# Pediatric asthma and related allergic and nonallergic diseases: patient-oriented evidence-based essentials that matter

*Miles Weinberger*
*University of Iowa Children's Hospital, Director, Pediatric Allergy & Pulmonary Division, Iowa City, IA 52242, USA*
*Tel.: +1 319 356 3485;*
*Fax: +1 319 353 6217;*
*E-mail: miles-weinberger@uiowa.edu*

Asthma is the most common medical diagnosis among hospitalized children. In the USA, asthma has accounted for approximately 15% of nonsurgical admissions to hospital in the pediatric age group. Asthma is also one of the leading causes for emergency care requirements, one of the leading causes for missed school, and a cause for considerable morbidity, disability and occasional mortality at all ages. Despite these discouraging statistics, convincing data indicate that this failure of asthma management is not the result of inadequate therapeutic potential, but instead represents ineffective delivery of medical care. Management of asthma and its major co-morbidities, allergic and nonallergic rhinitis, and atopic dermatitis requires a knowledge of the alternative therapies, natural history, and educational techniques for providing patients and families with the ability to manage these troublesome chronic disorders.

Asthma is the most common medical diagnosis among hospitalized children. In the USA, asthma has accounted for approximately 15% of nonsurgical admissions to the hospital in the pediatric age group. Asthma is also one of the leading causes for emergency care requirements, one of the leading causes for missed school, and a cause for considerable morbidity, disability, and occasional mortality at all ages [1].

Despite these discouraging statistics, convincing data indicate that this failure of asthma management is not the result of inadequate therapeutic potential, but instead represents ineffective delivery of medical care [2,3]. Guidelines proposed by the National Asthma Education and Prevention Program (NAEPP) have been published as Expert Panel Reports beginning in 1991, with updates in 1997 and 2002 [4–6]. A 415 page 2007 Expert Panel Report 3 with a 60 page summary has now been released [7,8]. An international guideline, the Global Initiative for Asthma (GINA) is a somewhat less weighty 92 pages; a 24 page 'Pocket Guide' version provides guidelines for treating children with asthma [201]. Despite the considerable efforts and ambitious goal of these various guidelines for improving asthma outcome, indications are that these lengthy and complex guidelines are not followed by primary care physicians [9,10], and published reports continue to show little decrease in urgent care requirements, hospitalizations or deaths from asthma [11,12].

Several specialist guided and team-directed model programs involving selected primary care physicians have been shown to impact positively on the outcome of asthma in children [13–15]. However, the greatest degree of effectiveness for asthma management has been documented for care programs directed by subspecialists that utilized continuity of care, an organized plan for effective therapeutic decisions, and patient education to carry out the plan [2,16–20]. Even among particularly difficult groups of patients where socio-economic factors complicate care, controlled clinical trials have demonstrated that specialized programs substantially improve outcome [2,19].

Rhinitis, allergic and nonallergic, and atopic dermatitis are comorbid conditions frequently associated with asthma in addition to occurring independent of asthma. Published guidelines for these troublesome clinical problems have also been published in an attempt to improve care of these related disorders in primary care settings [21–27].

The purpose of this review is to identify those measures with accepted potential benefit for these disorders that are the most important and should be utilized in primary care. Additional measures that go beyond the common scope of primary care will also be discussed to identify where specialty care may provide additional benefit.

## Asthma

### *Diagnosis*

Diagnosis of asthma has no lower age limit. However, the diagnosis of asthma in the young child has been particularly associated with controversy [28]. Misdiagnosis, by calling acute exacerbations bronchitis or pneumonia, and alternative diagnostic terminology, such as reactive airway disease (RAD) [29], is a frequent

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consequence of this. Symptoms resulting from airway inflammation associated with asthma have been all too frequently misdiagnosed as pneumonia and bronchitis [30]. This results in ineffective and unnecessary use of antibiotics [31,32]. On the other hand, asthma is also overdiagnosed, which results in unnecessary and ineffective medication [33–35].

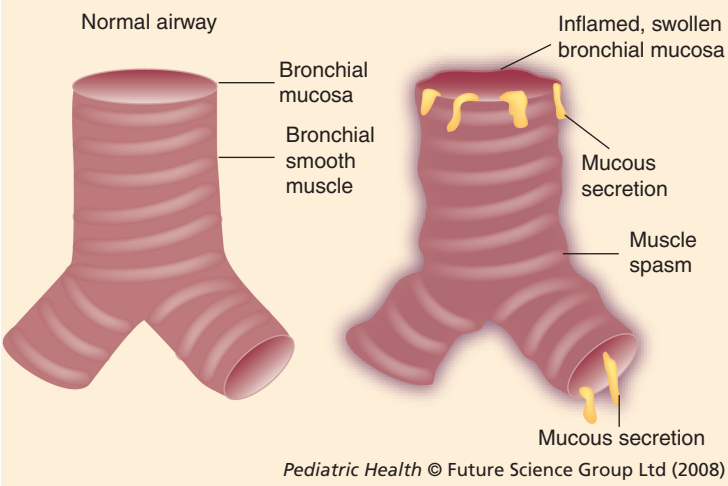
Asthma is defined as a disease characterized by hyper-responsiveness of the airways to various stimuli, resulting in airway obstruction that is reversible to a substantial degree either spontaneously or as a result of treatment. The airway obstruction is a result of varying degrees of bronchospasm and inflammation. Inflammation results in mucosal edema and mucous secretion (**Figure 1**).

Asthma should be considered when patients present with the following symptoms:

- Recurrent or chronic wheezing most prominent on expiration
- Recurrent or chronic coughing
- Repeated diagnoses of bronchitis
- Repeated diagnoses of pneumonia not clinically consistent with pyogenic infection

The diagnosis of asthma is most efficiently confirmed by demonstrating the complete response of symptoms or spirometric measurement of airway obstruction to an inhaled β2 agonist or a 5–10 day course of high-dose oral corticosteroids (**Table 1**). Patients that are not clearly made asymptomatic or having substantial reversibility of airway obstruction with these measures should be referred to an appropriate subspecialist for further investigation of other inflammatory or occasionally functional disorders that can cause similar symptoms [36]. These can include such varied disorders as cystic fibrosis, primary ciliary dyskinesia [37], tracheal or bronchial malacia [38], foreign body aspiration, vocal cord dysfunction [39], hyperventilation [33] or habit cough syndrome [40].

**Figure 1. Two components of airway obstruction in asthma.**




Bronchospasm and inflammation with mucosal edema and mucous secretions are illustrated on the right.

## Clinical characterization of asthma

### *Phenotypical patterns*

Owing to the heterogeneous nature of asthma, making the diagnosis just of asthma is not sufficient for the development of the most appropriate treatment plan. Planning effective and efficient strategies for managing asthma requires identification of the clinical pattern of disease in the patient to be treated. These clinical patterns or phenotypes can generally be determined by even a brief history that addresses the following questions:

- Age of onset of lower respiratory symptoms
- Are symptoms of asthma only associated with the clinical symptoms of a viral respiratory infection?
- Are there extended periods between episodes of respiratory symptoms where there is no cough or wheeze?
- Is there a seasonal variation in symptoms, and does the season match those of inhalant allergens or the season of increased viral respiratory infections?
- Are respiratory symptoms related to specific environmental exposures?
- Are lower respiratory symptoms occurring daily for extended periods?

From the responses to those questions, a clinical pattern of asthma can be determined.

#### Intermittent

This asthma pattern is characterized by episodic symptoms. The most common phenotype are those patients whose asthma is solely triggered by viral respiratory infections with completely asymptomatic periods between the viral respiratory infections. Typically parents will say, 'every time he/she gets a cold, it goes into his/her chest'. Generally, this pattern of asthma begins in the first 1 or 2 years of life. The typical course is the onset of coryza from a common cold virus followed by cough, wheezing and respiratory distress of varying severity that progresses over the next 1 to 2 days. The duration of symptoms, without effective intervention, can be days,

**Table 1. Doses of prednisone or prednisolone to obtain maximal effect on asthmatic airways.**

| Age | Dose* |
|---|---|
| Infant | 15 mg twice daily |
| 1–3 years of age | 20 mg twice daily |
| 3–13 years of age | 30 mg twice daily |
| >13 years of age | 40 mg twice daily |

**Reduce dose to morning only if irritability or insomnia is problematic after the initial 1 or 2 days of treatment.*

*Since there are insufficient dose–response data to support recommendations based on weight or body size, these are empirical doses based solely on experience that lower doses less reliably provide complete cessation of symptoms, with the goal of a 5- to 10-day course. Lower doses almost certainly will be adequate for some patients, and minor side effects require dosage to be limited in some patients to once daily in the morning only. There is no reason to taper short courses [63–65].*

weeks or months. During asymptomatic periods between colds, these patients have no evidence of airway inflammation when examined by bronchoalveolar lavage [41].

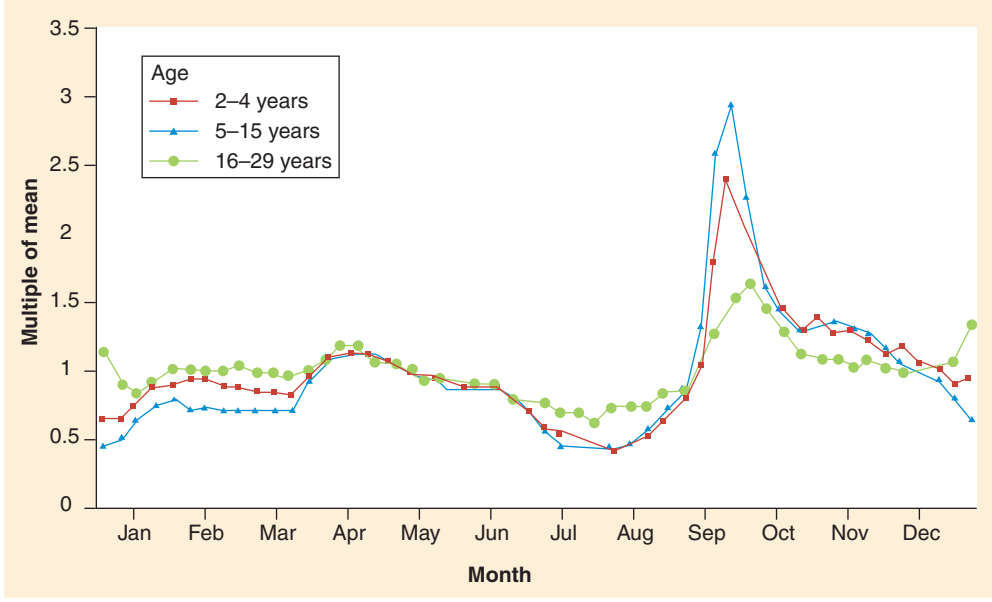
The frequency of colds in the preschool age period is increased for those in daycare or where there is an older sibling in school. The seasonal pattern for this asthma phenotype parallels the seasonal pattern of cold viruses that begin with the onset of the school year and continues throughout the Fall, Winter and Spring (**Figure 2**) [42]. An average of seven colds per year with 15% of children experiencing 12 or more colds per year [43] can result in the appearance of almost continuous symptoms for a period of time, but summer time is generally associated with periods free of symptoms in children with asthma limited to exacerbations from viral respiratory infection. Distinguishing this pattern of asthma from a chronic or seasonal allergic pattern is important because, unlike the latter, the most effective of maintenance therapies will not prevent the viral respiratory infection-induced asthma that characterizes this common intermittent pattern [44–46].

The absence of allergen-specific IgE in an infant or toddler with a pattern of intermittent viral respiratory infection-induced asthma is generally predictive of a future associated with a greatly reduced frequency of symptoms or remission over time. While most infants and toddlers with asthma have this intermittent viral respiratory infection-induced pattern, allergy testing is effective in identifying those who have an allergic component currently contributing to their disease or those who are at risk for more persistent symptoms in the future [47]. Contrary to the belief of some, there is no age limitation for allergy testing and some children can have evidence for inhalant allergy contributing to asthma even in infancy (**Figure 3**).

### Chronic

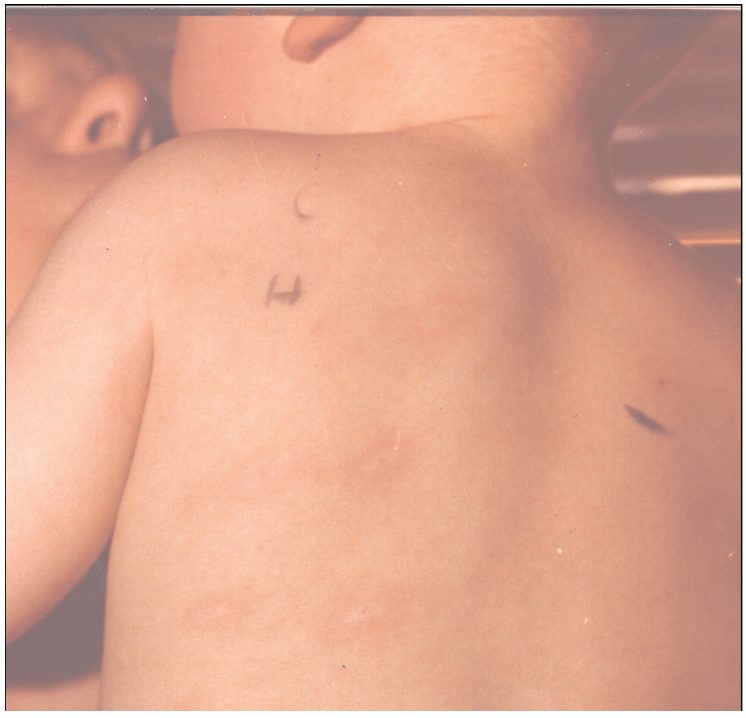
Patients with chronic asthma experience virtually daily year-round symptoms and, in the absence of effective maintenance therapy, do not have extended symptom-free periods. These children

**Figure 2. Typical autumnal increase in asthma at the beginning of the school year.**




The younger school-age children show signs of asthma first and are followed by their older siblings. Reproduced with permission from [42].

**Figure 3. This 11-month-old infant was hospitalized at 9 months of age with severe acute asthma preceded by rhinoconjunctivitis during the peak of the grass pollen season in a Northern California valley area where grass pollen is a major inhalant allergen.**



The typical wheal and flare of the multiple related species of grass pollen native to that area are seen on the left side of the infants back. They are much larger than the histamine control with no reactivity to the diluent control. Skin tests on the right side of the back to other common inhalant allergens were all negative. While immunotherapy using injections of allergenic extracts is rarely indicated at this age, this infant illustrates a striking exception where benefit could reasonably be expected.

may have begun with the viral respiratory infection-induced intermittent pattern of symptoms with subsequent evolution to persistent daily symptoms. Most, but not all, have an allergic component to their asthma.

### Seasonal allergic

These patients experience virtually daily symptoms during an inhalant allergy season. In north-central USA, this is most commonly from outdoor molds that grow on decaying vegetation from early Spring through late Fall, with peaks particularly in the Spring and Fall. In the valley areas of the Pacific northwest and northern California, grass pollens are the major allergens causing seasonal allergic asthma, generally accompanied by rhinoconjunctivitis. Allergens and seasonal patterns will vary with the geographic region. In other parts of the world, seasonal symptoms may be from molds, pollens, flying insects or a combination of those airborne allergens.

There is potential overlap among these clinical patterns. For example, patients with chronic disease often have intermittent exacerbations from viral respiratory illness and may have seasonal allergic exacerbations. Nonetheless, identification of the clinical pattern contributes to the determination of a therapeutic strategy.

### Severity

All of the above clinical patterns can vary in severity from trivial to life-threatening. Questions to assess severity include:

- Do respiratory symptoms interfere with sleep?
- Do respiratory symptoms interfere with activity?
- Frequency of rescue medication with bronchodilator and systemic corticosteroids;
- Frequency of urgent care requirements to a physician's office or emergency room;
- Frequency of hospitalization;
- Requirement for intensive care;
- Requirement for ventilatory assistance;
- Acute life-threatening events.

## Treatment of asthma

Treatment of asthma can be divided into two therapeutic strategies, intervention measures for acute symptoms (**Table 2**) and maintenance measures for prevention of future symptoms (**Table 3**).

### *Intervention medication*

An inhaled $\beta_2$ agonist is typically the initial intervention measure for acute symptoms. While older children can generally use a metered-dose inhaler (MDI) successfully, use of a nebulizer in young children and in emergency rooms has been common. However, the MDI utilized in young children with a valved holding chamber can provide equal or better efficacy in the emergency care setting [48,49]. The simplicity, more rapid administration, lower cost and the greater portability of the MDI with a valved holding chamber for younger children, have made this the method of choice for aerosol administration in children under 6 years of age with asthma. Whether nebulizer or MDI with a valved holding chamber is used, proper instruction and a tight fitting mask for those too young to seal their mouth on a mouthpiece are essential. Additionally, it is important to realize that a crying child gets little medication by either method.

**Table 2. Intervention medication: dosage and decisions for usual treatment of acute symptoms of asthma.**

| Medication | Dosage | When to use |
|---|---|---|
| Albuterol (salbutamol), levalbuterol terbutaline, or pirbuterol by metered dose inhaler *(see* **Figure 4** *for administration issues)*. | Two to four inhalations is usual, but up to six inhalations can be used (one at a time) and is equivalent to the most common dosage by nebulizer. | As needed for cough, wheezing and labored breathing. Scheduled use has no advantage over use as needed and may be deleterious for some patients. Repeated requirements for bronchodilator use during an exacerbation generally warrants a short course of an oral corticosteroid. |
| Prednisone, prednisolone, methylprednisolone and dexamethasone as tablets. Liquid formulations and oral disintegrating tablets of prednisolone for young children (*parenteral forms indicated only when concerned about oral retention)*. | Dosage as prednisone or prednisolone: see **Table 1**. | If bronchodilator subresponsiveness is identified by incomplete resolution of symptoms and signs from even repeat use of the bronchodilator, continue till asymptomatic; re-evaluate if not improving within 5 days or asymptomatic within 10 days. Don't taper [63–65]. |
| Ipratropium aerosol | 0.5 mg with 2.5–5 mg albuterol by nebulizer. | Indicated for severe acute asthma in the emergency room or hospital when response to a $\beta_2$ agonist is inadequate for relief of respiratory distress. |

While providing rapid onset of bronchodilatation, the $\beta_2$ agonists do not alter the inflammatory component of asthma that contributes to airway obstruction by causing mucosal edema and mucous secretions.

Albuterol (salbutamol) is the most common of these medications. A closely related pharmacologic agent that is essentially a therapeutic equivalent to albuterol, pirbuterol, is present in the Maxair Autohaler® (Graceway Pharmaceuticals, MN, USA). This device activates with an inspiratory effort, thereby eliminating the need to coordinate manual activation with inspiration. A similar device by Teva Pharmaceuticals is marketed outside the USA with anticipated US marketing in the near future. Marketing of the active optical isomer of albuterol, levalbuterol, has focused on the potential for the traditional racemic preparation of albuterol to have adverse effects that are not present with levalbuterol. However, clinical studies have not supported this claim [50,51], and levalbuterol should be considered just as

**Table 3. Maintenance medication: initial dosage and decisions for treatment of persistent symptoms of chronic or seasonal allergic asthma.**

| Medication | Dosage | When to use |
|---|---|---|
| Inhaled corticosteroid | Flovent 44 HFA® MDI (fluticasone suspension aerosol), two inhalations b.i.d.<br>QVAR 40® MDI (beclomethasone solution microaerosol), two inhalations b.i.d.<br>Pulmicort Flexhaler® (budesonide dry powder inhaler), one inhalation b.i.d. | First-line medication for persistent symptoms; use the Flovent or QVAR MDI with a valved holding chamber and mask for infants and toddlers; most can use a chamber without a mask by 4 years of age; the dry powder inhaler formulations can be used effectively in most children by 6 years of age. |
| Montelukast | 4 mg sprinkle, 4 and 5 mg chewable, or 10 mg tablets (similar blood levels for each) once daily. | An alternative to an inhaled corticosteroid for mild persistent symptoms; modest additional benefit as an add-on to inhaled corticosteroids. |
| Long-acting $\beta_2$ agonist | Advair 100/50® (fluticasone/salmeterol dry powder inhaler) one inhalation b.i.d. or Symbicort® (budesonide/formoteral MDI), two inhalations b.i.d. | When a conventional dose of inhaled corticosteroid does not maintain control; monitoring for the occasional patient made worse from the addition of long-acting $\beta_2$ agonist is essential. |
| Slow-release theophylline | Begin with 10 mg/kg/day divided b.i.d. to a maximum of 150 mg b.i.d.; increase in increments if tolerated to 16 mg/kg/day to a maximum of 300 mg b.i.d.; monitor serum theophylline concentrations to attain peak serum concentrations of 10–15 μg/ml [95]. | As an additive agent to an inhaled corticosteroid for the occasional patient where a long-acting $\beta_2$ agonist worsens rather than improves asthma control. Awareness of drug interactions and effect of fever on theophylline levels is essential for safety [95]. |

*Acute exacerbations, especially when induced by viral respiratory infection, require the intervention measures in* Table 2.
*b.i.d.: Twice daily; MDI: Metered-dose inhaler.*

therapeutically equivalent to the racemic preparation when given in a dosage equivalent to the levalbuterol component of racemic albuterol, specifically 2 mg of racemic albuterol contains 1 mg of levalbuterol, the active optical isomer [52]. The one study suggesting therapeutic advantage over racemic albuterol for children with acute asthma seen in an emergency room [53] was not supported in two subsequent studies [54,55].

Since the $\beta_2$ agonists do not alter the inflammatory component of airway obstruction, anti-inflammatory therapy is essential to relieve airway obstruction that is subresponsive to bronchodilators. Inhaled corticosteroids, even in high doses, have been shown to be ineffective for acute exacerbations of asthma [56], most of which are caused by viral respiratory infections [57]. In contrast to the little or no effect of inhaled corticosteroids on acute exacerbations of asthma, several studies have demonstrated that early aggressive use of systemic steroids provides impressive clinical benefit for children having an acute exacerbation of asthma [58–62].

Early administration of systemic corticosteroids for acute asthma permits earlier discharge from the hospital [58], decreases the likelihood of admission in patients coming for emergency care of asthma [59,60], and prevents progression of exacerbations of asthma in ambulatory patients at risk for requiring urgent care [61]. These courses of oral corticosteroids average 5–7 days and should not exceed 10 days. Tapering is not indicated [63–65]. Additionally, administration of oral corticosteroids during the early symptoms of a viral respiratory infection prevents progression to severe acute asthma in children with a history indicating a high risk for requiring hospitalization [62]. Despite previous controversies regarding the use of oral corticosteroids [66], consideration of the data reviewed above now support early administration of systemic corticosteroids as the standard of care for acute exacerbations of asthma [67]. Concerns regarding the sometimes repeated requirements for short courses of oral corticosteroids for viral respiratory infection-induced exacerbations that young children frequently experience have been examined, and sustained adverse effects appear not to occur [68].

The most appropriate place to treat acute symptoms of asthma is where they occur, at home, at school or at play. Treatment in the doctor's office, emergency room or hospital should generally be considered as damage control for manifestations of treatment failure. In point of fact, the most effective measures for treating acute asthma are inhaled and oral medications. These measures are more effective when used prior to the need for urgent medical care than waiting until evaluation and treatment is performed in the emergency room, clinic or physician's office.

When care is required in the emergency care setting, ipratropium, an anticholinergic aerosol, has been of value when added to inhaled albuterol for severe acute asthma not fully responsive to albuterol alone [69]. However, it has no documented clinical role in ambulatory patients. Intravenous magnesium may also have some value for severe acute asthma, although routine use is not indicated [70,71]. Oxygen is also indicated to correct hypoxemia. Measurement of pH and $pCO_2$ is indicated when hypoxemia is present. Early in the course of acute asthma, ventilation–perfusion mismatching causes hypoxemia. As airway obstruction progresses, $pCO_2$ may gradually increase. This constitutes respiratory failure. While ventilation–perfusion mismatching requires only continued oxygen and pharmacologic intervention measures, respiratory failure requires admission to an intensive care setting where assisted ventilation is available if sufficiently rapid reversal of the airway obstruction does not occur.

### *Maintenance medication*

Maintenance medication is indicated for those with chronic asthma and for those with prolonged seasonal allergic asthma. The goal is to safely utilize daily medication that effectively suppresses asthmatic symptoms and maintains normal lung function. Inhaled corticosteroids have become the maintenance medication with the greatest degree of efficacy. In pre-school age children with persistent asthma, these agents can be effectively delivered by both MDI via a valved holding chamber (**Figure 4**) and by nebulizer, with efficacy in decreasing asthmatic symptoms [72–74]. Although an aerosol corticosteroid is available as a nebulizer solution (Pulmicort Respules, AstraZeneca LP, DE, USA), there is no evidence that this offers any therapeutic advantage over the simpler and more rapid administration from a pressurized MDI with a valved holding chamber. Whichever inhaled corticosteroid preparation is used, careful attention to individualized instruction is essential for efficacy. For infants and toddlers, a tight fitting mask [75] and quiet breathing are required for effective delivery as a crying child gets little delivery of aerosolized medication to the lungs [76].

**Figure 4. Children using a pressurized metered dose inhaler.**

Upper left: Note mist leaking from child's mouth illustrating the difficulty young children have coordinating use of metered-dose inhalers (MDIs) even when cooperative. Upper middle: Maxair Autohaler® is a pressurized MDI that actuates automatically upon inspiration. Upper right: MDI through AeroChamber® with a mouthpiece (a mask is not needed for this 5-year old girl). Lower left: MDI through AeroChamber with soft flexible face mask. Lower middle: MDI through Pari Vortex® with soft flexible face mask. Lower right: Proper hand position to maintain seal of face mask for a child who wiggles (the hand and mask will move with the face).

Although there is evidence for dose-related systemic effects [77], conventional low doses have an established safety record [78,79]. A minimal degree of hypothalamic–pituitary axis suppression and a small degree of transient growth suppression is detectable at modest doses, but neither clinically detectable adverse effects nor sustained effect on growth are apparent except at higher doses [80]. Montelukast has potential benefit for some with milder manifestations of asthma [81] and also has some additive effect with inhaled corticosteroids [82]. However, the additive effect of montelukast does not appear to be as great as is seen with a long-acting inhaled $\beta_2$ agonist (LABA) [82]. Adding a LABA to an inhaled corticosteroid is generally more effective than a higher dose of the inhaled steroid [83,84]. However, concerns have been raised regarding tolerance to the subsequent bronchoprotective effect of inhaled $\beta_2$ agonists with continued stimulation of the $\beta_2$ adrenergic receptors [85,86].

A small subset of patients appear to be at particular risk for adverse effects from LABAs. Increased fatalities associated with LABAs has been reported and resulted in a US FDA 'black box' warning regarding this class of medications [87,88]. A report of two patients who had life-threatening symptoms and were poorly responsive to $\beta_2$ agonist bronchodilators while receiving salmeterol had dramatic improvement after stopping the salmeterol [89]. This was consistent with studies showing that certain genetic polymorphisms of the $\beta_2$-receptor were associated with downregulation of that receptor during regular administration of $\beta_2$-adrenergic agents [90–94]. Theophylline is an alternative additive agent with similar efficacy to the addition of a LABA, although less convenient to use [95]. Rational medication selection and careful monitoring of the patient with regularly scheduled return visits permits optimal management for meeting criteria for control.

Immunotherapy (allergy shots) can provide benefit for asthma in highly selected cases where the symptoms can be convincingly related to a limited number of well-defined inhalant allergens to which immunotherapy has been shown to be of benefit [96,97]. Another measure of

potential benefit for the allergic component of asthma is the monoclonal anti-IgE preparation, omalizumab (Xolair®). Although quite costly, severely symptomatic asthma that has a major allergic component may benefit substantially from this medication (**Figure 5**) [98].

## Environmental considerations

Of relevance to the characterization of asthma is an assessment of the environment and its role in contributing to symptomatology. The following questions can quickly identify the presence of relevant allergens and irritants:

- Urban or rural home
- Age of home
- Presence of a basement and dampness or water leakage problems
- Forced air heating; central air conditioning
- Pets in home
- Smokers in home
- Nearby industrial or agricultural source of air pollution

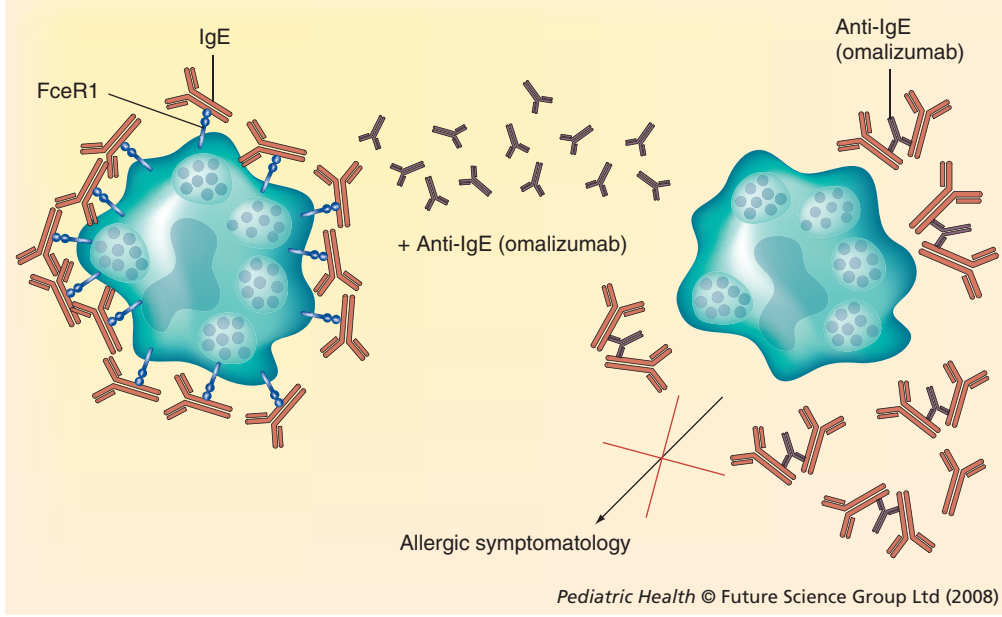
Rural homes, especially those on a farm, can result in more intense exposure to outdoor molds during procedures that stir up decaying vegetation, such as in harvesting. Very old homes may be plagued by indoor mold, especially if there is a basement with dampness or water leakage. Forced air heating can distribute aeroallergens throughout the home but also provides an opportunity to utilize a high efficiency air filter to minimize aeroallergens in the indoor environment. Pets are a common contributing factor to asthma, but these family members should not be blamed for symptoms without demonstrating allergen-specific IgE and obtaining a convincing history that exposure contributes to morbidity. Indoor fireplaces and outdoor bonfires or leaf burning are important nonallergenic major irritants that contribute to asthmatic symptoms. Exposure to tobacco smoke is a major irritant that increases the frequency and severity of acute and chronic asthmatic symptoms (**Figure 6**) [3].

Clinically important aero-allergens vary with the region and include pollens, outdoor and indoor molds, animal dander, cockroaches and dust mites. Knowledge of allergen-specific IgE in the patient and the aerobiology of the patient's environment are essential to assess the importance of this component.

## Treatment of co-morbidities

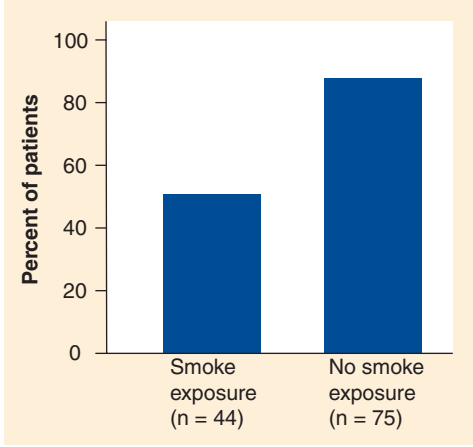
Treating co-morbidities may also benefit the control of chronic asthma. This is suggested for chronic rhinitis treated with topical nasal

**Figure 5. Mechanism of omalizumab (Xolair®), a humanized anti-IgE that binds to the portion of the IgE molecule that would otherwise attach to the high-affinity IgE receptor (FcεRI) on mast cells.**




Small inert circulating complexes of IgE and anti-IgE result, and the mediator release that would occur from allergens attaching to IgE on mast cells cannot occur.

**Figure 6. Patients meeting criteria for control of asthma during a 1-year observation period.**




Patients meeting criteria (as defined in **Box 1**) during care in a specialty care program among those exposed or not exposed to cigarette smoke. Cigarette smoke exposure was associated with a significantly lower likelihood of meeting criteria for control despite receiving care at the same specialty clinic ($p < 0.001$).
Adapted from [3].

steroids [99], although the validity of that report has been questioned [100]. There is a great deal of controversy regarding the role of sinusitis and gastroesophageal reflux as comorbities that contribute to asthma. While both sinusitis and gastroesophageal reflux are associated with asthma, evidence that treating them benefits asthma is only anecdotal [101–103]. While chronic rhinitis should be treated with topical nasal steroids in patients experiencing discomfort from nasal congestion, and gastroesophageal reflux should be treated in those experiencing the substernal discomfort associated with that disorder, there is little reason to expect clinically important benefit for the asthma itself. As to sinusitis, symptoms attributed to that disorder are predominantly those of rhinitis, and there is little correlation between radiological evidence of sinusitis and clinical symptomatology [101,104–105].

**Box 1. Criteria for control of asthma.**

- Absence of hospitalization
- Absence of urgent-care requirements
- Absence of interference with sleep
- Absence of interference with activity
- Infrequent use of inhaled $\beta_2$ agonists for acute symptoms
- Infrequent use of oral corticosteroids (except for unavoidable viral respiratory infection-induced exacerbations)
- Normal or near normal pulmonary function by spirometry

## Monitoring the clinical course

Successful management of asthma does not stop with writing the prescriptions. There should rarely be a need to see the patient during acute symptoms, since the patient or family should have been taught, with verbal and written instructions, successful management by use of the inhaled bronchodilator for symptom relief, and early intervention with a short course of systemic corticosteroid for an exacerbation identified by sub-responsiveness to the inhaled $\beta_2$ agonist. However, scheduled return visits are essential to review adherence to the treatment plan, to check inhaler technique, to assess if the patient meets criteria for control (Box 1), and to make adjustments in treatment when appropriate to meet those criteria with the least amount of medication.

While the peak flow meter is touted by some as a useful means for monitoring a patient, the weight of evidence indicates that symptom monitoring (and consequent need for intervention with an inhaled $\beta_2$ agonist) has been demonstrated to be generally equal to [107,108] or better [109,110] than peak flow monitoring in providing early warning of an exacerbation that requires intervention. The only patients where a home peak flow meter might be useful are the occasional underperceiver, usually with very severe chronic asthma, who does not recognize worsening airway obstruction, or the overperceiver, who confuses anxiety or hyperventilation attacks with asthma.

There is current interest in the utilization of exhaled nitric oxide as a marker of asthmatic inflammation [111,112]. Although the commercial device available to measure exhaled nitric oxide may have some clinical usefulness, troublesome asthmatic inflammation is generally adequately detectable by the presence of active symptoms and the measurement of the extent to which pulmonary function does not fully reverse with a bronchodilator.

General medical care for asthma should include routine immunizations, particularly the varicella vaccine. The varicella vaccine is important because of the small but serious risk of disseminated varicella that has been reported when the infection is incubating during a course of high-dose systemic corticosteroids as may be necessary for exacerbations of asthma [113]. A yearly influenza vaccine is now a general recommendation for children and is especially appropriate

for children with asthma [114]. A small risk from influenza vaccine is present for those with allergy to egg. However, the presence of clinically important adverse affects appears unlikely [115].

The best decision-making by the physician willl fail unless family and/or patient is adequately educated about the benefits and risks, if any, of each medication and in the implementation of the treatment plan [202]. Of special importance is having a simple written action plan that deals with periods of increased symptoms and exacerbations (**Box 2**). There is no advantage to complex plans with traffic light cartoon illustrations [116]. Seasonal allergic increases in symptoms may warrant an increase or additional maintenance medication. Viral respiratory infection-induced symptoms are likely to require a short course of oral corticosteroids.

## Evaluating & managing difficult asthma

Difficult asthma is that which does not meet criteria for control despite appropriate therapy [203]. The reason for such poor control is variable. In some cases, the asthma is truly poorly responsive to usual measures. However, more often, poor control is a result of poor adherence to the medical regimen. When poorly controlled symptoms of asthma are present despite appropriately prescribed medication, adherence to the prescribed medication can be verified by asking for a record of medication refills from their pharmacy. For example, a month's supply of the maintenance medication that lasted 6 months can readily explain inadequate control. The technique of using inhaled medication can also be an issue. Observing technique during a routine office visit can be both revealing and provides an opportunity for appropriate education. In some cases, poor control is because the patient does not have asthma at all – the symptoms are from some other problem with symptoms that mimic those of asthma [36] (see comments in the above section on Diagnosis of Asthma). Placing the difficult patient in a hospital situation for a period of time to observe the patient around-the-clock may be necessary in some cases to sort out these various confounding problems.

## Natural history of asthma

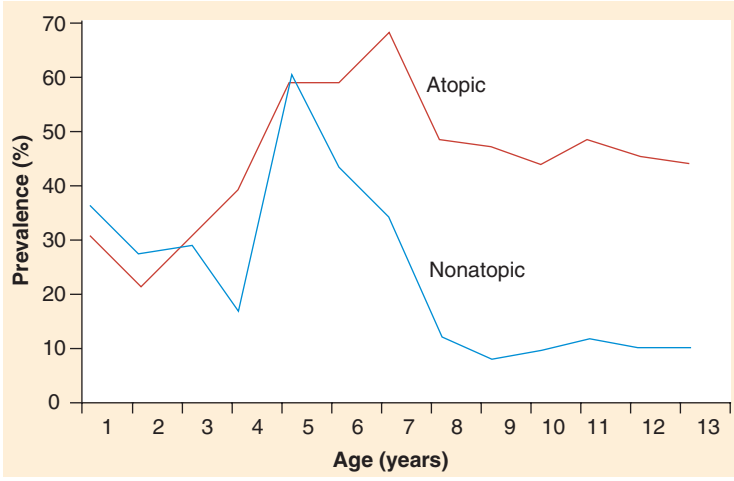
Will my child outgrow the asthma? This is a frequently asked question. In the preschool age child with episodic wheezing, the presence of atopy identified by the presence of allergen-specific IgE is highly associated with continued symptoms throughout childhood, while those with no presence of a potential allergic component are likely to have marked reduction or cessation of asthmatic symptoms by school age (**Figure 7**) [117].

The long-term clinical course of asthma in young children has been impressively examined in a prospective study with repeated evaluations for 35 years [118]. In 1963, all children aged 6 to 7 years in Melbourne, Australia, had a medical examination upon entering school that included a

**Box 2. Intervention action plan handout for acute exacerbations of asthma.**

- Acute symptoms of asthma including cough, wheeze, or shortness of breath should be dealt with promptly. They are particularly likely with a viral respiratory infection (common cold). Increasing cough following a day of runny nose is often the first sign of asthma triggered by a viral respiratory infection. While regularly taking medication will not prevent the acute flare of asthma from a viral respiratory infection, prompt intervention can shorten the course and generally prevent the need for urgent medical care or hospitalization.
- First: use your inhaled bronchodilator.
- If symptoms stop completely: repeat inhaled bronchodilator when necessary; consider a short course of oral corticosteroid after third dose for acute symptoms within 8 h or if more than four in 24 h (other than for preventative use before exercise).
- If symptoms are not completely relieved: repeat inhaled bronchodilator
- If symptoms still not completely relieved: a short course of oral corticosteroids may be needed. If uncertain what to do, call for advice. Otherwise, take first dose of oral corticosteroid and contact us (dosage and instructions should already be on hand).
- Response to oral corticosteroids is slow. In patients who have required emergency care or hospitalization, oral corticosteroid should be started at least 12 to 24 h before symptoms become that severe.
- Once corticosteroids are begun, inhaled bronchodilator can be repeated when needed.
- Maintenance medications should be continued.
- Continued increase in the frequency of inhaled bronchodilator use or continued difficulty breathing may require hospitalization. Call us if there is continued difficulty breathing. Frequent intervention treatment for episodes of asthma requires reassessment of the management plan.

**Figure 7. Prevalence of symptoms by age in atopic and nonatopic asthma.**




Reproduced with permission from [117].

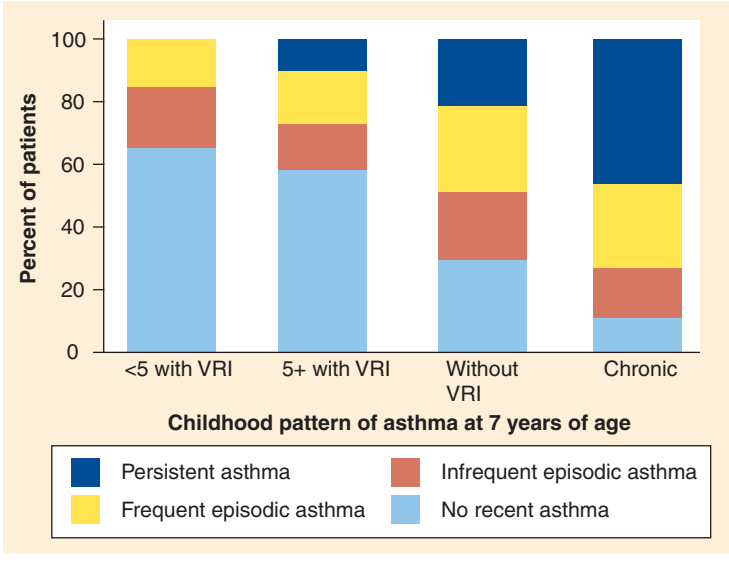
short questionnaire and interview. As part of that questionnaire, parents were asked if their child had experienced episodes of wheezing or asthma and whether that had been associated with symptoms of a viral respiratory infection. Based on that survey, an overall community prevalence for asthma symptoms in childhood was estimated to be approximately 20%, a rate similar to that described more recently in the USA [119,120]. A stratified sample was then randomly selected the following year from the approximately 30,000 7-year old children in the survey. This included 105 second graders who had never wheezed to serve as controls, 75 with less than five episodes of previous wheezing with viral respiratory infections, 104 with five or more episodes of previous wheezing with viral respiratory infections, and 113 with recurrent wheezing not limited to association with viral respiratory infections. The investigators also entered 83 children from the same population who had severe chronic asthma since before 3 years of age with persistent symptoms, barrel chest deformity, and/or forced expiratory volume in 1 sec that was 50% or less than the forced vital capacity. The children were re-evaluated at ages 14, 21, 28, 35 and 42 years (**Figure 8**) [121–124].

Of the sample followed longitudinally, 75% had infrequent episodes while 25% had frequent episodes. Of the initial children with asthma, 40% were free of respiratory symptoms by 10 years of age and 50% were asymptomatic by 14 years of age. The remainder continued into adult life, but symptoms were frequently not troublesome and present only with viral respiratory infections or exercise for many. However, 10% who had ceased wheezing in childhood had recurrences as young adults, and some of those had troublesome symptoms. The group with severe chronic asthma had growth failure and delayed puberty but eventually attained normal adult height. While 50% of that group with severe chronic asthma improved considerably at puberty, only 5% became totally asymptomatic.

When the subjects were examined at 42 years of age, a correlation between the nature of the symptoms in childhood and the subsequent outcome was apparent (**Figure 8**). Over half of those with symptoms of asthma limited to an association with viral respiratory infection prior to 7 years of age were asymptomatic at 42 years of age. Others were still having episodic asthma, and a few had developed persistent asthma. The frequency of all patterns of active asthma at 42 years of age was greater among those in whom wheezing without viral respiratory infections had been reported in childhood. Approximately half of those with severe chronic asthma as children continued to have persistent symptoms at 42 years of age with only 11% of that group reporting no recent asthma.

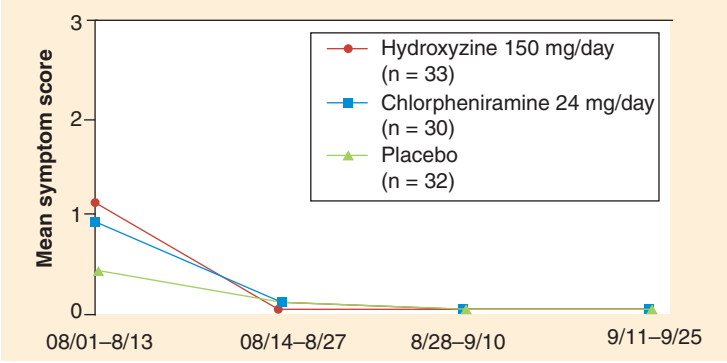
There has been speculation that early treatment with inhaled corticosteroids could modify the course of subsequent asthma. The hypothesis that inhaled steroids for episodic wheeze might alter the subsequent course of asthma was examined in a randomized, double-blind study of infants without demonstrable benefit either for acute symptoms or the frequency of recurrent episodes [125]. This

**Figure 8. Clinical expression of childhood asthma at 42 years.**




VRI: Viral respiratory infection.
Adapted from [118].

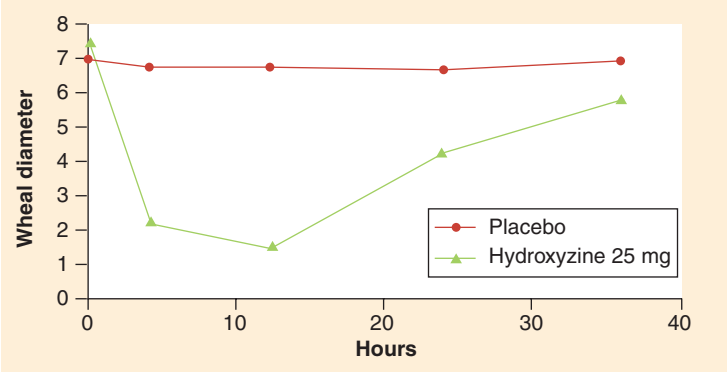
**Figure 9. Assessment of sedative effects.**




Double-blind, placebo-controlled study with gradually increasing doses of hydroxyzine from 25 mg at bedtime to 75 mg twice daily, and chlorpheniramine from 4 mg at bedtime to 12 mg twice daily during the mid-west ragweed season.
0 = none; 1 = present but annoying; 2 = annoying but no interference with activities; 3 = interence with activities.
Both provided suppression of rhinoconjuncitivitis to a much greater extent than placebo, with hydroxyzine somewhat more effective than chlorpheniramine. While 50% of subjects complained of some sedative effects during the first 2-week period on both antihistamines compared with 30% having similar complaints on placebo, none found it sufficiently troublesome to discontinue medication, and there was no sedation observed during the subsequent 6 weeks of the ragweed season.
Adapted from [133].

hypothesis has also been tested in a group of 2- and 3-year old children randomly assigned to receive fluticasone aerosol or placebo over a 1-year period. While symptoms were significantly less in the inhaled corticosteroid-treated group, the frequency of asthmatic symptoms became identical to the placebo-treated group once the inhaled corticosteroids were stopped, indicating the absence of any sustained effect on the disease [126].

**Figure 10. Time course of a single 25 mg dose of hydroxyzine.**




Sedative effect appears to be limited to a period approximately 2–6 h after a dose, while antihistamine effect as measured by suppression of histamine induced wheal lasts for more than 24 h.
Adapted from [136].

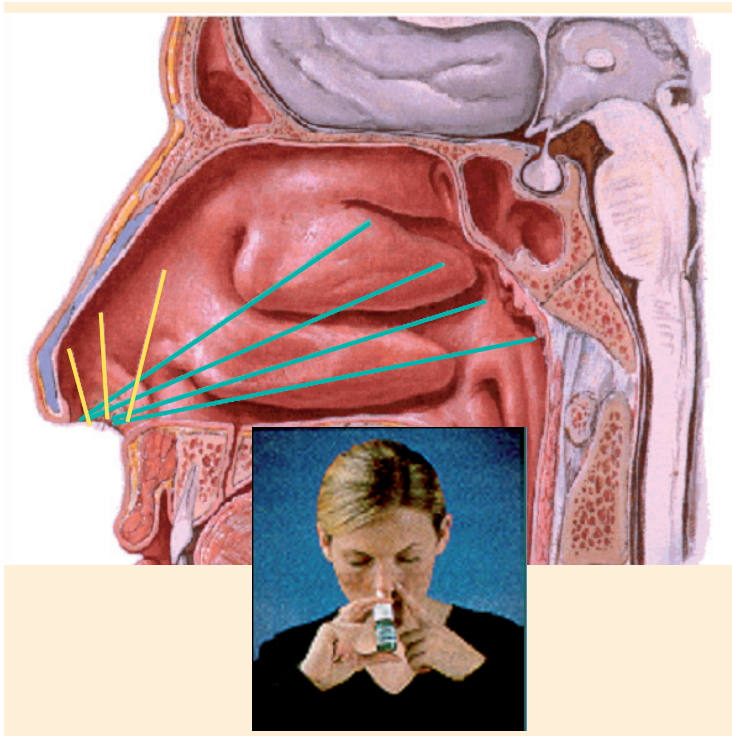
## Rhinitis

Rhinitis is commonly associated with asthma in addition to being a prevalent independent airway inflammatory disorder. It is associated with symptoms that can include, to varying degrees, rhinorrhea, sneezing, itchy nose, postnasal drainage and obstruction of the nasal passages. Symptoms can be induced by inhalant allergens and can be accompanied also by allergic conjunctivitis. However, nonallergic chronic rhinitis is quite common, resulting in many of the same nasal symptoms. Acute rhinitis from common cold viruses frequently precedes viral respiratory infection-induced asthma. The frequency of acute viral rhinitis from common colds in young children can result in the false impression of chronic rhinitis during the season of peak viral respiratory infections.

Treatment options for acute viral rhinitis are limited. Pseudoephedrine has a modest effect on nasal obstruction [127]. Oral phenylephrine, substituted recently for pseudoephedrine in many nonprescription cold preparations, does not decrease nasal airway resistance and will thus be ineffective at decreasing symptoms of nasal stuffiness [128]. Other ingredients in common nonprescription cold preparations have little benefit [129]. Topical nasal decongestants, such as oxymetazoline, can rapidly relieve nasal stuffiness, but prolonged usage is associated with rebound congestion. Ipratropium, a topical anticholinergic (Atrovent® nasal spray), stops rhinorrhea from all causes, including the common cold [130,131], although it has no effect on nasal stuffiness.

Treatment options for chronic rhinitis, allergic or nonallergic, include antihistamines and topical nasal steroids. Antihistamines have their predominant effect on conjunctivitis, sneezing, itchy nose and rhinorrhea with little effect on nasal stuffiness. While so-called second-generation antihistamines are associated with little or no sedation with initial therapy, sedation from the much less expensive classical antihistamines is transient, even in higher than usual doses (**Figure 9**) [132,133]. A classic antihistamine, hydroxyzine, appears to have the most favorable pharmacodynamic effects with a greater intensity and duration of action than others [134,135]. Initial sedation from hydroxyzine appears to be from 2–6 h after a dose, while duration of suppression of a histamine-induced wheal is 24 h (**Figure 10**) [136]. This permits the strategy of beginning doses at bedtime to minimize even the initial sedating effect. Increases can then be given if needed and tolerated. Of the second-generation

**Figure 11. Lateral nasal wall illustrating the common vertical direction (yellow lines) of a nasal spray that occurs when a patient is not appropriately instructed.**



Green lines illustrate the proper direction that will reach the posterior nasopharynx and all turbinates. A head down position permits the near vertical position for the spray device to operate properly while aiming towards the occiput.

antihistamines, cetirizine, an active metabolite of hydroxyzine, has been demonstrated to have greater potency than desloratadine, an active metabolite of the popular loratadine [137].

While antihistamines can be useful agents for chronic nonallergic rhinitis and allergic rhinoconjunctivitis, topical anti-inflammatory corticosteroids are even more effective and are the agents of choice for nasal airway obstruction [138]. Administration of a topical vasoconstrictor such as phenylephrine or oxymetazoline, provides a quick and easy test in the physician's office to distinguish anatomic nasal obstruction, for example, from enlarged adenoids or choanal stenosis, from inflammatory changes that cause swelling of the nasal mucous membrane and turbinates. Engorged nasal mucosa from inflammation will shrink within minutes of applying the vasoconstrictor. Failure to substantially improve nasal airflow warrants referral to an otolaryngologist. Prompt improvement in nasal airflow is predictive of success from treatment with a properly delivered topical nasal steroid.

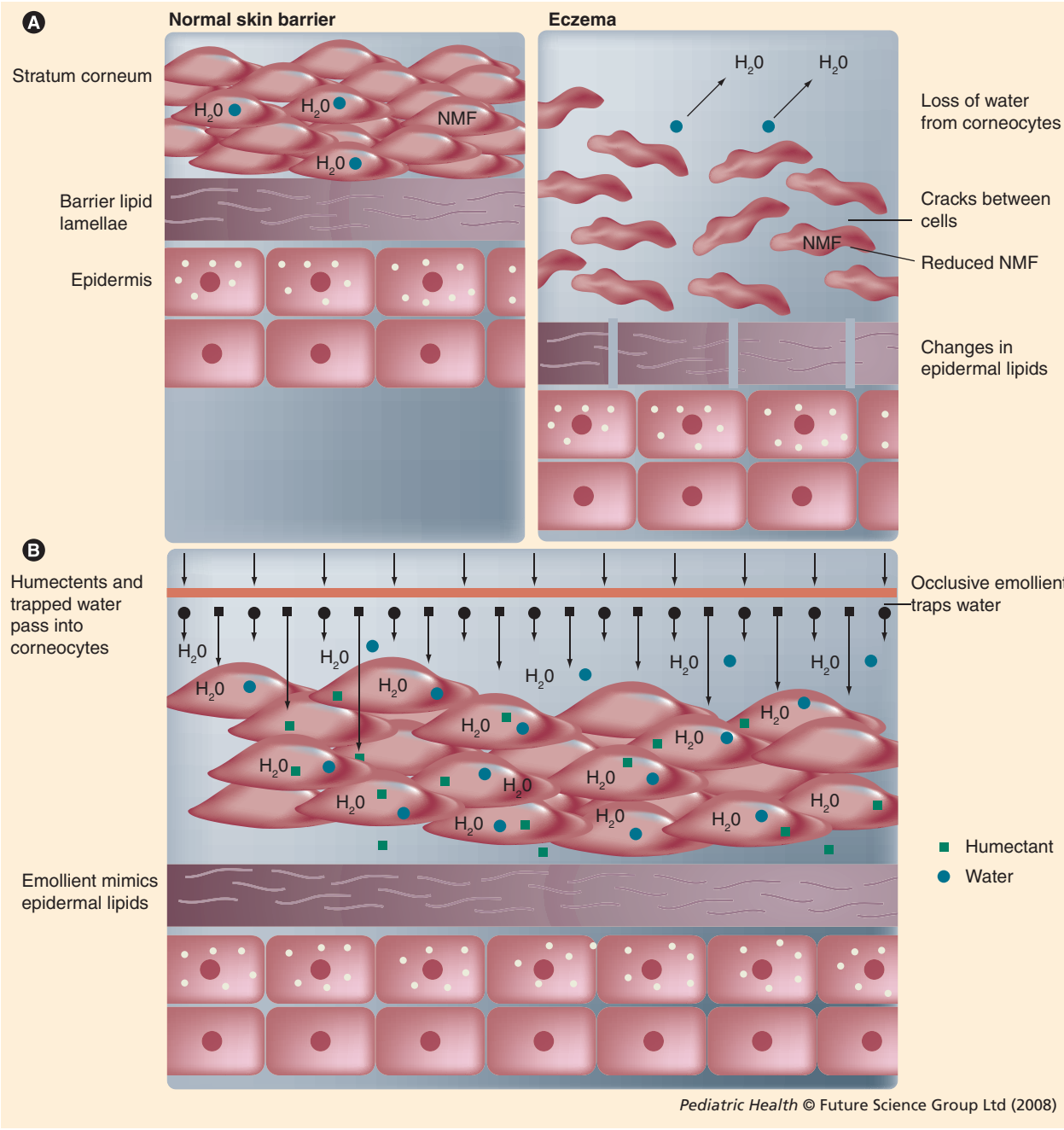
Failures from use of topical nasal corticosteroids are frequently caused by incorrect usage. While patients tend to assume the nasal passage is vertical and spray upward, the nasal passage actually goes posteriorly, and the nozzle of the spray needs to be aimed towards the occiput. To satisfactorily aim the spray towards the posterior nasopharynx, the head must be down so that the device is in a near vertical position (**Figure 11**). Treating chronic rhinitis with topical nasal steroids has been reported to benefit coexisting asthma [99], although the validity of that report has been questioned [100].

## Atopic eczema

Atopic eczema, also known as atopic dermatitis, is a chronic relapsing inflammatory skin rash characterized by dry skin and extreme pruritus [23]. Since the pruritus leads to extensive excoriation and worsening dermatitis, it is often called 'the itch that rashes' [139]. Symptoms most frequently have onset in infancy. It has a characteristic distribution that changes with age. There is a frequent association with IgE-mediated food and inhalant allergy. The inhalant allergy can be associated with asthma and/or allergic rhinoconjunctivitis. Approximately two-thirds of children remit after 3 years of age, but the remaining third can continue the problem into adult life. Even those who remit frequently continue to have the xerosis and sensitivity of the skin that is typically part of the disorder. Whether or not the atopic dermatitis remits, these children are at high risk for developing allergic asthma and/or rhinoconjunctivitis.

The food allergy that is so commonly associated with atopic dermatitis can result in anaphylactic reactions or less dramatically apparent reactions that just increase pruritus and worsen the eczema. Since these less dramatic reactions may not be readily apparent without a supervised challenge, allergy testing is indicated for eczema that is difficult to control in the form of skin prick testing or *in vitro* tests that identify and quantitate allergen-specific IgE to foods. The most common foods to which children with atopic dermatitis develop allergen-specific IgE are milk, egg, soy, peanut and wheat, but other foods can also be involved. Since the majority of children with atopic dermatitis do not have foods contributing to their skin disease, blind elimination is unlikely to provide clinical benefit [140]. However, since approximately 40% of children with moderate-to-severe atopic dermatitis who attended a

**Figure 12. The normal skin barrier and the lack of the natural moisturizing factor, ceramide and perhaps other substances in eczema.**




The lower figure illustrates the goal of absorbing water into the skin and retaining it with an emollient barrier, with the goal of restoring normal skin architecture and eliminating the xerosis that contributes to the severe pruritus of atopic dermatitis.
NMF: Natural moisturizing factor.

university pediatric dermatology clinic were found to have food allergy; evaluation and management can substantially contribute to the management of those children [141]. This involves, first, identification of allergen-specific IgE to foods, and then confirming the clinical relevance of those foods for atopic dermatitis by a medically supervised food challenge for those foods where no history of an anaphylactic reaction is obtained.

Dry skin (xerosis), appears to be the result of a deficiency of ceramide, which is responsible for retaining water in the skin [142]. Associated with

## Executive summary

### *Introduction*

- Asthma is the most common chronic disease of children.
- Asthma causes more hospitalizations than any other medical problem in children.
- Asthma is associated with rhinitis and atopic dermatitis as important co-morbidities.

### *Diagnosis of asthma*

- Asthma is both under- and over-diagnosed.
- There are conflicting definitions of asthma, particularly in young children, but a common definition can be applied to this complex of clinical patterns with similar end-organ responses.

### *Clinical characteristics of asthma*

- Intermittent asthma is most commonly a viral respiratory infection-induced phenotype in pre-school age children, but is seen at all ages.
- The chronic phenotype is characterized by the absence of extended symptom-free periods.
- The seasonal allergic phenotype is characterized by being limited to seasons that correspond to allergen-specific IgE released in response to seasonal inhalant allergens.

### *Severity of asthma*

- Interference with activity from exercise limitation.
- Interference with sleep from repeated nocturnal waking.
- Frequency of requirements for intervention measures, inhaled bronchodilators and oral corticosteroids.

### *Treatment of asthma*

- Intervention measures for relief of acute symptoms, albuterol and oral corticosteroids.
- Maintenance medications for those with chronic or extended seasonal symptoms, inhaled corticosteroids, long-acting bronchodilators, leukotriene modifiers, immunotherapy and anti-IgE.

### *Treatment of co-morbidities*

- Rhinitis, allergic and nonallergic, are commonly associated with asthma but also occur independently.
- Atopic eczema, also known as atopic dermatitis, often precedes inhalant allergy-induced rhinitis and asthma.

### *Monitoring the clinical course of asthma*

- Symptom identification by patient is essential to early intervention to prevent progression of exacerbations.
- Scheduled re-evaluations for assessment and education are required to evaluate adequacy of treatment and assess adherence to the treatment plan.

### *Evaluating & managing difficult asthma*

- Determine if difficulty is poor adherence.
- Determine if diagnosis is incorrect.

### *Natural history of asthma*

- How to respond to the question, 'Will my child outgrow his/her asthma?'.
- Predicting the clinical course and outcome.

### *Rhinitis*

- Allergic and nonallergic rhinitis.
- Selection of antihistamines.
- Topical nasal steroids.

### *Atopic eczema (a.k.a. atopic dermatitis)*

- Definition, a relapsing, highly pruritic, inflammatory skin disease associated with xerosis.
- Nature of the cutaneous defect and relationship to morbidity, ceramide deficiency and defects in innate immunity.
- Moisturizing and use of emollients for skin care hydration are the mainstay of therapy.
- Topical corticosteroids and calcineurin inhibitors used judiciously are effective and safe.

### *Conclusion & future perspective*

- Asthma and its co-morbidities, often undertreated, are generally manageable with knowledgeable selection of therapy and adequate instruction of patients.
- Careful ongoing evaluation, and an understanding of the disease on the part of the patient, is essential for a successful outcome.

this defect is a defect in the innate immunity of the skin resulting in a predisposition to excessive *Staphylococcus* on the skin with an increased frequency of impetigo. There is also a predisposition to certain viral infections, including *Molluscum contagiosum*, *Verucca vulgaris*, *Eczema herpeticum* and disseminated vaccinia [143].

Treatment of atopic dermatitis involves first and foremost restoration of the skin barrier (**Figure 12**) [26]. This involves nightly soaking in lukewarm water with soap substitutes followed by application of an emollient to still-damp skin. Use of ceramide-rich lipids may improve skin barrier function and reduce severity of atopic dermatitis [144]. For the areas of active dermatitis, judicious use of topical corticosteroids, topical calcineurin inhibitors and antibiotics, combined with skin barrier restoration, can control most cases [26].

## Conclusion & future perspective

Asthma and its related disorders, rhinitis and atopic dermatitis, are chronic troubling medical problems that require careful attention to evidence-based data with a focus on the measures most likely to have the greatest impact. The care of these requires patient adherence to the medical regimens, patient education, careful ongoing evaluation and an understanding of the disease.


### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.*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