

# Atopy and Asthma

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Advanced article

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**Atopy is the genetic propensity to develop an immunoglobulin E antibody response to common allergens. The most common clinical manifestations of atopy are allergic rhinitis, asthma and atopic dermatitis. Asthma is a complex disorder of the airways, involving airway hyperresponsiveness, airflow obstruction that is at least partially reversible, and inflammation of the airways. Although atopy has been identified as the strongest predisposing factor for the development of asthma, not all asthma is allergic in nature. The overall prevalence of asthma has been increasing worldwide for the past few decades, and continues to increase globally. Guidelines for the evaluation and treatment of asthma were developed in the early 1990s, and are revised periodically as research into effectiveness of available medications emerges, and development of new therapies arise.**

## Mechanisms of Immunoglobulin E (IgE) Production and IgE-mediated Inflammation

Atopic individuals develop immunologic responses to various glycoproteins (allergens). At the cellular level, the allergen is internalised by antigen-presenting cells, including macrophages, dendritic cells and B lymphocytes (Figure 1). The allergen is then processed, and peptide fragments of the allergen are presented with class II major

histocompatibility complex (MHC) molecules of the host antigen-presenting cells to T-helper lymphocytes. This interaction results in the release of cytokines. **See also:** [Allergens](#); [Antigen-presenting Cells](#)

T-helper lymphocytes (CD4 cells) include: T<sub>H1</sub>, T<sub>H2</sub>, T<sub>H17</sub> and other cells. When CD4+ T cells that recognise the allergen are of the T<sub>H2</sub> class, cytokines including granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin 3 (IL-3), IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 are released (Figure 1). IL-4, IL-5 and IL-6 are involved in B-cell proliferation and differentiation. Activated B lymphocytes are stimulated by these cytokines to proliferate and initially secrete immunoglobulin M (IgM). **See also:** [B Lymphocytes](#); [Hypersensitivity: Immunologic](#); [Interleukins](#); [T Lymphocytes: Helpers](#)

The selective expansion of T<sub>H2</sub> cells plays a critical role in inducing the IgE synthesis and eosinophilia associated with allergic disease. T<sub>H2</sub> cells produce IL-4 and IL-13, which cause immunoglobulin gene switching to IgE and IgG4 antibody synthesis. IL-5 induces the proliferation and differentiation of eosinophils. Therefore, atopy appears to be the result of a genetic predisposition towards T<sub>H2</sub>-type responses, which results in the formation of large quantities of allergen-specific IgE. **See also:** [Immunoglobulin Gene Rearrangements](#)

After IgE antibodies specific for a certain allergen are synthesised and secreted, they bind to mast cells and basophils. When allergen is inhaled, the allergen (or a hapten–allergen complex) crosslinks these allergen-specific IgE antibodies bound to the mast cell surface that induce the mast cell to rapidly degranulate (Figure 1). **See also:** [Haptens](#); [Mast Cells](#)

## Mediators of immediate hypersensitivity

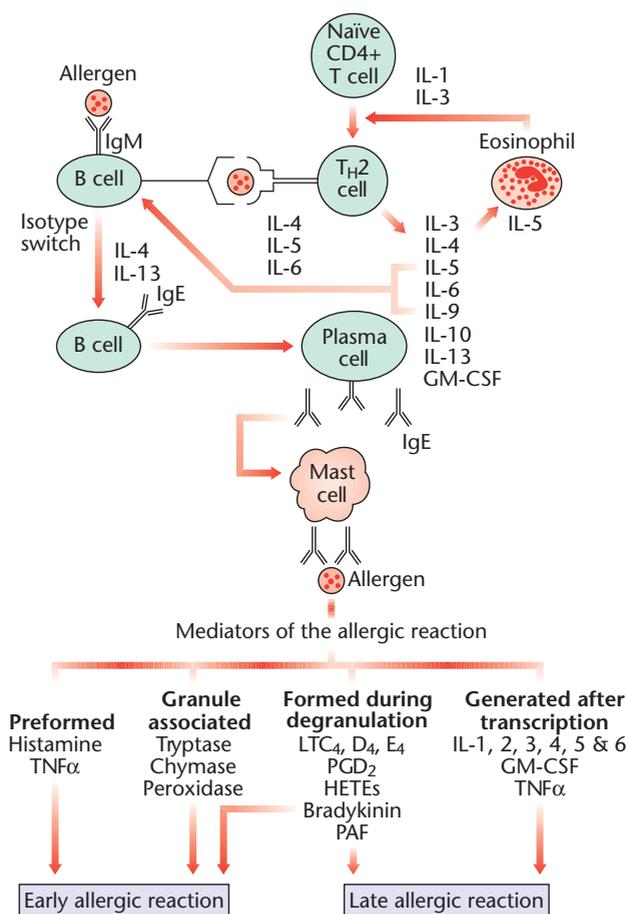
Mast cell mediators are of the following types: preformed, granule-associated, formed during degranulation or generated after transcription (Figure 1). The most important preformed mediator is histamine, which reproduces the symptoms of acute allergic asthma when inhaled by asthmatic patients. Histamine causes vasodilation, mucous secretion, bronchospasm and increased vascular

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**Figure 1** Mechanisms of allergic reaction. IL, interleukin; GM-CSF, granulocyte–macrophage colony-stimulating factor; IgE, immunoglobulin E; TNF $\alpha$ , tumour necrosis factor  $\alpha$ ; LTC $_4$ , leucotriene C $_4$ ; PGD $_2$ , prostaglandin D $_2$ ; HETEs, hydroxyeicosatetraenoic acids; PAF, platelet-activating factor.

permeability, which in turn leads to tissue oedema. **See also:** [Histamine Biosynthesis and Function](#)

Mast cells have secretory granules that contain fully active enzymes, which are released in parallel with histamine during degranulation. Tryptase is the primary granule-associated enzyme in human mast cells. Tryptase is clinically useful as a marker for acute mast cell activation during anaphylaxis, because it is elevated in the serum for at least 2–4 h. Histamine levels are maximal 5 min after mast cell release, then rapidly decline. **See also:** [Hypersensitivity: Anaphylactic \(Type I\)](#)

The activation of mast cells results in the release of arachidonic acid from cell membrane substrates. Arachidonic acid is metabolised through the cyclo-oxygenase pathway to form prostaglandin and thromboxane mediators or through the lipoxygenase pathway to form leucotrienes. Prostaglandin D $_2$  (PGD $_2$ ), the leucotrienes LTC $_4$ , LTD $_4$  and LTE $_4$ , platelet-activating factor and bradykinin are formed during degranulation. LTC $_4$ , and its metabolites LTD $_4$  and LTE $_4$ , cause bronchospasm, increased vascular

permeability and constriction of arterial, arteriolar and intestinal smooth muscle. PGD $_2$  causes vasodilation and bronchoconstriction, inhibits platelet aggregation and stimulates neutrophil chemotaxis. **See also:** [Hypersensitivity: Immunological](#)

Activated mast cells and basophils generate and release the cytokines GM-CSF, tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), IL-4, IL-5, IL-6 and IL-13, which promote further IgE production, mast cell growth and eosinophil growth, chemotaxis and survival. In turn, eosinophils secrete IL-1, which favours T $_H$ 2-cell proliferation, and the mast cell growth factor IL-3. Eosinophils release oxygen radicals and proteins, including eosinophil major basic protein, which are toxic to the mucosal tissues. **See also:** [Tumour Necrosis Factors](#)

## Immediate and late allergic reactions

Mast cells and basophils are the principal effector cells of IgE-mediated (immediate hypersensitivity) reactions. These cells bind IgE using their Fc $\epsilon$  receptors. Immediate allergic reactions are accompanied by an increase in local levels of histamine and tryptase, an enzyme produced only by mast cells. Soon after degranulation begins, arachidonic acid is mobilised and converted to LTC $_4$  in both mast cells and basophils, and to PGD $_2$  in mast cells but not basophils.

In many allergic patients, symptoms associated with the immediate reaction to allergen occur 15–20 min after exposure, only to be followed 4–8 h later by a second reaction associated histopathologically with leucocyte infiltration. Mast cell activation and mediator-cytokine secretion in the immediate reaction contribute to recruitment of basophils, eosinophils, neutrophils and macrophages. These cells produce additional inflammatory mediators and cytokines, the sum total of which is the inflammatory response. For instance, in asthmatic subjects, bronchoalveolar lavage fluid obtained several hours after inhaled allergic challenge contains histamine, tosyl-L-arginine methyl ester (TAME)-esterase activity and LTC $_4$ . Mast cell products PGD $_2$  and tryptase are absent, suggesting that basophils play a major role in late-phase reactions. The mechanism of asthma where allergen is not an obvious trigger is unclear. Identical mediators and cytokines appear to be present and the end result, eosinophilic bronchitis, is the same. **See also:** [Cytokines](#); [Hypersensitivity: Immunological](#)

## Asthma as a Model of Atopic Disease

Asthma is a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and in the early morning. These episodes are associated with widespread but variable obstruction to bronchial air flow that improves either spontaneously or with treatment. In the past 30 years, a significant change in the treatment of chronic asthma has followed appreciation that asthma is

not primarily a disease of the muscle surrounding the bronchi, but one involving inflammation of the airways. Chronic inflammation contributes to airway hyperresponsiveness (discussed later), bronchoconstriction, airway oedema, mucous plug formation and eventually airway wall remodelling. **See also:** [Inflammation: Chronic](#)

Asthma is a multifactorial disease with the inheritance pattern of a complex genetic disorder. Numerous factors contribute to the development of asthma, including exposure to allergens, irritants (smoke, chemicals), viruses, cold air and exercise. Asthma often begins in childhood, in association with allergy to common environmental allergens. However, asthma may develop at any age. In adult-onset asthma predisposing factors may include atopy, aspirin sensitivity or occupational exposure to various materials (animal products, biological enzymes, plastic resin, wood dusts or metals). Although atopy has been identified as the strongest predisposing factor for developing asthma, many adults and some children have no detectable allergens responsible for their asthma. **See also:** [Allergens](#); [Asthma](#); [Asthma: Genetics](#)

### Conditions that may influence asthma severity

Exposure to inhalant allergens ([Table 1](#)) to which an asthma patient is sensitive increases airway inflammation and symptoms. Any patient with persistent asthma should be evaluated for allergy as a possible contributing factor. This is done by history and *in vivo* (skin test) or *in vitro* testing for allergen-specific IgE. Simple measures reduce allergen exposure ([Table 2](#)). Gastro-oesophageal reflux, the ingestion of aspirin and other nonsteroidal anti-inflammatory drugs, foods that contain sulphites, or nonselective beta blockers (taken systemically or ophthalmically) may exacerbate asthma. The clinical triad of steroid-dependent asthma, nasal polyps and sinusitis is particularly suggestive of aspirin sensitivity.

## Epidemiology and Natural History

The global prevalence of asthma ranges from 1% to 18% of the population in different countries (GINA Report, 2009). The United Kingdom, Australia and New Zealand have the highest recorded prevalence rates for asthma, and the lowest was found in Albania, China, Ethiopia, Indonesia and Turkey (Patel *et al.*, 2008). The lack of a universally accepted definition of asthma makes the comparison of prevalence

**Table 1** Common allergens

Grass, tree and weed pollens
Mould spores
House dust mite and cockroach excretions
Animal dander and proteins
Foods – especially nuts, peanuts, seafood and milk
Occupational allergens

**Table 2** Reduction of indoor allergen exposure

1	Reduce indoor relative humidity levels to 50% or less to limit growth of house dust mites and moulds
2	Keep windows closed
3	Use air conditioners in warm areas, and change or wash the filter at least once a month
4	Encase the mattress, box spring and pillows in allergen-impermeable covers
5	Avoid foam or feather pillows
6	Wash bed linens weekly in hot water (> 55°C)
7	Remove carpet from the patient's bedroom, and carpets that are laid on concrete
8	Remove stuffed toys
9	Remove pets from the home (if animal allergic)
10	Regularly exterminate cockroaches, and do not have exposed food or refuse

data from different countries difficult. The prevalence of asthma increased worldwide from the late 1970s to the mid-1990s. In the USA, asthma increased 74% from 1980 to 1996, but no further increase was seen from 2001 to 2004 (Moorman *et al.*, 2007). Asthma prevalence also increased in other industrialised countries (Aberg, 1989; Burney *et al.*, 1990; Reijula *et al.*, 1996). The International Study of Asthma and Allergies in Childhood (ISAAC) Phase One (done between 1992 and 1998) and Phase Three (done between 1999 and 2004) showed an overall continued increase in the prevalence of asthma in children worldwide, especially Asia Pacific and India. However, in the 13–14 year old group in Western Europe, decreases in prevalence significantly outnumbered increases (Asher *et al.*, 2006).

The rise in asthma prevalence is greatest in inner-city populations, and may be largely due to socioeconomic factors, such as underutilisation of anti-inflammatory medications, poor access to care and high levels of environmental allergens in homes. Exposure to parental smoking during childhood is also associated with increased asthma prevalence. Smoking cessation either during or after pregnancy reduces the risk of the child developing asthma (Slezak *et al.*, 1998).

The 'Hygiene Hypothesis' is a theoretical construct to explain the increased prevalence of atopic diseases, including asthma, in developed countries (Strachan, 1989; Strachan, 2000). The major premise is that lower exposure to environmental microbes (i.e. endotoxin and muramic acid found in bacterial cell walls) earlier in life and the widespread receipt of vaccines in developed countries shifts the immune-response to one that is T<sub>H</sub>2 predominant and predisposes to the production of IgE. This is thought to occur largely by microbes stimulating the innate immune system through Toll-like receptors, and downregulation of regulatory T cells. Although epidemiologic studies have often supported this hypothesis, the results are variable, as are studies of cellular biology (Schaub *et al.*, 2006).

Mortality from asthma increased worldwide in the last 4 decades, but has begun to decrease in many developed

countries in the last decade. For instance, in the USA it increased from 0.8 per 100 000 in 1977 to 2 per 100 000 in 1998, but had decreased to 1.3 per 100 000 in 2004 (Moorman *et al.*, 2007). Undertreatment of chronic inflammation is a likely reason for the upward trend in asthma mortality (Sly, 1994). Risk of asthma in the USA is highest in Puerto Ricans and African-Americans. Mortality from asthma is more than double for African-American children than for Caucasian children (Slezak *et al.*, 1998). The prevalence of asthma in African-American children is higher than that in white children, but the difference is not as striking as for mortality. It is not known if the association between race and asthma is genetic or environmental. Poverty within an inner-city environment may produce higher exposure to certain aeroallergens, thereby leading to higher morbidity from asthma in this population (Crain *et al.*, 1994).

## Pathology

Examination of the lungs of patients with status asthmaticus and respiratory failure reveal airway inflammation, hyperinflation of the lungs and plugs in the airway lumen composed of mucous, serum proteins, inflammatory cells and cellular debris. Microscopically, bronchi are infiltrated with eosinophils, mast cells, lymphocytes, macrophages and plasma cells. The entire bronchial wall may be thickened with tissue oedema, vasodilation, epithelial disruption and microvascular leakage. There is often hypertrophy of the airway smooth muscle, with new blood vessel formation, increased numbers of goblet cells and deposition of collagen in the subbasement membrane. The latter finding has been associated with chronic abnormalities of lung function. **See also:** [Respiratory Failure and Assisted Respiration](#)

Bronchial biopsy of adult patients with mild-to-moderate asthma shows airway inflammation and epithelial injury in about half of the patients. Six hours after local allergen challenge, the numbers of eosinophils, mast cells, lymphocytes and neutrophils in the airway mucosa are increased. Many of the cells present in the airway appear to be in an activated state. Bronchoalveolar lavage fluid in patients with asthma shows increased activated T lymphocytes (greater expression of CD25 and HLA-DR), a greater number of activated mast cells, eosinophils and epithelial shedding. These results provide strong evidence for airway inflammation in patients with mild and moderate asthma, and support the recommendation for the routine use of anti-inflammatory medication even in patients with mild asthma. **See also:** [Cells of the Immune System](#)

## Diagnosis and Assessment

### Spirometry

A clinical diagnosis of asthma is confirmed by the demonstration of airway obstruction on pulmonary function

testing. In seniors with asthma who have fewer clinical symptoms, pulmonary function testing may supplant the utility of clinical symptoms in the diagnosis of asthma (Stupka and deShazo, 2009). Regardless, the demonstration of reversible obstructive airways disease, where possible, is the gold standard for the diagnosis of asthma. Objective measurement of lung function by spirometry is therefore recommended both to confirm the initial diagnosis, and for periodic assessment to monitor response to therapy and to track the severity of disease. Because of an inability to exhale, patients with obstructive lung disease have a decreased forced expiratory volume in 1 s (FEV<sub>1</sub>), and decreased ratio of FEV<sub>1</sub> to FVC (forced vital capacity), among other findings. When these findings are noted, an inhaled short-acting bronchodilator is given and spirometry is repeated to determine the amount of reversibility of airway obstruction. An increase in FEV<sub>1</sub> of at least 12% is considered a significant response to bronchodilator and is diagnostic of asthma.

If the baseline FEV<sub>1</sub> is close to normal, patients with mild asthma who are asymptomatic at the time of spirometry may have little or no change in FEV<sub>1</sub> after a bronchodilator. Some patients with long-term asthma may have irreversible airway obstruction from chronic inflammation and collagen deposition in the subbasement membrane of the airways like that seen in smokers with emphysema. In such patients, a several week course of oral corticosteroids may demonstrate reversible obstruction.

### Airway hyperresponsiveness

An important feature of asthma is an exaggerated bronchoconstrictor response to a wide variety of stimuli, manifested clinically by chest tightness, cough and wheezing. Exposure to allergens, irritants, cold air, exercise or viral infection may trigger such symptoms. The level of airway responsiveness usually correlates with the degree of airways inflammation. Airway hyperresponsiveness can be demonstrated by pulmonary function testing showing decreased air flow on inhalation challenge testing with methacholine, histamine, cold dry air or after exercise.

## Therapy of Asthma

### Goals of therapy

At all levels of asthma severity, goals of therapy must be established. The primary goals should be (1) to prevent chronic symptoms such as coughing or breathlessness, (2) maintain normal to near-normal pulmonary function, (3) maintain normal activity levels (including exercise), (4) prevent recurrent exacerbations and frequent use of short acting bronchodilators (<2 days a week), (5) provide pharmacotherapy with minimal or no adverse effects, (6) meet patients' and families' expectations and satisfaction with asthma care, (7) minimise the need for emergency department visits and hospitalisations and (8) prevent progressive loss of lung function.

## Bronchodilators

### $\beta$ -Adrenergic agonists

$\beta$ -Adrenergic agonists are the most potent and rapid-acting bronchodilators used. They are available in metered-dose inhalers (hand actuated, gas-pressurised canisters containing drug), nebuliser solutions, dry powder inhalers and as liquid or tablets for oral ingestion. Short-acting bronchodilators such as albuterol are useful for acute relief of bronchospasm. They may be used every 4–6 h as needed.  $\beta$ -Agonists are useful for prophylaxis of exercise-induced asthma. The long-acting  $\beta$ -agonists salmeterol and formoterol are also useful for exercise prophylaxis, and have a duration of effect of 9–12 h. Salmeterol must be used 2 h before exercise, whereas formoterol may be used 15 min before exercise. Long-acting bronchodilators are not used for acute bronchoconstriction.

When either short- or long-acting  $\beta$ -agonists are used on a regular basis, there is the potential for the development of tolerance to their bronchodilating effects by decreasing the production of  $\beta_2$  receptors on cell membranes. Studies on the adverse effects of regular use of short-acting  $\beta_2$ -agonists have shown conflicting results. No study has shown any long-term improvement of asthma with their regular use. Thus daily use of short-acting  $\beta_2$ -agonists as the sole treatment of asthma is not appropriate or approved. When combined with inhaled corticosteroids in severe asthma, long-acting bronchodilators provide better asthma control than inhaled steroid alone (Pearlman *et al.*, 1992).

### Theophylline

Theophylline is a mild-to-moderate bronchodilator, and may have mild anti-inflammatory effects as well. Theophylline inhibits the early- and late-phase response to allergens, but does not reduce allergen-induced airway hyperresponsiveness. It can be useful in nocturnal asthma, and improves exercise tolerance. It is available in liquid, capsules (that may be sprinkled on soft food and eaten) and tablets. Sustained-release formulations can be given at 8–24 h intervals. Theophylline is metabolised in the liver, so serum levels are affected by age, diet, disease states and drug interactions. Febrile illnesses, high-carbohydrate diets, macrolide antibiotics, cimetidine, ciprofloxacin and oral contraceptives all decrease theophylline metabolism. Tobacco exposure, phenytoin, phenobarbital, carbamazepine and rifampin all increase theophylline metabolism. Dose-related adverse effects of theophylline include gastrointestinal symptoms of nausea, vomiting or abdominal cramping (which can occur even at low doses in some individuals) and exacerbation of gastro-oesophageal reflux. Seizures or cardiac arrhythmias occur at higher doses, sometimes at doses just above the therapeutic range. Because of its narrow therapeutic window of 5–15  $\mu\text{g mL}^{-1}$ , serum levels must be monitored periodically.

Theophylline adds very little to the bronchodilator effect of high-dose inhaled  $\beta$ -adrenergic agonists (with or without steroids) in the management of acute asthma

exacerbations. Therefore, theophylline is not recommended in the acute management of asthma. Moreover, because of its narrow therapeutic window, and the availability of newer and more effective agents for the treatment of asthma, it is rarely used as a preventive agent.

### Anticholinergics

Ipratropium bromide is an atropine derivative with a longer duration of action and fewer adverse side effects. It can be useful in some patients with severe asthma exacerbation when combined with an inhaled  $\beta$ -adrenergic agent. Its role in chronic asthma management is unclear, but may be useful in patients with coexisting chronic bronchitis or with chronic obstructive pulmonary disease. Ipratropium is available in a solution for nebulisation or as a metered-dose inhaler.

## Anti-inflammatory agents

### Cromolyn and nedocromil

These are two structurally different medications that have similar anti-inflammatory effects. They inhibit mast cell release of inflammatory mediators, prevent early- and late-phase allergen-induced bronchoconstriction and reduce airway hyperresponsiveness. They are available in metered-dose inhalers and for nebulisation (cromolyn), are safe, and best used prophylactically, either just before exposure to an asthma triggering factor, or on a daily basis (dosed three to four times daily). They have no bronchodilating properties.

### Glucocorticoids

Corticosteroids are the most potent and effective anti-inflammatory agents used in the treatment of asthma. They are available in oral, injectable or inhaled forms. Corticosteroid molecules bind to a specific cytoplasmic glucocorticoid receptor inside cells. This glucocorticoid-receptor complex then moves to the cell nucleus where it binds to specific sites on the deoxyribonucleic acid (DNA) called glucocorticoid response elements. This regulates transcription of target genes.

Corticosteroids inhibit the production of many inflammatory cytokines, and increase the degradation of other mediators. Corticosteroids also increase production of  $\beta$ -adrenergic receptors on inflammatory cells.

### Inhaled corticosteroids

Inhaled corticosteroids are recommended as preferred therapy for all patients with persistent asthma. Used chronically, inhaled corticosteroids improve symptoms and pulmonary function test results, and reduce  $\beta$ -agonist use and asthma exacerbations.

The most common adverse effects of inhaled corticosteroids are hoarseness and fungal infection of the mouth (thrush). Side effects are reduced by using a spacer device on metered-dose inhalers to reduce oral deposition of the drug, use of a dry powder inhaler, rinsing the mouth after

each use and decreasing the dose frequency. Suppression of adrenal gland function occurs in some patients using inhaled corticosteroids, particularly at higher doses. Inhaled corticosteroids at high doses can also reduce bone density, and may predispose to glaucoma. High-dose inhaled corticosteroid may decrease the growth rate in children. This issue is complicated by the finding that children with asthma have delayed onset of puberty, which results in a delay in the adolescent growth spurt. However, a meta-analysis evaluating studies of inhaled corticosteroids in children with asthma found that when attained heights were compared to predicted heights of these children with asthma, there was no significant association between the use of low- to moderate-dose inhaled steroids and diminished stature (Allen *et al.*, 1994). Regardless, the potential problems above warrant use of the lowest dose of inhaled steroids that produces effective asthma control.

Doubling the dose of inhaled corticosteroid in patients already using inhaled corticosteroids has not been shown to reduce the severity or prevent the progression of acute exacerbations. However, quadrupling the dose of inhaled corticosteroid for 7 days at the first onset of worsening symptoms has been shown to reduce the need for oral corticosteroid use in one study (Foresi *et al.*, 2000).

### Systemic corticosteroid therapy

Oral corticosteroids combined with a short-acting  $\beta$ -agonist are effective for outpatient treatment of acute asthma exacerbations. The early use of oral corticosteroids for asthma exacerbation in children and adults has been shown to reduce hospitalisation. Those who do require hospitalisation usually require systemic corticosteroids. Daily or alternate-day oral corticosteroid therapy is recommended for patients with severe asthma who are not well controlled by bronchodilators and inhaled corticosteroids. The dosage and schedule of systemic steroids for acute asthma must be determined on an individual basis.

Adverse effects of oral corticosteroids tend to be more pronounced than those seen with the inhaled route. Short-term use of systemic corticosteroids can be associated with reversible abnormalities of glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer disease and, rarely, aseptic necrosis of the hip. Long-term use of systemic corticosteroids may result in all of the above, plus adrenal gland suppression, growth suppression, dermal thinning, diabetes, fat redistribution, cataracts, glaucoma and impaired immune function. Alternate-day dosing produces less toxicity than everyday dosing, and should be attempted in patients requiring long-term oral corticosteroids.

### Leucotriene antagonists

Leucotrienes are chemical mediators of inflammation produced from the oxidative metabolism of arachidonic acid, located in the cell membrane. Eosinophils, mast cells and basophils all release leucotrienes, which cause contraction of airway smooth muscle, increase vascular

permeability, increase mucous secretion and attract inflammatory cells into the airways.

Three leucotriene antagonists are currently available. Zileuton inhibits the enzyme 5-lipoxygenase and blocks the formation of  $LTB_4$ ,  $LTC_4$ ,  $LTD_4$  and  $LTE_4$  from cell membrane phospholipids. Zileuton causes reversible liver enzyme elevation, and can reduce the metabolism of the drugs terfenadine, warfarin and theophylline. Zafirlukast and montelukast are both leucotriene ( $LTD_4$ ) receptor antagonists (LTRA). They reduce the airway obstruction response to allergen, mildly improve  $FEV_1$  and improve symptom scores.  $LTD_4$  antagonism inhibits both the early- and late-phase asthmatic response.

Leucotriene receptor antagonists may be used in the management of chronic mild asthma, in aspirin-sensitive individuals and in those with exercise-induced bronchospasm. LTRAs or Zileuton may be combined with inhaled corticosteroid in moderate to severe asthma. Zileuton is not FDA approved for use in children. All three drugs may be hepatotoxic in some individuals.

### Monoclonal anti-IgE therapy

Omalizumab is a recombinant humanised monoclonal anti-IgE antibody of the IgG1  $\kappa$  subclass. It is produced in mice, but is 95% humanised. Anti-IgE has anti-inflammatory effects mediated by suppression of free IgE levels (although the total serum IgE is increased, due to IgE-anti-IgE complexes). After subcutaneous injection, omalizumab forms complexes with IgE (mostly trimers, and some hexamers), that prevent IgE from binding to IgE receptors on mast cells and basophils.

Omalizumab is currently indicated for moderate-to-severe perennial allergic asthma that is inadequately controlled with conventional therapy. Long-term treatment with omalizumab in these patients reduces the frequency of asthma exacerbations, and allows reduction of inhaled corticosteroid and other asthma medications.

### Allergen immunotherapy

Allergen immunotherapy is useful in patients with allergic rhinitis, and some patients with asthma who have clear evidence of a relationship between symptoms and exposure to unavoidable allergens to which IgE is present and there is difficulty controlling symptoms with pharmacological management. Immunotherapy involves the subcutaneous (SCIT) or sublingual (SLIT) administration of increasing concentrations of allergen to which the patient has demonstrated sensitisation by skin test (or radioallergosorbent test, RAST) and history. It is time-consuming and associated with a risk of anaphylaxis, especially when administered by healthcare professionals not properly trained in its use. Allergen immunotherapy reduces both the immediate- and the late-phase allergic reaction. The specific mechanism by which it relieves symptoms is unclear, although we do know that it increases allergen-specific IgG, reduces allergen-specific IgE, decreases allergen-induced mediator release, decreases eosinophil chemotaxis and appears to

**Table 3** Asthma classification by severity and risk

Level	Components of severity and risk
Intermittent	Symptoms $\leq 2$ times a week, asymptomatic between exacerbations, exacerbations last a few hours to a few days, nocturnal symptoms $\leq 2$ times a month, $FEV_1 \geq 80\%$ predicted and $FEV_1/FVC$ normal.
Mild persistent	Systemic corticosteroid use $\leq$ once per year. Symptoms $> 2$ times a week but not daily, minor limitation of activity, nocturnal symptoms 3–4 times a month, $FEV_1 \geq 80\%$ predicted with normal $FEV_1/FVC$ .
Moderate persistent	Systemic corticosteroid use $\geq 2$ times a year. Daily symptoms, daily use of inhaled short-acting $\beta_2$ -agonist, exacerbations affect activity, exacerbations $\geq 2$ times a week (may last days), nocturnal symptoms $> 1$ time a week, $FEV_1 > 60\% - < 80\%$ predicted with $FEV_1/FVC$ reduced up to 5%.
Severe persistent	Systemic corticosteroid use $\geq 2$ times per year. Continual symptoms, very limited physical activity, frequent exacerbations, frequent nocturnal symptoms, $FEV_1 \leq 60\%$ predicted with $FEV_1/FVC$ reduced $> 5\%$ . Systemic corticosteroid use $\geq 2$ times per year.

favour a shift to cytokine profiles associated with  $T_H1$  responses to allergen. **See also:** [Tumours: Immunotherapy](#)

Experimental forms of immunotherapy, such as administration of allergen proteins capable of binding receptors (but not IgE), are under investigation.

## Stratification of Asthma by Severity

Asthma may be classified as mild intermittent, mild persistent, moderate persistent or severe persistent, based on the frequency and severity of asthma symptoms and pulmonary function tests. This classification is helpful in developing a management plan (Table 3).

## Management of Chronic Asthma

A stepwise approach to medication therapy is recommended to gain and maintain control of asthma (Figure 2). There are two ways to utilise this stepwise approach. Some experts believe that all patients with asthma should receive anti-inflammatory therapy regardless of severity. They treat aggressively with anti-inflammatory therapy to achieve disease control, then gradually reduce (or 'step-down') the amount of anti-inflammatory medication, once pulmonary function has normalised. This is the approach

preferred by the National Asthma Education and Prevention Program in the USA. This Expert Panel recommends that the dose of inhaled corticosteroid be reduced by 25% every 2–3 months once control is achieved. Once the lowest dose required to maintain control is reached, that dose is continued with chronic monitoring to ascertain that the patient's asthma remains under good control.

An alternative approach is to start treatment at the step appropriate to the current severity of the patient's disease, and gradually step up the medications if control is not achieved. In this approach, mild intermittent asthma is treated only with a short-acting  $\beta_2$ -agonist. As the level of asthma severity increases, the amount of anti-inflammatory medication used also increases.

There are currently no studies directly comparing the two approaches. However, suppression of inflammation is more likely to be achieved with the step-down approach. And once the disease is controlled, the amount of anti-inflammatory medication is reduced. This may allow for earlier suppression of airway inflammation, and thereby reduce the amount of anti-inflammatory medication used over the long term.

The use of symptoms for assessment of response to therapy may be supplanted by improvement of pulmonary functions in seniors (deShazo and Stupka, 2009).

### Intermittent asthma

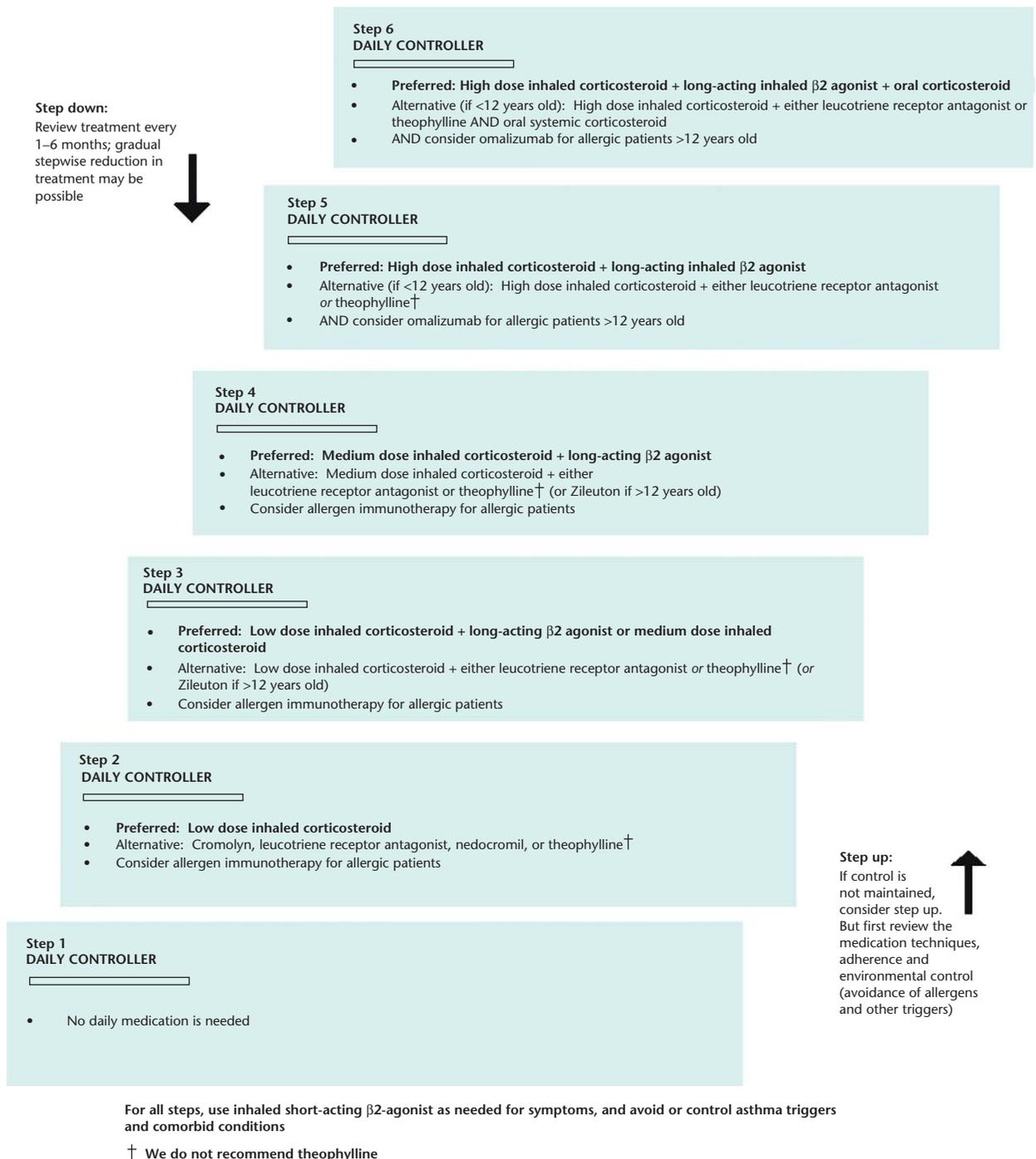
These patients use a short-acting  $\beta_2$ -agonist as needed for symptoms, and do not need daily preventive medication. Those with exercise-induced bronchospasm may use a short-acting  $\beta_2$ -agonist, cromolyn or nedocromil shortly before exercise. Likewise, cromolyn or nedocromil may be used prior to an unavoidable exposure to an allergen that is known to trigger the patient's asthma.

### Mild persistent asthma

Long-term control treatment with an anti-inflammatory drug is indicated in this group. A low dose of inhaled corticosteroid is the preferred agent. Young children may begin with a trial of cromolyn, nedocromil or a leucotriene receptor antagonist due to the safety profiles of these medications. Theophylline is an alternative, but we do not recommend theophylline due to the potential for toxicity and drug interactions.

### Moderate persistent asthma

Patients with moderate asthma should receive daily long-term anti-inflammatory medications. Low- to medium-dose inhaled corticosteroid combined with a long-acting inhaled  $\beta_2$ -agonist is the preferred treatment. Alternative treatment includes use of a medium-dose inhaled corticosteroid alone, or a low- to medium-dose inhaled corticosteroid combined with a leucotriene antagonist, sustained-release theophylline or in those aged 12 years and above Zileuton may be added. We do not recommend theophylline for routine use.



**Figure 2** A step-care approach to managing asthma in adults and children. Preferred treatments are in bold type. Note: Patients at any level of severity can have mild, moderate or severe exacerbations. Some patients with intermittent asthma may experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. Adapted from National Asthma Education and Prevention Program (2007).

## Severe persistent asthma

These patients should receive a high-dose inhaled corticosteroid and a long-acting inhaled  $\beta_2$ -agonist. Some patients with severe asthma may also require continuous oral

corticosteroid therapy for control of asthma. Alternate day therapy is preferred over daily therapy with oral corticosteroid whenever possible. Omalizumab (anti-IgE monoclonal antibody) should be considered in allergic asthmatic patients who meet the treatment criteria.

## All patients

An inhaled short-acting  $\beta_2$ -agonist is used as needed to relieve acute symptoms. Daily or increasing use of a short-acting  $\beta_2$ -agonist indicates the need for additional long-term control therapy.

## Management of Acute Asthma

Acute asthma exacerbations are manifest as increased cough, wheezing, shortness of breath, chest tightness and chest pain caused by worsening airway obstruction. In seniors, it may manifest as loss of function, including decreased mobility and exercise tolerance. Pulmonary function test results progressively decrease. Exacerbations may develop slowly over days to weeks, or suddenly over 1–2 h.

Risk factors for life-threatening acute asthma include: a previous life-threatening asthma exacerbation, more than two emergency room visits or hospitalisations for asthma in the past year, admission to an intensive care unit for asthma, mechanical ventilation for asthma, use of more than two canisters per month of short-acting inhaled  $\beta_2$ -agonist, recent withdrawal from systemic corticosteroids, poor perception of hypoxia or airway obstruction or a coexisting chronic illness such as cardiovascular disease, chronic obstructive pulmonary disease or psychiatric disorder. Early intervention improves the outcome in most cases. **See also:** Cardiovascular Disease and Congenital Heart Defects; Diffuse Parenchymal Lung Disease; Hypoxia; Respiratory Failure and Assisted Respiration

## Emergency treatment of asthma

Since other medical problems may cause cough, wheeze and abnormal pulmonary function tests, the first step is confirmation that asthma is the cause of symptoms. If the history, examination of the patient and ancillary data confirm asthma as the diagnosis, a  $\beta_2$ -selective bronchodilator, such as albuterol, is given by inhalation as a first step. Albuterol can be repeated every 20 min. The oxygen saturation level and vital signs are monitored in an ongoing fashion. Oxygen is given, if needed, to maintain oxygen saturation. Systemic corticosteroids speed the resolution of airway obstruction and reduce the rate of relapse.

Patients who respond to therapy (clinically and by pulmonary function tests) may be discharged. Additional  $\beta_2$ -agonist and oral steroid may be required for several days, during which time outpatient evaluation and reassessment occurs.

## Asthma action plan

All patients should have a daily self-management plan, and an action plan for treatment of exacerbations. Action plans are especially important for patients with moderate to severe persistent asthma. Asthma action plans may be based on peak expiratory flow rates, symptoms or a

combination of both. A partnership between the clinician and the patient/family provides education about asthma at every opportunity. This promotes open communication, improves understanding and allows better control of asthma.

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