The Clinical Complications of Asthma and its Pharmacotherapy

Atta Abbas1,2, Sadaf Shahid2, Arif Sabah3, Anwar Ejaz Beg2, Farrukh Rafiq Ahmed2, Sidra Tanwir3, Syed Waqar Ahmed4, Muhammad Kashif4, Aijaz Hussain Jatoi5, Syed Ata Rizvi6 and Muhammad Amir Qidwai7

1Department of Pharmacy, Health and Well-being, University of Sunderland, England, United Kingdom.
2Faculty of Pharmacy, Ziauddin University, Karachi, Sindh, Pakistan
3Department of Pharmacy, Seven Day Adventist Hospital, Karachi, Sindh, Pakistan.
4Abbott Pharmaceutical laboratories Private Limited, Karachi, Sindh, Pakistan
5Health Department, High Commission of Pakistan, London, England, United Kingdom
6Faculty of Pharmacy, Hamdard University, Karachi, Sindh, Pakistan
7Department of Pharmacy, Al Sharq Hospital, Fujairah, United Arab Emirates

ABSTRACT

Asthma is a disease characterized by wide variations in pathogenesis that cause resistance to flow in intrapulmonary airways. The dramatic changes in the architecture of the airway walls are usually connected to allergic reaction or other forms of hyper sensitivity, causing marked spasms that lead to difficulty in breathing. It is possible to relieve or remove the symptoms in the majority of patients by adopting the clinical guidelines for pharmacotherapy of asthma which include inhaled corticosteroids, long and short acting beta agonists, muscarinic antagonists, leukotriene modifiers, xanthine drugs and some allergy medicines. The proper use of these agents can aid in reducing or reversing many symptoms of asthma. Certain methods of using medicines, for example the correct use of the inhaler for relief and maintenance therapy, are also associated with a significant reduction in symptoms. This can be achieved by a pharmacist’s intervention that can provide a detailed understanding of the current rational drug choices and proper medication use to the patient. Nowadays massive resources are being ploughed into research in a concerted effort to halt the progress of this illness that can strike in all ages.

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Introduction

Asthma is a disease characterized by recurrent attacks of breathlessness and wheezing that vary in severity and frequency from person to person. It is a respiratory condition marked by attacks of spasm in the bronchi of the lungs, causing difficulty in breathing. It is usually connected to allergic reaction or other forms of hypersensitivity. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs. Evidence-based medicine is employed considering new approaches to the disease management of asthma. Clinical guidelines must be taken into the consideration for the direct assessment of patients with Asthma and COPD.¹

These clinical guidelines help to achieve improved quality of care (and thereby Improved outcomes), decreased practice variations (especially if unnecessary and inappropriate), controlled healthcare costs, faster evidence-based decision making, accelerated application and translation of advances in medical science to everyday clinical practice (especially in large medical practices).²

Epidemiological studies of asthma and COPD have shown that the two diseases over time may develop physiological features that are quite similar. The rapid rate of decline in pulmonary function is a characteristic of subjects with COPD, also seen in asthmatic subjects as well. Therefore, the progression in severity of asthma symptoms, and the overlap of symptoms seen in some patients with asthma and COPD have led to a hypothesis that asthma may be a risk factor for the subsequent development of COPD.³

Epidemiology of Asthma

An estimated 20.5 million persons in the United States have asthma (approximately 7% of the population).³ Asthma is the most common chronic disease among children in the United States, with approximately 6.5 million children affected. The prevalence of asthma in the United States and worldwide has continued to increase. The prevalence rate is highest in children 5-17 years at 9.6%.³ In the United States, as well as Western industrialized countries, the prevalence of asthma has reached epidemic proportions.³

Although asthma is the third leading cause of preventable hospitalization in the United States, hospitalizations for asthma have decreased only slightly over the past 10 years to 17 per 10,000 populations. Children younger than 15 years of age have the highest rate of hospitalization at 31 per 10,000 populations. Asthma accounts for more than 10 million missed school days per year. The prevalence of disabling asthma in children has increased 23.2% over the past 20 years compared with a 113% increase from all other chronic conditions in childhood. In young children (0 to 10 years of age), the risk of asthma is greater in boys than in girls, becomes about equal during puberty, and then is greater in women than in men.¹,³ In Pakistan only limited data are available among few age groups under one ISAAC study, which revealed that the frequency of diagnosed (previously seen by physicians) cases of asthma stood at 15.8% among school children in Karachi, Pakistan.⁴ The epidemiological aspects are highlighted in graph 1 and 2.

Etiology of Asthma

For a variety of reasons, in an asthma episode the bronchial tubes become narrow, or even blocked. As a result, air cannot get in or out of the lungs easily, and the patient begins to breathe heavily, wheeze or cough. There are two reasons behind narrowing of
the bronchi. They are squeezed by muscles from the outside or they are blocked by mucus and swelling inside the bronchial tubes. The condition when bronchi are narrowed by squeezing is called bronchoconstriction, in which muscles are wrapped around the bronchi like a series of elastic bands that tighten and restrict the passage of air. It is normal for these muscles to occasionally close the airway. But in asthmatics these muscles sometimes overreact, become twitchy and constrict or block the bronchi. Inflammation, for many years, was thought to be the main cause of asthma.5

Bronchial Inflammation occurs when the walls of the bronchi swell up and produce mucus, in reaction to some sort of irritation. It's normal for the bronchi to produce mucus in order to trap breathed-in irritants, and protect the lungs, but some asthmatics can produce an overabundance of mucus, and the bronchi can become chronically inflamed, resulting in blocked airways and asthmatic symptoms as shown in Figure 1.

These are some of the main causes of asthma, some other causes responsible for asthma are allergens, which are certain substances that can cause an allergic reaction in some people and it is sometimes a major trigger in patients.5 Common allergens include dust mites (microscopic bugs that live in dust), molds, pollen, animal dander, and cockroaches. Certain airborne irritants and pollutants, substances in air such as chalk dust or smoke, can trigger asthma because they irritate the airways. Cigarette smoke is a major cause of asthma symptoms and not just for smokers but it can trigger asthma symptoms in nonsmoking individuals present around smokers, which causes them to become secondary smokers. Scented products such as perfumes, cosmetics, and cleaning solutions can trigger symptoms, as well as strong odors from fresh paint or gasoline fumes.5 High levels of air pollutants such as ozone may irritate the sensitive tissues in the bronchial tubes and can possibly aggravate the symptoms of asthma in some people with the condition. Exercise-induced asthma is triggered by physical activity. Although unbearable, most cases of exercise-induced asthma can be treated. Cold or dry air can sometimes trigger asthma symptoms in certain people, as well as extreme heat or humidity. Colds, flu, and other viral infections can also trigger asthma in some people.1,5

Pathophysiology of Asthma

The major characteristics of asthma include a variable degree of airflow obstruction (related to bronchospasm, edema, and hyper secretion), Basal heart rate (BHR), and airways inflammation. Evidence of inflammation arises from nonspecific BHR, bronchoalveolar lavage, bronchial biopsies, and induced sputum, as well as postmortem observations of patients with asthma as a mortality cause. To understand the pathogenesis that underline variants of asthma, it is critical to identify factors that initiate, intensify, and modulate the inflammatory response of the airways and determine how these immunological and biological processes produce the characteristic airways abnormalities. Immune responses mediated by immunoglobulin IgE antibodies are of foremost importance.1,6 The pathophysiology is demonstrated in Figure 2.

Acute Inflammation

Add inhaled allergen challenge models contribute most to the understanding of acute inflammation in asthma. Inhaled allergen challenge in allergic patients leads to an early phase allergic reaction that, in some cases, followed by a late-phase reaction. The activation of cells bearing allergen-specific IgE initiates the early phase reaction. It is characterized primarily by the rapid activation of airway mast cells and macrophages. The
activated cells rapidly release pro-inflammatory mediators such as histamine, eicosanoids, and reactive oxygen species that induce contraction of airway smooth muscle, mucus secretion, and vasodilatation. The bronchial microcirculation has an essential role in this inflammatory process. Inflammatory mediators induce microvascular leakage with exudation of plasma in the airways. Acute plasma protein leakage induces microvascular leakage with exudation of plasma in the airways. Plasma exudation may compromise epithelial integrity, and the presence of plasma in the lumen may reduce mucus clearance. Plasma proteins also may promote the formation of exudative plugs mixed with mucus and inflammatory and epithelial cells. Together these effects contribute to airflow obstruction. The late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves the recruitment and activation of eosinophils, CD4\(^+\) T cells, basophils, neutrophils, and macrophages. There is selective retention of airway T cells, the expression of adhesion molecules, and the release of selected pro-inflammatory mediators and cytokines involved in the recruitment and activation of inflammatory cells. The activation of T cells after allergen challenge leads to the release of TH\(_2\) like cytokines that may be a key mechanism of the late-phase response. The release of preformed cytokines by mast cells is the likely initial trigger for the early recruitment of cells. This cell type may recruit and induce the more persistent involvement by T cells. The enhancement of nonspecific BHR usually can be demonstrated after the late-phase reaction but not after the early phase reaction following allergen or occupational challenge.

**Chronic Inflammation**

Airways inflammation has been demonstrated in all forms of asthma, an association between the extent of inflammation and the clinical severity of asthma has been demonstrated where it is accepted that both central and peripheral airways are inflamed. In asthma, all cells of the airways are involved and become activated. Including eosinophils, T cells, mast cells, macrophages, epithelial cells, fibroblasts, and bronchial smooth muscle cells. These cells also regulate airway inflammation and initiate the process of remodeling by the release of cytokines and growth factors.

**Epithelial Cells**

Bronchial epithelial cells traditionally have been considered as a barrier, participating in mucociliary clearance and removal of noxious agents. However, epithelial cells also participate in inflammation by the release of eicosanoids, peptidases, matrix proteins, cytokines, and nitric oxide (NO). Epithelial cells can be activated by IgE-dependent mechanisms, viruses, pollutants, or histamine. In asthma, especially fatal asthma, extensive epithelial shedding occurs. The functional consequences of epithelial shedding may include heightened airways responsiveness, altered permeability of the airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading pro-inflammatory neuropeptides. The integrity of airway epithelium may influence the sensitivity of the airways to various provocative stimuli. Epithelial cells also may be important in the regulation of airway remodeling and fibrosis.

**Eosinophils**

Eosinophils play an effectors role in asthma by release of pro-inflammatory mediators, cytotoxic mediators, and cytokines. Circulating eosinophils migrate to the airways by cell rolling, through interactions with selectins, a family of cell adhesion molecules or (CAMs) that have
divergent roles in pathophysiological processes and eventually adhere to the endothelium through the binding of integrins to adhesion proteins (vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]). As eosinophils enter the matrix of the membrane, their survival is prolonged by interleukin IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, eosinophils release inflammatory mediators such as leukotrienes and granule proteins to injure airway tissue.\(^7\)

**Lymphocytes**

Mucosal biopsy specimens from patients with asthma contain lymphocytes, many of which express surface markers of inflammation. There are two types of T helper CD 4\(^+\) cells. TH\(_1\) cells produce IL-2 and interferon-\(\gamma\) (INF-\(\gamma\)), both essential for cellular defense mechanisms. TH\(_2\) cells produce cytokines (IL-4, IL-5, and IL-13) that mediate allergic inflammation. It is known that TH\(_1\) cytokines inhibit the production of TH\(_2\) cytokines, and vice versa. It is hypothesized that allergic asthmatic inflammation results from a TH\(_2\)-mediated mechanism (an imbalance between TH\(_1\) and TH\(_2\) cells).\(^7\)

**TH\(_1\) and TH\(_2\) Cell Imbalance**

It has been postulated that the TH\(_1\)/TH\(_2\) imbalance contributes to the cause and evolution of atopic diseases, including asthma. The T cell population in the cord blood of newborn infants is skewed toward a TH\(_2\) phenotype. The extent of the imbalance between TH\(_1\) and TH\(_2\) cells (as indicated by diminished INF-\(\gamma\) production) during the neonatal phase may predict the subsequent development of allergic disease, asthma, or both. It has been suggested that infants at high risk of asthma and allergies should be exposed to stimuli that up-regulate TH\(_1\)-mediated responses in order to restore the balance during a critical time in the development of the immune system and the lung. The basic premise of the hygiene hypothesis is that the newborn’s immune system is skewed toward TH\(_2\) cells and needs timely and appropriate environmental stimuli to create a balanced immune response. Factors that enhance TH\(_1\)-mediated responses include infection with *Mycobacterium tuberculosis*, measles virus, and hepatitis A virus, increased exposure to infections through contact with older siblings, attendance at day care during the first 6 months of life; and a reduction in the production of INF-\(\gamma\). Restoration of the balance between TH\(_1\) and TH\(_2\) cells may be impeded by frequent administration of oral antibiotics, with concomitant alterations in gastrointestinal flora. Other factors favoring the TH\(_2\) phenotype include lifestyle, urban environment, diet, and sensitization to house-dust mites and cockroaches. Immune “imprinting” may begin in uterus by transplacental transfer of allergens and cytokines.\(^7\)

**Mast Cells**

Mast cell degranulation is important in the initiation of immediate responses following exposure to allergens. Mast cells are found throughout the walls of the respiratory tract, and increased numbers of these cells (three- to five fold) have been described in the airways of asthmatics with an allergic component. Once binding of allergen to cell-bound IgE occurs, mediators such as histamine; eosinophil and neutrophil chemotactic factors; leukotrienes (LTs) C4, D4, and E4; prostaglandins PGs; platelet-activating factor PAF; and others are released from mast cells. Histological examination has revealed decreased numbers of granulated mast cells in the airways of patients who have died from acute asthma attacks, suggesting that mast cell degranulation is a contributing factor in the progression of the disease. Sensitized mast cells also may be activated by
osmotic stimuli to account for exercise-induced bronchospasm (EIB).⁷

Alveolar Macrophages
The primary function of alveolar macrophages in the normal airway is to serve as “scavengers,” engulfing and digesting bacteria and other foreign materials. They are found in large and small airways, ideally located for affecting the asthmatic response. A number of mediators produced and released by macrophages have been identified, including platelet-activating factor, LTB⁴, LTC⁴, and LTD⁴. Additionally alveolar macrophages are able to produce neutrophil chemotactic factor and eosinophil chemotactic factor, which, in turn, augment the inflammatory process.⁷

Neutrophils
The role of neutrophils in the pathogenesis of asthma remains somewhat unclear because they normally may be present in the airways and usually do not infiltrate tissues showing chronic allergic inflammation despite the potential to participate in late-phase inflammatory reactions. However, high numbers of neutrophils have been reported to be present in the airways of patients who died from sudden-onset fatal asthma and in those with severe disease. This suggests that neutrophils may play a pivotal role in the disease process, at least in some patients with long-standing or corticosteroid-dependent asthma. The neutrophil also can be a source for a variety of mediators, including platelet-activating factor PAF, prostaglandins PGs, thromboxanes TBX, and leukotrienes LTs, that contribute to BHR and airway inflammation.⁶,⁷

Fibroblasts and Myofibroblasts
Fibroblasts are found frequently in connective tissue. Human lung fibroblasts may behave as inflammatory cells on activation by IL-4 and IL-13. The myofibroblast may contribute to the regulation of inflammation via the release of cytokines and to tissue remodeling. In asthma, myofibroblasts are increased in numbers beneath the reticular basement membrane, and there is an association between their numbers and the thickness of the reticular basement membrane.⁷

Inflammatory Mediators
Associated with asthma for many years, histamine is capable of inducing smooth muscle constriction and bronchospasm and is thought to play a role in mucosal edema and mucus secretion. Lung mast cells are an important source of histamine. The release of histamine can be stimulated by exposure of the airways to a variety of factors, including physical stimuli (such as exercise) and relevant allergens. Histamine is involved in acute broncho-spasm following allergen exposure; however, other mediators, such as leukotrienes, are also involved. Besides histamine release, mast cell degranulation releases interleukins, proteases, and other enzymes that activate the production of other mediators of inflammation. Several classes of important mediators, including arachidonic acid ARA and its metabolites (i.e., prostaglandins, LTs, and platelet-activating factor), are derived from cell membrane phospholipids. Once arachidonic acid is released, it can be metabolized by the enzyme cyclo-oxygenase COX to form prostaglandins. Although prostaglandin D2 is a potent bronchoconstricting agent, it is unlikely to produce sustained effects and its role in asthma remains to be determined. Similarly, prostaglandin F2α is a potent bronchoconstrictor in patients with asthma and can enhance the effects of histamine. However, its pathophysiologic role in asthma is unclear. Another cyclo-oxygenase product, prostacyclin (prostaglandin), is known to be produced in the lung and may contribute to
inflammation and edema owing to its effects as a vasodilator. Thromboxane A₂ is produced by alveolar macrophages, fibroblasts, epithelial cells, neutrophils, and platelets within the lung. Indirect evidence from animal models suggests that thromboxane A₂ may have several effects, including bronchoconstriction, involvement in the late asthmatic response, and involvement in the development of airway inflammation and BHR.⁶,⁷

The 5-lipoxygenase pathway of arachidonic acid metabolism is responsible for the production of the cysteinyl leukotrienes. LTC₄, LTD₄, and LTE₄ are released during inflammatory processes in the lung. LTD₄ and LTE₄ share a common receptor (LTD₄ receptor) that, when stimulated, produces bronchospasm, mucus secretion, microvascular permeability, and airway edema, whereas LTB₄ is involved with granulocyte chemotaxis. Thought to be produced by macrophages, eosinophils, and neutrophils within the lung. Platelet-activating factor is involved in the mediation of bronchospasm, sustained induction of BHR, edema formation, and chemotaxis of eosinophils.⁶,⁷

**Adhesion Molecules**

An important step in the inflammatory process is the adhesion of the various cells to each other and the tissue matrix to facilitate infiltration and migration of these cells to the site of inflammation. To promote this, cell membranes express a number of glycoproteins, or adhesion molecules. Adhesion molecules have additional functions involved in the inflammatory process aside from promoting cell adhesion, including activation of cells and cellular communication, and promoting cellular migration and infiltration. The adhesion molecules are divided into families on the basis of their chemical structure. These families are the integrins, cadherins, immunoglobulin supergene family, selectins, vascular adressins, and carbohydrate ligands. Those assumed important in inflammation include the integrins, immunoglobulin supergene family, selectins, and carbohydrate ligands, including ICAM-1 and VCAM-1. Adhesion molecules are found on a variety of cells, such as neutrophils, monocytes, lymphocytes, basophils, eosinophils, granulocytes, platelets, endothelial cells, and epithelial cells, and can be expressed or activated by the many inflammatory mediators present in asthma.⁶,⁷

**Clinical Consequences of Chronic Inflammation**

Chronic inflammation is associated with nonspecific BHR and increases the risk of asthma exacerbations. Exacerbations are characterized by increased symptoms and worsening airways obstruction over a period of days or even weeks, and rarely hours.⁸ Hyper responsiveness of the airways to physical, chemical, and pharmacological stimuli is a hallmark of asthma. BHR also occurs in some patients with chronic bronchitis and allergic rhinitis. Normal healthy subjects also may develop a transient BHR after viral respiratory infections or exposure to ozone. However, the degree of BHR is quantitatively greater in asthmatic patients than in other groups. Bronchial responsiveness of the general population fits a unimodal distribution that is skewed toward increased reactivity. Patients with clinical asthma represent the extreme end of the distribution. The degree of BHR within asthmatics correlates with the clinical course of their disease and medication requirement necessary to control symptoms. Patients with mild symptoms or in remission demonstrate lower levels of responsiveness, although greater than the normal population. It is currently understood that the increased BHR seen in asthma is at least in part owing to an inflammatory response within the airways.⁸
Early investigations found correlations with inflammatory cells in bronchoalveolar lavage fluids and degree of BHR. Newer evidence suggests that airways remodeling, subepithelial fibrosis, or collagen deposition also correlates with BHR, although the precise link is unknown. BHR therefore is in part related to the extent of inflammation in the airways.8

Remodeling of the Airways

Acute inflammation is a beneficial, nonspecific response of tissues to injury and generally leads to repair and restoration of the normal structure and function. In contrast, asthma represents a chronic inflammatory process of the airways followed by healing. That result in an altered structure referred to as a remodeling of the airways.8

Repair involves replacement of injured tissue by parenchymal cells of the same type and replacement by connective tissue and its maturation into scar tissue. In asthma, the repair process can be followed by complete or altered restitution of airways structure and function, presenting as fibrosis and an increase in smooth muscle and mucus gland mass.8 The exact mechanisms of remodeling of the airways are still not established and are currently under study. Airways remodeling is of concern because it may represent an irreversible process that can have more serious consequence such as the development of chronic obstructive pulmonary disease. Observations in children with asthma indicate that some loss of lung function may occur during the first 5 years of life. One of the greatest concerns is that no current therapies have been shown to alter either early decreased lung growth or later increased loss of lung function.8

Mucus Production

The mucociliary system is the lung’s primary defense mechanism against irritants and infectious agents. Mucus, composed of 95% water and 5% glycoproteins, is produced by bronchial epithelial glands and goblet cells. The lining of the airways consists of a continuous aqueous layer controlled by active ion transport across the epithelium in which water moves toward the lumen along the concentration gradient. Catecholamine’s and vagal stimulation enhance the ion transport and fluid movement. Mucus transport depends on the visco-elastic properties of the mucus. Mucus that is either too watery or too viscous will not be transported optimally.9

The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. The bronchial glands are increased in size and the goblet cells are increased in size and number in asthma. Expectorated mucus from patients with asthma tends to have a high viscosity. The mucus plugs in the airways of patients reaching mortality by status asthmatics were observed to be tenacious and were connected by mucous strands to the goblet cells. Asthmatic airways also may become plugged with casts consisting of epithelial and inflammatory cells. Although it is tempting to speculate that death from asthma attacks is a result of the mucus plugging that resulted in irreversible obstruction, there is still no evidence of such. Autopsies of asthmatics reaching mortality by other causes have shown similar pathology. In addition, some subjects that reached mortality due to sudden severe asthma did not show the characteristic mucus plugging on necropsy.9

Airway Smooth Muscle

The smooth muscle of the airways does not form a uniform coat around the airways but is wrapped around in a connecting network best described as a spiral arrangement. The muscle contraction displays a sphincteric action that is capable of completely occluding the airway lumen. The airway smooth muscle extends from the trachea through the respiratory bronchioles.
When expressed as a percentage of wall thickness, the smooth muscle represents 5% of the large central airways and up to 20% of the wall thickness in the bronchioles. Total smooth muscle mass decreases rapidly past the terminal bronchioles to the alveoli, so the contribution of smooth muscle tone to airway diameter in this region is relatively small. In the large airways of asthmatics, smooth muscle may account for 11% of the wall thickness. It is possible that the increased smooth muscle mass of the asthmatic airways is important in magnifying and maintaining BHR in chronic asthma. However, it appears that the hypertrophy and hyperplasia are secondary processes caused by chronic inflammation and are not the primary cause of BHR.¹⁰

**Neural Control/Neurogenic Inflammation**

The airway is innervated by parasympathetic, sympathetic, and non-adrenergic inhibitory nerves. Parasympathetic innervations of the smooth muscle consist of efferent motor fibers in the vagus nerves and sensory afferent fibers in the vagus and other nerves. The normal resting tone of human airway smooth muscle is maintained by vagal efferent activity.

Maximum broncho-constriction mediated by vagal stimulation occurs in the small bronchi and is absent in the small bronchioles. The nonmyelinated C fibers of the afferent system lie immediately beneath the tight junctions between epithelial cells lining the airway lumen. These endings probably represent the irritant receptors of the airways. Stimulation of these irritant receptors by mechanical stimulation, chemical and particulate irritants, and pharmacologic agents such as histamine produces reflex bronchoconstriction.¹¹ The nonadrenergic noncholinergic (NANC) nervous system has been described in the trachea and bronchi. Substance P, Neurokinin A (NK-A), Neurokinin B (NK-B), and vasoactive intestinal peptide are the best-characterized neurotransmitters in the NANC nervous system. Vasoactive intestinal peptide is an inhibitory neurotransmitter in the system. Inflammatory cells in asthma can release peptidases that can degrade vasoactive intestinal peptide, producing exaggerated reflex cholinergic bronchoconstriction. NANC excitatory neuropeptides such as substance P and Neurokinin A (NK-A) are released by stimulation of C-fiber sensory nerve endings.¹¹ The NANC system may play an important role in amplifying inflammation in asthma by releasing nitric oxide.¹²

**Nitric Oxide**

Nitric Oxide is produced by cells within the respiratory tract. It has been thought as a neurotransmitter of the NANC nervous system. Endogenous NO is generated from the amino acid L-arginine by the enzyme NO synthase. There are three isoforms of NO synthase. One isoform is induced in response to proinflammatory cytokines, inducible NO synthase, in airway epithelial cells and inflammatory cells of asthmatic airways. NO produces smooth muscle relaxation in the vasculature and bronchial; however, it appears to amplify the inflammatory process and is unlikely to be of therapeutic benefit. The measurement fraction of exhaled NO (FeNO) concentrations is a useful measure of ongoing lower airways inflammation in patients with asthma and for guiding asthma therapy.¹²

**Clinical Features of Asthma**

General features of asthma include intermittent wheezing, coughing and breathlessness, triggering factors, symptoms that follow a diurnal pattern where nocturnal cough may be the only symptom, morning tightness and wheezing that occurs usually within seconds of wakening and may take minutes or hours to resolve may also be seen.
Characteristically asthmatic patients suffer early morning attacks - morning dips. These may occur in the early hours, e.g. 3 or 4 am, and the patient may disrupt sleep with chest tightness, cough and wheezing. These attacks may be confused with paroxysmal nocturnal dyspnea due to left ventricular failure. The symptom of nocturnal chest tightness is a diagnostic pointer to asthma.13

Clinical features that occur in between attack include sometimes no signs, sometimes signs of chronic asthma like Harrison's sulcus and may be features of Churg-Strauss syndrome, i.e. nasal polyps and skin rashes. Clinical features that occur during an attack include decreased peak flow, tachypnoea, use of accessory muscles of respiration, hyperinflation, barrel chest, prolonged expiration, on auscultation there are widespread polyphonic and high pitched wheezes.13

In a severe attack the patient may be fearful and exhausted. Various clinical features are significant in assessing its severity such as difficulty in speaking in which the patient is so tachypnoeic and breathless that they have difficulty in forming phrases or sentences, besides this tachycardia occurs (greater than 110 per minute) where as in a very severe attack the pulse becomes bradycardic, pulsus paradoxus occurs-this indicates severe airflow limitation, silent chest - in a patient who is extremely breathless this implies that airflow restriction is severe enough to totally restrict airflow to parts of the lung, drowsiness due to hypercapnia- this occurs only in a preterminal attack and is a very sinister sign, cyanosis may also occur in the preterminal state also investigations may reveal type II respiratory failure.13

Diagnostic Test for Asthma

During the process of being diagnosed with asthma or during the course of treatment, a patient undergoes different types of tests. Some of the tests are undergone fairly frequently, while some patients never undergo others. Peak Flow is probably the simplest test that patients use it to see how well an asthmatic is responding which is an integral part of asthma care plan. Peak flows can easily be done at home with an inexpensive device called a peak flow meter. Peak flow measure how fast air can be removed from lungs. Spirometry is slightly more complicated than peak flow in that it is usually done at a clinic and measures how fast a measured amount of air is removed from lungs. It is vital in both the diagnosis and management of asthma over time. The asthma care provider may want to determine the lung volumes and diffusing capacity. This is often done if diagnosis is unclear. The test requires a patient to sit inside a special box that determines how much air is breathed in and out. The asthma care provider may order body plethysmography test to determine lung volumes. Asthma can cause certain changes in lung volumes that assist in diagnosing or treating asthma.14 Diffusion capacity measures how well oxygen flows from the lungs into blood. Poor diffusion indicates damage to the lung where the oxygen and blood meet in the lungs. Diffusion capacity is usually normal in asthmatics. A chest x-ray is a test commonly performed for patients who wheeze. An asthma care provider will usually order one to make sure there is not some other condition that may be causing symptoms like a lung infection. When an asthma care provider orders a broncho provoked test, you will inhale a specific substance through a nebulizer, often methacholine or histamine. This is done to see if lungs become irritated, hyper-responsive, and lead to the development of asthma symptoms. This test has a high negative predictive value. It means that if the test is negative it is unlikely the patient has asthma. Pulse oximetry is a non-invasive way to measure oxygenation of blood or how well oxygen is being exchanged between the lungs and the blood. A sensor is
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placed on the fingertip or other thin part of the body with blood vessels close to the skin. The sensor measures changes in wavelengths of light and is able to estimate oxygenation in the blood.\textsuperscript{14}

An arterial blood gas (ABG) is an arterial blood sample is used to determine how well blood is oxygenated; a biomarker for oxygen exchange between the lungs and the blood. Commonly, a blood sample will be obtained from one of the arteries near the wrist. This test may likely be performed during an acute asthma exacerbation and is more reliable than pulse oximetry.\textsuperscript{14}

The relationship between allergies and asthma has been known for a long time. Allergens normally breathed in increase the inflammatory reaction and hyper-responsiveness in lungs. However, a doctor cannot reliably determine if a particular allergen is responsible for symptoms on clinical grounds alone. Because of this, an asthma care provider may recommend allergy testing. Not all asthmatics are tested. But if a patient has persistent asthma, an asthma care provider will recommend further testing.\textsuperscript{14}

**Treatment**

**Aerosol Delivery of Drugs**

Topical application of drugs to the lungs can be accomplished by use of aerosols. In theory, this approach should produce a high local concentration in the lungs with a low systemic delivery, thereby significantly minimizing systemic side effects.\textsuperscript{15} The drugs used most commonly in the treatment of asthma, adrenergic receptor agonists and glucocorticoids, have potentially serious side effects when delivered systemically. Since the pathophysiology of asthma appears to involve the respiratory tract alone, the advantages of aerosol treatments with limited systemic effects are substantial. Indeed, in clinical practice, probably more than 90% of asthmatic patients who are capable of manipulating inhaler devices can be managed by aerosol treatments alone.

The critical determinant of the delivery of any particulate matter to the lungs is the size of the particles. Particles larger than 10 um are deposited primarily in the mouth and oropharynx, whereas particles smaller than 0.5 mm are inhaled to the alveolae and subsequently exhaled without being deposited in the lungs. Particles with a diameter of 1 to 5 mm allow deposition of drugs in the small airways and therefore are the most effective. There is no aerosol system in clinical use can produce uniform particles limited to the appropriate size range. A number of factors in addition to particle size determine effective deposition of drugs in the bronchial tree, including the rate of breathing and breath-holding after inhalation. It is recommended that a slow, deep breath be taken and held for 5 to 10 seconds when administering drugs to the lungs.\textsuperscript{15}

In ideal circumstances only a small fraction of the aerosolized drug is deposited in the lungs, typically 2% to 10%. Most of the remainder is swallowed.\textsuperscript{14} Therefore, to minimize systemic effects, an aerosolized drug should be either poorly absorbed from the gastrointestinal system or rapidly inactivated via first-pass hepatic metabolism. Furthermore, any maneuvers that increase deposition in the lungs or decrease the percentage of drug reaching the gastrointestinal system should enhance the desired effects and reduce undesired systematic effects. For example, with metered-dose inhalers, a large-volume "spacer" can be attached to the inhaler. A spacer is a tube or expandable bellows that fits between the inhaler and the patient's mouth; the inhaler discharges into the spacer, and the patient inhales from it. A spacer can improve markedly the ratio of inhaled to swallowed drug by limiting the amount of larger particles (>10 um) that reach the mouth and by reducing the need for the patient to coordinate accurately inhalation with inhaler
activation. More than 50% of patients using inhalers do not use proper technique and thus deposit too small a fraction of inhaled drug into the lungs.\textsuperscript{15}

The two types of devices used for aerosol therapy are metered-dose inhalers and nebulizers. Both devices provide a range of particle sizes that includes the desired 1 to 5 \(\mu\text{m}\) range. When used appropriately, they are equally effective in drug delivery to the lungs, even in the setting of fairly severe asthma exacerbations. Nevertheless, some clinicians and many patients prefer to use nebulizers for severe asthma exacerbations with poor inspiratory ability. Metered-dose inhalers offer the advantages of being cheaper and portable; nebulizers offer the advantage of not requiring hand-breathing coordination. In addition, nebulizer therapy can be delivered by facemask to young children or older patients who are confused. A substantial disadvantage of metered-dose inhalers is that most contain chlorofluorocarbons. Temporary exemptions have been given for these devices until safe alternative propellants can be developed.\textsuperscript{14} An albuterol metered-dose inhaler using hydrofluoroalkane as a propellant (Proventil HFA\textsuperscript{\textregistered}\textsuperscript{15}) is available for clinical use in the United States.\textsuperscript{16}

An alternative to aerosolized delivery is the use of dry-powder inhalers. These typically use lactose or glucose powders to carry the drugs. One disadvantage of these devices is that a relatively high airflow is needed to suspend the powder properly. Young children, the elderly, and those suffering from a significant asthma exacerbation may be unable to generate such airflow rates. The dry powder can be irritating when inhaled. Storage of dry-powder inhalers in areas where there are wide temperature fluctuations or high humidity can impair their performance.\textsuperscript{15} The asthma treatment scheme is given in Figure 3.

### \(\beta_2\) Adrenergic Receptor Agonists

**Mechanism of Action and Use in Asthma**

The \(\beta_2\) adrenergic receptor agonists available for the treatment of asthma are selective for the \(\beta_2\) receptor subtype. With few exceptions, they are delivered directly to the airways via inhalation. The agonists can be classified as short or long-acting. This subclassification is useful from a pharmacological perspective: Short-acting agonists are used only for symptomatic relief of asthma, whereas long-acting agonists are used prophylactically in the treatment of the disease. The mechanism of the anti-asthmatic action of \(\beta\) adrenergic receptor agonists is linked to the direct relaxation of airway smooth muscle and consequent bronchodilation. Although human bronchial smooth muscle receives little or no sympathetic innervation, it nevertheless contains large numbers of \(\beta_2\) adrenergic receptors. Stimulation of these receptors activates the Gs adenylyl cyclase-cyclic AMP pathway with a consequent reduction of smooth muscle tone. \(\beta_2\) Adrenergic receptor agonists also increase the conductance of large \(\text{Ca}^{2+}\)-sensitive \(\text{K}^+\) channels in airway smooth muscle, leading to membrane hyperpolarization and relaxation. This occurs at least partly by mechanisms independent of adenylyl cyclase activity and cyclic AMP production and may involve the regulation of capacitative \(\text{Ca}^{2+}\) entry by small G proteins.\textsuperscript{17} The mechanism is given in Figure 4.

There are \(\beta_2\) adrenergic receptors on cell types in the airways other than bronchial smooth muscle. Of particular interest, stimulation of \(\beta_2\) adrenergic receptors inhibits the function of numerous inflammatory cells, including mast cells, basophils, eosinophils, neutrophils, and lymphocytes. In general, stimulating \(\beta_2\) adrenergic receptors in these cell types increases intracellular cyclic AMP, activating a signaling cascade that inhibits the release of inflammatory mediators and
cytokines. As noted below, long-term exposure to β₂ agonists may desensitize some of these receptor-response pathways; thus there is little evidence that these drugs, used chronically, reduce airway inflammation.¹⁷

**Short-Acting β₂ Adrenergic Receptor Agonists**

Drugs in this class include albuterol (Proventil®, Ventolin®), levalbuterol, the (R)-enantiomer of albuterol (Xopenex®), metaproterenol (Alupent®), terbutaline (Brethaire®), and pirbuterol (Maxair®). These drugs are used for acute inhalation treatment of bronchospasm. Terbutaline (Brethine®, Bricanyl®), albuterol, and metaproterenol also are available in oral dosage form. Each of the inhaled drugs has an onset of action within 1 to 5 minutes and produces bronchodilation that lasts for about 2 to 6 hours. When given in oral dosage forms, the duration of action is somewhat longer (oral terbutaline, for example, has a duration of action of 4 to 8 hours). Although there are slight differences in the relative β₂/β₁-receptor potency ratios among the drugs, all of them are selective for the β₂ subtype.¹⁷

The most effective drugs in relaxing airway smooth muscle and reversing bronchoconstriction are short-acting β₂ adrenergic receptor agonists. They are the preferred treatment for rapid symptomatic relief of dyspnea associated with asthmatic bronchoconstriction. Although these drugs are prescribed on an as-needed basis, it is imperative that guidelines be given to the patient so that reliance on relief of symptoms during times of deteriorating asthma does not occur. When the asthma symptoms become persistent, the patient should be reevaluated so that those drugs that control this disease can be prescribed.¹⁷

**Long-Acting β Adrenergic Receptor Agonists**

Salmeterol xinafoate Serevent® and formoterol (Foradil®) are long-lasting adrenergic agents with very high selectivity for the β₂-receptor subtype. Inhalation of salmeterol provides persistent bronchodilation lasting over 12 hours. The mechanism underlying the extended duration of action of salmeterol is not yet fully understood. The extended side chain on salmeterol renders it 10,000 times more lipophilic than albuterol. The lipophilicity regulates the diffusion rate away from the receptor by determining the degree of partitioning in the lipid bilayer of the membrane. Subsequent to binding the receptor, the less lipophilic, short-acting agonists are removed rapidly from the receptor environment by diffusion in the aqueous phase. Unbound salmeterol, by contrast, persists in the membrane and only slowly dissociates from the receptor environment. Long-acting β adrenergic receptor agonists relax airway smooth muscle and cause bronchodilation by the same mechanisms as short-duration agonists. Chronic treatment with a receptor agonist often leads to receptor desensitization and a diminution of effect. The rate and degree of β₂ adrenergic receptor desensitization depend on the cell type. Several studies have evaluated the effect of adding a long-acting β₂ adrenergic agonist to inhaled glucocorticoid treatment in patients with persistent asthma. Combinations examined include salmeterol-fluticasone and formoterol-budesonide. The data suggest that adding a long-acting β₂ adrenergic agonist to the inhaled steroid regimen is more effective than doubling the steroid dose. Thus, current management guidelines for asthma recommend that long-acting β₂ adrenergic agonists be added if symptoms persist in patients on low or medium doses of inhaled steroids. Because chronic treatment with long-lasting inhaled β₂...
adrenergic agonists does not decrease airway inflammation significantly, most experts do not use them as sole agents for asthma treatment.\textsuperscript{17}

**Toxicity**

A portion of inhaled drug is inevitably absorbed into the systemic circulation. At higher doses, therefore, these drugs may lead to increased heart rate, cardiac arrhythmias, and central nervous system (CNS) effects associated with $\beta_2$ adrenergic receptor activation. This is of particular concern in patients with poorly controlled asthma, in whom there may be excessive and inappropriate reliance on symptomatic treatment with short-acting $\beta$ receptor agonists.\textsuperscript{17}

**Oral Therapy with $\beta_2$ Adrenergic Receptor Agonists**

The use of orally administered $\beta_2$ adrenergic agonists for broncho-dilation has not gained wide acceptance largely because of the greater risk of side effects, especially tremulousness, muscle cramps, cardiac tachyarrhythmias, and metabolic disturbances. There are two primary situations in which oral $\beta_2$ adrenergic agonists are used. First, brief courses of oral therapy (albuterol or metaproterenol syrups) are well tolerated and effective in young children (<5 years old) who cannot manipulate metered-dose inhalers yet have occasional wheezing with viral upper respiratory infections. Second, in some patients with severe asthma exacerbations, any aerosol, whether delivered via a metered-dose inhaler or a nebulizer, can worsen cough and bronchospasm owing to local irritation. In this setting, oral therapy with $\beta_2$ adrenergic agonists (e.g., albuterol, metaproterenol, or terbutaline tablets) can be effective. However, the frequency of adverse systemic side effects with orally administered agents is higher in adults than in children. Even though stimulation of $\beta_2$ adrenergic receptors inhibits the release of inflammatory mediators from mast cells, long-term administration of $\beta_2$-agonists, either orally or by inhalation, does not reduce bronchial hyper responsiveness. Thus, other approaches are preferred for the treatment of chronic symptoms. As discussed below under "Pharmacogenetics," polymorphisms of the $\beta_2$ adrenergic receptor may correlate with response to therapy and adverse effects with $\beta_2$-agonists.\textsuperscript{17}

**Glucocorticoids**

Systemic glucocorticoids long have been used to treat severe chronic asthma or severe acute exacerbations of asthma. The development of aerosol formulations significantly improved the safety of glucocorticoid treatment, allowing it to be used for moderate asthma.\textsuperscript{26}

**Mechanism of Glucocorticoid Action in Asthma**

Asthma is associated with airway inflammation, airway hyper reactivity, and acute bronchoconstriction. Glucocorticoids do not directly relax airway smooth muscle and thus have little effect on acute bronchoconstriction. By contrast, these agents are singularly effective in inhibiting airway inflammation. Very few mechanisms of inflammation escape the inhibitory effects of these drugs. The anti-inflammatory effects of glucocorticoids in asthma include modulation of cytokine and chemokine production; inhibition of eicosanoid synthesis; marked inhibition of accumulation of basophils, eosinophils, and other leukocytes in lung tissue; and decreased vascular permeability.\textsuperscript{26} The mechanism of glucocorticoid action in asthma is given in Figure 5.

**Inhaled Glucocorticoids**

Although glucocorticoids are very effective in controlling asthma, treatment with systemic glucocorticoids comes at the cost of considerable adverse effects. A major advance in asthma therapy was the
development of inhaled glucocorticoids that targeted the drug directly to the relevant site of inflammation. There are currently five glucocorticoids available in the United States for inhalation therapy: beclomethasone dipropionate (Beclovent®), triamcinolone acetonide (Azmacort®), flunisolide (Aerobid®), budesonide (Pulmicort®), and fluticasone propionate (Flovent®). While they differ markedly in their affinities for the glucocorticoid receptor, with fluticasone and budesonide having much higher affinities than beclomethasone, they are all effective in controlling asthma at the appropriate doses. Inhaled glucocorticoids are used prophylactically to control asthma rather than acutely to reverse asthma symptoms. The newer, highly potent drugs (e.g., fluticasone, flunisolide, and budesonide) can be effective with as little as one or two puffs administered twice or even once daily. The appropriate dose of steroid must be determined empirically. Important variables that influence the effective dose include the severity of disease, the particular steroid used, and the device used for drug delivery, which determines the actual quantity of drug delivered to the lungs. Asthmatic patients maintained on inhaled glucocorticoids show improvement in symptoms and lowered requirements for "rescue" with β2 adrenergic agonists. Beneficial effects may be seen within 1 week; however, improvement, in terms of reduced bronchial hyper reactivity, may continue for several months. Inhaled glucocorticoids are superior to inhaled β2-agonists for symptom control.

Systemic Glucocorticoids

Systemic glucocorticoids are used for acute asthma exacerbations and chronic severe asthma. Substantial doses of glucocorticoids (e.g., 40 to 60 mg prednisone or equivalent daily for 5 days; 1 to 2 mg/kg per day for children) often are used to treat acute exacerbations of asthma. Although an additional week at somewhat reduced dosage may be required, the steroids can be withdrawn abruptly once control of the symptoms by other medications has been restored; any suppression of adrenal function dissipates within 1 to 2 weeks. More protracted bouts of severe asthma may require longer treatment and slower tapering of the dose to avoid exacerbating asthma symptoms and suppressing pituitary/adrenal function. Previously, alternate-day therapy with oral prednisone was employed commonly in persistent asthma. Now most patients with asthma are better treated with inhaled glucocorticoids.

Toxicity Inhaled Glucocorticoids

Some portion of any inhaled drug is swallowed. Therefore, inhaled drugs can reach the circulation by direct absorption from the lung or by absorption from the gastrointestinal tract. The newer glucocorticoids have extremely low oral bioavailability owing to extensive first-pass metabolism by the liver and reach the circulation almost exclusively by absorption from the lung. In contrast to the beneficial effects on asthma, which plateau at about 1600 µg/day, the probability of adverse effects continues to increase at higher doses. Oropharyngeal candidiasis and, more frequently, dysphonia can be encountered. The incidence of candidiasis can be reduced substantially by rinsing the mouth and throat with water after each use and by employing spacer or reservoir devices attached to the dispenser to decrease drug deposition in the oral cavity. Apprecciable suppression of the hypothalamic-pituitary-adrenal axis is difficult to document at doses below 800 µg/day and probably is rarely of physiologic importance even at doses up to 1600 µg/day. Others have shown increases in markers for bone mineral turnover (serum osteocalcin and urine hydroxyl-proline levels) during treatment with inhaled glucocorticoids.
Systemic Glucocorticoids
The adverse effects of systemic administration of glucocorticoids are well known, but treatment for brief periods (5 to 10 days) causes relatively little dose-related toxicity. The most common adverse effects during a brief course are mood disturbances, increased appetite, impaired glucose control in diabetics, and candidiasis.26

Leukotriene-Receptor Antagonists and Leukotriene-Synthesis Inhibitors
Zafirlukast (Accolate\textsuperscript{833}) and montelukast (Singulair\textsuperscript{834}) are leukotriene-receptor antagonists. Zileuton (Zyflo\textsuperscript{835}) is an inhibitor of 5-lipoxygenase, which catalyzes the formation of leukotrienes from arachidonic acid.32

Pharmacokinetics and Metabolism
The leukotriene-modifying drugs are administered orally. Zafirlukast is absorbed rapidly, with greater than 90% bioavailability. At therapeutic plasma concentrations, it is over 99% protein-bound. Zafirlukast is metabolized extensively by hepatic CYP2C9. The parent drug is responsible for its therapeutic activity, with metabolites being less than 10% as effective. The half-life of zafirlukast is approximately 10 hours. Montelukast is absorbed rapidly, with about 60% to 70% bioavailability. At therapeutic concentrations, it is highly protein-bound (99%). It is metabolized extensively by CYP3A4 and CYP2C9. The half-life of montelukast is between 3 and 6 hours. Zileuton is absorbed rapidly on oral administration and is metabolized extensively by CYPs and by UDP-glucuronosyl transferases. The parent molecule is responsible for its therapeutic action. Zileuton is a short-acting drug with a half-life of approximately 2.5 hours and also is highly protein-bound (93%).32

Mechanism of Action in Asthma
Leukotriene-modifying drugs act either as competitive antagonist of leukotriene receptors or by inhibiting the synthesis of leukotrienes.

Leukotriene-Receptor Antagonists
Cysteinyl leukotrienes (cys-LTs) include leukotriene C4 (LTC\textsubscript{4}), leukotriene D4 (LTD\textsubscript{4}), and leukotriene E4 (LTE\textsubscript{4}). All the cys-LTs are potent constrictors of bronchial smooth muscle. On a molar basis, LTD\textsubscript{4} is approximately 1000 times more potent than is histamine as a broncho-constrictor. The receptor responsible for the broncho-constrictor effect of leukotrienes is the cys-LT\textsubscript{1} receptor. Although each of the cys-LTs is an agonist at the cys-LT\textsubscript{1} receptor, LTE\textsubscript{4} is less potent than either LTC\textsubscript{4} or LTD\textsubscript{4}. Zafirlukast and montelukast are selective high-affinity competitive antagonists for the cys-LT\textsubscript{1} receptor. Pranlukast is another cys-LT\textsubscript{1} receptor antagonist used in some countries in the treatment of asthma, but it is not approved for use in the United States. Inhibition of cys-LT\textsubscript{1}-induced bronchial smooth muscle contraction likely is involved in the therapeutic effects of these agents to relieve the symptoms of asthma. The effects of cys-LTs that are potentially relevant to bronchial asthma are not limited to bronchial smooth muscle contraction. Cys-LTs can increase micro vascular leakage, increase mucous production, and enhance eosinophil and basophil influx into the airways. The extent to which inhibiting these non-smooth muscle effects of leukotrienes contributes to the therapeutic effects of the drugs is not known.32

Leukotriene-Synthesis Inhibitors
The formation of leukotrienes depends on lipoxygenation of arachidonic acid by 5-lipoxygenase. Zileuton is a potent and selective inhibitor of 5-lipoxygenase activity and thus inhibits the formation of all 5-lipoxygenase products. Thus, in addition to inhibiting the formation of the cys-LTs,
zileuton also inhibits the formation of leukotriene B₄ (LTB₄), a potent chemotactic autacoid, and other eicosanoids that depend on leukotriene A₄ (LTA₄) synthesis. In theory, the therapeutic effects of a 5-lipoxygenase inhibitor would include all those observed with the cys-LT-1 receptor antagonists, as well as other effects that may result from inhibiting the formation of LTB₄ and other 5-lipoxygenase products. The pharmacological actions of cys-LTs are not fully accounted for by activation of the cys-LT-1 receptor. For example, cys-LT-induced contraction of vascular smooth muscle and stimulation of expression of P-selection by endothelial cells occur via cys-LT-2 receptors. This provides another theoretical advantage of zileuton over zafirlukast and montelukast because 5-lipoxygenase inhibitors would inhibit cys-LT effects regardless of the receptor subtypes involved. These theoretical advantages to date do not prove that zileuton is significantly more efficacious than the cys-LT-1 receptor antagonists in the treatment of asthma.

Toxicity

There are few adverse effects directly associated with inhibition of leukotriene synthesis or function. This likely is due to the fact that leukotriene production is limited predominantly to sites of inflammation.

Zafirlukast and Montelukast

In large clinical studies the adverse-effect profiles of these drugs were similar to that observed with placebo treatment. Very rarely, patients taking these drugs develop systemic eosinophilia and a vasculitis with features similar to Churg-Strauss syndrome. This problem, often associated with a reduction in glucocorticoid therapy, may represent the unmasking of a preexisting disease. Zafirlukast, but not montelukast, may interact with warfarin and increase prothrombin times, which should be monitored in patients subject to this interaction.

Zileuton

The adverse-effect profile in patients taking zileuton is similar to that in patients taking placebo. In about 4% to 5% of patients taking zileuton, however, there is an elevation in liver enzymes, generally within the first 2 months of therapy. Zileuton decreases the steady-state clearance of theophylline, substantially increasing its plasma concentrations. Zileuton also decreases warfarin clearance.

Use in Asthma

Although leukotriene inhibitors are effective prophylactic treatment for mild asthma, their role in asthma therapy is not clearly defined. Most clinical trials with these drugs have studied patients with mild asthma who were not taking glucocorticoids. In general, the studies show a modest but significant improvement in pulmonary function and a decrease in symptoms and asthma exacerbations. In a meta-analysis of clinical trials with zafirlukast, there was decrease in the rate of asthma exacerbations, with an average reduction of 50%. When zafirlukast and montelukast were compared with low-dose inhaled glucocorticoid therapy, the improvement in lung function and decreased dependence on short-acting β₂ adrenergic receptor agonist therapy was found to be greater in the glucocorticoid treated subjects. There was little difference, however, between the steroid and montelukast treated subjects in the reduction in rate of asthma exacerbations.

Anti-IgE Therapy

Omalizumab (Xolair®) is the first "biological drug" approved for the treatment of asthma. Omalizumab is a recombinant humanized monoclonal antibody targeted against IgE. IgE bound to omalizumab cannot
bind to IgE receptors on mast cells and basophils, thereby preventing the allergic reaction at a very early step in the process.\textsuperscript{36}

**Pharmacokinetics and Metabolism**

Omalizumab is delivered as a single subcutaneous injection every 2 to 4 weeks. It has a bioavailability of about 60%, reaching peak serum levels after 7 to 8 days. The serum elimination half-life is 26 days, with a clearance rate of about 2.5 ml/kg per day. The elimination of omalizumab-IgE complexes occurs in the liver reticuloendothelial system at a rate somewhat faster than that of free IgG. Some intact omalizumab is also excreted in the bile. There is little evidence of specific uptake of omalizumab by any tissue.\textsuperscript{36,37}

**Mechanism of Action**

The Fc region of IgE binds with high affinity to the Fc epsilon receptor I (Fc and RI). Fc and RI is expressed on the surfaces of mast cells and basophils, as well as several other cell types. When an allergen interacts with the antigen-binding domains of IgE bound to Fc & RI on mast cells and basophils, it cross-links the receptors and activates the cell. This, in turn, triggers the release of preformed granule-associated mediators such as histamine and tryptase. In addition, it results in the immediate production of eicosanoids, most notably LTC-4 and prostaglandin D\textsubscript{2} (PGD\textsubscript{2}) and, on a time scale of hours instead of minutes, the synthesis of various cytokines. Omalizumab is an IgG antibody for which the antigen is the Fc region of the IgE antibody; thus it is an "anti-antibody antibody." Omalizumab binds tightly to free IgE in the circulation to form omalizumab-IgE complexes that have no affinity for Fc and RI. At the recommended doses, omalizumab reduces free IgE by more than 95%, thereby limiting the amount of IgE bound to Fc&RI bearing cells. Omalizumab treatment also decreases the amount of Fc and RI expressed on basophils and mast cells. For example, after treatment with omalizumab, the number of Fc and RIs expressed on the surfaces of basophils decreased by more than 95% from a starting value of about 200,000 receptors per cell.\textsuperscript{36,37} This decrease in surface Fc and RIs results from increased turnover of unbound receptors rather than decreased Fc and RI synthesis. Thus the effectiveness of omalizumab in reducing the amount of allergen-specific IgE bound to mast cells and basophils depends on the reduction of both free IgE and available Fc and RIs on cell surfaces. Normally, IgE-mediated basophil activation is extremely efficacious, requiring antigen to interact with only a small fraction of the bound IgE to evoke a half-maximal response. This predicts that drugs such as omalizumab will have little clinical effect until doses are given that reduce free IgE by greater than 90%. Besides mast cells and basophils, monocytes, lymphocytes, certain antigen presenting cells, and eosinophils express Fc and RI. The effects of omalizumab on decreasing IgE binding and Fc and RI expression on these cells also may contribute to the therapeutic effect of omalizumab.\textsuperscript{37}

**Toxicity**

The safety of omalizumab so far has been evaluated in only three large, randomized, placebo-controlled multicenter studies. Omalizumab generally was well tolerated in several large, placebo-controlled trials. The most frequent adverse effect was injection-site reactions (e.g., redness, stinging, bruising, and induration), but these reactions also were seen at comparable frequencies with placebo. Low titers of antibodies against omalizumab developed in 1 of 1723 treated patients, whereas anaphylaxis was seen in 0.1% of treated patients.\textsuperscript{37}

**Use in Asthma**

Omalizumab is indicated for adults and adolescents older than 12 years of age with allergies and moderate-to-severe
persistent asthma. In this population, omalizumab has proven to be effective in reducing the dependency on inhaled and oral corticosteroids and in decreasing the frequency of asthma exacerbations. Omalizumab is not an acute bronchodilator and should not be used as a rescue medication or as a treatment of status asthmaticus. Based on its mechanism of action, omalizumab has been used in the treatment of other allergic disorders, such as nasal allergy and food allergy, but large-scale clinical trials are limited to asthma.

**Cromolyn Sodium and Nedocromil Sodium**

**Mechanism of Action**

Cromolyn and nedocromil have a variety of activities that may relate to their therapeutic efficacy in asthma. These include inhibiting mediator release from bronchial mast cells; reversing increased functional activation in leukocytes obtained from the blood of asthmatic patients; suppressing the activating effects of chemotactic peptides on human neutrophils, eosinophils, and monocytes; inhibiting parasympathetic and cough reflexes; and inhibiting leukocyte trafficking in asthmatic airways. The mechanism of action of cromolyn and nedocromil in asthma is not known.

**Pharmacokinetics**

For asthma, cromolyn is given by inhalation using either solutions (delivered by aerosol spray or nebulizer) or, in some countries except the United States, powdered drug (mixed with lactose and delivered by a special turboinhaler) is given. The pharmacological effects result from the topical deposition of the drug in the lung, since only about 1% of an oral dose of cromolyn is absorbed. Once absorbed, the drug is excreted unchanged in the urine and bile in about equal proportions. Peak concentrations in plasma occur within 15 minutes of inhalation, and excretion begins after some delay such that the biological half-life ranges from 45 to 100 minutes.

**Toxicity**

Cromolyn and nedocromil generally are well tolerated by patients. Adverse reactions are infrequent and minor and include bronchospasm, cough or wheezing, laryngeal edema, joint swelling and pain, angioedema, headache, rash, and nausea. Such reactions have been reported at a frequency of less than 1 in 10,000 patients. Very rare instances of anaphylaxis also have been documented. Nedocromil and cromolyn can cause a bad taste.

**Use in Asthma**

The main use of cromolyn (Intal) and nedocromil (Tilade) is to prevent asthmatic attacks in individuals with mild to moderate bronchial asthma. These agents are ineffective in treating ongoing bronchoconstriction. When inhaled several times daily, cromolyn inhibits both the immediate and the late asthmatic responses to antigenic challenge or to exercise. With regular use for more than 2 to 3 months, bronchial hyper reactivity is reduced, as measured by response to challenge with histamine or methacholine. Nedocromil generally is more effective than cromolyn in animal models and human beings. Nedocromil is approved for use in asthmatic patients 12 years of age and older; cromolyn is approved for all ages.

Cromolyn and nedocromil generally are less effective than inhaled glucocorticoids in controlling asthma. Cromolyn (2 mg inhaled four times daily) was less effective than 200 µg twice daily of beclomethasone or 4 mg four times daily of nedocromil. Although necrodomil was roughly comparable with 200 µg beclomethasone inhaled twice daily, nedocromil was not as effective in controlling
symptoms, reducing bronchodilator use, or improving bronchial hyperreactivity.\textsuperscript{38} 4 mg nedocromil four times daily is as effective as 100 µg beclomethasone four times daily.\textsuperscript{38} Also nedocromil is useful in patients with mild to moderate asthma as added therapy, as an alternative to regularly administered oral and inhaled β adrenergic agonists and oral methylxanthines, and possibly as an alternative to low-dose inhaled glucocorticoids. In patients with systemic mastocytosis who have gastrointestinal symptoms owing to an excessive number of mast cells in the gastrointestinal mucosa, an oral preparation of cromolyn (Gastrocrom\textsuperscript{41}) is effective in reducing symptoms. The benefits reflect local action rather than systemic absorption; cromolyn is poorly absorbed, and only the gastrointestinal symptoms are improved in the treated patients.\textsuperscript{38}

**Theophylline**

Theophylline, a methylxanthine, is among the least expensive drugs used to treat asthma, and consequently, it remains a commonly used drug for this indication in many countries. In industrialized countries, the advent of inhaled glucocorticoids, β\textsubscript{2} adrenergic receptor agonists, and leukotriene-modifying drugs has diminished theophylline use significantly, and it has been relegated to a 3\textsuperscript{rd} or 4\textsuperscript{th} line treatment in patients whose asthma is otherwise difficult to control.\textsuperscript{42}

**Mechanism of Action**

Theophylline inhibits cyclic nucleotide PDEs, thereby preventing breakdown of cyclic AMP and cyclic GMP to 5'-AMP and 5'-GMP, respectively. Inhibition of PDEs will lead to an accumulation of cyclic AMP and cyclic GMP, thereby increasing signal transduction through these pathways. The cyclic nucleotide PDEs are members of a super family of genetically distinct enzymes. Theophylline and related methylxanthines are relatively nonselective in the PDE subtypes they inhibit. Cyclic nucleotide production is regulated by endogenous receptor-ligand interactions leading to activation of adenylyl cyclase and guanylyl cyclase. Inhibitors of PDEs therefore can be thought of as drugs that enhance the activity of endogenous autocoids, hormones, and neurotransmitters that signal via cyclic nucleotide messengers. Theophylline is a competitive antagonist at adenosine receptors. Adenosine can act as an autocoid and transmitter with myriad biological actions of particular relevance to asthma are the observations that adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells.\textsuperscript{42}

Theophylline also may owe part of its anti-inflammatory action to its ability to activate histone deacetylases in the nucleus. In theory, the deacetylation of histones could decrease the transcription of several proinflammatory genes and potentiate the effect of corticosteroids.

**Pulmonary System**

Theophylline effectively relaxes airway smooth muscle; this bronchodilation likely contributes to its acute therapeutic efficacy in asthma. Both adenosine receptor antagonism and PDE inhibition are likely involved in the bronchodilating effect of theophylline. Adenosine does not contract isolated human bronchial smooth muscle directly, but when it is inhaled, it acts as a potent bronchoconstrictor in asthmatic subjects. Therefore, inhibition of this function of adenosine may contribute to theophylline-induced bronchodilation in some asthmatic subjects. Inhibition of PDE-4 and PDE-5 effectively relaxes human isolated bronchial smooth muscle. It thus seems likely that inhibition of PDEs also contributes to the bronchodilating effect of theophylline. Methyl xanthine enprofylline (3-
propylxanthine), in treatment of asthma in Europe population, also support a mechanistic role for PDE inhibition in the bronchodilator actions of theophylline. Enprofylline is more potent than theophylline as a bronchodilator but is much less potent in inhibiting most types of adenosine receptors. The latter point, however, must be interpreted cautiously. Activation of the A<sub>2</sub>B subtype of adenosine receptor causes several proinflammatory effects, and both theophylline and enprofylline are potent competitive antagonists of A<sub>2</sub>B adenosine receptors.

Theophylline also inhibits synthesis and secretion of inflammatory mediators from numerous cell types, including mast cells and basophils. This effect of theophylline likely is due to PDE inhibition and can be mimicked in large part with drugs that selectively inhibit PDE-4 isozyme. At therapeutic concentrations, the antiinflammatory effect of theophylline may be more relevant to the drug's therapeutic actions than direct bronchodilation, but this remains unproven. Consistent with an important role of PDE-4 in obstructive lung disease, selective PDE-4 inhibitors have been evaluated in clinical trials for the treatment of asthma and chronic obstructive pulmonary disease (COPD). In one study, cilomilast (Ariflo<sup>®</sup>; 15 mg twice daily for 10 weeks) decreased inflammatory cell infiltration significantly in bronchial biopsies of patients with COPD. Further studies are needed to define the role of PDE-4 inhibitors in asthma and COPD, but these drugs are promising candidates for new approaches to asthma therapy.

**Toxicology**

Fatal intoxications with theophylline have been much more frequent than with caffeine. Rapid intravenous administration of therapeutic doses of aminophylline (500 mg) sometimes results in sudden death that is probably due to cardiac arrhythmias, and the drug should be injected slowly over 20 to 40 minutes to avoid severe toxic symptoms. These include headache, palpitation, dizziness, nausea, hypotension, and precordial pain. Additional symptoms of toxicity include tachycardia, severe restlessness, agitation, and emesis; these effects are associated with plasma concentrations of more than 20 µg/ml. Focal and generalized seizures also can occur, sometimes without prior signs of toxicity. Most toxicity results from repeated administration of theophylline by either oral or parenteral routes. Although convulsions and death have occurred at plasma concentrations as low as 25 µg/ml, seizures are relatively rare at concentrations below 40 µg/ml. Patients with long-term theophylline intoxication appear to be much more prone to seizures than those who experience short-term overdoses. Treatment may include prophylactic administration of diazepam, perhaps in combination with phenytoin or phenobarbital; phenytoin also may be a useful alternative to lidocaine in the treatment of serious ventricular arrhythmias.

**Use in Asthma**

Theophylline has proven efficacy as a bronchodilator in asthma and formerly was considered first-line therapy. It now is relegated to a far less prominent role primarily because of the modest benefits it affords, its narrow therapeutic window, and the required monitoring of drug levels. Nocturnal asthma can be improved with slow-release theophylline preparations, but other interventions such as inhaled glucocorticoids or salmeterol probably are more effective. Therapy usually is initiated by the administration of 12 to 16 mg/kg per day of theophylline (calculated as the free base) up to a maximum of 400 mg/day for at least 3 days. Children younger than 1 year of age require considerably less; the dose in milligrams per kilogram per day may be calculated as 0.2 µ (age in weeks) + 5. Starting with these low doses minimizes the
early side effects of nausea, vomiting, nervousness, and insomnia that often subside with continued therapy and virtually eliminates the possibility of exceeding plasma concentrations of 20 µg/ml in patients older than age 1 year who do not have compromised hepatic or cardiac function.42 Thereafter, the dosage is increased in two successive stages to between 16 and 20 and, subsequently, 18 and 22 mg/kg per day (up to a maximum of 800 mg/day) depending on the age and clinical response of the patient and allowing at least 3 days between adjustments. The plasma concentration of theophylline is determined before a further adjustment in dosage is made. Although extended-release preparations of theophylline usually allow twice-daily dosing, variations in the rate and extent of absorption of such preparations require individualized calibration of dosing regimens for each patient and preparation.42

**Anticholinergic Agents**

With the advent of inhaled β adrenergic agonists, use of anticholinergic agents declined. Renewed interest in anticholinergic agents paralleled the realization that parasympathetic pathways are important in bronchospasm in some asthmatics and the availability of ipratropium bromide (Atrovent®), a quaternary muscarinic receptor antagonist that has better pharmacological properties than prior drugs. A particularly good response to ipratropium may be seen in the subgroup of asthmatic patients who experience psychogenic exacerbations. The cholinergic receptor subtype responsible for bronchial smooth muscle contraction is the muscarinic M₃ receptor. Although ipratropium and related compounds block all five muscarinic receptor subtypes with similar affinity, it is likely that M₃ receptor antagonism alone accounts for the bronchodilating effect. The bronchodilation produced by ipratropium in asthmatic subjects develops more slowly and usually is less intense than that produced by adrenergic agonists. Some asthmatic patients may experience a useful response lasting up to 6 hours.44

The variability in the response of asthmatic subjects to ipratropium presumably reflects differences in the strength of parasympathetic tone and in the degree to which reflex activation of cholinergic pathways participates in generating symptoms in individual patients. Combined treatment with ipratropium and β₂ adrenergic agonists results in slightly greater and more prolonged bronchodilation than with either agent alone in baseline asthma. In acute bronchoconstriction, the combination of a β₂ adrenergic agonist and ipratropium is more effective than either agent alone and more effective than simply giving more β₂ adrenergic agonist. A large multicenter study showed that certain asthma patients that had worst initial lung function benefited most from combination therapy.44 Thus the combination of a selective β₂ adrenergic agonist and ipratropium should be considered in acute treatment of severe asthma exacerbations. Ipratropium is available in metered-dose inhalers and as a nebulizer solution. A metered-dose inhaler containing a mixture of ipratropium and albuterol (Combivent®) also is available in the United States. In Europe, metered-dose inhalers containing a mixture of ipratropium and fenoterol are available (Duovent®, Berodual®). Recently, tiotropium (Spiriva®), a structural analogue of ipratropium, has been approved for the treatment of COPD and emphysema. Like ipratropium, tiotropium has high affinity for all muscarinic receptor subtypes, but it dissociates from the receptors much more slowly that ipratropium. In particular, binding and functional studies indicate that tiotropium dissociates from muscarinic M₃ receptors more slowly than from muscarinic M₂ receptors. The high affinity of tiotropium for muscarinic receptors, combined with its very
slow dissociation rate, permits once-daily dosing. The slow dissociation rate also provides a theoretical advantage in that it limits the capacity of large concentrations of the endogenous agonist acetylcholine to surmount the receptor blockade.\textsuperscript{44} According to the NICE guidelines, overview current asthma drugs is given in Table 1.

\textbf{Conclusion}

In conclusion, it is very essential to understand the complexities of asthma, its epidemiology, types, symptoms, and the underlying pathophysiology which can form a basis of understanding of the action of drugs used to treat this disease and its association with COPD. The symptoms of asthma and the diagnosis of asthma must be taken into special consideration in order to understand the underlying cause. The pharmacotherapy of asthma is complex and evolving, an understanding of the pharmacologic properties of the numerous agents involved in the treatment of asthma is critical for making rational drug choices and understanding potential side effects.\textsuperscript{1} Education regarding optimal medication use can help to improve asthma control by a pharmacist intervention which can significantly improve therapeutic outcomes in asthma patients, having a positive effect on the symptoms.\textsuperscript{49} The proper use and adherence to the right medication to patients with the help of a pharmacist physician collaboration can lead to substantial reduction in disease symptoms and improved clinical outcomes.\textsuperscript{49} Research is still going on various aspects associated with the disease which can become helpful in managing asthma more effectively.\textsuperscript{1,5}

\textbf{Conflict of Interests}

The authors declare no conflict of interest exists.

\textbf{Author’s Contribution}

All authors contributed equally in all aspects.

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### Table 1. Current Asthma Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Uses</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂ Agonists (albuterol, salmeterol)</td>
<td>Relaxation of bronchial smooth muscle</td>
<td>Long-acting inhaled forms for moderate to severe asthma</td>
<td>Skeletal muscle tremor, tachycardia, tolerance?</td>
</tr>
<tr>
<td>Corticosteroids (budesonide)</td>
<td>Broad antiinflammatory actions</td>
<td>Mild, moderate persistent asthma by inhaler</td>
<td>Cough, oral candidiasis, Systemic effects: growth suppression, adrenal suppression, osteoporosis</td>
</tr>
<tr>
<td>Methylxanthines (theophylline)</td>
<td>Relaxation of bronchial smooth muscle, effects on eosinophils &amp; T-cells, ↑ mucociliary clearance</td>
<td>Orally for severe asthma</td>
<td>Dose-dependent cardiac stimulation, CNS stimulation, gastric upset, weak diuresis</td>
</tr>
<tr>
<td>Cromolyn, Nedocromil</td>
<td>Inhibit release of inflammatory mediators</td>
<td>Mild persistent asthma</td>
<td>Cough, dryness, unpleasant taste. Rare dermatitis and myositis</td>
</tr>
<tr>
<td>Leukotriene Modifiers (zafirlukast, montelukast)</td>
<td>Antagonize the actions of the leukotrienes in the airways</td>
<td>Secondary choice in mild to moderate persistent asthma</td>
<td>Minor G.I complaints, headache, nausea</td>
</tr>
<tr>
<td>Mucociliary Antagonists (ipratropium)</td>
<td>Mucociliary blockade in the airways</td>
<td>Acute treatment of severe exacerbations with a β₂ agonist</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Monoclonal Antibodies (omalizumab)</td>
<td>Block IgE binding to mast cells</td>
<td>Patients with refractory severe asthma with IgE-mediated sensitivity</td>
<td>Injection site reactions drug antibodies increased malignancies?</td>
</tr>
</tbody>
</table>

Source: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2064896/table/T1/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2064896/table/T1/)

Graph 1. Epidemiological data of asthma in the United States

- **Population**: 7%
- **Prevalence Rate**: 9.60%
Graph 2. Epidemiological data of childhood asthma in Pakistan

Figure 1. Etiology of asthma, Pathogenesis

Source: http://Evvcomasthmapathogensis.jpg
**Figure. 2.** Pathophysiology of Asthma

Source: www.epgonline.org. altanaimages1388_011.jpg

**Figure. 3.** Treatment Scheme of Asthma

Source: http://www.erj.ersjournals.com/cgi/
Figure. 4. Mechanism of Action of Bronchodilators


Figure. 5. Mechanism of Glucocorticoid Action in Asthma

Source: wikimedia.org