# 5 The Pediatric Asthmatic

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***Contents***



## KEY POINTS

- The incidence of asthma has increased dramatically during the past 20 years, with the highest increases in the urban areas of developed countries.
- Asthma treatment goals in children include decreasing mortality and improving quality of life.

From: *Bronchial Asthma: A Guide for Practical Understanding and Treatment, 6th ed.*
Edited by: M. E. Gershwin and T. E. Albertson, DOI 10.1007/978-1-4419-6836-4_5

- Specific treatment goals include but are not limited to decreasing inflammation, improving lung function, decreasing clinical symptoms, reducing hospital stays and emergency department visits, reducing work or school absences, and reducing the need for rescue medications.
- Nonpharmacological management strategies include allergen avoidance, environmental evaluation for allergens and irritants, patient education, allergy testing, regular monitoring of lung function, and the use of asthma management plans, asthma control tests, peak flow meters, and asthma diaries.
- Achieving asthma treatment goals reduces direct and indirect costs of asthma and is economically cost-effective.
- Developing optimal technique in the use of metered-dose inhalers (MDI) in young children is difficult. Ongoing instruction and review may be necessary to ensure good technique. The use of spacers may help.
- Asthma is a chronic disease with a potential psychological impact on the pediatric patient during critical years of development.

## INTRODUCTION

The incidence of allergies and asthma in the Western world has been increasing over the past 30 years. However, more recent data suggests that over the past 5–10 years, the overall global trends of asthma incidence have begun to stabilize *(1)*. Urbanization and industrialization has contributed to the increase in developed countries, but the reasons for this are still unclear. Asthma is estimated to be responsible for 1 in every 250 deaths worldwide. Many of these deaths are preventable, and specific issues have been identified that may contribute to this high mortality rate. Factors that contribute to high mortality and morbidity include slow access to care and medications, inadequate environmental control of allergens and irritants, dietary changes, genetic variations, cultural barriers, lack of education amongst patients and providers, insufficient resources, and improper use of health care dollars.

The Global Initiative for Asthma (GINA), initiated in 1989 for the World Health Organization (WHO) and the US National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) periodically establish guidelines for the diagnosis and treatment of asthma (*2, 3*). The most recent significant update to these recommendations appeared in the Expert Panel Review 3 (EPR-3) published by the National Asthma Education and Prevention Program (NAEPP) coordinating committee of the NHLBI of the NIH *(3)*. A historical timeline of these revisions is shown in Fig. 1.

The development of newer medications and delivery devices over the past 25 years has made a significant impact on our ability to decrease morbidity of childhood asthma. Hospitalizations for asthma have clearly decreased as a result of the use of controller medications. Quality of life has been identified as a significant metric to measure asthma treatment success. On the other hand, despite our improved knowledge of the pathogenesis of asthma, newer medications with fewer adverse effects, and increased standardization of treatment protocols, there has been a paradoxical increase in asthma mortality. The reasons for this observation are debatable, but may include lifestyle changes, dietary changes, the increase in obesity rates in the Western Hemisphere, coding anomalies, poor patient and/or caregiver education, and the

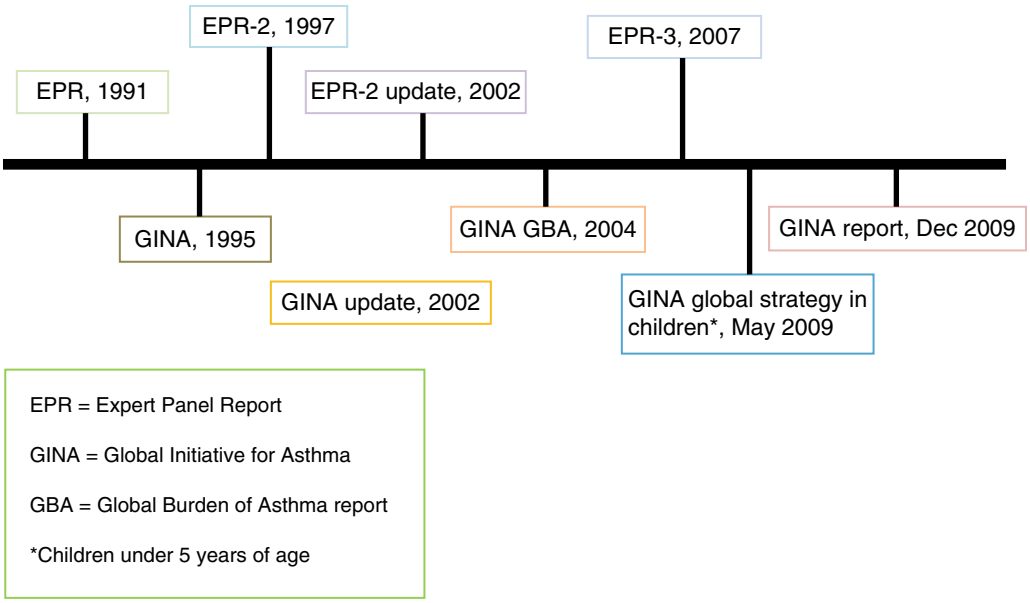



**Fig. 1.** Historical chart showing recommendations in asthma treatment worldwide.

overall increase in the incidence of allergies and asthma. What is clear, however, is that the development and introduction of new pharmaceuticals is not by itself the answer to improving outcomes in children with asthma. Patient education, environmental avoidance measures, proper use of medications, and immunotherapy are all equally important in the successful treatment of the pediatric asthmatic. The good news is that with our awareness of these factors, mortality has at least stabilized over the past 5 years.

Asthma in children has a unique set of characteristics that merit discussion (Table 1). The diagnosis of asthma in children may be difficult to make in the infant because of the prevalence of viral-associated wheezing in this age group of patients. The impact of viral illness on the development of asthma in later years is addressed later, along with the role of allergies in childhood asthma. Certain medications are not always appropriate for all ages, and devices that are used to evaluate asthma status may not be usable by young children. Exercise-induced asthma (EIA) is particularly important in childhood as physical activity is critical to controlling the epidemic of obesity in developed countries, especially the United States. Lifestyle changes, including the use of television, internet, and other video devices, may play a role in childhood asthma. Finally, the "hygiene hypothesis" has introduced the concept that early exposure to animals, foods, or endotoxin may actually be protective against allergic sensitization. While this is still a controversial issue, it illustrates the complexity of asthma as a heterogeneous disease, with genetic and environmental influences. Indeed, we now know that there is no single asthma gene, rather that there are multiple genetic variants that, under the proper environmental conditions, can result in asthma.

**Table 1**
**Special Considerations for Asthma in Children**

| |
|---|
| The increased significance of allergies in childhood asthma |
| The role of passive smoking (ETS exposure) in infancy and pregnancy in the development of asthma |
| The role of respiratory syncytial virus (RSV) and other viral bronchiolitis in pediatric asthma |
| Genetics (host factors) vs. environmental exposures in childhood asthma |
| Vocal cord dysfunction (VCD) in teenage athletes with or without concurrent asthma |
| The increase in obesity in children and its impact on childhood asthma |
| Gender predisposition for asthma in children is reversed that in adults |
| Availability of asthma medications and indications in the pediatric age group |
| The role of immunotherapy in the very young child |
| The use of biologics in children (omalizumab and new drugs) |
| Corticosteroids and growth retardation |
| Exercise induced asthma (EIA) and sports in children |

## EPIDEMIOLOGY AND THE PREVALENCE OF CHILDHOOD ASTHMA

The prevalence of asthma is now estimated to be more than 300 million worldwide, or about 5% of the global population. The incidence of asthma has been steadily increasing since the 1970s, with the greatest increase occurring in modern, developed countries. Asthma accounts for about 1 in every 250 deaths worldwide. The national prevalence of asthma in different countries varies between 1 and 19% (Table 2). It has been observed that developed countries have the higher incidences, while third world countries have the lower rates, but in recent years, the gap is decreasing due to an increasing incidence of asthma in Asia, South America, and Africa.

The gender predominance is reversed in children from that in adults. In children under the age of 14, there is a 2:1 male to female prevalence of asthma, approximately opposite that in adults. Obesity appears to be a risk factor for asthma. Diet is more complicated, and the initial observation that breast feeding protects against asthma is being challenged. Exposure to Western diets comprising high levels of processed foods with increased levels of *n*-6 polyunsaturated fatty acids, decreased antioxidant levels, and decreased *n*-3 polyunsaturated fatty acids has been associated with the increase in asthma and allergies observed over the past few decades.

## GENETICS AND ASTHMA

Asthma is heritable. Children born to asthmatic parents have an increased likelihood of developing asthma themselves. Asthma is polygenic, and multiple phenotypes exist. It is estimated that up to 70% of asthma in children is associated with atopy or allergies. Airway hyperresponsiveness, serum IgE levels, inflammatory mediator expression, and Th1/Th2 balance are four areas that may be influenced by genetics. The genes involved in regulating these processes may differ between ethnic groups. Some of these processes, such as airway hyperresponsiveness and serum IgE levels, may be co-inherited in

**Table 2**
**Asthma Prevalence by Country[a]**

| *Country* | *Prevalence (% population)* |
|---|---|
| Scotland | 18.5 |
| Wales | 16.8 |
| England | 15.3 |
| New Zealand | 15.1 |
| Australia | 14.7 |
| Republic of Ireland | 14.6 |
| Canada | 14.1 |
| Peru | 13.0 |
| Trinidad and Tobago | 12.6 |
| Costa Rico | 11.9 |
| Brazil | 11.4 |
| United States | 10.9 |
| Fiji | 10.5 |
| Paraguay | 9.7 |
| Uruguay | 9.5 |
| Israel | 9.0 |
| Panama | 8.8 |
| Kuwait | 8.5 |
| Ukraine | 8.3 |
| Ecuador | 8.2 |
| South Africa | 8.1 |
| Finland | 8.0 |
| Czech Republic | 8.0 |
| Columbia | 7.4 |
| Turkey | 7.4 |
| Germany | 6.9 |
| France | 6.8 |
| Norway | 6.8 |
| Japan | 6.7 |
| Hong Kong | 6.2 |
| United Arab Emirates | 6.2 |
| Spain | 5.7 |
| Saudi Arabia | 5.6 |
| Argentina | 5.5 |
| Chile | 5.1 |
| Italy | 4.5 |
| South Korea | 3.9 |
| Mexico | 3.3 |
| Denmark | 3.0 |
| India | 3.0 |
| Cyprus | 2.4 |
| Switzerland | 2.3 |
| Russia | 2.2 |
| China | 2.1 |
| Greece | 1.9 |
| Georgia | 1.8 |
| Romania | 1.5 |
| Albania | 1.3 |
| Indonesia | 1.1 |

[a] Selected countries.

**Table 3**
**A Few Selected Candidate Genes for Asthma and Their Impact on Disease or Treatment**

| *Gene* | *Target response/asthma phenotype* | *Population/location* |
|---|---|---|
| CTLA-4 | Response to corticosteroids | European |
| Arginase 1 and 2 | Response to bronchodilators | Netherlands |
| Glutathione *S*-transferase | With air pollution as interactive risk factors | Italy |
| ADAM-33 | Risk for asthma, elevated IgE, and increased specific IgE to dust mite species | Columbia |
| IL-4R | Specific asthma phenotype, eczema, and allergic rhinitis | Sweden |
| DENND1B | Increased susceptibility to asthma (GWAS study) | North America |
| LTA4H and ALOX5AP | Gene–gene interactions convey variants in asthma susceptibility | Latinos (Mexico and Puerto Rico) |
| TLR4 | Gene polymorphisms convey risk of asthma (IRAK1, NOD1, MAP3K7IP1 gene–gene interactions) | Netherlands |
| PHF11 and DPP10 | Risk for asthma | Chinese, European and Latin American |
| NOS-1 | Increased IgE levels, increase in frequency of asthma phenotype | Taiwanese |
| ECP | Allergy and asthma symptoms, smoking | From the European Community Respiratory Health Survey (ECRHS) |
| TSLP | Higher risk of childhood and adult asthma | Japan |
| RANTES | Higher risk of asthma in subgroup analysis by atopic status | Global |

*TLR4* Toll like receptor 4; *PHF11* plant homeodomain zinc finger protein 11; *DPP10* dipeptidyl-peptidase 10; *ADAM-33* a disintegrin and metalloprotein 33; *LTA4H* leukotriene A (4) hydrolase; *ALOX5AP* arachidonate 5 lipooxygenase activating protein; *IL-4R* interleukin 4 receptor; *CTLA-4* cytotoxic T-lymphocyte antigen 4; *NOS-1* nitric oxide synthase 1; *ECP* eosinophil cationic protein; *TSLP* thymic stromal lymphopoetin; *RANTES* regulated upon activation, normal T cell expressed and secreted. DENND1B=DENN/MADD domain containing 1B protein.

some individuals, possibly as a result of close proximity of genes affecting both processes (e.g., chromosome 5q).

Genes can also affect an asthmatic child's response to medications. This has been found to be the case for β-adrenergic agonists, glucocorticoids, and leukotriene modifiers. While studies of pharmacogenetics have so far produced more questions than answers, this is an exciting area of research because it promises the capability of generating customized care plans, or personalized medicine, that will match optimal treatment with each individual asthmatic child. Genes that are involved in asthma are now too numerous to count. An example of genes associated with asthma is given in Table 3.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

Making the diagnosis of childhood asthma requires taking a thorough history and doing a complete physical examination on the patient. There are many conditions that may mimic asthma. Some of these diagnoses are age dependent. A complete list of conditions in the differential diagnosis is given in Table 4. Asthma is still a clinical diagnosis, as there is no pathognomonic marker for diagnosing asthma. Taking a good history is critical. A good history includes current or past history of cough, wheezing, viral respiratory diseases, accompanying allergy symptoms or signs, shortness of breath, and sinus problems. The intensity and characteristics of any breathing sounds should be determined. It is also important to obtain an exposure history to attempt to clarify relevant triggers for asthma exacerbations. This can include indoor allergen exposures,

**Table 4**
**Differential Diagnosis of Cough, Wheezing, and Other Bronchial Sounds**

| |
|---|
| Asthma |
| Foreign body aspiration |
| Aspiration pneumonia |
| Bronchopulmonary dysplasia |
| Heart disease |
| Infections (may be viral, bacterial, fungal, or mycobacterial) |
| Pneumonia |
| Bronchitis |
| Bronchiolitis |
| Epiglottitis (stridor, respiratory distress) |
| Sinusitis |
| Exposures |
| Allergies |
| Smoke inhalation |
| Toxic inhalations |
| Hypersensitivity pneumonitis |
| Gastroesophageal reflux |
| Genetic disorders |
| Cystic fibrosis |
| Iatrogenic |
| ACE inhibitor related cough |
| Anatomical abnormalities |
| Vocal cord dysfunction |
| Vocal cord anomalies (nodules) |
| Subglottic stenosis (stridor) |
| Laryngotracheal malacia (in infants) |
| Vascular anomalies of the chest |
| Endotracheal fistulas and tracheal anomalies |
| Other |
| Immunodeficiency syndromes |
| Obesity |
| Alpha-1 antitrypsin deficiency |

outdoor pollens, viral upper respiratory infections and exercise, exposure to foods, and an occupational history of both the child (if old enough to be working) and the parents or caregivers. Exposure to day care is also important and environmental tobacco smoke and pollution exposure should also be documented. A past medical history asking about previous hospitalizations, doctor visits, frequent otitis media, sinusitis or pneumonia, and a complete medication history, including use of nebulizers or inhalers and any other pertinent medications should be elicited. The family history is also important, as asthma has a genetic component.

In addition to taking a good history, a complete physical examination should also be conducted to rule out any other possible diagnoses. While the presence of a wheeze may suggest asthma, foreign body aspiration may also be a possibility if the wheeze is unilateral. The presence of a heart murmur may suggest a coarctation with compression of the trachea. Clubbing of the fingers may be suggested of a more chronic condition such as cystic fibrosis. These are only some of the many observations one may glean from a physical examination that can help in establishing or ruling out the diagnosis of asthma.

Procedures and laboratory tests have a role in the diagnosis of asthma. Allergy testing may be indicated if the history is consistent with an allergic component or trigger. Spirometry should certainly be done, with the response to bronchodilators examined as well. Exercise challenge tests can be done in the child or adolescent who suspects EIA or bronchospasm (EIB). Other tests that may be helpful in monitoring the condition of an asthmatic may be fractional exhaled of nitric oxide (FeNO). A complete blood count, chest X-ray, or sinus CT scan may also be indicated in some cases. Components of a diagnostic scheme and clinical assessment of asthma are shown in Fig. 2.

While we think of wheezing as a hallmark of asthma, it can be present in children without asthma, and absent in those with asthma. In children under 5 years of age, wheezing can be categorized into three groups: transient early wheezing, persistent early onset wheezing, and late-onset wheezing/asthma. These are discussed in more detail later.

## TRIGGERS OF ASTHMA IN CHILDREN

### *Allergens*

It is estimated that between 60 and 70% of asthma in children is allergic asthma. Conversely, children with allergies have a 30% chance of having asthma as well. The atopic march describes a commonly seen paradigm in which children who are atopic (genetically predisposed to developing allergies) present early in life with atopic dermatitis, then asthma, and finally allergic rhinitis and conjunctivitis. Common allergens can be categorized into either indoor or outdoor allergens. The outdoor allergens are mostly linked to seasonal allergic rhinitis, whereas indoor allergens are linked to perennial allergic rhinitis. There are geographical differences in the seasonal distribution of pollen allergens. Recently, it has been suggested that climate change may be impacting the prevalence of various outdoor allergens through different mechanisms. In addition, environmental exposures and host factors can lead to changes in an individual's sensitivities throughout life. Certain allergens, such as dust mite, cat and dog dander, and *Aspergillus* are independent risk factors for the development of symptoms of asthma in children under 3 years of age *(4)*.


**Fig. 2.** Diagnosis and clinical assessment of the asthmatic child – the appropriate parts of the history and physical examination should be performed depending on the circumstances (e.g., is this a new patient with a history of cough presenting to the office as a consult, or is this a patients with known asthma who is in the midst of an asthma exacerbation presenting to the emergency room).

On the other hand, the "hygiene hypothesis" has been used to explain why in some cases, exposure to dogs and/or cats leads to a decrease in allergic sensitization *(5)*. These inconsistencies in studies on allergen sensitivity have not been adequately resolved, and it is likely that other factors, possibly related to the timing of exposure or host factors play a significant role in the effect of allergen exposure on sensitization. In addition to cats and dogs, other pets such as guinea pig, gerbils, hamsters, mice, rats, and rabbits can also trigger asthma attacks in susceptible individuals.

It has been suggested that exposure to endotoxin may play a protective role in allergen sensitization, though this is not universally observed. Cockroach and mouse

**Table 5**
**Common Allergenic Determinants**

| *Determinant* | *Source* | *Source scientific name* | *Protein class/function* |
|---|---|---|---|
| Der p 1 | Dust mite | *Dermatophagoides pteronyssinus* | Cysteine protease |
| Der p 2 | Dust mite | *D. pteronyssinus* | Serine protease |
| Der f 1 | Dust mite | *D. farina* | Cysteine protease |
| Der f 2 | Dust mite | *D. farina* | Serine protease |
| Der m 1 | Dust mite | *D. microcerax* | Cysteine protease |
| Blo t 1 | Dust mite | *Blomia tropicalis* | Cysteine protease |
| Fel d 1 | Cat | *Felis domesticus* | Salivary glycoprotein |
| Can f 1 | Dog | *Canis familiaris* | Salivary lipocalin proteins |
| Bla g 1 | Cockroach | *Blattella germanica* | Unknown |
| Bla g 2 | Cockroach | *B. germanica* | Aspartic proteinase |
| Rat n 1 | Rat | *Rattus norvegicus* | Major urinary protein |
| Mus m 1 | Mouse | *Mus muscularis* | Major urinary protein |
| Per a 7 | Cockroach | *Periplaneta americana* | Tropomyosin |
| Lol p 1 | Ryegrass | *Lolium perenne* | Unknown |
| Amb a 1 | Ragweed | *Ambrosia artemisiifolia* | Polysaccharide lyase 1 family |
| Aln g 1 | Alder | *Alnus glutinosa* | Pathogenesis-related protein |
| Bet v 1 | Birch | *Betula verrucosa* | Pathogenesis-related protein |
| Que a 1 | Oak | *Quercus alba* | Pathogenesis-related protein |
| Ole e 1 | Olive | *Olea europea* | Unknown |
| Cyn d 1 | Bermuda grass | *Cynodon dactylon* | Expansin family |
| Art v 1 | Mugwort | *Artemisia vulgaris* | Unknown |
| Dac g 3 | Orchard grass | *Datylus glomerata* | Expansin family |

allergen have both been found to play a significant role in allergic sensitization in children living in inner city environments *(6)*. Both early and late phase reactions have occurred in places where cockroach infestation is a problem, such as highly populated urban areas in warm climates.

Food allergens can be a significant cause of allergic sensitization in children, especially in the younger age range. Foods are typically associated with eczema in infants and toddlers, but eczema is a feature of atopy, and the earliest manifestation of the "atopic march." These patients can subsequently develop asthma or allergic rhinoconjunctivitis as they grow older.

In order to treat allergic asthma effectively, it is therefore important to identify a child's current allergic sensitization patterns. This can be done by skin testing or by a blood test that measures specific IgE. There are advantages and disadvantages to both forms of testing. Skin testing is more sensitive and specific, although the blood test methodology is improving. The blood test can be done if there are contraindications to skin testing, such as in the very young child who may not be able to tolerate skin testing, a patient on antihistamines or β-blockers, or a patient with a severe rash. Available now are "multitest" devices that facilitate skin testing and make it possible to perform in the very young child. A list of common environmental allergens is given in Table 5.

While food allergens can also trigger asthma, these are less likely triggers, and testing for food allergens is not as sensitive or specific as environmental allergens. A complete discussion on the role of allergies in asthma can be found in chapter 4 on the diagnosis and management of allergies.

### *Irritants*

Most air pollutants are irritants, although some can have immunomodulatory effects. The most extensively studied airborne pollutant is environmental cigarette smoke. Gaseous irritants include nitric oxide, sulfur dioxide, formaldehyde, ozone, and other volatile organic compounds (VOC). Airborne particulates can vary in size, ranging from course particulates to fine particles, to ultrafine particles or nanoparticles. The smaller the particle, the greater the penetration into the airway. Particles greater than 10 μm in diameter are generally cleared in the upper airway. Although these larger particles can indirectly trigger early or late phase asthma reactions by virtue of their action in the upper airways, fine and ultrafine particles present a more significant problem due to their deeper penetration into the smaller airways *(7)*. Recently, evidence has surfaced that these ultrafine particles indeed possess effects on inflammatory cells such as neutrophils or eosinophils that can lead to asthma symptoms. This can occur through several different mechanisms and are reviewed extensively elsewhere *(7)*.

### *Exercise-Induced Asthma or Bronchospasm*

Exercise is a common trigger for asthma in children. However, exercise is essential to the physical and psychological development of all children. Lack of exercise also promotes obesity, which has been linked to asthma *(8)*. Therefore, we no longer recommend that children with asthma stop exercising. In fact, exercise can help to build lung reserve. With proper control of asthma using controller medications, a patient with EIA can almost always participate in regular cardiovascular training without adverse effects. Asthma can even be managed successfully in the elite athlete. The severity of a patient's EIA can be evaluated using an exercise challenge test. Historically, the methodology of exercise challenge tests has been very inconsistent, but recently the American Thoracic Society (ATS) has proposed a set of criteria that should be met in order to ensure an accurate and valid test *(9)*. These criteria and a typical protocol are illustrated in Fig. 3.

### *Viral Respiratory Illness and Asthma*

The link between viral respiratory infections and asthma has been well established *(10)*. In infants, the most well-known viral respiratory illness associated with wheezing is respiratory syncytial virus (RSV). However, rhinovirus is the more common virus in children *(11)*, and wheezing can be associated with other viruses as well, including parainfluenza virus, influenza virus, metapneumonia virus, adenovirus, coronavirus, and picornavirus. Rhinovirus is the major pathogen associated with hospital admissions for asthma in children *(12)*.

Transient early wheezing develops in infancy and usually resolves by 3 years of age. Risk factors include low birth weight, prematurity, maternal exposure to tobacco smoke, male gender, and upper respiratory viral infections. A second phenotype is that of the atopic wheezer. These are school age children who have a history or family history of atopy. Their wheezing may or may not be triggered by a viral infection, but they have a

### A) An exercise challenge protocol

Equipment needed:

1. Spirometry equipment
2. Exercise challenge protocol
3. Exercise challenge result sheet
4. Stethoscope
5. Pulse oximeter
6. Calculator
7. Printer
8. Treadmill or place to run

**C) Guidelines/criteria for exercise challenge testing:**

1. >= 10-15% decrease for + test
2. Pulmonary medications withdrawn prior to test
3. No vigorous exercise 4 hours before testing
4. 4 hours separate sequential exercise challenges
5. Treadmill testing with target intensity reached within 2-4 minutes
6. HR = 80-90% predicted or minute ventilation = 40-60% predicted maximum
7. Target HR or minute ventilation maintained for 4-6 minutes
8. Relative humidity <50%
9. Air temp = 20-25oC
10. Use nose clip to ensure smooth air flow
11. Post-exercise spirometry up to 15-20 minutes post exercise
12. Use of higher of minimum 2 FEV1 values

Protocol:

1. Prepare pre-printed results form. Enter demographics
2. Listen to the child's lungs for wheezing – chart results
3. Record pulse and oxygen saturation
4. Have child perform spirometry three times. Record results
5. Have child run for 6 minutes. Heart rate should reach 85% maximum heart rate.
6. Auscultate child's chest
7. Record pulse and oxygen saturation
8. Perform spirometry one time (0 minutes after exercise). Immediately calculate % change in FEV1. Record result. If FEV1 decreases > 12% compared to pre-exercise test, skip to step 13
9. After 2 minutes, repeat step 8
10. After 5 minutes, repeat step 8
11. After 10 minutes, repeat step 8
12. After 15 minutes, repeat step 8
13. Auscultate child's chest. If child is not wheezing, is not in respiratory distress and FEV1 did not at anytime drop >12% compared to pre-exercise levels, then test is finished
14. Administer a unit dose bronchodilator nebulization treatment
15. After completion of the treatment, wait five minutes and repeat spirometry 3 times. Record results.
16. Auscultate child's lungs

### B) Exercise challenge test results sheet- sample

Date: _____ Patient name: _____ DOB: _____

Test performed by: _____

How to calculate %change:
(post FEV1-best pre FEV1) x 100% = % change

| *Event* | *Time* | *O2 Saturation* | *Pulse* | *FEV1* | *%change* |
|---|---|---|---|---|---|
| **Pre** | | | | | |
| **0 min post** | | | | | |
| **2 min post** | | | | | |
| **5 min post** | | | | | |
| **10 min post** | | | | | |
| **15 min post** | | | | | |
| **After neb treatment (if indicated)** | | | | | |

**Fig. 3.** (**A**) An exercise challenge protocol. (**B**) Exercise challenge test results sheet – sample. (**C**) Guidelines/criteria for exercise challenge testing.

strong probability of continued wheezing into adolescence or adulthood. It is in this group that one would be able to detect chronic inflammatory changes in the airways. A third category, persistent early onset wheezing, includes preschool aged children and is usually not associated with a family history of asthma or atopy, but instead is associated with acute viral respiratory infections. This group has a better long-term prognosis and symptoms may disappear when they reach school age.

Bronchiolitis in infancy can lead to decreased FEV1 and FEF25–75% in childhood *(13)*. A connection between asthma and RSV bronchiolitis was supported by an observation that there is elevated eosinophil cationic protein (ECP) and leukotriene C4 in the nasal lavage fluid of infants with RSV bronchiolitis *(14)*. It is not clear whether the occurrence of RSV bronchiolitis as an infant significantly increases the risk of developing asthma at a later age, although one prospective study of 47 children hospitalized for RSV bronchiolitis in infancy showed a higher incidence of airway hyperreactivity at age 13 compared to 93 matched controls *(15)*. Continued follow-up of these patients revealed a persistent increase in allergic asthma into early adulthood among patients who had RSV bronchiolitis in infancy *(16)*.

## INTERPRETING THE NEW ASTHMA GUIDELINES IN CHILDREN

The new EPR guidelines were released in 2007 *(3)*. These guidelines contain revisions that were aimed at improving the overall care of asthmatics. There are several important changes. Firstly, the main goal of asthma treatment is control of symptoms and disease. A list of specific goals to target control is given in Table 6. Better distinction is made between monitoring asthma control and classifying asthma severity. Severity is defined as the intrinsic intensity of asthma and is still grouped into the original classification of mild intermittent, mild persistent, moderate persistent, or severe persistent. Categorizing severity in this manner is helpful for initiating therapy. Control

**Table 6**
**Treatment Goals in Asthma**

| |
|---|
| Decreasing mortality |
| Decreasing morbidity and improving quality of life |
| Fewer nighttime awakenings |
| Ability to participate in sports with no limitations |
| Fewer school or work days lost |
| Reduction of symptoms of cough or wheezing |
| Reduction in the need for rescue medications |
| Easy compliance with medications with minimal disruptions in daily life |
| Reduction in side effects of asthma medications |
| Reduction in the number and severity of asthma exacerbations |
| Reduction in emergency or unscheduled office or clinic visits |
| Reduction in the need for systemic steroids |
| Prevention of “airway remodeling” and long-term sequelae of asthma |
| Economic goals |
| Reducing costs of treating asthma by improving preventative measures |

is defined as the response to therapy, in terms of the degree to which manifestations of asthma are kept to a minimum. Therapy should be adjusted periodically in order to maintain control.

The second major change is the focus on impairment and risk. These are the two key domains of control and severity, and provide additional information or parameters to assess response to treatment. Impairment is defined as the extent to which standard goals of asthma treatment are maintained, so this includes the frequency and intensity of symptoms and interference with good quality of life, such as an inability to conduct normal daily activities. Risk can include several parameters – the likelihood of developing an asthma exacerbation, the risk of side effects of medications, and the risk of declining lung function or lung growth.

In order to address the change in focus, the treatment recommendations have also been adjusted. The stepwise approach is still utilized, but now there are six steps, with clearly defined actions, instead of having progressive actions within each step. The treatment recommendations have also been divided into three groups depending on age, a group for children 0–4 years of age, another group addressing children 5–11 years of age, and the third group consisting of adults and children 12 and over. This was done because the evidence for the various treatment modalities may be different between age groups.

Other important recommendations address environmental control, with the recommendation for these actions being present in all age groups. Inhaled corticosteroids are the first-line control drug for all ages. The use of combination inhaled steroid and long acting β-agonists (LABAs) is considered an equal alternative to increasing the dose of inhaled corticosteroids in patients 5 years of age and older. Omalizumab is also recommended in patients with allergic asthma who are 12 years of age and older who require step 5 or 6 therapy. A black box warning for anaphylaxis accompanies omalizumab. The breakdown of the stepwise approach for children under 12 is given in Table 7.

## NONPHARMACOLOGIC MANAGEMENT OF CHILDHOOD ASTHMA

An asthma management plan involves approaching the problem from three different angles – environmental control, pharmacologic intervention, and immunotherapy. In addition, objective measurement of asthma status is important, and ongoing monitoring is also of benefit. It is clear that the development of new drugs is only a part of a more comprehensive strategy to treat asthma. In addition to drugs, nonpharmaceutical modes of treatment need to be incorporated into the asthmatic child's treatment plan. Nonpharmaceutical modes of therapy for asthma are discussed below and listed in Table 8.

### *Environmental Control*

Allergen challenge studies have shown that exposure to an allergen to which an asthmatic has been sensitized is likely to bring about an asthma exacerbation *(17)*. Conversely, avoidance of such allergens may lead to resolution of the exacerbation. Thus, allergen avoidance has been recognized as an important part of an asthma management plan. The effectiveness of an allergen avoidance plan requires knowledge of the patient's sensitivities and exposure pattern.

Table 7
EPR-3 Guidelines for the Diagnosis and Treatment of Asthma in Children[a]

**a) 0-4 years of age**

**Determine severity when initiating therapy**

| Components of severity | | Classification of Asthma Severity (0-4 years of age) | | | |
|---|---|---|---|---|---|
| | | Intermittent | Persistent | | |
| | | | Mild | Moderate | Severe |
| Impairment | **Symptoms** | <= 2 days/wk | >2 days/wk | Daily | Throughout day |
| | **Nighttime awakenings** | < 2x/month | 3-4x/month | >1x/wk | Nightly |
| | **SABA use for symptom control (not EIA)** | <= 2days/wk | >2days/wk, <1x/day | Daily | Several times/day |
| | **Interference with normal activity** | None | Minor | Some | Extreme |
| Risk | **Exacerbations requiring oral corticosteroids** | 0-1/year | >=2 exacerbations in 6m requiring oral steroids, or >= 4 wheezing episodes/year lasting >1day and risk factors for persistent asthma. Exacerbations of any severity can occur in asthmatics in any severity category | | |
| Recommended Step for Initiating Therapy | | Step 1 | Step 2 | Step 3 and consider short course of steroids | |
| | | Evaluate level of asthma in 2-6 weeks. Adjust therapy if no clear benefit, reconsider diagnosis | | | |

**Once control is achieved, continue to assess control on ongoing basis (approx every 1-6 months)**

| Components of Control | | Classification of Asthma Control (0-4 years of age) | | |
|---|---|---|---|---|
| | | Well controlled | Not Well Controlled | Very Poorly Controlled |
| Impairment | **Symptoms** | <= 2 days/wk | >2days/wk | Throughout the day |
| | **Nighttime awakenings** | <=1x/month | >1x/month | >1x/wk |
| | **SABA use for symptom control (not EIA)** | <= 2 days/wk | > 2 days/wk | Several times/day |
| | **Interference with normal activity** | None | Some | Extreme |
| Risk | **Exacerbations requiring oral corticosteroids** | 0-1/year | 2-3/year | >3/year |
| | **Treatment related adverse effects** | Can vary from none to very troublesome. Consider in overall assessment of risk | | |

*(Continued)*

Table 7 *(Continued)*

**Stepwise treatment approach**

| Intermittent Asthma | Persistent Asthma: Daily Medication<br>If Step 3 or higher is required, should refer to asthma specialist | | | | |
|---|---|---|---|---|---|
| **Step 1**<br>***Preferred***<br>SABA prn | **Step 2**<br>***Preferred***<br>Low dose ICS<br>***Alternative***<br>Cromolyn or montelukast | **Step 3**<br>***Preferred***<br>Medium dose ICS | **Step 4**<br>***Preferred***<br>Medium dose ICS + either LABA or montelukast | **Step 5**<br>***Preferred***<br>High dose ICS + either LABA or montelukast | **Step 6**<br>***Preferred***<br>High dose ICS + either LABA or montelukast<br>Oral systemic corticosteroids |

**Patient Education and Environmental Control at each Step**

- Quick-Relief Medications for All Patients
- SABA as need for symptoms. With viral respiratory infections, SABA q4-6h. Consider short course of oral/parenteral steroids if severe

**b) 5-11 years of age**

**Determine severity when initiating therapy**

| Components of severity | | Classification of Asthma Severity (0-4 years of age) | | | |
|---|---|---|---|---|---|
| | | Intermittent | Persistent | | |
| | | | Mild | Moderate | Severe |
| Impairment | **Symptoms** | <= 2 days/wk | >2 days/wk | Daily | Throughout day |
| | **Nighttime awakenings** | < 2x/month | 3-4x/month | >1x/wk | Nightly |
| | **SABA use for symptom control (not EIA)** | <= 2days/wk | >2days/wk, <1x/day | Daily | Several times/day |
| | **Interference with normal activity** | None | Minor | Some | Extreme |
| | **Lung function** | Normal FEV1 between exacerbations FEV1>80% predicted FEV1/FVC>85% | FEV1 =>80% predicted FEV1/FVC>80% | FEV1=60-80% predicted FEV1/FVC=75-80% | FEV1<60% predicted FEV1/FVC<75% |
| Risk | **Exacerbations requiring oral corticosteroids** | 0-1/year | >=2 exacerbations in 6m requiring oral steroids, or >= 4 wheezing episodes/year lasting >1day and risk factors for persistent asthma. Exacerbations of any severity can occur in asthmatics in any severity category | | |
| Recommended Step for Initiating Therapy | | Step 1 | Step 2 | Step 3 and consider short course of steroids | Step 3 or 4 and consider short course of steroids |
| | | Evaluate level of asthma in 2-6 weeks. Adjust therapy if no clear benefit, reconsider diagnosis | | | |

**Once Control is achieved, continue to assess control on ongoing basis (approx every 1-6 months)**

| Components of Control | | Classification of Asthma Control (0-4 years of age) | | |
|---|---|---|---|---|
| | | Well controlled | Not Well Controlled | Very Poorly Controlled |
| Impairment | **Symptoms** | <= 2 days/wk | >2days/wk | Throughout the day |
| | **Nighttime awakenings** | <=1x/month | >1x/month | >1x/wk |
| | **SABA use for symptom control (not EIA)** | <= 2 days/wk | > 2 days/wk | Several times/day |
| | **Interference with normal activity** | None | Some | Extreme |
| Risk | **Exacerbations requiring oral corticosteroids** | 0-1/year | 2-3/year | >3/year |
| | | Consider severity and interval since last exacerbation | | |
| | **Reduction in lung growth** | Evaluation requires long term follow-up | | |
| | **Treatment related adverse effects** | Can vary from none to very troublesome. Consider in overall assessment of risk | | |

*(Continued)*

**Stepwise treatment approach**

| Intermittent Asthma | Persistent Asthma: Daily Medication<br>If Step 3 or higher is required, should refer to asthma specialist | | | | |
|---|---|---|---|---|---|
| **Step 1**<br>***Preferred***<br>SABA prn | **Step 2**<br>***Preferred***<br>Low dose ICS<br>***Alternative***<br>Cromolyn, nedocromil, theophylline or montelukast | **Step 3**<br>***Preferred***<br>Low dose ICS + either LABA, LTRA or theophylline<br>***Alternative***<br>Medium dose ICS | **Step 4**<br>***Preferred***<br>Medium dose ICS + either LABA<br>***Alternative***<br>Medium dose ICS + either LTRA or theophylline | **Step 5**<br>***Preferred***<br>High dose ICS + either LABA or montelukast<br>***Alternative***<br>High dose ICS + either LTRA or theophylline | **Step 6**<br>***Preferred***<br>High dose ICS + either LABA + oral systemic corticosteroids<br>***Alternative***<br>High dose ICS + either LTRA or theophylline + oral systemic corticosteroids |

**Patient Education and Environmental Control at each Step**

- Quick-Relief Medications for All Patients
- SABA as need for symptoms. Intensity of treatment depends on severity of symptoms, up to 3 treatments at 20 minute intervals as needed. Short course of corticosteroids may be required.
- Caution: Increasing use of SABA or use greater than 2 days per week for symptom relief not related to EIA indicates inadequate control and need to step up treatment

**The above tables were adapted from NAEPP EPR-3 guidelines**

[a]The tables were adapted from NAEPP EPR-3 guidelines.

**Table 8**
**Nonpharmacologic Treatment Modalities for Asthma**

| |
|---|
| Objective measurement of asthma status |
| Peak flow monitoring |
| Pulmonary function testing |
| Spirometry |
| Environmental control and identifying sensitivities |
| Allergy skin testing |
| Environmental exposure assessment |
| Allergen avoidance |
| Monitoring and prevention |
| Asthma diary sheets |
| Asthma action or management plans |
| Education |
| Asthma education |
| Exercise regimen |
| Asthma camps for children |
| Dietary assessment |
| Tobacco prevention counseling for parents |
| Internet |
| Printed material |
| Special help for children |
| Use of spacer devices |
| Small volume nebulizer machines |

Avoidance of seasonal allergens, mainly pollens, is difficult without making unreasonable changes to one's lifestyle, because these allergens are windborne and can travel for miles. On the other hand, there are well-established strategies developed for avoidance of indoor allergens. Because we spend up to a third of our time sleeping in close quarters with dust mites, the bedroom should have a high priority when developing an indoor allergen avoidance program. Dust mites require water to survive, and damp environments allow them to reproduce and proliferate. Keeping the relative humidity of the home around 50–55% will help keep dust mite concentrations down. In addition, the uses of mattress and pillow encasings, as well as high-efficiency particulate air (HEPA) filters are additional control measures that may provide benefit. The child with asthma should also not be the one to vacuum as the action of vacuuming can disturb dust mite reservoirs and release these particulates into the breathing zone. Good ventilation and filtration systems in the home can also help to reduce exposure. Additional measures of allergen avoidance are illustrated in Fig. 4.

Avoidance of pet allergen is best accomplished by getting rid of the pet altogether. This is often an insurmountable task because of the emotional attachment that patients, especially children, have towards their pets. If getting rid of the pet is not possible, then at least keeping the pet out of the bedroom may help. Washing the pet regularly is of


**Fig. 4.** Avoidance measures for common allergens.

questionable benefit. Numerous "denaturing" preparations are also available, but again, their effectiveness is controversial.

Molds are common allergens that originate from the outdoor environment and are particularly prevalent in moist climates. The presence of a high indoor to outdoor mold count ratio is probably indicative of a water leak or at least of excessive humidity indoors. As in the case of dust mites, keeping the relative humidity of the indoor environment at around 50% helps to reduce mold spore exposure. Substrates for mold growth include decaying living material, damp paper or books, or household plants. Removal of these substrates may reduce indoor mold spore levels.

As mentioned earlier, pollens are more difficult to avoid, but patients and their parents can glean information regarding outdoor exposures by accessing the American Academy of Allergy, Asthma and Immunology (AAAAI) National Allergy Bureau

(NAB) website (http://www.aaaai.org/nab). The site contains information on pollen and mold counts derived from counting stations run by certified counters. As of October 2010, there were 85 counting stations throughout the United States, as well as 2 in Canada and 2 in Argentina.

### *Spirometry in Children*

Spirometry provides information on lung mechanics. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), the FEV1/FVC ratio, and peak expiratory flow (PEF) are the four main parameters measured during spirometry. Measurement of spirometry before and after bronchodilation treatment can help determine if there is reversibility of lung function. Because sometimes patient history, especially in children, can be inaccurate, spirometry provides an objective assessment of the child's condition. Spirometry can be attempted at about 4–5 years of age, but at these very young ages, obtaining reliable results depends on the child's ability to follow instructions and their physical coordination. Data on predicted values of spirometry parameters have been obtained by several investigators and are dependent on age, gender, height, and ethnic background. However, as in the case of peak flow measurement, there is significant individual variability, and it is important to establish each child's baseline spirometry. Obviously, as the child grows, this will change, so frequent updates may be needed. While spirometry is not diagnostic of asthma, it serves as a complementary test to the history and physical that can be used to support the diagnosis of asthma.

### *The Use of Peak Flow Meters in Childhood Asthma*

Measurement of peak flow may part of an asthma management plan. Peak flow measurements provide objective evaluation of an asthmatic's condition. With the proper teaching, even a 5 year old can learn to use a peak flow meter effectively (Fig. 5). Usually, peak flow measurements are done in the morning and in the evening, but the peak flow meter can be used throughout the day or night, whenever necessary. Most new peak flow meters are small enough to fit in a pocket or a purse. Traditional peak flow meters are available for children and adults. The low range peak flow meters usually measure up to about 450 L/m, while the high range measure up to 800 L/m. The peak flow zonal system, based on the child's personal best peak flow, is a convenient and simple method for parents and patients to assess how they are doing, whether to administer a breathing treatment, and whether to seek additional help. Electronic versions of peak flow meters are also available. These have the advantage of being able to record and store data that can be analyzed and trended on a computer. Some of the newer electronic versions can also measure FEV1, which is considered to be a more reliable measurement of airway obstruction as it is not as dependent on patient technique or effort. An assortment of peak flow meters and spacers is shown in Fig. 6.

### *Asthma Diary Sheets and Asthma Assessment Questionnaires*

Asthma diary sheets (illustrated in Fig. 7) provide patients with a means to keep track of their symptoms and their peak flows. The recent availability of electronic peak flow meters with memory is an alternative way to monitor a patient's asthma status, which is

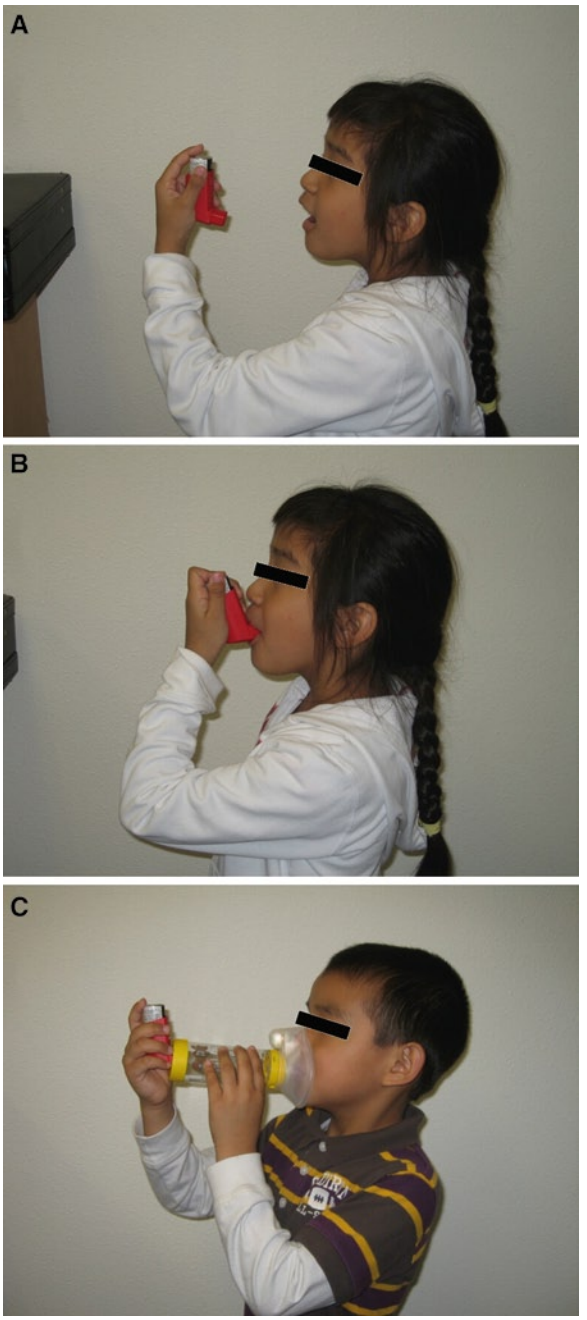



**Fig. 5.** Inhaler technique. (**A**) Open mouth technique. (**B**) Closed mouth technique. (**C**) Using a spacer and a mask.

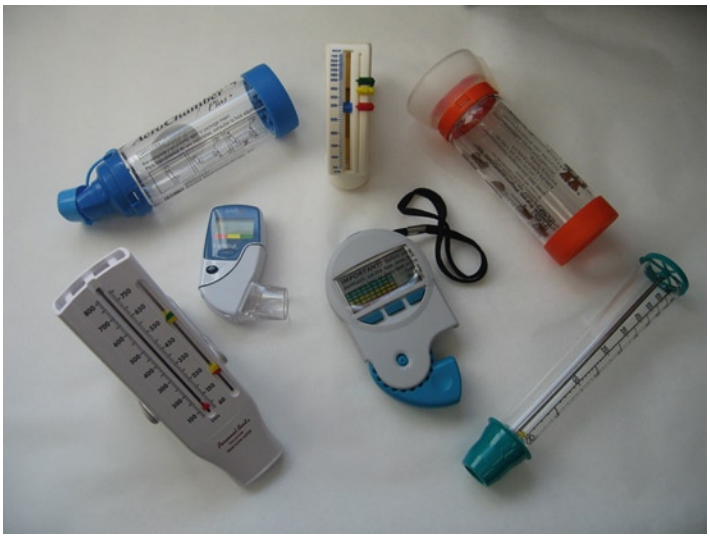


**Fig. 6.** A sampling of peak flow meters and spacer devices.

similar to monitoring blood pressure with an automatic blood pressure cuff or diabetes with a home glucose monitoring kit. Monitoring of peak flows not only gives a continuous assessment of the patient's condition, but also may help as a reminder for patients to take their control medications, thus improving compliance. Patients should be instructed to bring their asthma diary sheets to their doctor visit, so that their progress can be reviewed. Besides symptoms and peak flows, there is space to record other pertinent information, such as β-agonist use, exposures that are out of the ordinary, addition of new medications, etc.

In addition to home monitoring, patients should complete an asthma assessment questionnaire each time they visit their asthma care provider. The asthma assessment questionnaire is a tool that can be used to evaluate control, impairment, and can also help to identify gaps in patient education. From the asthma assessment questionnaire, a great deal of important information can be obtained, such as whether the patient is compliant with medications, if they are overusing their rescue inhaler, are they having too many nighttime awakenings, is their daily activity restricted, and so on, all of which addresses asthma control. Figure 8 shows an independently developed asthma assessment questionnaire, which has not been validated. Some questionnaires, such as the ACT (Allergy Control Test) or ATAQ (Allergy Therapy Assessment Questionnaire), have been validated and have been distributed for use by physicians and patients.

### *Asthma Action Plans*

The components of an asthma management plan are shown in Fig. 9. Asthma action plans are an important part of successful asthma management. They provide written guidance for parents and patients once they leave the doctor's office or hospital. This is important because sometimes asthma treatment can be complicated for patients, and parents and patients can become overwhelmed with all the instructions about multiple

| Week 1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***Date*** | | | | | | | | |
| | | **Sunday** | **Monday** | **Tuesday** | **Wednesday** | **Thursday** | **Friday** | **Saturday** |
| **Morning** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| **Afternoon** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| **Evening** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| SABA use | | | | | | | | |
| Regular medications | | | | | | | | |
| New medications | | | | | | | | |
| Exposures | | | | | | | | |
| Comments | | | | | | | | |
| **Week 2** | | | | | | | | |
| ***Date*** | | | | | | | | |
| | | **Sunday** | **Monday** | **Tuesday** | **Wednesday** | **Thursday** | **Friday** | **Saturday** |
| **Morning** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| **Afternoon** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| **Evening** | Peak flow | | | | | | | |
| | FEV1 | | | | | | | |
| | Symptoms | | | | | | | |
| SABA use | | | | | | | | |
| Regular medications | | | | | | | | |
| New medications | | | | | | | | |
| Exposures | | | | | | | | |
| Comments | | | | | | | | |

**Fig. 7.** An asthma diary.

medications, how to use a peak flow meter, and what to do in an emergency. The asthma action plan can also serve as a refresher course for patients, who have recently been discharged from the hospital after an admission for an asthma exacerbation. Involving schoolteachers in a child's asthma action plan can also help to improve the overall asthma control and quality of life *(18)*.

Name:_____Date:_____Age:

_____

Date of previous assessment:_____

Asthma control parameters

| | | |
|---|---|---|
| 1 | # days in the past week with wheezing, coughing, shortness of breath, chest tightness | |
| 2 | # nights in the past week awakening with symptoms listed in (1) | |
| 3 | Days in the past week that asthma has restricted physical activity | |
| 4 | # asthma attacks since last assessment | |
| 5 | # emergency department visits since last assessment | |
| 6 | # doctor visits for acute attacks since last assessment | |
| 7 | # puffs of rescue medications used in the past week | |
| 8 | # school days or work days lost since last visit | |
| Total score | | |

How would you characterize your asthma?

Poorly controlled Fair control Good control Well control

Have you been using your peak flow meter? Y_____N_____

Have you been charting your peak flows? Y____N_____

What is your best peak flow?_____Average peak flow?_____

**Would like to receive more information on:**

Medications

Avoidance or environment control

Immunotherapy

Inhaler technique

Exacerbations

**Fig. 8.** A sample asthma assessment tool.

**An Asthma Action Plan developed for**_____ Date: _____ DOB: _____ Gender: M/F

Address: _____ Tel: _____ E-mail: _____

Date of diagnosis: _____ Age at diagnosis: _____ Personal best PF: _____ Date measured: _____

Asthma disease classification: Mild intermittent _____ Persistent: Mild _____ Moderate _____ Severe _____

Pulmonary Function Test: Date: _____ FVC: _____ FEV1: _____ PEF: _____

Known triggers: Exercise _____ Viral infections: ____ Allergies:_____ Other: _____

Allergic triggers: Dust mite Dog Cat Mold Pollen Cockroach Mouse Other: _____

**Nonpharmacological intervensions**

Avoidance measures (Circle applicable measures): Dust mite proof encasings HEPA filters Relative humidity/temperature gauge

Dehumidifier HEPA vacuum Removal of pet Cockroach abatement Professional cleaning Home remodeling

**Medications**

Regular control medications: _____

_____

Rescue medications: _____

| Health care provider | Telephone number | Pager number |
|---|---|---|
| | | |

## Asthma Exacerbation Management Plan

1. Awareness of increased exposure or condition which may lead to an asthma attack
2. Evaluation of symptoms: a) Respiratory rate, b) Retractions, c) Mental status changes
3. Measure peak expiratory flow (or FEV1)
4. Zonal system for evaluating asthma status

| | | |
|---|---|---|
| ***Green zone – all clear***<br>No symptoms<br>Normal daily activities<br>Control medications effective | Peak flow above_____ | Take regular control medications |
| ***Yellow zone – action***<br>Increased symptoms<br>Unable to perform certain tasks<br>Increased use of β-agonist | Peak flow between_____and _____ | Increase inhaled steroid _____ to _____ puffs per day. Take β-agonist inhaler and measure peak flow. If improved, monitor closely. If not improved, repeat β-agonist, proceed to seek professional help |
| ***Red zone – alert***<br>Symptoms > 24 hours<br>Difficulty breathing<br>Ineffective relief with β-agonists | Peak flow below | Add oral steroid_____mg/day (_____mg/kg/day). Take β-agonist inhaler or nebulization treatment. If symptoms persist or not improvement in peak flow, proceed to seek professional help |

Call 911 or proceed to hospital if danger signs occur, such as lack of response, difficulty breathing or ambulating due to respiratory distress or if lips or fingernails are blue

**Fig. 9.** An asthma management plan. An asthma action plan must include information on how to assess the child's condition. Known triggers should be listed and the PEF zonal system can be used to provide easy instructions for patients and parents. The form also allows for entering medication doses.

One of the reasons for the persistently high asthma morbidity in the face of newly developed asthma medications is that patients do not usually follow all the instructions to ensure effective asthma control. Written action plans help circumvent this problem, making it easier for patients to be compliant. Besides medication instructions, asthma

action plans can also give instructions on environmental control and avoidance of triggers. Instructions on when to seek professional help is also entered on an asthma action plan.

## OBJECTIVE METHODS OF ASSESSING AIRWAY INFLAMMATION

### *Nitric Oxide*

Fractional exhaled nitric oxide (FeNO) is elevated in children with asthma. It has been demonstrated to be a marker of eosinophilic airway inflammation in children with asthma, and it also responds to glucocorticoid therapy *(19)*. Measurement of FeNO may be an effective way of monitoring airway inflammation and bronchial hyperresponsiveness. Recently, increased levels of FeNO have been found to correlate with risk of asthma in children *(20)*. Equipment to measure FeNO is currently available, but this test has not yet been widely adopted, mainly because there is still controversy regarding its value in managing the asthmatic child, but also because insurance companies have been slow to reimburse for this test adequately. As these issues are sorted out, FeNO may yet prove to be a valuable tool to assess airway inflammation.

### *Eosinophil Cationic Protein*

Elevated ECP levels in cord blood are predictive of atopy. ECP is a marker of eosinophil activation. Serum ECP levels correlate with airway inflammation in wheezing children *(21)*. In a retrospective study of 441 patients with respiratory disease, the sensitivity and specificity for asthma was 70 and 74%, respectively. ECP was not predictive for any other respiratory disease *(22)*. When patients with asthma are bronchial challenged with allergen, activation of eosinophils and generation of specific eosinophilic mediators result. Evaluation and continued monitoring of eosinophil and ECP may be a way to assess efficacy of asthma therapy and airway inflammation in children with allergic asthma *(23)*. Both leukotriene receptor antagonists and inhaled corticosteroids have been associated with a reduction in sputum ECP levels in patients with mild to moderate persistent asthma *(24)*. A response of serum ECP levels to glucocorticoid treatment has also been observed *(25)*.

## PHARMACOLOGIC MANAGEMENT

### *Controller Medications*

#### Inhaled Corticosteroids

The beneficial effect of ACTH in the treatment of asthma was shown in 1949 *(26)*. Subsequently, oral corticosteroids were also shown to be beneficial but side effects limited their widespread use. The introduction of inhaled corticosteroids in 1972 heralded a new age in asthma treatment, and inhaled corticosteroids have been the first-line treatment in the control of asthma since then. Corticosteroids work by switching off inflammatory genes through their interaction with the glucocorticoid receptor and recruitment of histone deactylase-2 (HDAC-2). By regulation of transcription of

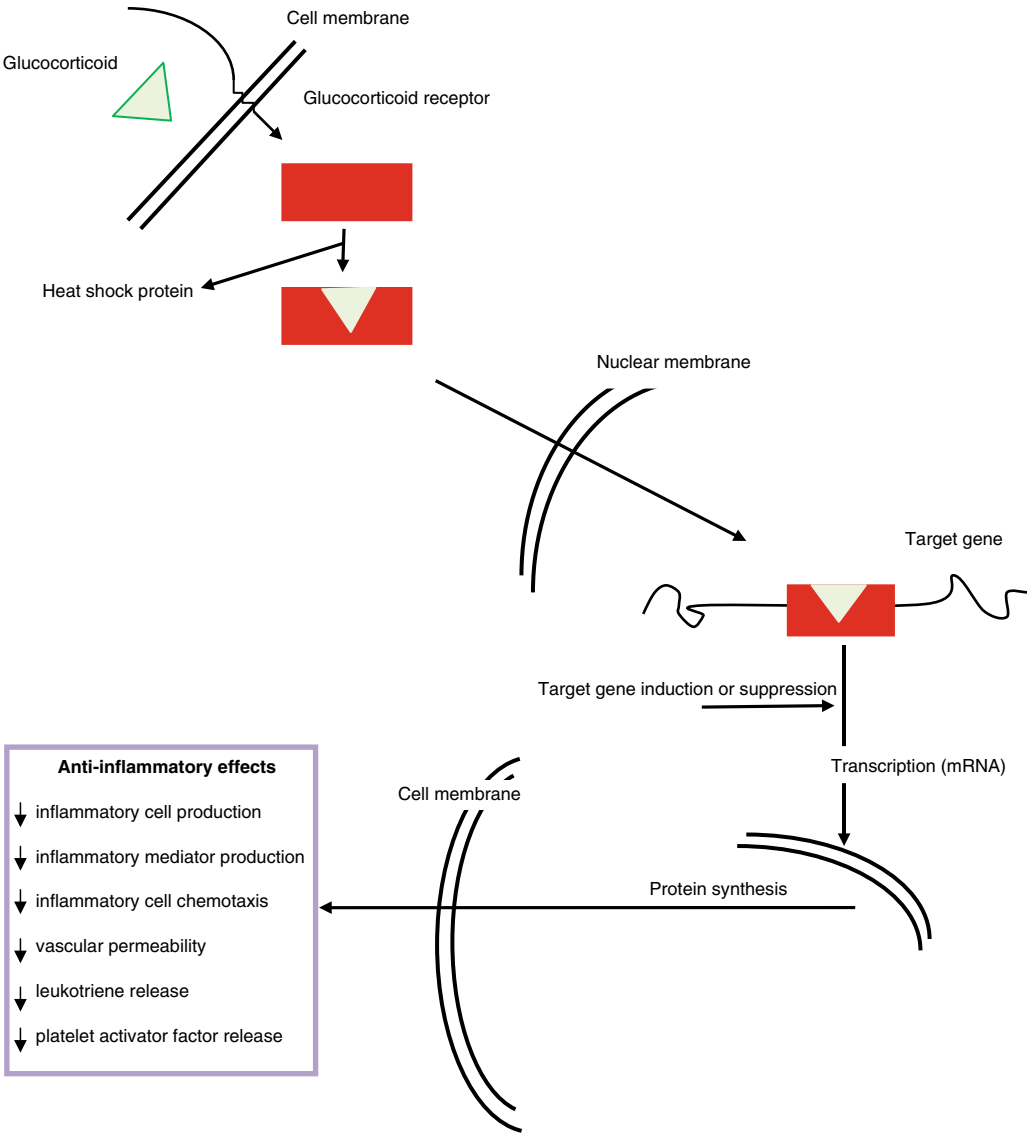



**Fig. 10.** Mechanism of action of glucocorticoids.

inflammatory genes or their promoters, they exert a number of anti-inflammatory effects (as illustrated in Fig. 10). The relative potency of the various steroids is given in Table 9.

All of the different inhaled corticosteroids can be used in children. Budesonide is also available in nebulized form, in three strengths, 0.25, 0.5, and 1.0 mg. A multicenter study of 481 children demonstrated improvement in daytime and nighttime symptoms when treated with nebulized budesonide. Inhaled corticosteroids are now the first-line drug for treatment of mild, moderate, and severe persistent asthma.

**Table 9**
**Steroid Dose Equivalency**

| *Scientific name* | *Dose equivalency (mg)* | *Relative potency* | *Half-life (h)* | *Comment* |
|---|---|---|---|---|
| Cortisone | 25 | 0.8 | 8–12 | |
| Hydrocortisone | 20 | 1 | 8–12 | |
| Prednisone | 5 | 4 | 12–36 | Available in liquid or tablet form |
| Prednisolone | 5 | 4 | 12–36 | Available in liquid or tablet form |
| Methylprednisolone | 4 | 5 | 12–36 | Used in ED or hospitalized patients |
| Triamcinolone | 4 | 5 | 12–36 | |
| Paramethasone | 2 | 10 | 36–72 | |
| Dexamethasone | 0.75 | 26.67 | 36–72 | |
| Betamethasone | 0.6 | 33.34 | 36–72 | |

The issue of adverse effects of inhaled steroids in children has been extensively studied. Steroids are associated with numerous side effects (*see* Table 10). Most of these have been attributed to oral or parenteral steroids. In children with asthma, the major concerns regarding inhaled or nebulized steroids have been the effect on growth *(27)*. Studies to determine if inhaled corticosteroids indeed have such an effect are difficult to conduct because asthma itself has been associated with growth retardation *(28)*. Results have therefore been inconsistent; however, the bulk of the evidence suggests that even if there is growth retardation, this is usually reversible, and there is a period of "catch-up" growth. Moreover, even if corticosteroids do indeed affect growth, the extent of growth retardation is minimal. Thus, the risk of growth retardation is small compared to the potential for serious asthma exacerbations. Adrenal suppression in children on inhaled steroids is also not a significant problem. In a study of 14 children on a dry-powder beclomethasone dipropionate inhaler, there was no suppression of the hypothalamic-pituitary-adrenal (HPA) axis *(29)*. The dose of beclomethasone was 12–25 μg/kg/day. Other studies have failed to demonstrate adverse effects on the HPA axis *(30)*. On the other hand, use of high doses of fluticasone has been shown to cause HPA axis suppression *(31)*. It is not known if there is any clinical significance to these observed effects. A list of the available inhaled corticosteroids and their daily dosing regimens in pediatrics is given in Table 11.

### Long Acting β-Agonists

LABAs are available either alone or in combination with an inhaled corticosteroid. The two available LABAs currently available are salmeterol xinafoate and formoterol fumarate. Salmeterol xinafoate possesses a long hydrocarbon chain connecting the binding site with the active site of the molecule. Theoretically, this conformation allows repetitive interaction between the active site and the target receptor, as the binding site is firmly attached to an alternate site on the cell membrane and the long chain acts as a

**Table 10**
**Adverse Effects of Asthma Medications**

| β-*Agonists* | *Inhaled steroids* | *Systemic steroids* | *Anticholinergics* | *Leukotriene pathway modifiers* | *Theophylline* | *Anti-IgE* |
|---|---|---|---|---|---|---|
| Tremors | Dysphonia | Hyperglycemia | Dry mouth | Elevated liver enzymes | Gastritis | Anaphylaxis |
| Tachycardia | Oral thrush | Hypertension | Blurry vision | Churg–Strauss syndrome | Seizures | |
| Muscle spasms[a] | Growth retardation[a] | Osteonecrosis | Increased wheezing | Risk of suicide | Tremors[a] | |
| Hypokalemia | Adrenal suppression[a] | Osteoporosis | | | Insomnia | |
| Tachyphylaxis | | Cushing's syndrome | | | Nausea/vomiting | |
| Hyperglycemia | | Adrenal suppression[a] | | | Tachycardia | |
| Headache | | Moon facies[a] | | | Hypokalemia | |
| Hyperactivity[a] | | Gastritis[a] | | | Hypoglycemia | |
| Increase in asthma mortality[b] | | Psychological disturbances[a] | | | Central nervous system stimulation | |
| | | Acne[a] | | | Headache | |
| | | Cataracts | | | Hyperactivity[a] | |
| | | Hirsutism[a] | | | | |
| | | Decreased platelet function | | | | |
| | | Growth retardation[a] | | | | |

[a] Of particular importance in children.
[b] Not clearly established, may be related to other confounding issues.

**Table 11**
**Daily Pediatric Doses of Inhaled Corticosteroids**

| | | | | *Mild persistent* | *Moderate persistent* | *Severe persistent* |
|---|---|---|---|---|---|---|
| *Medication* | *Pediatric indication* | *Dose/ actuation (μg)+* | *Dosing frequency* | *Number of actuations/day* | *Number of actuations/day* | *Number of actuations/day* |
| Beclomethasone dipropionate | 5–11 Year | 40 | Bid | 2 | 2–4 | |
| | | 80 | Bid | | 2 | 2 |
| Triamcinolone[a] | 6–12 Year | 100 | Bid to qid | 4–8 | 8–12 | 8–12 |
| Flunisolide | 6–15 Year | 250 | Bid | 4 | 4 | 4 |
| Budesonide | 6 Year and older | 200 | Bid | 1 | 2 | 4 |
| Nebulized budesonide | 12 Month to 8 year | Ampules of 250, 500, and 1,000 mg | Bid | 1 mg total daily dose | | |
| Fluticasone | 12 Year and older | 44 | Bid | 2–4 | 4–10 | |
| | | 110 | | | 2–4 | 4–8 |
| | | 220 | | | 2–4 | 4–8 |
| Fluticasone diskus | 4–11 Year | 50 | Bid | 2–4 | | |
| | | 100 | | | 1–4 | 2–4 |
| | | 250 | | | 1–4 | 2–4 |
| Mometasone furoate | 4–11 Year | 110 | Bid | 1 | 2 | 4 |
| | | 220 | Bid | | 1 | 2 |

[a] Triamcinolone inhaler is no longer commercially available.
[+] These are suggested doses modified from the package inserts of each drug.

tether. Salmeterol is indicated down to age 4. It used to be available as an MDI and the diskus, but now only the diskus is available. The dose per puff in the diskus is 50 μg and should be taken twice daily. The terminal elimination half-life of salmeterol is 5.5 h. Formoterol is available in an aerolizer, a dry powder device in which a capsule must be punctured in a specialized chamber. A total of 12 μg of drug is contained in one capsule. Formoterol is also dosed twice daily. The mean elimination half-life of formoterol in healthy subjects is 10 h. The structures of salmeterol and formoterol are illustrated in Fig. 11.

The LABAs are not generally considered first-line treatment for persistent asthma and the current recommendation is that it be used as an add-on therapy. Recently, case reports appeared in the literature of asthma-related deaths associated with salmeterol use. The FDA subsequently attached a black box warning on increased asthma-related deaths to the LABA class of drugs. The issue is, however, still under significant debate due to the presence of other confounding variables that may or may not have been taken into account in the studies. The recommendation for the use of LABAs is to discontinue the LABA once the patient's asthma has been stabilized and control of his/her asthma has been achieved. It remains to be seen if there will be adverse consequences of such a recommendation *(32)*.

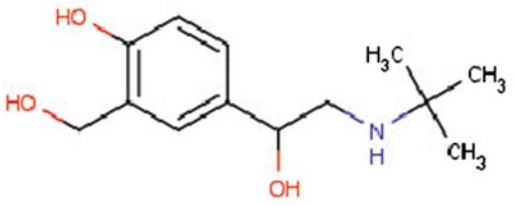
### Cromolyn and Nedocromil

These two unrelated compounds have an excellent safety profile. Their chemical structures are illustrated in Fig. 12. Both are mast cell stabilizers, and both also inhibit the activation and release of inflammatory mediators from eosinophils. This appears to be mediated through blockage of chloride channels *(33)*. Both early and late phase reactions to allergen challenge are inhibited. Cromolyn is derived from the plant, *Ammi visnaga*, or bishop's weed. The commercial product can be administered in either nebulized form or by MDI. The dose of cromolyn via MDI is 1 mg/actuation, where as the dose of nedocromil is 2 mg/actuation delivered from the valve and 1.75 mg/actuation delivered from the mouth piece of the inhaler. The dose of cromolyn delivered via nebulizer is 20 mg/treatment. The terminal elimination half-life of nedocromil sodium is 3.3 h. Nedocromil sodium is indicated in children 6 years of age or older. Cromolyn sodium is regularly used in very young children via nebulizer.

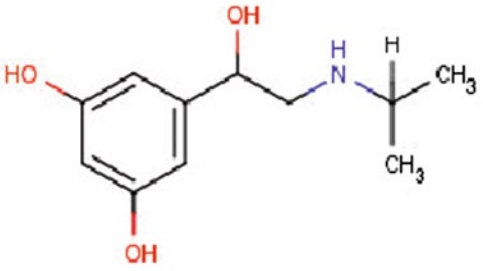
Because of the unfavorable dosing schedule, Cromolyn, a previously widely used medication, has given way to other nebulized anti-inflammatory medications, such as the glucocorticoids. Nedocromil has an unpleasant taste, and along with cromolyn, has fallen out of favor recently.

### Leukotriene Pathway Drugs

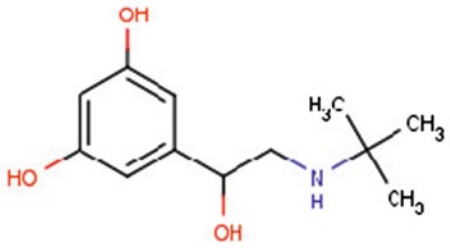
Drugs that block the effects of leukotrienes were first introduced in the early 1990s. Two strategies were used in the development of these drugs, inhibiting their synthesis or blocking their action at the Cys-LT receptor level. Drugs that block leukotriene synthesis, such as zileuton, have been associated with liver toxicity. The leukotriene receptor antagonists have a much better safety profile and dosing schedule, and have been the more widely used medications. The mechanism of action of leukotrienes is shown in Fig. 13.



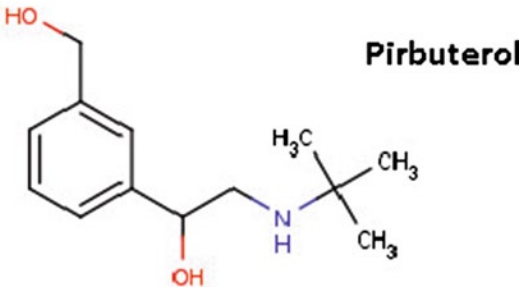

Albuterol




Metaproterenol




Terbutaline




Pirbuterol

**Fig. 11.** Structure of the β-adrenergic agonists. Comparison of the structures of albuterol and salmeterol helps to explain the long half-life of salmeterol. The long chain connects the binding site to the active site of the molecule. Once bound at the binding site, the long chain is theorized to swing back and forth, allowing the active site to repeatedly come in contact with the receptor site, prolonging the action of the drug.

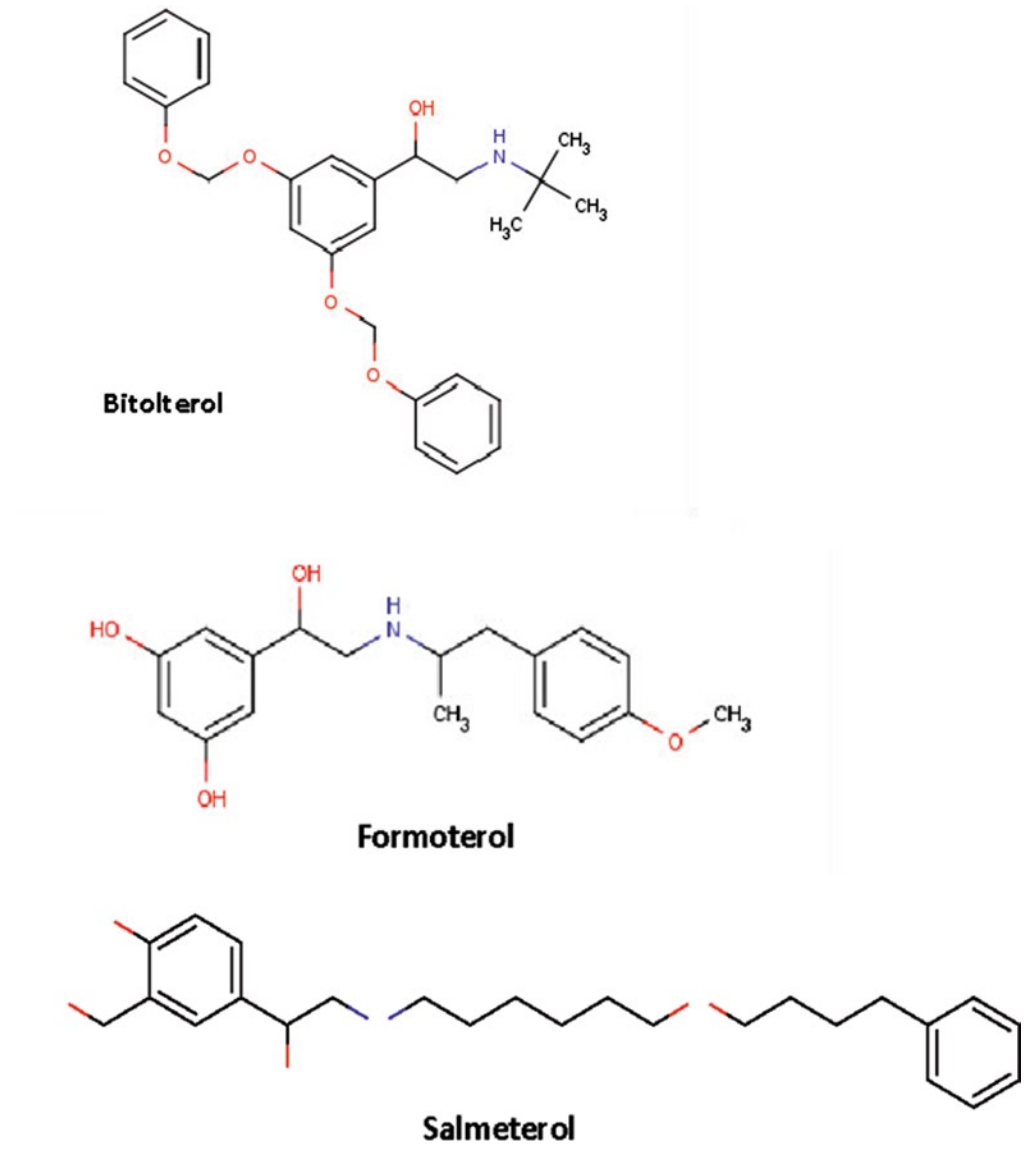



**Fig. 11.** *(Continued)*

As an inflammatory mediator in asthma, leukotrienes are 1,000 times more potent than histamine *(34)*. The effects of LTC4, LTD4, and LTE4 on the Cys-LT receptor include an increase in mucous production, constriction of bronchial smooth muscle, augmentation of neutrophil and eosinophil migration, and stimulation of monocytes aggregation. In general, side effects of the leukotriene receptor antagonists are mild, with the exception of Churg–Strauss syndrome, a vasculitis associated with peripheral eosinophilia, elevated serum total IgE, patchy pulmonary infiltrates, cutaneous purpuric lesions, and pleural effusions. Leukotriene pathway modifiers can also affect metabolism of theophylline and a number of other drugs.

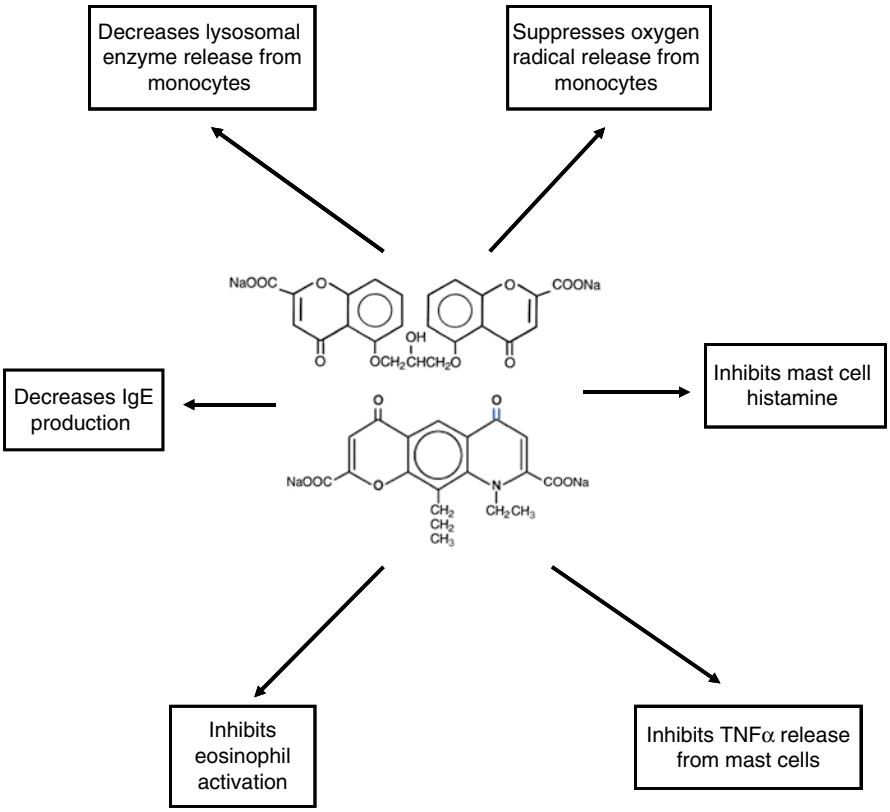



**Fig. 12.** Structure and anti-inflammatory effects of cromolyn and nedocromil.

Montelukast, the most commonly used leukotriene pathway drug is approved in children 1 year and older for asthma, 6 months and older for perennial allergic rhinitis, and 24 months and older for seasonal allergic rhinitis. Montelukast has been particularly useful in the treatment of cough variant asthma in children *(35)*. Early reports of an association between suicide and montelukast have been re-assessed, and the conclusion is that the risk of suicidal ideation in montelukast use is low. However, it was recommended that patients should be screened for behavioral anomalies including suicide ideation, which are generally more common in adolescents and the elderly.

### Antihistamines

Whether to use antihistamines in children with asthma has been a hotly debated topic. The FDA originally had a warning on using antihistamines in asthma which was a class effect, so any newer antihistamines that were introduced all carried the same warning. However, while the first-generation antihistamines had side effects that could potentiate an asthma exacerbation, such as the anticholinergic effects of drying, as well as the

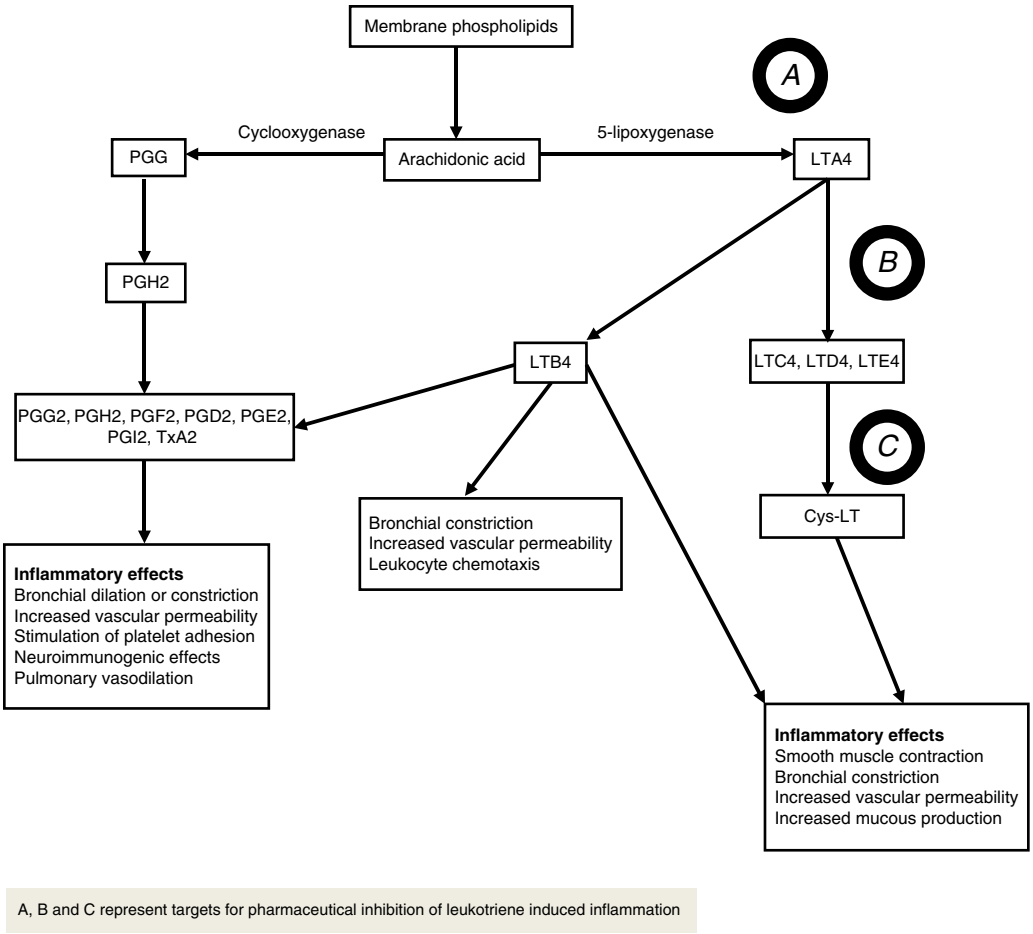



**Fig. 13.** Mechanism of action of leukotriene pathway modifiers.

sedative effects, the second-generation antihistamines have much less of these adverse effects and should be safe in asthmatics. They should also provide some benefit, especially in children, where the greater proportion of asthma is associated with allergies *(36)*. The currently available second-generation antihistamines in the United States are cetirizine, levocetirizine, loratidine, desloratidine, and fexofenidine. These drugs block the allergic effect of environmental allergens, but cetirizine also inhibits leukocyte recruitment and activation and eosinophil migration *(37)*, and has been shown to decrease late leukocyte migration into antigen-challenge skin blister fluid chambers *(38)*. All three inflammatory cell lines, including neutrophils, eosinophils, and basophils were affected.

### Theophylline in Childhood Asthma

Theophylline and aminophylline had their heyday in the 1980s, when almost every child with an asthma exacerbation requiring hospital admission was started on an

aminophylline drip. Similarly, most patients with asthma were placed on theophylline as a maintenance therapy. The use of this class of medications has decreased significantly since then, due to its narrow therapeutic window, and potentially severe side effects (Table 10). Aminophylline is metabolized to theophylline, which is then metabolized to caffeine.

Theophylline acts as a phosphodiesterase inhibitor (Fig. 14). Its efficacy in improving symptom scores and pulmonary function test parameters is similar to inhaled steroids. Therefore, despite the undesirable effects of theophylline, there may still be role for its use as a steroid sparing agent in children with severe persistent asthma, especially those on systemic steroids. Theophylline levels should be monitored regularly every 2–3 months or more frequently if there are dosage changes, signs of adverse effects, or lack of efficacy. A list of factors and agents that influence theophylline levels and their effect is given in Table 12.

#### Monoclonal Anti-IgE

Omalizumab (Xolair) is a recombinant DNA-derived humanized IgG1a monoclonal antibody, which binds specifically to human IgE. Binding of IgE by omalizumab inhibits both early and late-phase reactions of asthma. Effects of omalizumab include a reduction in serum IgE levels and a decrease in allergen-induced bronchoconstriction *(39)*. Omalizumab is indicated for patients 12 years of age or older who have moderate to severe persistent allergic asthma with a positive skin or blood allergy test, who have IgE levels between 30 and 700 IU/mL. Table 13 shows the dosing schedule for omalizumab. Side effects include malignancies, anaphylactic reactions, and local injection reactions. The high cost of Xolair can be potentially offset by savings in the cost of asthma exacerbations, e.g., hospital costs, outpatient emergency department visits, rescue medications, and indirect costs from loss of productivity by the patient.

### *Reliever Medications (Rescue Medications)*

#### Short Acting β-Agonists

The mechanism of action of the β-agonists is through activation of the β2-adrenergic receptors on airway smooth muscle cells, which leads to activation of adenyl cyclase. This, in turn, leads to an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A, causing inhibition of phosphorylation of myosin and lowering of intracellular calcium concentrations, which then results in relaxation of bronchial smooth muscle. β2-Adrenergic receptors are present in all airways, from the trachea to the terminal bronchioles. Another effect of the increase in cAMP concentration is the inhibition of mediator release from mast cells. Adverse effects of β-agonists include paradoxical bronchospasm, cardiovascular effects, central nervous system stimulation, fever, tremors, nausea, vomiting, and an unpleasant taste (Table 10).

The short acting β-agonist (SABA) used include albuterol, levalbuterol, pirbuterol, bronkosol, isoproterenol, metaproterenol, and terbutaline (Fig. 11). The more recently developed β-agonists are more specific to β2-adrenergic receptors, optimizing the effects on bronchial smooth muscle while reducing cardiac side effects, and have made

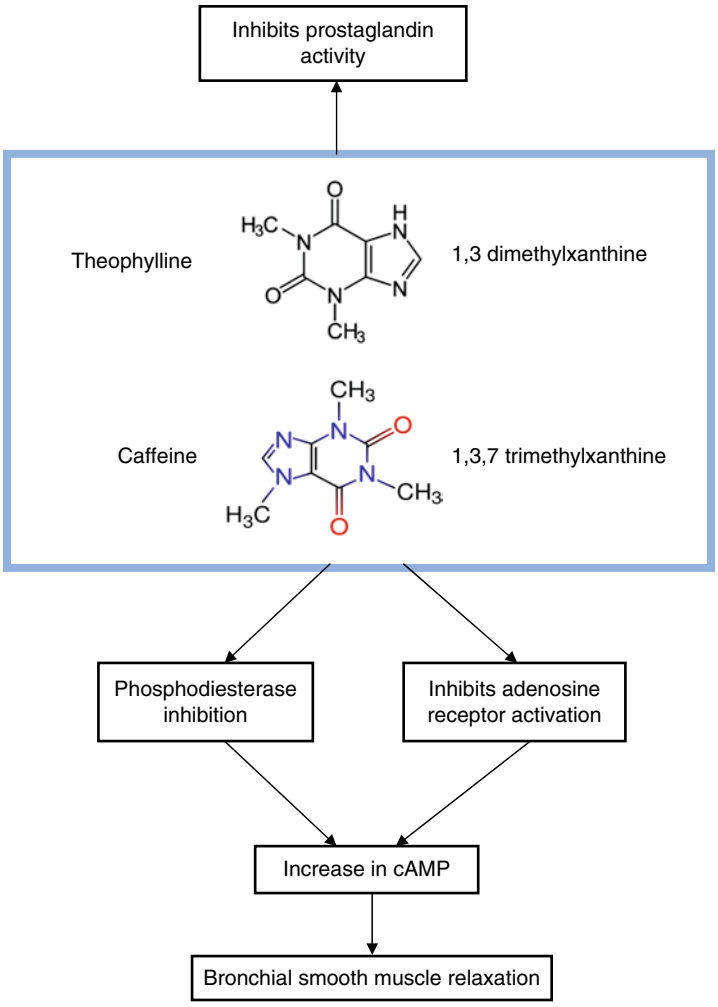



**Fig. 14.** Structure and bronchodilatory effects of theophylline and known actions of theophylline and caffeine. Actual mechanism for the bronchodilatory effect of methylxanthines is not completely understood. Phosphodiesterase inhibition appears to be the most likely mechanism, but theophylline is known to have other activity, as shown.

older less-specific drugs such as metaproterenol and isoproterenol obsolete. Dosing recommendations for SABA inhalers are given in Table 14. Albuterol, the most commonly used β-agonist, is available as a 0.083% nebulization solution. The use of β-blockers is a relative contraindication in children with asthma. β-Blockers have been associated with worsening asthma *(40)*.

Albuterol is a 50–50 racemic mixture of the stereoisomers R-albuterol (levalbuterol) and S-albuterol. Levalbuterol is available in both inhaler and nebulizer solution form. There are three available doses of levalbuterol, 0.31, 0.63, and 1.25 mg for nebulization. Levalbuterol increases mean FEV1 by 31–37% in children between the ages of 6 and 11 *(41)*. The elimination half life of levalbuterol is 3.3 h compared to 1.5 h for albuterol.

**Table 12**
**Factors Affecting Theophylline Metabolism**

| *Factor or drug* | *Effect on theophylline levels* |
|---|---|
| **Antibiotics** | |
| Ketolides | Increase |
| Ciprofloxacin | Increase |
| Rifampin | Decrease |
| Macrolides: erythromycin, clarithromycin | Increase |
| **Antiepileptics** | |
| Phenobarbital | Decrease |
| Carbamazepine | Decrease |
| Phenytoin | Decrease |
| **Other drugs** | |
| Aminoglutethimide | Decrease |
| Disulfiram | Increase |
| Ticlopidine | Increase |
| Propranolol | Increase |
| Cimetidine | Increase |
| Allopurinol | Increase |
| Calcium channel blockers | Increase |
| Methotrexate | Increase |
| **Other factors** | |
| Diet | Increase/decrease |
| Obesity | Increase |
| Hypoxia | Increase |
| Smoking | Decrease |
| Viral illness | Usually increase |
| Pediatric and geriatric population | Usually increase |

**Table 13**
**Dosing Schedule for Omalizumab[a]**

| *Pretreatment serum IgE (IU/mL)* | *Body weight (kg)* | | | |
|---|---|---|---|---|
| | *30–60* | *>60–70* | *>70–90* | *>90–150* |
| **Every 4 weeks dosing** | | | | |
| ≥30–100 | 150 | 150 | 150 | 150 |
| >100–200 | 300 | 300 | 300 | See below |
| >200–300 | 300 | See below | See below | |
| >300–400 | See below | | | |
| >400–500 | | | | |
| >500–600 | | | | |
| **Every 2 weeks dosing** | | | | |
| ≥30–100 | See above | See above | See above | See above |
| >100–200 | | | | 225 |
| >200–300 | | 225 | 225 | 300 |
| >300–400 | 300 | 300 | 375 | Do not dose |
| >400–500 | 300 | 375 | Do not dose | |
| >500–600 | 375 | Do not dose | | |

Adapted from Omalizumab package insert.
[a]Omalizumab is FDA approved in children over 12 years of age.

**Table 14**
**Characteristics of Inhaled or Nebulized Bronchodilator Preparations[a]**

| *Generic name* | *Dosage/inhalations or puff* | *Available delivery devices* | *Dosing frequency* | *Max puffs/day* | *Half life (h)* | *Onset of action (min)* | *Time to peak effect (min)* | *Duration of action (h)* |
|---|---|---|---|---|---|---|---|---|
| Albuterol | 90 μg/puff or 2.5 mg/ nebulization | MDI, D, C, N | 2 Puffs q4 h prn, 1 tmt q4 h prn | 12 | 1.5 | 6 | 55–60 | 3 |
| Levalbuterol | 0.31, 0.63 or 1.25 mg/ nebulization or 90 μg/MDI puff | MDI, N | 2 Puffs q4 h prn, 1 tmt q4 h prn | 12 | 3.3 | 10–17 | 90 | 8 |
| Metaproterenol | 630 μg/puff or 15 mg nebulization | MDI, N | 2 Puffs q4 h prn or 1 tmt q4 h prn | 12 | N/A | 5–30 | 60–75 | 1–2.5 |
| Pirbuterol | 200 μg | A | 2 Puffs q4–6 h prn | 12 | N/A | 5 | 50 | 5 |
| Bitolterol | 370 μg | MDI, N | 2 Puffs q6 h prn | 12 | N/A | 3–4 | 30–60 | 5–8 |
| Formoterol | 12 μg | D | 2 Puff q12 h | 2 | 10 | 5 | 60 | 12 |
| Salmeterol | 25 μg | MDI, D | 2 Puffs q12 h | 4 | 5.5 | 10–20 | 45 | 12[b] |
| Ipratropium | 18 μg/puff or 500 μg/ nebulization | MDI, C, N | 2 Puffs q6 h prn or 1 tmt q6 h | 12 | 2 | 15 | 60–120 | 3–4 |

[a] Some of these are no longer commercially available.
[b] Late phase reaction may be inhibited up to 30 h.
*MDI* Metered-dose inhaler (only HFA available now); *A* autoinhaler; *D* dry-powder inhaler; *C* combination inhaler; *N* solution for small volume nebulizer.

Albuterol is also available in oral form, either as a 2 mg/5 mL syrup or a sustained release 4 mg tablet. The oral dose in children is 0.03–0.06 mg/kg/day in three divided doses (no more than 8 mg/day). Terbutaline is also available orally in 2.5 and 5 mg tablets and is indicated for use in children over 12 years of age.

### Anticholinergics

Anticholinergic inhalers are indicated for the treatment of chronic obstructive pulmonary disease (COPD), but may be of some value in the treatment of the asthmatic during an exacerbation. The mechanism of action of ipratropium bromide is through competitive inhibition of M2 and M3 muscarinic cholinergic receptors. This leads to a decrease in airway vagal tone and decreased mucous gland secretion. Bronchoconstriction is also inhibited by anticholinergic agents *(42)*. Ipratropium bromide is available in nebulized form (2.5 mL of a 0.02% solution = 500 μg), or by HFA MDI (17 μg/dose from the mouthpiece). Ipratropium bromide is not well absorbed in the gastrointestinal tract. The elimination half-life of ipratropium bromide is 1 h when taken by MDI or administered intravenously.

### Mucolytics

The use of mucolytics, such as *N*-acetylcysteine and *S*-carboxymethylcysteine, in childhood asthma is controversial. Mucolytics exert their action by breaking up the disulfide bonds between mucin chains and allowing for easier clearance of mucous. On the other hand, they can cause bronchoconstriction. Although animal studies have demonstrated that *N*-acetylcysteine can improve gas exchange after methacholine challenge *(43)*, there is currently no clinical indication for the use of mucolytics in the treatment of childhood asthma.

### Oral or Parenteral Steroids

Fortunately, the use of systemic steroids in the treatment of asthma has decreased in countries where access to preventative, controller medications is easy and unrestricted. Systemic steroids, administered orally or parenterally on a chronic basis, are associated with a long list of adverse effects, many of which are potentially more serious than the disease they are being used to treat. These side effects are listed in Table 10. One important side effect that is sometimes forgotten is osteonecrosis. While corticosteroid-induced osteonecrosis is more common in autoimmune diseases and transplant patients than in asthma, one should still have a high index of suspicion when treating an asthmatic child who has been on steroids for a long time *(44)*. Generally speaking, a short course of steroids to treat an asthma exacerbation is acceptable from a risk benefit standpoint. In this case, if the corticosteroid course is less than 7 days, no tapering of dose is needed. A tapering schedule should be formulated for those patients in whom steroids are being used for longer than 1 week. If the patient requires multiple courses of steroids, then the possibility of developing serious side effects should be considered.

There are several corticosteroids available to treat asthma exacerbations. These are given in Table 9. Many of the oral preparations have a very bad taste and may need to be disguised in foods in order to be able to administer them to young children. There is also available at least one form in an oral disintegrating tablet (ODT), which will facilitate compliance in young children.

## TREATMENT OF EXERCISE-INDUCED ASTHMA

Exercise is a common trigger for asthma, and is particularly relevant in children, as many children are active in sports. SABAs are widely used, whereby the child takes two puffs of an albuterol inhaler prior to exercising. This has the effect of shifting the stimulus–response curve to the right. Inhaled albuterol or terbutaline provides relief for up to 1 h during exercise. Other short-acting bronchodilators that have been used in EIA include fenoterol and bitolterol. Oral bronchodilators have provided longer relief, up to 6 h for albuterol and 2–5 h for terbutaline. Cromolyn and nedocromil have been found to protect against EIA for 120 and 300 min, respectively. Theophylline has also been used in EIA, but the narrow therapeutic window and the lack of benefit observed at lower doses has hindered its widespread use. The use of ipratropium bromide in EIA has not produced consistent results. Controller medications that have played a role in preventing EIA include inhaled corticosteroids and the long-acting bronchodilators salmeterol and formoterol. Leukotriene receptor antagonists have also been shown to be of some value in preventing EIA in children. The data on ketotifen, calcium channel blockers, and antihistamines in the treatment of EIA is conflicting.

## INHALATION DEVICES IN CHILDREN

MDIs were first introduced in 1955 to deliver a predetermined amount of drug to the airways. The devices have undergone significant evolution since then and now are the most common device to carry and administer drugs to treat asthma. Dry powder inhalers (DPI) are an alternative to MDIs. While the ability to deliver drug straight to the airways has revolutionized asthma treatment, the use of these devices in children presents some special considerations. The most important of these is the ability of young children to use these devices effectively. Specifically, this is the ability of the child to (1) understand how to use them and (2) be coordinated enough to use them accurately and effectively. MDIs require considerable more coordination than DPIs, although spacer devices do help. If a child is found to be unable to effectively use one of these devices, then it would be much more beneficial to the asthmatic child to continue with the use of nebulizers. A comparison of the various drug delivery devices is given in Table 15. The table also shows the most common age at which these inhalers can typically be used, although it is important to appreciate that there is a significant variability to these ages.

## IMMUNOTHERAPY IN CHILDHOOD ASTHMA

Also referred to as hyposensitization, desensitization, or allergy shots, immunotherapy plays a significant role in the treatment of pediatric asthma. Studies done in children who were allergic to dust mite, cat, dog, mold, grass, ragweed, olive tree, and other allergens have demonstrated a beneficial effect of subcutaneous immunotherapy (SCIT). A study of 215 patients with dust mite allergy demonstrated that those patients with an FEV1 greater than 90% were 4 times as likely to benefit from immunotherapy to house dust mite, compared with patients with FEV1 less than 60%. Moreover, patients under the age of 20 years were 3 times more likely to

**Table 15**
**Comparison of Inhaler Devices**

| | *CFC inhalers* | *HFA inhalers* | *Autoinhalers* | *Dry powder inhalers (DPIs)* | *Spacer devices* | *Nebulizers* |
|---|---|---|---|---|---|---|
| Availability | No longer available | Widespread | Rare | Increasing | Common | Widespread |
| Portability | Easy | Easy | Easy | Easy | Some are cumbersome | Smaller devices are available |
| Ease of use | Difficult | Difficult | No need for coordination | Need for adequate breath actuation | Improves effectiveness of MDI | No coordination necessary |
| Age range of use | 5 Year and older | 5 Year and older | 4 Year and older | 4 Year and older | May allow for use of MDI at an earlier age | Any age |
| Available for | Not available | SABA, LABA, corticosteroids, ipratropium bromide | SABA (pirbuterol) | LABA, corticosteroids, combination products | N/A | SABA, cromolyn, nedocromil, iptratropium bromide, corticosteroids |
| Cost/value | N/A | Expensive/good | Expensive/fair | Expensive/good | Moderate/good | Expensive/good |
| Comments | CFCs no longer available | The standard for MDI devices | Difficult to find | Dose lost if child exhales through device | Improves drug delivery to airways | Most reliable way to deliver drug – less dependent on patient technique |

improve than those more than 51 years of age *(45)*. Indications for immunotherapy include clear evidence of symptom–exposure relationship, perennial symptoms, and inadequate control with medications. Recent advances in sublingual immunotherapy (SLIT) may provide another option for hyposensitization in children with allergic asthma.

## EMERGENCY TREATMENT OF STATUS ASTHMATICUS

A child may present to an emergency room or urgent care setting in respiratory distress but without a diagnosis of asthma. It is important for the emergency room physician or provider to be able to quickly formulate a differential diagnosis in order to administer the correct treatment. Assessment of respiratory distress involves the evaluation of patient symptoms and signs including heart rate, respiratory rate, retractions, mental status changes, presence of cough or wheezing, pulsus paradoxicus and if quickly available, peak flow measurement and pulse oximetry. A differential diagnosis of asthma is given in Table 4. If wheezing is present, other causes must be ruled out, including foreign body aspiration or bronchiolitis. A chest radiograph may help in this case, and also in identifying potential comorbidities of asthma, such as atelectasis or pneumothorax. An algorithm for the emergency treatment of the pediatric asthmatic is shown in Fig. 15.

A comprehensive initial evaluation of the patient in respiratory distress can be done fairly quickly, and if the respiratory distress is severe, then treatment must be initiated promptly. In an asthmatic in status asthmaticus, a SABA such as albuterol or levalbuterol should be administered quickly, preferably via a small volume nebulizer. If there is time, measurement of peak flow or spirometry done prior to and after the treatment can help to evaluate the effectiveness of the treatment, but one should not delay treatment if the child's condition is serious. If the child appears dyspneic, the patient should be placed on a cardiac monitor that can provide a rhythm and oxygen saturation. Intravenous (IV) access should be established in patients who are in respiratory distress or to maintain hydration status. Parenteral steroids may be initiated for moderate to severe asthma exacerbations. Methylprednisolone 1–2 mg/kg can be given intravenously or intramuscularly. This can be continued every 6 h if the child requires admission. If the child's condition improves quickly and he or she remains stable, the child may be discharged home on a short course of oral steroids (prednisone 1–2 mg/kg/day) with close follow-up and an action plan with detailed instructions. Measurement of peak flow and oxygen saturation should be done prior to discharge.

Epinephrine, although always important to consider, is less commonly used because of the abundance of other medications with lesser side effects. Side effects of epinephrine include tremors, hypertension, tachycardia, neutrophil demargination, and cardiac stimulation. In very severe cases, subcutaneous epinephrine (1:1,000) has been used in the treatment of the asthmatic child. The dose is 0.01 mL/kg to a maximum of 0.3 mL. The dose can be repeated if the response is inadequate. Having an epinephrine autoinjector available obviates the need to measure out the dose and saves time.

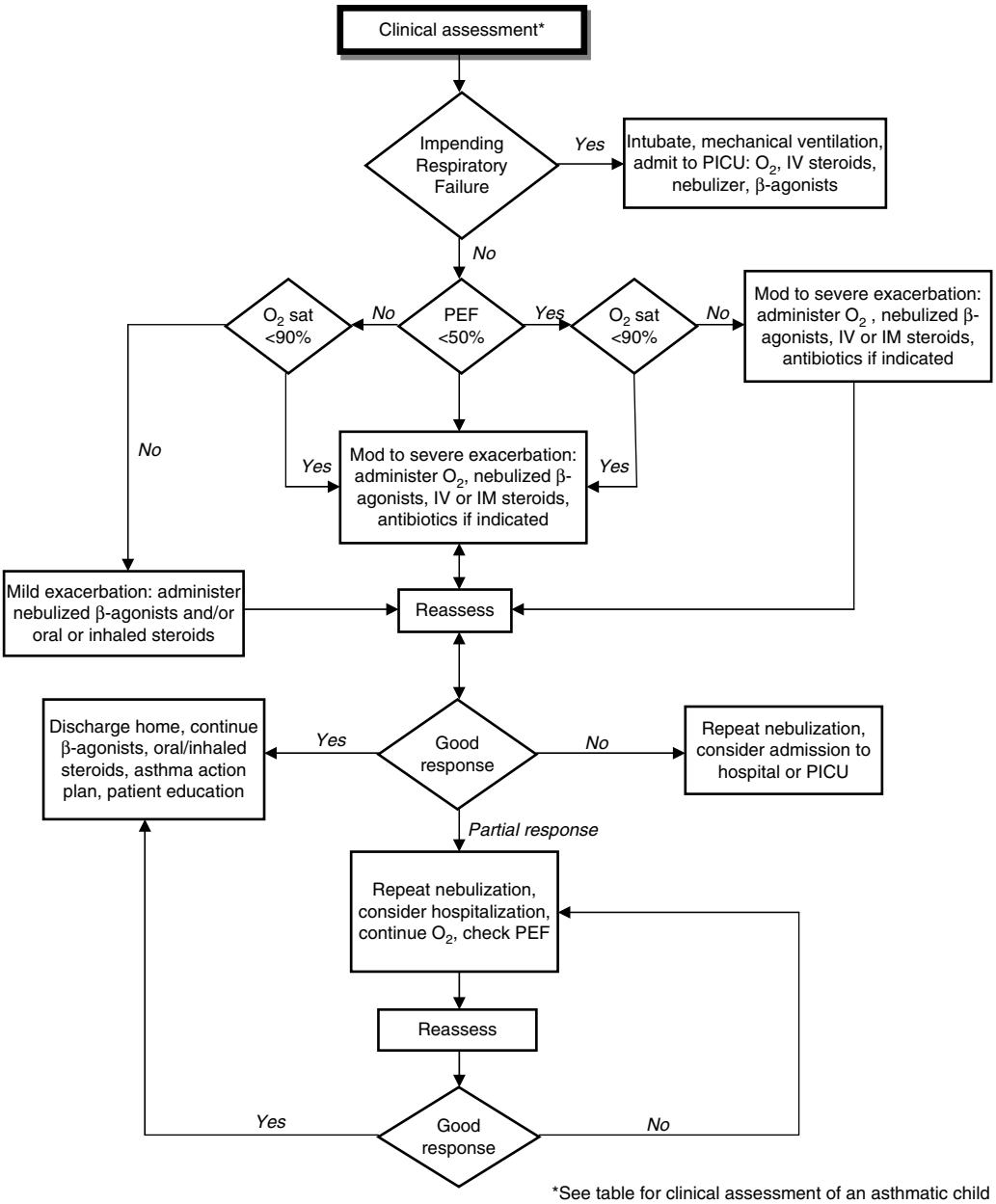



**Fig. 15.** Algorithm for the treatment of the acute asthmatic child.

Dehydration can be a factor in the successful treatment of the asthmatic child because it results in drying up of bronchial mucous and/or electrolyte imbalances, making the treatment of the asthmatic more difficult. Concomitant infection, such as pneumonia or sinusitis should be treated with antibiotics. Other medications used in

**Table 16**
**Emergency Equipment and Medication Doses in Children**

*Emergency medications*

| *Age* | *Weight (kg)* | *Epinephrine SQ 1:1,000 (mL)* | *Epinephrine IV 1:10,000 (mL)* | *Atropine 0.1 mg/mL (mL)* | *Sodium bicarbonate 0.5 mEq/mL (4.2%) for children <3 month, 1.0 mEq/L >3 month (mL)* |
|---|---|---|---|---|---|
| Newborn | 3.0 | 0.03 | 0.3 | 1.0 | 6.0 |
| 1 Month | 4.0 | 0.04 | 0.4 | 1.0 | 8.0 |
| 3 Month | 5.5 | 0.055 | 0.55 | 1.1 | 11.0 |
| 6 Month | 7.0 | 0.07 | 0.7 | 1.4 | 7.0 |
| 1 Year | 10.0 | 0.1 | 1.0 | 2.0 | 10.0 |
| 2 Year | 12.0 | 0.12 | 1.2 | 2.4 | 12.0 |
| 3 Year | 14.0 | 0.14 | 1.4 | 2.8 | 14.0 |
| 4 Year | 16.0 | 0.16 | 1.6 | 3.2 | 16.0 |
| 5 Year | 18.0 | 0.18 | 1.8 | 3.6 | 18.0 |
| 6 Year | 20.0 | 0.20 | 2.0 | 4.0 | 20.0 |
| 7 Year | 22.0 | 0.22 | 2.2 | 4.4 | 22.0 |
| 8 Year | 25.0 | 0.25 | 2.5 | 5.0 | 25.0 |
| 9 Year | 28.0 | 0.28 | 2.8 | 5.6 | 28.0 |
| 10 Year | 34.0 | 0.34 | 3.4 | 6.8 | 34.0 |

*Emergency equipment sizes*

| *Age* | *Weight (kg)* | *Self-inflating bag size* | *$O_2$ ventilation mask size* | *Endotracheal tube size* | *Laryngoscope blade size* |
|---|---|---|---|---|---|
| Premature newborn | <2.5 | Infant | Newborn small | <3.0 | 0 |
| Newborn | 2.5–4.0 | Infant | Newborn | 3.0–3.5 | 0–1 |
| 6 Month | 7.0 | Child | Child | 3.5–4.0 | 1 |
| 1–2 Year | 10–12 | Child | Child | 4.0–4.5 | 1–2 |
| 2–5 Year | 12–18 | Child | Child | 4.5–5.0 | 2 |
| 5–8 Year | 18–24 | Child | Child | 5.0–5.5 | 2 |
| 8–10 Year | 24–30 | Child/adult | Small adult | 5.5–6.0 | 2–3 |

the treatment of the acute asthmatic include nebulized corticosteroids, nebulized cromolyn, leukotriene-receptor antagonists, theophylline or aminophylline, and nebulized anticholinergic agents. The doses of emergency medications and the size of emergency equipment that is used in the pediatric population are summarized in Table 16.

Currently, theophylline is much less commonly used in the treatment of the acute asthmatic. However, if β-agonist nebulization is not effective in resolving respiratory distress, theophylline can be administered first as an intravenous bolus followed by a continuous intravenous drip. Once theophylline is started, the child

should be admitted to the hospital. Each milligram per kilogram of theophylline IV bolus results in about a 2 mg/dL rise in theophylline levels. The therapeutic window of theophylline serum levels is between 10 and 20 mg/dL. Thus, a commonly used bolus of 6 mg/kg results in a level that should fall well within the therapeutic window. An intravenous theophylline drip of 0.8–1 mg/kg/h will result in a steady state serum level. Theophylline levels must be monitored carefully because of the serious side effects that can occur at higher serum levels (Table 10). Another disadvantage of using theophylline is that multiple factors can affect theophylline metabolism, sometimes leading to unpredictable serum levels. These factors are given in Table 12.

The use of leukotriene receptor antagonists in the treatment of an asthma exacerbation has been reported. In a recent study of 201 patients, montelukast administered intravenously led to a significantly improved FEV1 after 20 min when compared to patients who were given placebo *(46)*. The effect lasted longer than 2 h, and patients in the treatment group received less β-agonist and had fewer treatment failures compared to the placebo group. Some success with the use of oral montelukast in the treatment of asthma exacerbations has also been reported *(47)*.

## INPATIENT MANAGEMENT OF CHILDHOOD ASTHMA

The decision to admit a child with an asthma exacerbation to the hospital or intensive care depends on several factors. These include the efficacy of treatment in the emergency room and the original severity of the asthma exacerbation. Persistent wheezing and retractions, dyspnea, reduced oxygen saturation, and abnormal blood gas parameters can all be indications for admission. Treatment that has been initiated in the emergency room can also lead to an admission, such as supplemental oxygen, theophylline drip, intubation, IV rehydration, or IV antibiotics. Intubation should not be delayed if the patient is in impending respiratory arrest because resuscitation is more difficult in patients who are in respiratory failure. If intubation is performed, arterial blood gas measurement and chest radiography to document placement of the endotrachael tube must be done.

Oxygen, nebulized steroids, oral or parenteral steroids, leukotriene-receptor antagonists, and theophylline can be continued as indicated, until the patient condition allows for weaning of medications. Oxygen saturation should be monitored either continuously or intermittently depending on the child's status. Particular attention should be paid to hydration status, fever, or signs of adverse effects of medications, such as tremors or electrolyte imbalances from nebulized steroids. Infections should be treated appropriately.

As the child improves, treatment can be weaned and discharge planning initiated. Children should be sent home with an asthma management plan, and instructions to return if conditions worsen. Discharge medications depend on the patient's history of present illness, and past history of asthma. Close follow-up as an outpatient by an asthma specialist is preferable to review ongoing treatment and preventative measures. Table 17 shows pediatric indications for the various asthma medications, according to the manufacturer's prescribing information (PI).

**Table 17**
**Pediatric Indications for Asthma Drugs**

| *Drug name (trade name)* | *Category* | *Components (scientific names)* | *Pediatric indication*[a] |
|---|---|---|---|
| Accolate | Leukotriene receptor antagonist | Zafirlukast | 5 Years and older |
| Advair Diskus | Combination (ICS + LABA) | Fluticasone propionate<br>Salmeterol xinafoate | 4 Years and older |
| Advair HFA | Combination (ICS + LABA) | Fluticasone propionate<br>Salmeterol xinafoate | 12 Years and older |
| Albuterol oral syrup | SABA | Albuterol sulfate | 2 Years and older |
| Alvesco | Inhaled ICS | Ciclesonide | 12 Years and older |
| Asmanex Twisthaler | Inhaled ICS | Mometasone furoate | 4 Years and older |
| Atrovent HFA | Anticholinergic | Ipratropium bromide | Not established |
| Dulera | Combination (ICS + LABA) | Mometasone furoate<br>Formoterol fumarate dihydrate | 12 Years and older |
| Foradil | LABA | Formoterol fumarate | 5 Years and older |
| Intal inhaler | Anti-inflammatory | Cromolyn | Discontinued in US, available still in other countries |
| Intal nebulization solution | Anti-inflammatory | Cromolyn | 2 Years and older |
| Pro-Air HFA | SABA | Albuterol sulfate | 4 Years and older |
| Proventil HFA | SABA | Albuterol sulfate | 4 Years and older |
| Pulmicort Flexhaler | Inhaled ICS | Budesonide | 6 Years and older |
| Pulmicort respules | Inhaled (nebulized) ICS | Budesonide | 12 Months to 8 years |
| QVAR | Inhaled ICS | Beclomethasone dipropionate | 5 Years and older |
| Seretide Accuhaler | Combination (ICS + LABA) | Fluticasone propionate<br>Salmeterol xinafoate | 4 Years and older (Australia) |
| Seretide MDI | Combination (ICS + LABA) | Fluticasone propionate<br>Salmeterol xinafoate | 4 Years and older (Australia) |
| Serevent Accuhaler | LABA | Salmeterol xinafoate | 4 Years and older (Australia) |
| Serevent Diskus | LABA | Salmeterol xinafoate | 4 Years and older (USA) |
| Serevent Inhaler | LABA | Salmeterol xinafoate | 4 Years and older (Australia) |
| Singulair | Leukotriene receptor antagonist | Montelukast | 12 Months and older (for asthma) |
| Spiriva HFA | Anticholinergic | Tiotropium bromide | Not indicated in children |
| Symbicort HFA | Combination (ICS + LABA) | Budesonide<br>Formoterol fumarate dihydrate | 12 Years and older |

*(Continued)*

Table 17 *(Continued)*

| *Drug name (trade name)* | *Category* | *Components (scientific names)* | *Pediatric indication*[a] |
|---|---|---|---|
| Tilade CFC free | Anti-inflammatory | Nedocromil sodium | 2 Years and older |
| Ventolin HFA | SABA | Albuterol sulfate | 4 Years and older |
| Xolair | Monoclonal anti-IgE | Omalizumab | 12 Years and older |
| Xopenex HFA | SABA | Levalbuterol tartrate | 4 Years and older |
| Xopenex nebulization solution | SABA | Levalbuterol HCl | 6 Years and older |
| Zyflo | Leukotriene receptor antagonist | Zileuton | 12 Years and older |

[a]These are current pediatric age indications by the FDA or corresponding regulatory agency if drug is available elsewhere.

## INTEGRATIVE MEDICINE IN PEDIATRIC ASTHMA

About one third of the population in the United States uses some form of alternative or complementary medicine. Techniques that have been utilized by patients to treat asthma include acupuncture *(48)*, herbal medicines, homeopathy, massage therapy, ayurvedic medicine, yoga, relaxation techniques, breathing exercises, and meditation *(49)* (Table 18). While popular, these modes of therapy have not been well studied, and at the present time, there is no scientific evidence to support their efficacy in the treatment of asthma. Although the majority of these techniques are themselves harmless, using them as a substitute for established asthma management may deny the pediatric asthmatic the proper care that he or she should be receiving. Special warning should be given to herbal medications, which in addition to the lack of evidence for efficacy, may actually be harmful either by themselves or in interaction with concurrent asthma medications. The use of these preparations in children should be especially discouraged until further evidence of safety and efficacy are available.

## NATURAL HISTORY AND PROGNOSIS OF CHILDHOOD ASTHMA

Although many patients believe that they have outgrown their asthma, this is never really the case, because asthma is at least partially genetically determined. On the other hand, a child's asthma can vary during their childhood and even into adulthood. Asthma is dependent on having a genetic predisposition and clinically, is modulated by the environment. Environmental modulation can stem from allergenic exposure, exposure to other agents such as endotoxin, irritants, ozone, particulates, and even temperature. Hormones can also play a role in asthma, as suggested by the interesting observation that in pregnancy, women who have asthma have an equal chance of their asthma worsening, improving, or remaining unchanged.

Table 18
Important Cytokines Targets in Asthma

| *Cytokine* | *Cellular expression (with particular relevance to asthma)* | *Cell targets* | *Function* | *New drug or drug target for asthma treatment* | *Results* |
|---|---|---|---|---|---|
| IL-3 | Activated T-cells | Bone marrow progenitors | Increases lifespan of eosinophils, stimulates differentiation of multiple cell types | None | N/A |
| IL-4 | Macrophages, Th2 cells | Naïve T cells, B cells, T cells | Upregulation of immunoglobulin E synthesis, Th2 lymphocyte differentiation, production of VCAM-1, effects low affinity CD23 IgE receptors | Soluble IL-4 receptors<br>Pitrakinra | Phase II trials show significant improvement in asthma<br>Successful asthma treatment in a monkey model |
| IL-5 | T helper 2 cells and mast cells | Eosinophils, B cells | Stimulates differentiation and activation of eosinophils | Monclonal antibody to IL-5 | Blockage of eosinophils, reduces eosinophil numbers |
| IL-6 | T cells, macrophages, fibroblasts | T cells, B cells, liver cells, mature B cells | Downregulation of inflammatory cell infiltration and enhancement of airway remodeling | None | N/A |
| IL-8 | Macrophages, epithelial cells, platelets | Neutrophils, macrophages, endothelial cells, keratinocytes, mast cells | Chemokine, angiogenic factor, may have a role in bronchiolitis, also known as neutrophil chemotactic factor | None | N/A |
| IL-9 | T helper cells | T helper cells, B cells | Th2 cytokine, activity in conjunction with IL-4, IL-1 and IL-3 | Anti-IL-9 | Inhibits asthma related features in antigen stimulated mice |

| | | | | | |
|---|---|---|---|---|---|
| IL-10 | Monocytes, lymphocytes, mast cells, Th2 cells, Treg cells, activated macrophages | T cells, mast cells, B cells | Inhibits allergen-induced airway hyperresponsiveness and inflammation | None | N/A |
| IL-12 | Activated macrophages and dendritic cells | Th cells, Tc cells, NK cells | Immunomodulatory cytokine | R848 (Resiquimod) | Reduces airway inflammation after antigen challenge |
| IL-13 | Th2 cells + many other cell types | B cells + others | Proinflammatory cytokine, Th1/Th2 balance, mediator of allergic inflammation | Anti-IL-13 | Antibody to IL-13 suppressed AHR, eosinophil infiltration, proinflammatory cytokine production, serum IgE in mice, poor results clinically |
| IL-17 | Th cells, NK cells, Treg cells, mast cells | Release of cytokines from many cells | Proinflammatory cytokine, chemokines, differentiation of Th17 cells, airway remodeling | Possibly under investigation for asthma | Unknown |
| IL-19 | Epithelial cells, endothelial cells, macrophages, monocytes | NK cells, T cells, B cells, monocytes | Function unknown, may alter balance of Th1/Th2 cells in favor of Th2 cells, increases proportion of IL-4 producing cells | None | N/A |
| IL-25 | Helper T cells, mast cells | Eosinophils (via stimulation of production of IL-4, IL-5 and IL-13) | Inflammatory bowel disease, mucosal immunity | None | N/A |
| IL-33 | Mast cells, bronchial smooth muscle cells, epithelial cells | Helper T cells, mast cells, eosinophils, basophils | Role in atopic dermatitis and asthma, gene | None | N/A |

*(Continued)*

Table 18 *(Continued)*

| *Cytokine* | *Cellular expression (with particular relevance to asthma)* | *Cell targets* | *Function* | *New drug or drug target for asthma treatment* | *Results* |
|---|---|---|---|---|---|
| GM-CSF | Macrophages, T cells, endothelial cells, fibroblasts, mast cells | Stem cells | Proinflammatory cytokine, potentially leading to increase in inflammatory cells | None | N/A |
| Interferon-γ | Th1 cells, Tc cells, dendritic cells, NK cells | Many cell types | Suppresses Th2 activity, activates inducible NOS | None | N/A |
| TNF-α | Macrophages, T cells + many other cells | Neutrophils, macrophages, T cells, B cells + others | Proinflammatory cytokine, activates neutrophils, stimulates phagocytosis, acute phase reactant | Has been studied extensively in asthma | Generally poor results |
| ADAM-33 | Vascular smooth muscle cells, fibroblasts, lung mesenchymal cells | Unknown | Type 1 transmembrane protein implicated in asthma and eczema | None | N/A |
| RANTES | Airway smooth muscle cells, mast cells, macrophages | T cells, basophils eosinophils | Chemotactic, leukocyte recruitment | None | N/A |
| CCR3 | Eosinophils, basophils, Th1 cells, Th2 cells, airway epithelial cells | Eosinophils and other inflammatory cells | Eosinophil chemotaxis | None | N/A |
| CXCR2 | Mast cells, human mesenchymal stem cells, endothelial cells | Endothelial cells, neutrophils | Neutrophil and monocytes chemotaxis | None | N/A |
| Matrix metalloproteinase-12 (metalloelastase) | Lung and alveolar macrophages | Extracellular matrix | Repair cycles influence airway changes in asthma, reduction of levels of chemotactic factors and other proinflammatory cytokines | MMP-12 specific inhibitor | Attenuates early airway response, blocks late airway response |

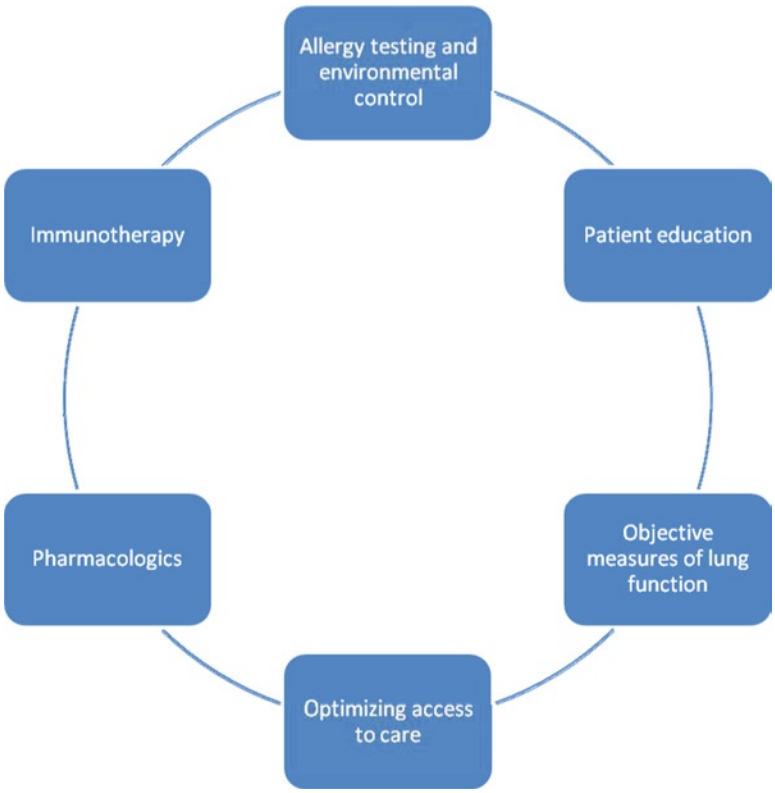



**Fig. 16.** A comprehensive asthma management program.

What is known, however, is that asthma is an inflammatory disease that results in bronchoconstriction. Successful treatment of the asthmatic means control of the inflammation. Failure to control inflammation results in chronic obstructive lung disease, as in the case of the cigarette smoker. The introduction of inhaled corticosteroids over the past few decades has greatly improved asthma care, and probably will prove to have a beneficial effect on long-term sequelae of asthma. The persistently high mortality from asthma is probably more related to patient and provider education and compliance than anything else. This is why treatment of asthma requires a comprehensive management plan that incorporates all facets of treatment, including environmental control, medications, education, and immunotherapy (Fig. 16). Regular monitoring is important to minimize the morbidity of chronic asthma.

## FUTURE DIRECTIONS

### *New Medications*

Targets for new treatment modalities in asthma include IgE, eosinophils, cytokines, chemokines, cell-signaling pathways, adhesion molecules, and inflammatory mediators such as leukotrienes, prostaglandins, and platelet activating factor. The development of airway inflammation is under the control of many biological modulators, many of which are targets of asthma research. Currently, phosphodiesterase-4 inhibitors, peroxisome proliferator-activated receptor-γ (PPAR) agonists, nuclear factor κB, phosphoinisotide-3-kinase γ, lipoxins, and p38 mitogen-activated protein kinase inhibitors are anti-inflammatory drugs that are being investigated in the treatment of asthma. It is unlikely that a single agent will be identified that will be a panacea for the treatment of asthma due to the redundancy of the immune system. A list of biologically active molecules that may have a role in asthma is given in Table 19.

Phosphodiesterase-4 inhibitors are currently being studied in the treatment of asthma. A study of airway responses to allergen challenge in 24 mild asthmatics treated with an inhaled phosphodiesterase-4 inhibitor showed an inhibition in the fall of minimum and weighted FEV1 compared to placebo *(50)*. Other phosphodiesterase-4 inhibitors are also under investigation.

Platelet activating factor has been associated with EIA and allergen-induced asthma. Inhibition of platelet activation diminishes the late phase reaction of asthma *(51)*. Several medications currently used to treat asthma, including the glucocorticoids and ketotifen, normalize platelet survival times *(52)*. Platelets also secrete platelet-factor 4, platelet-derived growth factor (PDGF), arginine-glycine-aspartic acid, thrombospondin, transforming growth factor-α and -β, 5-hydroxytryptamine, thromboxane A2, 12-hydroxyeicosatetranoic acid, β-lysin, adenosine diphosphate, and platelet derived histamine releasing factor, all of which may play a role in airway inflammation.

Platelets possess low-affinity receptors for IgG and IgE on their surface, and release adhesion molecules and inflammatory cell chemoattractants such as RANTES *(53)*. Cromolyn sodium *(54)*, nedocromil sodium *(55)*, and cetirizine *(56)* can all inhibit IgE-induced platelet activation. Platelet activation is associated with increased airway eosinophils. Despite the numerous inflammatory effects of platelets, and the potential for new drugs, there are currently no available platelet-related drugs for the treatment of

**Table 19**
**Integrative Medicine and Asthma**

| |
|---|
| Acupuncture |
| Herbal medicines |
| Homeopathy |
| Yoga |
| Ayurvedic medicine |
| Massage therapy |
| Relaxation techniques |
| Breathing exercises |

asthma. Interestingly, the recent furor over vitamin D has led to the identification of vitamin D as an inhibitor of thrombin and PDGF-induced airway smooth muscle proliferation *(57)*, suggesting that improvement in nutrition in young children may lead to normalization of vitamin D levels, and a decreased incidence of asthma.

Other targets for the future treatment of childhood asthma include the prostaglandins, specifically PGD2, a tyrosine kinase inhibitor (masitinib), and a number of potential cytokine-based therapies targeting Th2 cytokines such as IL-4, IL-5, IL-9, IL-13, IL-17, and TNF-α *(58)*. Other drugs that are continually being developed for asthma are anticholinergics and new glucocorticoid agents. There are many other potential targets that have not been mentioned here that are beyond the scope of this chapter.

### *New Forms of Immunotherapy*

SLIT has been used in Europe for several years. Early experience in the United States suggests that it is of comparable efficacy to SCIT, but with significantly diminished side effects or risk of anaphylaxis. One potential drawback of SLIT compared to SCIT is the lack of supervision associated with self-administration of oral or sublingual extracts. Better patient education may circumvent this objection, however, and SLIT may yet become widely used in the treatment of asthma. The other potential road block with SLIT is the absence of an established regimen for prescribing SLIT in polysensitized individual. A study of 51 polysensitized children with allergic rhinitis and/or mild to moderate asthma treated with SLIT for 1 year showed an improvement in symptoms of allergic rhinitis severity and classification, nasal, ocular and bronchial symptoms, and medication use. While the majority *(42)* of these children was treated with a single allergen, seven were treated with two or more extracts and experienced benefit as well *(59)*. Studies on the efficacy of SLIT have been done for dust mite, *Olea*, grass pollen, and others.

Other novel forms of immunotherapy include the development of allergen vaccines based on allergen-derived T cell peptides, recombinant allergens, and hypoallergeneic allergen derivatives. Another new chimeric Fc-γ allergen protein immunotherapy is being evaluated for cat and peanut allergy. Studies of these new forms of immunotherapy are still in the early phases and are not currently used clinically.

## GENETICS-BASED THERAPIES IN ASTHMA

Asthma is a polygenic disease with a great deal of heterogeneity. Multiple genes have been identified that convey risk of asthma. The list of asthma genes continues to grow. Single nucleotide polymorphisms (SNPs) have been found that play a role in asthma severity or response to medications. A current goal is matching the asthma phenotype with an existing drug or a drug in development to maximize the response in an individual patient.

The ability to perform Genome Wide Associations Studies (GWAS) provides a technology to rapidly analyze and compare genomes of many people to determine variations associated with specific diseases. Identification of genes that may play a role in multiple diseases or conditions has also been made possible, as in the analysis of the relationship between obesity and asthma *(60)*. This has opened the door to an infinite amount of research on asthma genetics.

## CHILDHOOD ASTHMA AND HEALTHCARE SYSTEMS

Delivery of care for allergies and asthma is highly dependent on the existing health care system within each country. There are clearly advantages and disadvantages to socialized medicine vs. fee for service medicine. Every country has its own health care system, and outcomes vary as a result of the efficiency and effectiveness of delivery of care.

In the United States, the issue of whether asthma should be managed by a generalist or a specialist has always been hotly debated. Multiple studies have shown that management by an asthma specialist (especially allergists) leads to reduced morbidity and mortality and improved quality of life. Treatment by a specialist leads to fewer hospitalizations, fewer exacerbations requiring emergency care, better quality of life, and better outcomes. However, the availability of financial resources, and more important, the failure to properly allocate such resources can be such an economic burden that optimal systems of healthcare are not implemented. As a result of this, many asthmatic children receive the bulk of their care from generalists and even mid-level practitioners, even in those cases where referral to a specialist may be indicated.

Unfortunately, in today's healthcare climate, generalists are being asked to see more and more patients and they simply do not have the time to formulate a comprehensive asthma treatment program as illustrated in Fig. 16. Asthma educators who may be nurses or even medical assistants who are specially trained may help, but no financial resources are actually devoted to this form of medical care. Too many patients with asthma are not well controlled and eventually end up in an urgent care or emergency department, at many times the cost of prevention. A list of recommendations for referral to a specialist is given in Table 20. These should be considered the very minimum requirements for referral to a specialist.

**Table 20**
**Indications for Referral to a Specialist**

| |
|---|
| Children requiring step 3 care of higher (step 2 for children under 4 years of age) |
| Children on or those who may be candidates for immunotherapy |
| Uncontrolled patients not meeting goals of therapy within 3 months of after initiation of treatment |
| Children who have had a life-threatening asthma exacerbation |
| Children in whom symptoms are atypical or if the diagnosis has not been established |
| Children with comorbid or complicating factors, including chronic sinusitis, nasal polyps, gastroesophageal reflux, allergic rhinitis, allergic bronchopulmonary aspergillosis, etc. |
| Children in whom additional diagnostic testing is needed, such as allergy testing, pulmonary function tests, rhinolaryngoscopy, provocation challenge or bronchoscopy |
| Children who require systemic corticosteroids on a chronic basis or who have more than two steroid bursts in 1 year |
| Children who have been hospitalized for asthma |
| Children with EIA or other special circumstances |
| Children and/or parents who require or desire counseling on issues related to compliance, environmental evaluation and control, medication usage, device usage, peak flow meter usage, or any other additional asthma education |
| Children who may have an unusual exposure which may be provoking or contributing to asthma |

## SUMMARY

Since our last edition, the treatment of asthma in children has become more standardized, at least amongst allergy and asthma specialists. Inhaled corticosteroids have become the first-line medical treatment of asthma in all age groups. There is still debate on the preferred add-on therapy, the options being increasing the dose of steroids, adding a leukotriene receptor antagonists, or adding a LABA, but all of these options are acceptable, and should be tailored and customized for each individual child with asthma. Future research may be able to identify which treatment might be preferred based on the patient's pharmacogenetics, but we have not yet reached this point. Environmental control has become a mainstay in asthma treatment, and new modes of immunotherapy have contributed to a significant less morbidity over the past two or three decades. Hospitalization rates of asthmatic children have decreased, drugs with high rates of side effects such as theophylline have been replaced, and quality of life has improved. Most children with asthma are able to enjoy very normal lives, compete in sports at a high level and have very few missed school or work days, as long as they are compliant with their asthma management plan.

There is continual ongoing improvement in the educational component of asthma. The development of the internet has facilitated the availability of multiple resources for physician, provider, ancillary staff, parents, and patients (Table 21). Publications for children to make it easier for them to understand their disease are now ubiquitous. With better education comes better compliance, and hopefully, better outcomes.

Some problems remain. Mortality has not decreased significantly since the last edition. One of the main remaining issues is related to patient education and compliance. It is now not a matter of availability of education materials, but acceptance and

**Table 21**
**Asthma Resources for Physicians, Patients and Parents**

| | |
|---|---|
| World Allergy Organization | http://www.worldallergy.org |
| American Academy of Allergy, Asthma and Immunology (AAAAI) | http://www.aaaai.org |
| American College of Allergy, Asthma and Immunology (ACAAI) | http://www.acaai.org |
| World Health Organization (WHO) | http://www.who.org |
| American Lung Association | http://www.lungusa.org |
| American Thoracic Society (ATS) | http://www.lungusa.org |
| Asthma and Allergy Foundation of America | http://www.aafa.org |
| National Technical Information Service | http://www.ntis.gov |
| National Asthma Education and Prevention Program (NAEPP) | http://www.nhlbi.nih.gov/about/naepp/ |
| National Heart, Lung and Blood Institute (NHLBI) | http://www.nhlbi.nih.gov |
| Allergy and Asthma Network/Mothers of Asthmatics | http://www.aanma.org |
| Center for Disease Control | http://www.cdc.gov |
| Global Initiative for Asthma (GINA) | http://www.ginaasthma.com |
| National Allergy Bureau (NAB) | http://www.aaaai.org/nab |
| Kidshealth | http://www.kidshealth.org |

utilization. Another main issue, which may become even more of a problem in the face of cost-cutting measures associated with a variety of health care reform ideas, involves the access to specialist care. There is also some concern that health care reform in the United States may lead to an overall reduction in access to care to any healthcare provider, let alone the asthma specialist.

From a scientific standpoint, the future of pediatric asthma is bright. Research is ongoing to better understand the pathophysiology of asthma, and in doing so, developing new pharmaceuticals to treat asthma. Knowledge of the genetic basis for asthma and how children react to asthma medications will help guide us in developing a personal care plan for the treatment of each child with asthma. Hopefully, this will lead to further improvements in the outcomes of asthmatic children.

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