings. The panel was charged with the responsibility of reviewing  
5 the available scientific literature and assigning evidence levels according to the methodology  
6 used in previous GINA documents (Four levels of evidence: Categories A, B, C and D based on  
7 the quality of available evidence.) Because of the relative paucity of randomized clinical trials in  
8 children 5 years and younger, many of the recommendations are identified as **Evidence D**  
9 (expert opinion). However, in many of these cases, the expert opinion is based on randomized  
10 clinical trial data from studies conducted in older children and adults. A summary of key  
11 messages is provided at the end of the document.  
12  
13  
14  
15  
16  
17  
18

19 Prior to completion of this report by the pediatric expert panel, the document was reviewed by H. Bisgaard,  
20 Denmark, J. de Blic, France, J. De Jongste, The Netherlands, R. Stein, Brazil, S. Szefler, USA and G. Wennergren,  
21 Sweden. All members of the GINA Assembly received a copy for review, and comments were received from C.  
22 Baena-Cagnani, H. E. Neffen Argentina; Y. Chen, C. Bai, China; H. Campos, Brazil; M. Ebisawa, S. Makino, S.  
23 Yoshihara, Japan; A. Koleilat, Lebanon; L. Lan, Viet Nam; E. Mantzouranis, Greece; Y. Mohammad, G. Dib, S.  
24 Mohammad, F. Dmeiraoui, Syria; L. Pereira, West Indies, P. Pohunek, Czech Republic; Y. Shim, Korea; H. Turktas,  
25 B. Karadag, B. Sekerel, H. Yuksel, Turkey. Final review was conducted by the GINA Executive Committee: E.  
26 Bateman, South Africa, L. P. Boulet, Canada, A. Cruz, Brazil, M. FitzGerald, Canada, T. Haahtela, Finland, M,  
27 Levy, UK, P. O'Byrne, Canada, K. Ohta, Japan, P. Paggiaro, Italy, S. Pedersen, Denmark, M. Soto-Quiroz, Costa  
28 Rica, G. Wong, Hong Kong ROC.  
29  
30  
31

## 32 **RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ASTHMA**

33  
34  
35

36 Epidemiologic studies have identified a number of risk factors associated with the development  
37 of asthma, including (but not limited to) sensitization to aeroallergens, maternal diet during  
38 pregnancy and/or lactation, pollutants (particularly environmental tobacco smoke), microbes and  
39 their products, and psychosocial factors. However, evidence for avoidance measures to prevent  
40 asthma is lacking in many cases.  
41  
42  
43  
44  
45  
46

### 47 **Aeroallergens**

48  
49

50 Atopic sensitization to common aeroallergens, especially perennial inhalant allergens, is an  
51 important risk factor associated with asthma<sup>8</sup>. For some children, the earlier in life they become  
52 sensitized to local allergens the greater their risk for asthma later in life<sup>6</sup>, especially when  
53 sensitization occurs in association with frequent lower respiratory illnesses<sup>9</sup>. Several types of  
54 aeroallergens are particularly important in relation to asthma.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
**House dust mites:** A Cochrane analysis questioned the effectiveness of house dust mite avoidance for the treatment of established asthma<sup>10</sup>. Moreover, there is no evidence that anti-house dust mite measures prevent the onset of asthma<sup>11-13</sup>.

10  
11  
12  
13  
14  
15  
16  
17  
**Companion animal allergens:** The relationship between exposure and sensitization to allergens from companion animals is not clear, and there are insufficient data to recommend for, or against, the presence of a pet in the home unless the child has become sensitized to the pet species<sup>8,14-16</sup>.

18  
19  
20  
21  
22  
23  
**Cockroaches:** Exposure to cockroach allergen in the living quarters is associated with the development of sensitization, and sensitization to cockroach allergen is associated with an increased risk of developing asthma<sup>17</sup>.

24  
25  
26  
27  
28  
29  
30  
**Fungi:** Sensitization to *Alternaria* is a major risk factor not only for the development of asthma in children, but also for its severity<sup>18,19</sup>. *Alternaria* is usually considered an outdoor aeroallergen, but outdoor and indoor concentrations may be similar<sup>20</sup>.

### 31 **Maternal Diet During Pregnancy and/or Lactation**

32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
At present, there are insufficient data to support a protective effect of any dietary intervention during pregnancy or lactation in preventing asthma or atopic disease<sup>21,22</sup>. Breastfeeding itself decreases early childhood wheezing syndromes associated with upper and lower respiratory infections. However, although recommended for its general health benefits, there is little evidence that breastfeeding prevents development of persistent asthma<sup>9,23-25</sup>.

### 45 **Pollutants**

46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Maternal smoking during pregnancy and exposure to environmental tobacco smoke early in life are associated with a greater risk of developing wheezing illnesses in childhood<sup>26</sup>, as well as with reduced lung function later in life<sup>5</sup>. Therefore, every effort should be made to avoid exposing children to tobacco smoke<sup>27</sup>.



1  
2  
3 Use of biomass fuels in the home has been associated with an increased risk of asthma, increased  
4 severity of asthma, and exercise-induced bronchospasm in children<sup>28,29</sup>. This presents a problem  
5 in much of the world where biomass fuels such as wood, charcoal, animal dung, and crop  
6 residues are used on a daily basis for cooking and/or heating. Outdoor air pollution related to  
7 traffic has been shown to trigger wheezing in the first 3 years of life<sup>30</sup>.

### 13 **Microbes And Their Products**

16 Wheezing in early childhood is predominately linked to viral infections, especially those due to  
17 rhinovirus, respiratory syncytial virus (RSV), Boca virus, and metapneumovirus (MPV)<sup>31-33</sup>.

21 The impact of bacterial products and their relationship to the development of asthma is  
22 increasingly a focus of interest and forms part of the so-called "hygiene hypothesis." Exposure  
23 to a farming environment in early life has been associated with a reduced risk of asthma and  
24 allergy in children compared to those who have not grown up on a farm<sup>34,35</sup>. In this regard,  
25 exposure to the lipopolysaccharide endotoxin from microorganisms encountered in the farming  
26 environment appears to be a potential protective factor, particularly in children with specific  
27 genetic polymorphisms<sup>36</sup>.

35 Since intestinal flora are the largest source of microbial exposure for most infants and children,  
36 the use of probiotics to modify the composition of intestinal flora has been proposed as a method  
37 for exploiting this asthma-protective effect of microbes. While probiotics have been shown to be  
38 of some benefit in the prevention of atopic dermatitis, no impact on the development of asthma  
39 has been demonstrated<sup>37</sup>.

46 Although the use of antibiotics also modifies the composition of intestinal flora, the impact of  
47 use of antibiotics early in life on the risk of developing asthma later in life is controversial<sup>38,39</sup>.  
48 Based on available data, it is recommended that particularly broad-spectrum antibiotics should  
49 be used with circumspection in this young age group, and only for recognized indications  
50  
51  
52  
53 **(Evidence D).**

### 57 **Psychosocial Factors**

1  
2  
3  
4  
5 A child's social environment may play a role in the development and severity of asthma<sup>40,41</sup>.  
6  
7 Stress in family or other primary caregivers during the first year of life is associated with an  
8  
9 atopic profile and wheeze in infants, and is also associated with asthma at age 6 to 8 years<sup>42</sup>.  
10  
11 Maternal distress in early life may play a role in the development of childhood asthma, especially  
12  
13 if the distress continues beyond the postpartum period<sup>43</sup>.  
14  
15  
16  
17

### 18 **Other Risk Factors**

19  
20  
21 Children born by Cesarean section have a higher risk of asthma than those born by vaginal  
22  
23 delivery<sup>44</sup>, particularly children of allergic parents<sup>45</sup>. Paracetamol (acetaminophen) use during  
24  
25 pregnancy<sup>46</sup> and for fever in the child's first year of life<sup>47</sup> have been associated with increased  
26  
27 prevalence of asthma in children.  
28  
29

### 30 **Summary**

31  
32  
33 Since the contributions of different risk factors to the development of asthma vary widely in  
34  
35 different societies and homes, their relative importance overall may be difficult to assess.  
36  
37 Avoidance of some risk factors requires societal and public health interventions. However,  
38  
39 measures to avoid other risk factors can be implemented by individual concerned parents as part  
40  
41 of their personal preventive strategies for asthma, and these include:

- 42 • Avoid exposures to atmospheric pollution and particularly tobacco smoke
  - 43 • Avoid unnecessary use of antibiotics in young children
  - 44 • Provide a calm and nurturing environment (**Evidence D**)
- 45  
46  
47  
48

### 49 **DIAGNOSIS**

50  
51  
52  
53 Making a diagnosis of asthma in children 5 years and younger may be difficult because episodic  
54  
55 respiratory symptoms such as wheezing and cough are also common in children who do not have  
56  
57 asthma, particularly in those younger than 3 years<sup>48,49</sup>. Furthermore, it is not possible to  
58  
59  
60

1  
2  
3 routinely assess both airflow limitation and inflammation in this age group. Nevertheless, a  
4 diagnosis of asthma in young children can often be made based largely on symptom patterns and  
5 on a careful clinical assessment of family history and physical findings. The presence of atopy  
6 or allergic sensitization provides additional predictive support, as early allergic sensitization  
7 increases the likelihood that a wheezing child will have asthma<sup>6</sup>.  
8  
9  
10  
11  
12

### 13 14 **Symptoms**

15  
16  
17 Symptoms in this age group that may indicate a diagnosis of asthma include wheeze, cough,  
18 breathlessness (typically manifested by patterns of activity limitation), and nocturnal  
19 symptoms/awakenings.  
20  
21  
22  
23

24  
25 **Wheeze:** Wheeze, the most common symptom associated with asthma in children 5 years and  
26 younger, has been strictly defined as a continuous high-pitched sound, sometimes with musical  
27 quality, emitting from the chest during expiration<sup>50</sup>. Wheezing occurs in several different  
28 patterns but a wheeze that occurs recurrently, during sleep, or with triggers such as activity,  
29 laughing, or crying is consistent with a diagnosis of asthma.  
30  
31  
32  
33

34  
35 Wheezing may be interpreted differently based on the individual observing it (e.g., parent versus  
36 clinician), when it is being reported (e.g., retrospectively versus in real time), the environmental  
37 context in which it is occurring (e.g., wheeze may have different presentation patterns in areas of  
38 the world where parasites with life cycles involving the lung are more prevalent), and the cultural  
39 context in which it is occurring (e.g., different cultures assign different relative importance to  
40 certain symptom sand to diagnosis and treatment of respiratory tract diseases in general).  
41  
42  
43  
44  
45  
46

47  
48 Viral respiratory infections are the most common factors responsible for acute wheezing  
49 episodes in young children, and some viral infections (RSV and rhinovirus) are associated with  
50 recurrent wheeze throughout childhood. Since many young children may wheeze with viral  
51 infections, deciding when the presence of wheezing with infections is truly an initial or recurrent  
52 clinical presentation of childhood asthma is difficult<sup>5</sup>.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
**Cough:** Cough due to asthma is recurrent and/or persistent, and is usually accompanied by some wheezing episodes and breathing difficulties. Nocturnal cough (occurring when the child is asleep) or cough occurring with exercise, laughing, or crying in the absence of an apparent respiratory infection, strongly supports a diagnosis of asthma. The common cold and other respiratory illnesses are also associated with cough.

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
**Breathlessness (Terms often used by parents include difficult breathing, heavy breathing, and shortness of breath):** Breathlessness that occurs during exercise and is recurrent increases the likelihood of the presentation being due to asthma. In infants and toddlers, crying and laughing are an exercise equivalent.

## 24 25 26 27 **Clinical History**

28  
29  
30  
31  
32  
33  
34  
35  
36  
For children 5 years and younger with a history of recurrent respiratory symptoms; a strong family history of asthma in first degree relatives (especially the mother); and/or atopy presenting as atopic dermatitis, food allergy, and/or allergic rhinitis also make a diagnosis of asthma more likely.

## 37 38 39 40 **Tests for Diagnosis**

41  
42  
43  
44  
45  
While no tests diagnose asthma with certainty in young children, the following may be considered as useful adjuncts in making a diagnostic decision.

46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
**Therapeutic Trial:** A trial of treatment with short-acting bronchodilators and inhaled glucocorticosteroids for at least 8 to 12 weeks may provide some guidance as to the presence of asthma (**Evidence D**). These interventions should be evaluated in terms of how they affect control of daytime and nocturnal symptoms as well as the frequency of exacerbations requiring increasing doses of inhaled or systemic glucocorticosteroids. Marked clinical improvement during the treatment and deterioration when it is stopped supports a diagnosis of asthma. Due to

the variable nature of asthma in young children, a therapeutic trial may need to be repeated more than once in order to be certain of the diagnosis.

**Tests for Atopy:** Sensitization to allergens can be assessed using either immediate hypersensitivity skin testing or an *in vitro* method that detects antigen-specific IgE antibody. Skin-prick testing is less reliable for confirming atopy in infants.

**Chest Radiograph (X-ray):** If there is doubt about the diagnosis of asthma in a wheezing child, a plain chest radiograph may help to exclude structural abnormalities of the airway (e.g., congenital malformations such as congenital lobar emphysema, vascular ring), chronic infection (e.g. tuberculosis), or other diagnoses.

Lung function testing, bronchial challenge, and other physiological tests do not have a major role in the diagnosis of asthma in children 5 years and younger due to the inability of children this age to perform reproducible expiratory maneuvers. Such tests are only possible in specialized centers, and are undertaken mainly for research purposes.

### Differential Diagnosis

Although a variety of tools have been described above to aid the clinician in making a diagnosis of asthma in children 5 years and younger, it must be emphasized that a definite diagnosis in this young age group is challenging and has important clinical consequences. Thus, alternative causes that can lead to respiratory symptoms of wheeze, cough, and breathlessness must be considered and excluded before an asthma diagnosis is arrived at<sup>48</sup> (Table 1).

**TABLE 1: Differential Diagnosis of Asthma in Children 5 Years and Younger**

Infections
<ul style="list-style-type: none"> <li>• Recurrent respiratory tract infections</li> <li>• Chronic rhino-sinusitis</li> <li>• Tuberculosis</li> </ul>
Congenital problems
<ul style="list-style-type: none"> <li>• Tracheomalacia</li> <li>• Cystic fibrosis</li> </ul>

- Bronchopulmonary dysplasia
- Congenital malformation causing narrowing of the intrathoracic airways
- Primary ciliary dyskinesia syndrome
- Immune deficiency
- Congenital heart disease

#### Mechanical problems

- Foreign body aspiration
- Gastroesophageal reflux

Neonatal or very early onset of symptoms (associated with failure to thrive), symptoms associated with vomiting, or focal lung or cardiovascular signs, suggest an alternative diagnosis and indicate the need for further investigations.

### Wheezing Phenotypes

Recurrent wheezing occurs in a large proportion of children five years and younger. However, not all of this wheezing indicates asthma. Several phenotypes of wheezing disorders in this age group have been recognized in epidemiologic studies.

Early childhood wheezing has been classified by a Task Group convened by the European Respiratory Society (ERS)<sup>2</sup> as either *episodic wheeze* (wheezing during discrete time periods, often in association with clinical evidence of a common cold, with absence of wheeze between episodes) or *multiple-trigger wheeze* (wheezing that occurs as episodic exacerbations as above, but also with symptoms including cough and wheeze occurring between these episodes, during sleep or with triggers such as activity, laughing, or crying).

Data from a U.S. cohort study<sup>5</sup> led to the description of three wheezing phenotypes: *transient wheeze* (symptoms begin and end before the age of 3 years), *persistent wheeze* (symptoms begin before the age of 3 years and continue beyond the age of 6 years), and *late-onset wheeze* (symptoms begin after the age of 3 years).

The clinical usefulness of the phenotypes described by the ERS Task Group<sup>2</sup> or based on data from the U.S. cohort study<sup>5</sup> remains a subject of active investigation. Children with asthma may

1  
2  
3 have any of these phenotypes, but asthma occurs much more rarely in the *episodic wheeze* and  
4 *transient wheeze* phenotypes compared to the other phenotypes. A number of other publications  
5 provide additional insights into wheezing phenotypes and their relationship to children 5 years  
6 and younger with asthma<sup>5,51,52</sup>.

7  
8  
9  
10  
11  
12 To aid in the early identification, in the clinical setting, of children 5 years and younger who  
13 wheeze and are at high risk of developing persistent asthma symptoms, a number of risk profiles  
14 have been evaluated<sup>53-56</sup>. One such predictive assessment, the Asthma Predictive Index (API), is  
15 recommended for children with four or more wheezing episodes in a year and is based on  
16 information obtained from the Tucson (USA) Respiratory Study<sup>54</sup>. One study has shown that a  
17 child with a positive API has a 4- to 10-fold greater chance of developing asthma between the  
18 ages of 6 and 13, while 95% of children with a negative API remained free of asthma<sup>54,56</sup>. The  
19 applicability and validation of the API in other countries and clinical situations is awaited.  
20  
21  
22  
23  
24  
25  
26  
27

## 28 **MANAGEMENT AND PHARMACOLOGIC TREATMENT**

29  
30  
31 For all patients with a confirmed diagnosis of asthma, the goal of treatment is to achieve control  
32 of the clinical manifestations of the disease, and maintain this control for prolonged periods, with  
33 appropriate regard to the safety and cost of the treatment required to achieve this goal. Control  
34 of asthma can be achieved in a majority of children 5 years and younger with a pharmacologic  
35 intervention strategy developed in partnership between the family/caregiver and the health care  
36 practitioner. As in older children and adults, inhaled therapy constitutes the cornerstone of  
37 asthma treatment in children 5 years and younger.  
38  
39  
40  
41  
42  
43  
44  
45

### 46 **Asthma Education**

47  
48  
49 Asthma education should be provided to family members and caregivers of wheezy children 5  
50 years and younger when wheeze is suspected to be caused by asthma. An educational package  
51 should contain a basic explanation about asthma and the factors that influence it, instruction  
52 about correct inhalation technique and the importance of adherence to the prescribed medication  
53 regime, and a description of how to recognize when asthma control is deteriorating and the  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 medications to administer when this occurs. Randomized controlled trials in older children and  
4 adults have demonstrated that the use of a written asthma management plan along with careful  
5 verbal explanation of the treatment regime can improve asthma control. For children 5 years and  
6  
7 younger who cannot reliably perform lung function measurements, asthma management plans  
8  
9 based on the levels of respiratory symptoms have been shown to be just as effective as plans  
10  
11 based on self-monitoring of lung function<sup>57</sup> (**Evidence B**). Crucial to a successful asthma  
12  
13 education program are a **patient-doctor partnership** featuring a high level of agreement  
14  
15 between family or caregiver and healthcare practitioner regarding the goals of treatment for the  
16  
17 child, as well as **intensive follow-up**<sup>58</sup> (**Evidence D**).  
18  
19

## 20 21 **Asthma Control**

22  
23  
24 For all patients with a confirmed diagnosis of asthma, the goal of treatment is to achieve control  
25  
26 of the clinical manifestations of the disease and maintain this control for prolonged periods, with  
27  
28 appropriate regard to the safety and cost of the treatment required to achieve this goal.  
29  
30

31  
32 The relevance of distinguishing between current control (as assessed by the control or  
33  
34 elimination of clinical features of asthma in the recent weeks or months) from “future risk” (the  
35  
36 likelihood of future worsening, exacerbations, impaired lung development), and the relationship  
37  
38 between these two concepts, have not been carefully studied in small children. However, a  
39  
40 combination of increased daytime cough, daytime wheeze, and nighttime  $\beta_2$ -agonist use has been  
41  
42 found to be a strong predictor of an exacerbation in children 5 years and younger (predicting  
43  
44 around 70% of exacerbations, with a low false positive rate of 14%<sup>59</sup>). In contrast, no individual  
45  
46 symptom was predictive of an imminent asthma exacerbation. This finding indirectly supports  
47  
48 the importance of good daily asthma control and the use of composite outcomes in the  
49  
50 assessment of asthma control in this age group.

51  
52 Although exacerbations may occur in children after months of apparent clinical control, the risk  
53  
54 is greater in patients whose current control is poor. On the other hand, the “future risk” of harm  
55  
56 caused by excessive doses of medications, or inappropriate treatment such as the prolonged use  
57  
58 of high doses of inhaled or systemic glucocorticosteroids, must also be avoided by ensuring that  
59  
60



treatment is appropriate and reduced to the lowest level that maintains satisfactory current clinical control.

Defining satisfactory current clinical asthma control in children 5 years and younger is problematic, since health care providers are almost exclusively dependent on the reports of the child's family members and caregivers who might be unaware either of the presence of asthma symptoms, or of the fact that they represent uncontrolled asthma. Moreover, as with the diagnosis of asthma, lung function testing is not feasible as a means to monitor control in children of this age. No objective measures to assess clinical control have been validated for children younger than 4 years (one such measure has been developed for children aged 4-11<sup>60</sup>). However, a working scheme based on current expert opinion presents characteristics of controlled, partly controlled, and uncontrolled asthma for children 5 years and younger based on (1) symptoms recognized by family members/caregivers and (2) the child's need for reliever/rescue treatment (**Table 2**) (**Evidence D**).

**Table 2. Levels of Asthma Control in Children 5 Years and Younger\***

<b>Characteristic</b>	<b>Controlled (All of the following)</b>	<b>Partly Controlled (Any measure present in any week)</b>	<b>Uncontrolled (Three or more of features of partly controlled asthma in any week)</b>
<b>Daytime symptoms: wheezing, cough, difficult breathing</b>	None (less than twice/week, typically for short periods on the order of minutes and rapidly relieved by use of a rapid-acting bronchodilator)	More than twice/week (typically for short periods on the order of minutes and rapidly relieved by use of a rapid- acting bronchodilator)	More than twice/week (typically last minutes or hours or recur, but partially or fully relieved with rapid-acting bronchodilator)
<b>Limitations of activities</b>	None (child is fully active, plays and runs without limitation or symptoms)	Any (may cough, wheeze, or have difficulty breathing during exercise, vigorous play, or laughing)	Any (may cough, wheeze, or have difficulty breathing during exercise, vigorous play, or laughing)
<b>Nocturnal symptoms/awakening</b>	None (including no nocturnal coughing during sleep)	Any (typically coughs during sleep or wakes with cough, wheezing, and/or difficult breathing)	Any (typically coughs during sleep or wakes with cough, wheezing, and/or difficult breathing.
<b>Need for reliever/rescue treatment</b>	≤ 2 days/week	> 2 days/week	> 2 days/week

\*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate. Although patients with current clinical control are less likely to experience exacerbations, they are still at risk during viral upper respiratory tract infections and may still have one or more exacerbations per year.

## Pharmacotherapy

Inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years and younger. A general strategy for choosing inhalers in children is provided in **Table 3**. A pressurized metered-dose inhaler (MDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system<sup>61</sup> (**Evidence A**). This recommendation is based on studies with performed with  $\beta_2$ -agonists.

Spacers come in different designs and, since the dose received may vary considerably from one device to another, a spacer device that has documented efficacy in young children is recommended. Nebulizers, the only viable alternative delivery systems in children, should be reserved for the minority of children who cannot be taught effective use of a spacer device.

**Table 3: Choosing an Inhaler Device for Children with Asthma**

Age Group	Preferred Device	Alternate Device
Younger than 4 years	Pressurized metered-dose inhaler <i>plus</i> dedicated spacer with face mask	Nebulizer with face mask
4 – 5 years	Pressurized metered-dose inhaler <i>plus</i> dedicated spacer with mouthpiece	Pressurized metered-dose inhaler <i>plus</i> dedicated spacer with face mask, <i>or</i> Nebulizer with mouthpiece or face mask

Controlled trials in children 5 years and younger are rather limited, the patient populations have often not been well characterized with respect to phenotype (including wheezy children who may or may not have asthma), and different studies have used different outcomes and definitions of exacerbations. However, based on literature that is available, and on expert opinion, the following sections provide recommendations for controller medications (taken daily on a long-term basis to keep asthma under control) and reliever medications (for use on an as-needed basis) for the pharmacologic treatment of asthma in children 5 years and younger.

## *Controller Medications*

### *Inhaled glucocorticosteroids*

**Efficacy:** As in older children, several placebo-controlled studies of inhaled glucocorticosteroids in children 5 years and younger with asthma have found statistically significant clinical effects on a variety of outcomes, including increased lung function and number of symptom-free days, and reduced symptoms, need for additional medication, caregiver burden, systemic glucocorticosteroid use, and exacerbations<sup>56,62-73</sup> (**Evidence A**). However, the dose-response relationships have been less well studied. The clinical response may differ depending on the specific device used for delivery and the child's ability to use it correctly. With correct use of a spacer device, twice the recommended initial low dose of inhaled glucocorticosteroid results in near-maximum benefits as regular, long-term treatment in the majority of patients (**Table 4**)<sup>63,67</sup>. In the daily clinic inhaled glucocorticosteroids was reported to reduce hospitalizations (mainly because of less readmissions in children younger than 24 months)<sup>74</sup>. Use of inhaled glucocorticosteroids for up to 2 years has not been documented to induce remission of asthma; symptoms almost always return when treatment is stopped<sup>56</sup> (**Evidence B**).

**Safety:** The majority of studies evaluating the systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5 years. However, the available data in children 5 years and younger suggest that, as in older children, clinically effective doses of inhaled glucocorticosteroids are safe and the potential risks are well balanced by the clinical benefits<sup>56,62,72</sup>. Generally, low doses of inhaled glucocorticosteroids (**Table 4**) have not been associated with any clinically serious adverse systemic effects in clinical trials and are considered safe<sup>56,62-72</sup> (**Evidence A**). However, higher doses have been associated with detectable systemic effects on both growth and the hypothalamic-pituitary-adrenal (HPA) axis<sup>56,62-72</sup>. These effects are similar to those reported in studies of older children, which find no evidence of long-term clinical impact<sup>75,76</sup>. Local side effects, such as hoarseness and candidiasis, are rare in children 5 years and younger<sup>67</sup>.

### *Leukotriene modifiers*

Efficacy: Leukotriene modifiers reduce viral-induced asthma symptoms in children ages 2-5 years with a history of intermittent asthma<sup>77</sup> by reducing the number of protocol-defined exacerbations, but do not reduce the frequency of hospitalizations, use of prednisolone, duration of exacerbations, or days without asthma symptoms. Moreover, no effect on post-bronchiolitic wheeze or cough is seen following hospitalization with RSV bronchiolitis<sup>78</sup>. In a three-month study of children with persistent wheeze, montelukast reduced symptoms and rescue  $\beta_2$ -agonist use by approximately 6%. The percentage of patients experiencing an asthma attack was not significantly reduced, but the need for a course of prednisolone was significantly reduced from 28% to 19% of patients<sup>79</sup>. Montelukast has also been shown to reduce airway hyperresponsiveness to methacholine<sup>77</sup> or hyperventilation with cold dry air<sup>80</sup>. A randomized, placebo-controlled trial of the addition of montelukast to usual asthma therapy among 42 children aged 2-5<sup>81</sup> found that this treatment reduced the number of days with worsening of asthma symptoms in boys but not in girls, the number of days with symptoms in the two groups being 7.8% and 3.5%, respectively. In summary, leukotriene modifiers improve some asthma outcomes in young children (**Evidence A**). However, the role of leukotriene modifiers as add-on therapy in children 5 years and younger whose asthma is uncontrolled on inhaled glucocorticosteroids has not been specifically evaluated.

Safety: No safety concerns have been demonstrated from the use of leukotriene modifiers in young children.

### *Theophylline*

Although a few studies in children 5 years and younger suggest clinical benefit from regular use of theophylline, the effects are small and mostly non-significant<sup>82</sup>. The efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids, and side effects are more common (**Evidence D**).

### *Long-acting inhaled $\beta_2$ -agonists*

1  
2  
3  
4  
5  
6 Long-acting inhaled  $\beta_2$ -agonists (LABAs) are bronchodilators, but as long-term therapy for  
7 asthma they are only prescribed in combination with an inhaled glucocorticosteroid and are  
8 therefore considered controller medications. The effect of long-acting inhaled  $\beta_2$ -agonists or  
9 combination (LABA/glucocorticosteroid) products has not been adequately studied in children 5  
10 years and younger. Formoterol and salmeterol have shown long-lasting bronchodilatory and  
11 bronchoprotective effects in this age group<sup>83</sup> (**Evidence D**). However, there are no published  
12 randomized placebo-controlled trials in this age group on the addition of long-acting inhaled  $\beta_2$ -  
13 adrenergic agents to inhaled glucocorticosteroids.  
14  
15  
16  
17  
18  
19

#### 20 21 22 *Cromolyn and nedocromil sodium*

23  
24  
25 A Cochrane Review concluded that there was no beneficial effect of cromolyn therapy in  
26 preschool children<sup>84,85</sup> (**Evidence A**) and nedocromil has not been studied in preschool children.  
27  
28 Therefore, cromones cannot be recommended in this age group.  
29  
30  
31

#### 32 33 *Oral and systemic glucocorticosteroids*

34  
35  
36 Because of the side effects associated with prolonged use, oral glucocorticosteroids in young  
37 children with asthma should be restricted to the treatment of acute severe exacerbations, whether  
38 viral-induced or otherwise (**Evidence D**).  
39  
40  
41  
42

#### 43 44 *Immunotherapy*

45  
46  
47 No studies of immunotherapy for asthma have been performed in this age group. Therefore,  
48 immunotherapy is not recommended for the treatment or prophylaxis of asthma in children 5  
49 years and younger (**Evidence D**).  
50  
51  
52

#### 53 54 *Comparisons Between Controller Medications*

### *Inhaled glucocorticosteroids and cromolyn*

In older children and adults, regular treatment with inhaled glucocorticosteroids has been well documented to be clinically more effective than other controller treatments for asthma. Moreover, they attenuate the decline in lung function seen in association with severe exacerbations<sup>86</sup>. Fewer comparative studies have been conducted in children 5 years and younger. However two studies of nearly 1,000 children in this age group<sup>87,88</sup> confirmed the superiority of inhaled glucocorticosteroids over cromones for almost all endpoints assessing asthma control (**Evidence A**).

### *Inhaled glucocorticosteroids and leukotriene modifiers*

Two studies have compared inhaled glucocorticosteroids with leukotriene modifiers. A one-year, randomized, open study compared montelukast with nebulized budesonide in 400 children; overall measures favored budesonide<sup>89</sup>. In a blinded, placebo-controlled study of 63 children, fluticasone propionate treatment significantly improved symptoms over placebo, whereas montelukast did not, and fluticasone propionate also improved lung function after three months<sup>90</sup> (**Evidence B**).

### *Inhaled glucocorticosteroids and demand bronchodilator/glucocorticosteroid combination*

Another study reported that regular inhaled glucocorticosteroid was more effective than on demand treatment with a bronchodilator/glucocorticosteroid combination in children aged 1-4 years with frequent wheeze<sup>91</sup>.

### ***Reliever Medications***

Rapid-acting inhaled  $\beta_2$ -agonists are the most effective bronchodilators available and therefore the preferred reliever treatment for asthma in children 5 years and younger. An MDI with spacer is, in most cases, an effective way for delivering reliever therapy<sup>61,92</sup> (**Evidence A**). When delivery is not optimal because of lack of cooperation or distress, or when the child is hypoxic,

nebulizer therapy is also an option. Oral therapy is not recommended due to its slower onset of action and its tendency to produce more side effects.

There is no evidence that inhaled ipratropium has an important role in the daily management of asthma in children 5 years and younger<sup>93</sup> (**Evidence A**).

### **Treatment Strategy**

The goal of asthma treatment, to achieve and maintain control of the disease, can be reached in a majority of children 5 years and younger with a pharmacologic intervention strategy<sup>87</sup> developed in partnership between the family/caregiver and the health care practitioner. Although validated tools for assessment of asthma control have not been developed for young children, it is recommended that both current impairment (day and night symptoms, activity level impairment, need for rescue medications) and future risk (likelihood of acute exacerbation in the future) be assessed and controlled (**Table 2**) (**Evidence B**).

### ***Who Should be Treated***

Regular controller treatment is normally recommended for children 5 years and younger whose frequency and severity of asthma symptoms without treatment indicates that their asthma is not controlled (**Table 2**).

### ***Selecting Initial Therapy***

A low-dose inhaled glucocorticosteroid is recommended as the preferred initial treatment to control asthma in children 5 years and younger<sup>56,69,89</sup> (**Table 4**) (**Evidence A**).

<b>Table 4. Low Daily Doses* of Inhaled Glucocorticosteroids for Children 5 Years and Younger</b>	
<b>Drug</b>	<b>Low Daily Dose (µg)</b>
Beclomethasone dipropionate	100
Budesonide MDI+spacer	200
Budesonide nebulized	500




†Ciclesonide	NS
Fluticasone propionate	100
†Mometasone furoate	NS
†Triamcinolone acetonide	NS

\* A low daily dose is defined as the dose which has not been associated with clinically adverse effects in trials including measures of safety. This is not a table of clinical equivalence.

†NS = Not studied in this age group.

This initial treatment should be given for at least 3 months to establish its effectiveness in reaching control. If at the end of this period the low dose of inhaled glucocorticosteroid does not control symptoms, and the child is using optimal technique and is adherent to therapy, doubling the initial dose of glucocorticosteroid given in **Table 4** may be the best option (**Evidence C**). Addition of a leukotriene modifier to the low-dose inhaled glucocorticosteroid may also be considered, although this has not been studied in this age group (**Evidence D**).

**Table 5** presents a management approach based on asthma control for children 5 years and younger.

<b>Table 5. Asthma Management Approach Based on Control for Children 5 Years and Younger</b>		
<i>Asthma education</i>		
<i>Environmental control</i>		
<i>As needed rapid-acting <math>\beta_2</math>-agonist</i>		
<b>Controlled on as needed rapid-acting <math>\beta_2</math>-agonists</b>	<b>Partly controlled on as needed rapid-acting <math>\beta_2</math>-agonists</b>	<b>Uncontrolled or only partly controlled on low-dose inhaled glucocorticosteroid*</b>
		
<b>Controller options</b>		
Continue as needed rapid-acting $\beta_2$ -agonists	Low-dose inhaled glucocorticosteroid	Double low-dose inhaled glucocorticosteroid
	Leukotriene modifier	Low-dose inhaled glucocorticosteroid <i>plus</i> leukotriene modifier

\*Oral glucocorticosteroids should be used only for treatment of acute severe exacerbations of asthma.

Shaded boxes represent the preferred treatment options.



1  
2  
3  
4  
5 ***When Control is not Achieved:*** When doubling the initial dose of inhaled glucocorticosteroids  
6 fails to achieve and maintain asthma control, the child's inhalation technique and compliance  
7 with the medication regimen should be carefully assessed and monitored, as these are common  
8 problems in this age group. Furthermore, control of environmental factors should be assessed  
9 and addressed appropriately, and the asthma diagnosis reconsidered.  
10  
11  
12  
13

14  
15  
16 The best treatment for children whose asthma is not controlled on twice the initial dose of  
17 inhaled glucocorticosteroid has not been established. Options to consider are to further increase  
18 the dose of inhaled glucocorticosteroid (perhaps combined with more frequent dosing), or to add  
19 a leukotriene modifier, theophylline, or a low dose of oral glucocorticosteroid for a few weeks  
20 until the control of the child's asthma improves (**Evidence D**). The need for this additional  
21 treatment should be re-evaluated at each visit and maintained for as short a period as possible.  
22 Furthermore, the treatment goal or level of control that is feasible for each child must be  
23 considered and discussed with the family/caregivers, since a compromise might be necessary -  
24 accepting a level of persisting symptoms to avoid excessive and harmful doses of oral and  
25 inhaled glucocorticosteroids or theophylline.  
26  
27  
28  
29  
30  
31  
32  
33

34  
35 ***Duration and Adjustments to Treatment:*** Asthma symptoms remit in a substantial proportion of  
36 children 5 years and younger, and marked seasonal variations are seen in chronic symptoms and  
37 the risk of exacerbations. For children with seasonal symptoms, if daily long-term control  
38 therapy is discontinued after the season a written action plan detailing specific signs of  
39 worsening asthma, and therapeutic interventions that should be subsequently initiated, should be  
40 reviewed with the caregivers. It is recommended that the continued need for asthma treatment in  
41 children under age 5 should be regularly assessed (e.g., every three to six months) (**Evidence D**).  
42 A follow-up visit should be scheduled 3-6 weeks after discontinuation of therapy to ascertain  
43 whether the remission of symptoms persists and there is no need for reinstatement of therapy.  
44  
45  
46  
47  
48  
49  
50  
51

52  
53 ***Approach to the Child with Intermittent Wheezing Episodes:*** Intermittent episodic wheezing of  
54 any severity may represent unrecognized uncontrolled asthma, an isolated viral-induced  
55 wheezing episode, or an episode of seasonal or allergen-induced asthma. The initial treatment is  
56  
57  
58  
59  
60

1  
2  
3 identical in any case: a dose of rapid-acting inhaled  $\beta_2$ -agonist every 4–6 hours as needed for a  
4 day or more until symptoms disappear (**Evidence A**). However, uncertainty surrounds the  
5 addition of other drugs, especially when the nature of the episode is unclear.  
6  
7  
8  
9

10 *If a detailed history suggests the diagnosis of asthma*, and wheezing episodes are frequent (e.g.,  
11 3 in a season), regular controller treatment should be initiated and the effect evaluated (**Evidence**  
12 **D**). Regular controller treatment may also be indicated in a child with less frequent, but more  
13 severe, episodes of viral-induced wheeze (**Evidence D**).  
14  
15  
16  
17

18  
19 *Where the diagnosis is in doubt*, and when rapid-acting inhaled  $\beta_2$ -agonist therapy needs to be  
20 repeated more frequently than every 6-8 weeks, a diagnostic trial of regular controller therapy  
21 should be considered to confirm whether the symptoms are due to asthma (**Evidence D**).  
22  
23  
24  
25

26 The best way to treat intermittent episodic wheezing that occurs in children where a diagnosis of  
27 asthma cannot be confirmed, or is unlikely, is controversial. The short-term addition of a  
28 controller medication - inhaled glucocorticosteroid, leukotriene modifier, or oral  
29 glucocorticosteroid - has demonstrated no effects on wheezing symptoms or progression to  
30 asthma<sup>94-102</sup>. However, in one study treating wheezing episode with 1,500  $\mu\text{g}$  of fluticasone  
31 propionate daily for 10 days reduced the need for oral glucocorticosteroids for the episode (18%  
32 in the untreated arm versus 8% in the treated arm)<sup>103</sup>. Therefore, although these treatments are  
33 widely practiced, based on current evidence, their continued use cannot be recommended  
34  
35  
36  
37  
38  
39  
40  
41 (**Evidence D**).  
42  
43

#### 44 **Acute Exacerbations**

45  
46  
47 The management of acute exacerbations of asthma in children 5 years and younger includes an  
48 action plan to enable the child's family members and caregivers to recognize an asthma attack  
49 and initiate treatment, recognize a severe episode, identify when urgent hospitalized treatment is  
50 necessary, and provide specific recommendations for follow-up (**Evidence D**).  
51  
52  
53  
54  
55

#### 56 **Definition**

1  
2  
3  
4  
5 An acute exacerbation of asthma in children 5 years and younger is defined as an acute or  
6 subacute deterioration in symptom control that is sufficient to cause distress or risk to health  
7 necessitating a visit to a health care provider or requiring treatment with systemic  
8 glucocorticosteroids<sup>104</sup>. Early symptoms of an acute exacerbation may include any of the  
9 following :

- 10 • An increase in wheeze and shortness of breath
- 11 • An increase in coughing, especially nocturnal cough
- 12 • Lethargy or reduced exercise tolerance
- 13 • Impairment of daily activities, including feeding
- 14 • A poor response to reliever medication

15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27 Upper respiratory symptoms frequently precede the onset of an asthma exacerbation, indicating  
28 the important role of upper respiratory tract viral infections in precipitating exacerbations in  
29 many, although not all, asthmatic children.

### 30 31 32 33 34 *Home Action Plan for Family/Caregivers*

35  
36  
37 An asthma action plan should be considered for use by the family/caregivers of children 5 years  
38 and younger (**Evidence D**). Developed through collaboration between an asthma educator, the  
39 health care provider, and the family, action plans have been shown to be of value in older  
40 children<sup>105-108</sup>, although they have not been sufficiently studied in this younger age group. An  
41 asthma action plan should contain details that will enable those who care for the child to  
42 recognize exacerbations early, and know what interventions are required, including when  
43 medical help should be sought. The home action plan should also provide details (including  
44 telephone numbers) of services available for emergencies – doctors' offices, emergency rooms  
45 and hospitals, ambulance services, and, where relevant, emergency pharmacies. Treatments that  
46 can be initiated at home are inhaled rapid-acting  $\beta_2$ -agonist and oral glucocorticosteroids, but  
47 specific instructions on their use must be provided in the action plan.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Initial home management: Inhaled rapid-acting  $\beta_2$ -agonist via a mask or spacer device and observation.* Treatment should be initiated with two puffs (200 $\mu$ g salbutamol or the equivalent) of inhaled rapid-acting  $\beta_2$ -agonist, given one puff at a time via a mask or spacer device (**Evidence D**). The child should be observed by the family/caregiver and maintained in a restful and reassuring atmosphere for an hour or more. Medical attention should be sought the same day if the inhaled bronchodilator is required for symptom relief more than every 3 hours or for more than 24 hours.

*Need for urgent medical attention.* Immediate medical attention should be sought:

- For children younger than 1 year requiring repeated rapid-acting inhaled  $\beta_2$ -agonists over the course of hours
- If the child is acutely distressed
- If the symptoms are not relieved promptly by inhaled bronchodilator
- If the period of relief after a dose of inhaled  $\beta_2$ -agonist becomes progressively shorter<sup>109</sup>

*Family/Caregiver Initiated Oral Glucocorticosteroids.* Although practiced in some parts of the world, the evidence to support the initiation of oral glucocorticosteroid treatment by family/caregivers in the home management of asthma exacerbations in children is weak, and should be considered only where the physician is confident that they will be used appropriately (**Evidence D**).

### *Assessment of Severity*

Features that indicate that an exacerbation is severe are provided in **Table 6** and the presence of any of these features is an indication of the need for urgent treatment (**Evidence A**). Agitation, drowsiness, and confusion are features of cerebral hypoxemia. Percutaneous oxygen saturation of 92% or less on presentation (before oxygen or bronchodilator treatment) is associated with higher morbidity and greater likelihood of the need for hospitalization. Other clinical features of a severe attack requiring immediate treatment are inability to talk in sentences or phrases, tachycardia (200 beats per minute or more for children 0-3 years, and 180 beats per minute or

more for children 4-5 years), central cyanosis, and a quiet chest on auscultation (indicating minimal ventilation – insufficient to produce a wheeze).

Symptoms	Mild	Severe <sup>a</sup>
Altered consciousness	No	Agitated, confused or drowsy
Oximetry on presentation <sup>b</sup> (SaO <sub>2</sub> )	≥ 94%	< 90%
Talks in <sup>c</sup>	Sentences	Words
Pulse rate	< 100 bpm <sup>d</sup>	> 200 bpm (0-3 years) >180 bpm (4-5 years)
Central cyanosis	Absent	Likely to be present
Wheeze intensity	Variable	May be quiet

<sup>a</sup> Any of these features indicates a severe asthma exacerbation

<sup>b</sup> Oximetry performed before treatment with oxygen or bronchodilator

<sup>c</sup> The normal developmental capability of the child must be taken into account.

<sup>d</sup> bpm = beats per minute.

### ***Indications for Hospitalization***

Indications for hospitalization of children 5 years and younger are presented in **Table 7**.

Children with features of a severe exacerbation that fail to resolve in 1 to 2 hours in spite of repeated dosing with rapid-acting inhaled  $\beta_2$ -agonists, with or without the addition of oral glucocorticosteroids, must be referred for observation and further treatment in the hospital (**Evidence D**). Other indications are respiratory arrest or impending arrest, lack of supervision in the home or emergency department, and recurrence of signs of severity within 48 hours of the initial exacerbation (particularly if treatment with systemic glucocorticosteroids has been given). In addition, early medical attention should be sought in children under 2 years of age where the risk of dehydration and respiratory fatigue is increased.

<p><i>ANY of the following:</i></p> <ul style="list-style-type: none"> <li>No response to three (3) administrations of an inhaled short-acting <math>\beta_2</math>-agonist within 1-2 hours</li> <li>Tachypnea (Normal respiratory rate &lt; 60 breaths per minute in children 0 – 2 months; &lt; 50 in children 2- 12 months; &lt; 40 in children 1 – 5 years) despite 3 administrations of an inhaled</li> </ul>
---

short-acting  $\beta_2$ -agonist

- Child is unable to speak or drink or is breathless
- Cyanosis
- Subcostal retractions
- Oxygen saturation when breathing room air < 92%
- Social environment that impairs delivery of acute treatment; caregivers unable to manage acute asthma at home

### ***Emergency Treatment and Pharmacotherapy***

*Treat hypoxemia:* The presence of hypoxemia must be treated urgently with oxygen delivered by face mask, to achieve and maintain percutaneous oxygen saturation above 94% (**Evidence A**). A 24% facemask is usually adequate with oxygen flow set to manufacturer's instructions (usually 4 L per minute). To avoid hypoxemia during changes in treatment, children who are acutely distressed should be treated immediately with oxygen and rapid-acting bronchodilator (2.5 mg of salbutamol or equivalent diluted in 3 ml of sterile normal saline) delivered by an oxygen-driven nebulizer (if available). This treatment should not be delayed, and may be given before the full assessment is completed.

*Bronchodilator therapy:* The initial dose of rapid-acting bronchodilator may be given by oxygen-driven nebulizer (as described above), or if hypoxemia is absent (or an oxygen-driven nebulizer not available) by either an air-driven nebulizer or a pressurized MDI with spacer and mask or mouthpiece. For most children, the MDI plus spacer is favored as it is more efficient than the nebulizer<sup>61,110,111</sup> (**Evidence A**) for bronchodilator delivery. The initial dose is two puffs of salbutamol (100  $\mu$ g per puff) or equivalent. A dose of 2.5 mg salbutamol solution is recommended when a nebulizer is used. The frequency of dosing depends on the response observed over 1 to 4 hours (see below).

*Inhaled glucocorticosteroids or leukotriene modifier:* Children who have been prescribed maintenance therapy with inhaled glucocorticosteroids, leukotriene modifier, or both should continue to take the prescribed dose during and after an exacerbation (**Evidence D**).

### *Assessment of Treatment Response*

Children with a severe exacerbation must be observed for at least 1 hour after initiation of treatment, at which time further treatment can be planned.

- If symptoms persist, a further 2 puffs of salbutamol may be given 20 minutes after the first dose and repeated at 20-minute intervals for an hour. Failure to respond to this at 1 hour, or earlier if the child deteriorates, should prompt urgent admission to the hospital and a short course of oral glucocorticosteroids (**Evidence D**).
- If symptoms improve at 1 hour, but recur within 3 or 4 hours, more frequent doses of bronchodilator may be given (2 or 3 puffs hourly), and oral glucocorticosteroids should be administered. The child should be observed by the family/caregiver and might need to remain in the emergency room or have ready access to emergency care. Children who fail to respond to 10 puffs of inhaled rapid acting  $\beta_2$ -agonist should be referred to the hospital (**Evidence D**).
- If the symptoms resolve rapidly and do not recur for 1 or 2 hours, no further treatment might be required. The dose of bronchodilator may be repeated every 3 to 4 hours (up to a total of 10 puffs per 24 hours) and, if symptoms persist beyond 1 day, other treatments including inhaled or oral glucocorticosteroids are indicated (**Evidence D**).

### *Additional Treatment*

When treatment in addition to short-acting bronchodilators is required for an exacerbation, the options available for children this age include inhaled glucocorticosteroids (if not already used, short-term or long-term, either nebulized or administered via a pressurized MDI), a short course of oral glucocorticosteroid, and leukotriene modifiers. Although such interventions have been shown to result in statistically significant benefits in several studies, their clinical benefit, particularly on such endpoints as hospitalizations and longer-term outcomes, have not been impressive<sup>95-102,112</sup>. The exception to this pattern is one study of 1,500  $\mu\text{g}$  of fluticasone



propionate daily, which reduced the need for oral glucocorticosteroids from 18% to 8% of subjects<sup>103</sup> (**Evidence D**).

*Inhaled glucocorticosteroids:* For children not previously on inhaled glucocorticosteroids, an initial dose of inhaled glucocorticosteroid twice the low daily dose indicated in **Table 4** may be given and continued for a few weeks or months (**Evidence D**). For those already on inhaled glucocorticosteroids, doubling the dose has *not* been documented to be effective in older children and there is no evidence for this approach in children 5 years and younger.

*Oral glucocorticosteroids:* Oral glucocorticosteroids (syrup or tablets) are as effective as systemic (intramuscular or intravenous) administration, but are most effective when administered early in an exacerbation. A dose equivalent to prednisolone 1-2 mg/kg/day, with a maximum of 20 mg in children under 2 year of age and 30 mg for children 2-5 years, is recommended (**Evidence D**). A 3-5 day course is sufficient in most children and can be stopped abruptly (**Evidence D**).

Regardless of the type of intervention, with either glucocorticosteroids or leukotriene modifiers, the severity of symptoms at the time the therapy is initiated must be carefully monitored. The sooner therapy is started in relationship to the onset of symptoms, the more likely the impending exacerbation may be clinically attenuated or abated.

**Table 8** provides a summary of management of acute severe asthma in children 5 years and younger.

<b>Table 8: Initial Management of Acute Severe Asthma in Children 5 Years and Younger*</b>	
<b>Therapy</b>	<b>Dose and Administration</b>
Supplemental oxygen	Deliver by 24% face mask (flow set to manufacturer's instructions, usually 4L/minute) Maintain oxygen saturation above 94%
Short-acting $\beta_2$ -agonist	6 puffs salbutamol by spacer or 2.5 mg salbutamol by nebulizer every 20 minutes for first hour <sup>a</sup>



Ipratropium	2 puffs every 20 minutes for first hour only
Systemic glucocorticosteroids	Oral prednisolone (1-2 mg/kg daily for up to 5 days) <i>or</i> Intravenous methylprednisolone 1 mg/kg 6 hourly on day 1; 12 hourly on day 2; then daily
Aminophylline <sup>b</sup>	Consider in ICU: loading dose 6-10mg/kg lean body weight Initial maintenance: 0.9 mg/kg/hour Adjustment according to plasma theophylline levels
Oral $\beta_2$ agonists	No
Long-acting $\beta_2$ -agonist	No

<sup>a</sup> If inhalation is not possible an intravenous bolus of 5  $\mu$ g/kg given over 5 minutes, followed by continuous infusion of 5  $\mu$ g/kg/hour. The dose should be adjusted according to clinical effect and side effects<sup>84</sup>.

<sup>b</sup> Loading dose should not be given to patients already receiving theophylline.

### *Follow-up of Exacerbations*

Children who have recently had an asthma exacerbation are at risk of further episodes and require follow-up to ensure complete recovery, to establish the cause of the exacerbation, and, when necessary, to establish appropriate maintenance treatment (**Evidence D**). Prior to discharge from the emergency department or hospital, family/caregivers should receive the following (all are **Evidence D**):

- Instruction on recognition of signs of recurrence and worsening of asthma. The factors that precipitated the exacerbation should be identified and strategies for future avoidance of these factors implemented
- A written individualized action plan including details of accessible emergency services
- A supply of bronchodilator and, where applicable, the remainder of the course of oral or inhaled glucocorticosteroids or leukotriene modifier
- Careful review of inhaler technique
- Further treatment advice:
  - The bronchodilator should be used on an as-needed basis, but the daily requirement should be recorded to assure it is being decreased over time to pre-exacerbation levels
  - Initiate or continued inhaled glucocorticosteroids (for first month after discharge, 3 times low initial dose, then adjust dose as needed)

- A follow-up appointment within 1 week and another within 1-2 months depending on the clinical, social, and practical context of the exacerbation

Before discharge, the condition of the patient should be stable, e.g., out of bed and able to eat and drink without problem.

### **Summary: Key Messages**

1. The goal of asthma treatment, to achieve and maintain control of the disease, can be reached in a majority of children 5 years and younger with a pharmacologic intervention strategy developed in partnership between the family/caregiver and the health care practitioner.
2. Maternal smoking during pregnancy and exposure to environmental tobacco smoke early in life are associated with a greater risk of developing wheezing illnesses in childhood, as well as with reduced lung function later in life. Therefore, every effort should be made to avoid exposing children to tobacco smoke.
3. Making a diagnosis of asthma in children 5 years and younger may be difficult because episodic respiratory symptoms such as wheezing and cough are also common in children who do not have asthma, particularly in those younger than 3 years.
4. A diagnosis of asthma in young children can often be made based largely on symptom patterns and on a careful clinical assessment of family history and physical findings. The presence of atopy or allergic sensitization provides additional predictive support, as early allergic sensitization increases the likelihood that a wheezing child will have asthma.
5. Asthma education should be provided to family members and caregivers of wheezy children 5 years and younger when wheeze is suspected to be caused by asthma.
6. For all patients with a confirmed diagnosis of asthma, the goal of treatment is to achieve control of the clinical manifestations of the disease and maintain this control for prolonged periods, with appropriate regard to the safety and cost of the treatment required to achieve this goal.
7. The prolonged use of high doses of inhaled or systemic glucocorticosteroids must be avoided by ensuring that treatment is appropriate and reduced to the lowest level that maintains satisfactory current clinical control.
8. A pressurized metered-dose inhaler (MDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

9. Several placebo-controlled studies of inhaled glucocorticosteroids in children 5 years and younger with asthma have found statistically significant clinical effects on a variety of outcomes, including increased lung function and number of symptom-free days, and reduced symptoms, need for additional medication, caregiver burden, systemic glucocorticosteroid use, and exacerbations.

10. Because of the side effects associated with prolonged use, oral glucocorticosteroids in young children with asthma should be restricted to the treatment of acute severe exacerbations, whether viral-induced or otherwise.

11. Rapid-acting inhaled  $\beta_2$ -agonists are the most effective bronchodilators available and therefore the preferred reliever treatment for asthma in children 5 years and younger.

12. A low-dose inhaled glucocorticosteroid is recommended as the preferred initial treatment to control asthma in children 5 years and younger.

13. If low dose of inhaled glucocorticosteroid does not control symptoms, and the child is using optimal technique and is adherent to therapy, doubling the initial dose of glucocorticosteroid may be the best option.

14. When doubling the initial dose of inhaled glucocorticosteroids fails to achieve and maintain asthma control, the child's inhalation technique and compliance with the medication regimen should be carefully assessed and monitored, as these are common problems in this age group.

15. Continued need for asthma treatment in children under age 5 should be regularly assessed (e.g., every three to six months).

#### REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-478.
2. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, de Jongste JC, Eber E, Everard ML, Frey U, Gappa M, Garcia-Marcos L, Grigg J, Lenney W, Le Souef P, McKenzie S, Merkus PJ, Midulla F, Paton JY, Piacentini G, Pohunek P, Rossi GA, Seddon P, Silverman M, Sly PD, Stick S, Valiulis A, van Aalderen WM, Wildhaber JH, Wennergren G, Wilson N, Zivkovic Z, Bush A. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32(4):1096-1110.
3. Bisgaard H, Szeffler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007;42(8):723-728.

- 1
- 2
- 3
4. Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;37(12):1738-1746.
5. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-138.
6. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, Gern JE, Gerritsen J, Hamelmann E, Helms PJ, Lemanske RF, Martinez F, Pedersen S, Renz H, Sampson H, von Mutius E, Wahn U, Holt PG. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372(9643):1100-1106.
7. Global Initiative for Asthma. *Global Strategy for Asthma Diagnosis and Prevention*. Global Initiative for Asthma (updated 2009). Available from <http://www.ginasthma.org>.
8. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: A population-based cross-sectional study. *Lancet* 2001;357(9258):752-756.
9. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: A systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139(2):261-266.
10. Gotzsche PC, Johansen HK, Hammarquist C, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2001(2):CD001187.
11. Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, Smit HA, Gerritsen J, Neijens HJ, de Jongste JC. House dust mite allergen reduction and allergy at 4 yr: Follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17(5):329-336.
12. Marks GB, Mhrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, Ampon RD, Crisafulli D, Belousova EG, Mellis CM, Peat JK, Leeder SR. Prevention of asthma during the first 5 years of life: A randomized controlled trial. *J Allergy Clin Immunol* 2006;118(1):53-61.
13. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, Simpson A, Custovic A. Early life environmental control: Effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170(4):433-439.
14. Bufford JD, Gern JE. Early exposure to pets: Good or bad? *Curr Allergy Asthma Rep* 2007;7(5):375-382.
15. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;288(8):963-972.
16. Platts-Mills JA, Custis NJ, Woodfolk JA, Platts-Mills TA. Airborne endotoxin in homes with domestic animals: Implications for cat-specific tolerance. *J Allergy Clin Immunol* 2005;116(2):384-389.
17. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, 3rd, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068-1080.
18. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, Sachs MI. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324(6):359-363.

19. Salo PM, Arbes SJ, Jr., Sever M, Jaramillo R, Cohn RD, London SJ, Zeldin DC. Exposure to *Alternaria alternata* in US homes is associated with asthma symptoms. *J Allergy Clin Immunol* 2006;118(4):892-898.
20. O'Connor GT, Walter M, Mitchell H, Kattan M, Morgan WJ, Gruchalla RS, Pongratic JA, Smartt E, Stout JW, Evans R, Crain EF, Burge HA. Airborne fungi in the homes of children with asthma in low-income urban communities: The Inner-City Asthma Study. *J Allergy Clin Immunol* 2004;114(3):599-606.
21. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121(1):183-191.
22. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006;3:CD000133.
23. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Poulton R. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: A longitudinal study. *Lancet* 2002;360(9337):901-907.
24. Takemura Y, Sakurai Y, Honjo S, Kusakari A, Hara T, Gibo M, Tokimatsu A, Kugai N. Relation between breastfeeding and the prevalence of asthma: The Tokorozawa Childhood Asthma and Pollinosis Study. *Am J Epidemiol* 2001;154(2):115-119.
25. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56(3):192-197.
26. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;159(2):403-410.
27. Bisgaard H, Loland L, Holst KK, Pippert CB. Prenatal determinants of neonatal lung function in high-risk newborns. *J Allergy Clin Immunol* 2009.
28. Khalequzzaman M, Kamijima M, Sakai K, Chowdhury NA, Hamajima N, Nakajima T. Indoor air pollution and its impact on children under five years old in Bangladesh. *Indoor Air* 2007;17(4):297-304.
29. Ng'ang'a LW, Odhiambo JA, Mungai MW, Gicheha CM, Nderitu P, Maingi B, Macklem PT, Becklake MR. Prevalence of exercise induced bronchospasm in Kenyan school children: An urban-rural comparison. *Thorax* 1998;53(11):919-926.
30. Andersen ZJ, Loft S, Ketzler M, Stage M, Scheike T, Hermansen MN, Bisgaard H. Ambient air pollution triggers wheezing symptoms in infants. *Thorax* 2008;63(8):710-716.
31. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005;24(11 Suppl):S217-222.
32. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E, Carlson-Dakes KT, Salazar LP, DaSilva DF, Tisler CJ, Gern JE, Lemanske RF, Jr. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178(7):667-672.
33. Lee KK, Hegele RG, Manfreda J, Wooldrage K, Becker AB, Ferguson AC, Dimich-Ward H, Watson WT, Chan-Yeung M. Relationship of early childhood viral exposures to



- 1  
2  
3  
4 respiratory symptoms, onset of possible asthma and atopy in high risk children: The  
5 Canadian Asthma Primary Prevention Study. *Pediatr Pulmonol* 2007;42(3):290-297.  
6 34. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D,  
7 Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E.  
8 Environmental exposure to endotoxin and its relation to asthma in school-age children. *N*  
9 *Engl J Med* 2002;347(12):869-877.  
10 35. von Mutius E, Radon K. Living on a farm: Impact on asthma induction and clinical  
11 course. *Immunol Allergy Clin North Am* 2008;28(3):631-647, ix-x.  
12 36. Eder W, Klimecki W, Yu L, von Mutius E, Riedler J, Braun-Fahrlander C, Nowak D,  
13 Holst O, Martinez FD. Association between exposure to farming, allergies and genetic  
14 variation in CARD4/NOD1. *Allergy* 2006;61(9):1117-1124.  
15 37. Bjorksten B. Evidence of probiotics in prevention of allergy and asthma. *Curr Drug*  
16 *Targets Inflamm Allergy* 2005;4(5):599-604.  
17 38. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic  
18 use in early life. *Chest* 2007;131(6):1753-1759.  
19 39. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, Marra CA. Does  
20 antibiotic exposure during infancy lead to development of asthma?: A systematic review  
21 and metaanalysis. *Chest* 2006;129(3):610-618.  
22 40. Chen E, Langer DA, Raphaelson YE, Matthews KA. Socioeconomic status and health in  
23 adolescents: The role of stress interpretations. *Child Dev* 2004;75(4):1039-1052.  
24 41. Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of  
25 wheezing in infancy: A prospective birth-cohort study. *Am J Respir Crit Care Med*  
26 2002;165(3):358-365.  
27 42. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression  
28 of atopy. *Curr Opin Allergy Clin Immunol* 2005;5(1):23-29.  
29 43. Kozyrskyj AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued  
30 exposure to maternal distress in early life is associated with an increased risk of  
31 childhood asthma. *Am J Respir Crit Care Med* 2008;177(2):142-147.  
32 44. Tollanes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe  
33 childhood asthma: A population-based cohort study. *J Pediatr* 2008;153(1):112-116.  
34 45. Roduit C, Scholtens S, de Jongste JC, Wijga AH, Gerritsen J, Postma DS, Brunekreef B,  
35 Hoekstra MO, Aalberse R, Smit HA. Asthma at 8 years of age in children born by  
36 caesarean section. *Thorax* 2009;64(2):107-113.  
37 46. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol  
38 and risk of wheezing and asthma in children: A birth cohort study. *Int J Epidemiol*  
39 2008;37(3):583-590.  
40 47. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, Stewart A.  
41 Association between paracetamol use in infancy and childhood, and risk of asthma,  
42 rhinoconjunctivitis, and eczema in children aged 6-7 years: Analysis from Phase Three of  
43 the ISAAC programme. *Lancet* 2008;372(9643):1039-1048.  
44 48. Doherty G, Bush A. Diagnosing respiratory problems in young children. *Practitioner*  
45 2007;251(1697):20, 22-25.  
46 49. Pedersen S. Preschool asthma--not so easy to diagnose. *Prim Care Respir J* 2007;16(1):4-  
47 6.  
48 50. Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA, Everard ML.  
49 Survey of respiratory sounds in infants. *Arch Dis Child* 2001;84(1):35-39.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 51. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP,  
4 Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life  
5 with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*  
6 2008;63(11):974-980.
- 7  
8 52. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing  
9 phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J*  
10 2008;31(5):974-981.
- 11 53. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current  
12 wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest*  
13 2005;127(2):502-508.
- 14 54. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define  
15 risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*  
16 2000;162(4 Pt 1):1403-1406.
- 17 55. Devulapalli CS, Carlsen KC, Haland G, Munthe-Kaas MC, Pettersen M, Mowinckel P,  
18 Carlsen KH. Severity of obstructive airways disease by age 2 years predicts asthma at 10  
19 years of age. *Thorax* 2008;63(1):8-13.
- 20 56. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF, Jr., Sorkness C, Szeffler SJ, Larsen  
21 G, Spahn JD, Zeiger RS, Heldt G, Strunk RC, Bacharier LB, Bloomberg GR, Chinchilli  
22 VM, Boehmer SJ, Mauger EA, Mauger DT, Taussig LM, Martinez FD. The Prevention  
23 of Early Asthma in Kids study: Design, rationale and methods for the Childhood Asthma  
24 Research and Education network. *Control Clin Trials* 2004;25(3):286-310.
- 25 57. Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled  
26 trials examining written action plans in children: What is the plan? *Arch Pediatr Adolesc*  
27 *Med* 2008;162(2):157-163.
- 28 58. Brouwer AF, Brand PL. Asthma education and monitoring: What has been shown to  
29 work. *Paediatr Respir Rev* 2008;9(3):193-199; quiz 199-200.
- 30 59. Swern AS, Tozzi CA, Knorr B, Bisgaard H. Predicting an asthma exacerbation in  
31 children 2 to 5 years of age. *Ann Allergy Asthma Immunol* 2008;101(6):626-630.
- 32 60. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, Rosenzweig JC,  
33 Manjunath R. Development and cross-sectional validation of the Childhood Asthma  
34 Control Test. *J Allergy Clin Immunol* 2007;119(4):817-825.
- 35 61. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with  
36 valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in  
37 children under 5 years of age: A systematic review with meta-analysis. *J Pediatr*  
38 2004;145(2):172-177.
- 39 62. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-  
40 dosing, placebo-controlled study of budesonide inhalation suspension given once or twice  
41 daily for treatment of persistent asthma in young children and infants. *Pediatrics*  
42 1999;103(2):414-421.
- 43 63. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone  
44 propionate in the treatment of young asthmatic children: A dose comparison study. *Am J*  
45 *Respir Crit Care Med* 1999;160(1):126-131.
- 46 64. Chavasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Persistent wheezing in  
47 infants with an atopic tendency responds to inhaled fluticasone. *Arch Dis Child*  
48 2001;85(2):143-148.
- 49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11
  - 12
  - 13
  - 14
  - 15
  - 16
  - 17
  - 18
  - 19
  - 20
  - 21
  - 22
  - 23
  - 24
  - 25
  - 26
  - 27
  - 28
  - 29
  - 30
  - 31
  - 32
  - 33
  - 34
  - 35
  - 36
  - 37
  - 38
  - 39
  - 40
  - 41
  - 42
  - 43
  - 44
  - 45
  - 46
  - 47
  - 48
  - 49
  - 50
  - 51
  - 52
  - 53
  - 54
  - 55
  - 56
  - 57
  - 58
  - 59
  - 60
65. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993;68(1):85-87.
66. Hofhuis W, van der Wiel EC, Nieuwhof EM, Hop WC, Affourtit MJ, Smit FJ, Vaessen-Verberne AA, Versteegh FG, de Jongste JC, Merkus PJ. Efficacy of fluticasone propionate on lung function and symptoms in wheezy infants. *Am J Respir Crit Care Med* 2005;171(4):328-333.
67. Ilangovan P, Pedersen S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. *Arch Dis Child* 1993;68(3):356-359.
68. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): Double-blind, randomised, controlled study. *Lancet* 2006;368(9537):754-762.
69. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1500-1506.
70. Pao CS, McKenzie SA. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med* 2002;166(7):945-949.
71. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108(4):540-546.
72. Teper AM, Colom AJ, Kofman CD, Maffey AF, Vidaurreta SM, Bergada I. Effects of inhaled fluticasone propionate in children less than 2 years old with recurrent wheezing. *Pediatr Pulmonol* 2004;37(2):111-115.
73. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009;123(3):e519-525.
74. Korhonen K, Dunder T, Klaukka T, Reijonen TM, Korppi M. Use of inhaled corticosteroids decreases hospital admissions for asthma in young children. *World J Pediatr* 2009;5(3):177-181.
75. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343(15):1064-1069.
76. Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001;164(4):521-535.
77. Hakim F, Vilozni D, Adler A, Livnat G, Tal A, Bentur L. The effect of montelukast on bronchial hyperreactivity in preschool children. *Chest* 2007;131(1):180-186.
78. Bisgaard H, Flores-Nunez A, Goh A, Azimi P, Halkas A, Malice MP, Marchal JL, Dass SB, Reiss TF, Knorr BA. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008;178(8):854-860.
79. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, Michele TM, Reiss TF, Nguyen HH, Bratton DL. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.
80. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. *Am J Respir Crit Care Med* 2000;162(1):187-190.
81. Johnston NW, Mandhane PJ, Dai J, Duncan JM, Greene JM, Lambert K, Sears MR. Attenuation of the September epidemic of asthma exacerbations in children: a



- 1  
2  
3 randomized, controlled trial of montelukast added to usual therapy. *Pediatrics*  
4 2007;120(3):e702-712.  
5  
6 82. Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance  
7 treatment for asthma in children. *Cochrane Database Syst Rev* 2006(1):CD002885.  
8  
9 83. Nielsen KG, Bisgaard H. Bronchodilation and bronchoprotection in asthmatic preschool  
10 children from formoterol administered by mechanically actuated dry-powder inhaler and  
11 spacer. *Am J Respir Crit Care Med* 2001;164(2):256-259.  
12  
13 84. Tasche MJ, van der Wouden JC, Uijen JH, Ponsioen BP, Bernsen RM, van Suijlekom-  
14 Smit LW, de Jongste JC. Randomised placebo-controlled trial of inhaled sodium  
15 cromoglycate in 1-4-year-old children with moderate asthma. *Lancet*  
16 1997;350(9084):1060-1064.  
17  
18 85. van der Wouden JC, Tasche MJ, Bernsen RM, Uijen JH, de Jongste JC, Ducharme FM.  
19 Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev*  
20 2003(3):CD002173.  
21  
22 86. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and  
23 decline in lung function in asthma. *Am J Respir Crit Care Med* 2008.  
24  
25 87. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety  
26 and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent  
27 wheezing. *Pediatrics* 2004;113(2):e87-94.  
28  
29 88. Leflein JG, Szeffler SJ, Murphy KR, Fitzpatrick S, Cruz-Rivera M, Miller CJ, Smith JA.  
30 Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer  
31 solution for asthma in young children: Results of a randomized outcomes trial. *Pediatrics*  
32 2002;109(5):866-872.  
33  
34 89. Szeffler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of  
35 budesonide inhalation suspension and montelukast in young children with mild persistent  
36 asthma. *J Allergy Clin Immunol* 2007;120(5):1043-1050.  
37  
38 90. Kooi EM, Schokker S, Marike Boezen H, de Vries TW, Vaessen-Verberne AA, van der  
39 Molen T, Duiverman EJ. Fluticasone or montelukast for preschool children with asthma-  
40 like symptoms: Randomized controlled trial. *Pulm Pharmacol Ther* 2008;21(5):798-804.  
41  
42 91. Papi A, Nicolini G, Baraldi E, Boner AL, Cutrera R, Rossi GA, Fabbri LM. Regular vs  
43 prn nebulized treatment in wheeze preschool children. *Allergy* 2009;64(10):1463-1471.  
44  
45 92. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-  
46 agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006(2):CD000052.  
47  
48 93. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F, Mayowe V. Anticholinergic  
49 drugs for wheeze in children under the age of two years. *Cochrane Database Syst Rev*  
50 2005(3):CD001279.  
51  
52 94. Bacharier LB, Phillips BR, Zeiger RS, Szeffler SJ, Martinez FD, Lemanske RF, Jr.,  
53 Sorkness CA, Bloomberg GR, Morgan WJ, Paul IM, Guilbert T, Krawiec M, Covar R,  
54 Larsen G, Mellon M, Moss MH, Chinchilli VM, Taussig LM, Strunk RC. Episodic use of  
55 an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with  
56 moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122(6):1127-  
57 1135.  
58  
59 95. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled  
60 corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998-  
2005.

- 1  
2  
3 96. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: Prevention of attacks with  
4 short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics*  
5 1988;81(5):624-629.
- 6  
7 97. Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in  
8 infancy with oral salbutamol and prednisolone. *Eur J Pediatr* 1996;155(6):512-516.
- 9  
10 98. Grant CC, Duggan AK, DeAngelis C. Independent parental administration of prednisone  
11 in acute asthma: A double-blind, placebo-controlled, crossover study. *Pediatrics*  
12 1995;96(2 Pt 1):224-229.
- 13  
14 99. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral  
15 prednisolone for viral wheeze in children aged 1-5 years: Randomised controlled trial.  
16 *Lancet* 2003;362(9394):1433-1438.
- 17  
18 100. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, Grigg J. Oral  
19 prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med*  
20 2009;360(4):329-338.
- 21  
22 101. Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, Lee AJ, Turner J,  
23 Sant M. Short-course montelukast for intermittent asthma in children: A randomized  
24 controlled trial. *Am J Respir Crit Care Med* 2007;175(4):323-329.
- 25  
26 102. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18  
27 months. *Arch Dis Child* 1986;61(1):15-19.
- 28  
29 103. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, Savdie C, Collet JP,  
30 Khomenko L, Rivard G, Platt RW. Preemptive use of high-dose fluticasone for virus-  
31 induced wheezing in young children. *N Engl J Med* 2009;360(4):339-353.
- 32  
33 104. National Asthma Council Australia. *Written Asthma Action Plans*. 2006. Available from  
34 [http://www.nationalasthma.org.au/html/management/action\\_plans/index.asp](http://www.nationalasthma.org.au/html/management/action_plans/index.asp) (assessed  
35 11/14/08).
- 36  
37 105. Agrawal SK, Singh M, Mathew JL, Malhi P. Efficacy of an individualized written home-  
38 management plan in the control of moderate persistent asthma: A randomized, controlled  
39 trial. *Acta Paediatr* 2005;94(12):1742-1746.
- 40  
41 106. Burkhart PV, Rayens MK, Revelette WR, Ohlmann A. Improved health outcomes with  
42 peak flow monitoring for children with asthma. *J Asthma* 2007;44(2):137-142.
- 43  
44 107. Gibson PG, Ram FS, Powell H. Asthma education. *Respir Med* 2003;97(9):1036-1044.
- 45  
46 108. McGrath AM, Gardner DM, McCormack J. Is home peak expiratory flow monitoring  
47 effective for controlling asthma symptoms? *J Clin Pharm Ther* 2001;26(5):311-317.
- 48  
49 109. Asthma Management Handbook. National Asthma Council Australia  
50 2006:<http://www.nationalasthma.org.au/cms/index.php> (accessed 11/14/08).
- 51  
52 110. Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S,  
53 Samransamruajkit R. Randomized controlled trial of salbutamol aerosol therapy via  
54 metered dose inhaler-spacer vs. jet nebulizer in young children with wheezing. *Pediatr*  
55 *Pulmonol* 2005;39(5):466-472.
- 56  
57 111. Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers vs metered-dose inhalers with  
58 spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a  
59 pediatric emergency department. *Arch Pediatr Adolesc Med* 2003;157(1):76-80.
- 60  
112. Bacharier LB, Phillips BR, Zeiger RS, Szeffler SJ, Martinez FD, Lemanske Jr RF,  
Sorkness C, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

antagonist in preschool children with intermittent wheezing. J Allergy Clin Immunol  
2008;in press.

For Peer Review