Asthma - A Brief Outlook

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ABSTRACT
Asthma is disease of the human respiratory system in which the airways constrict and become narrow, often in response to a “trigger” such as exposure to an allergen, cold air, exercise or emotional stress. Due to rapid industrialization and urbanization, asthma prevalence is predicted to increase more rapidly in the coming years. Asthma is a common disease and acute severe asthma exacerbation can be lifethreatening. This article aims to review recent advances in understanding of risk factors, pathophysiology, diagnosis and treatment of severe asthma exacerbation.

Keywords: Asthma, Trigger, Exacerbation

INTRODUCTION
Asthma is a most common chronic disease of the airways that makes breathing difficult. With asthma, there is inflammation of the air passages that result in a temporary narrowing of the airways that carry oxygen to the lungs. This results in asthma symptoms, including coughing, wheezing, shortness of breath, and chest tightness. Some people refer to asthma as "bronchial asthma." Asthmatics usually experience these symptoms most frequently during the night and the early morning[1]. Pharmacists, as part of the health care team, help improve the pharmacologic management of asthma by teaching patients about their medications, how to use them, and the importance of using them as prescribed. Alert physicians to suspected problems, such as under using anti-inflammatory therapy or overusing inhaled bronchodilators, will provide an opportunity for the physician to consider changes in a patient's management plan when appropriate. Acting in these educational and information-sharing roles, pharmacists contribute to improving the control of asthma and enabling patients to live full, active, and productive lives.[2]

WHO Definition
Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become
worse during physical activity or at night. During an asthma attack, the lining of the bronchial tubes swell, causing the airways to narrow and reducing the flow of air into and out of the lungs. Recurrent asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism. Asthma has a relatively low fatality rate compared to other chronic diseases.\[^2\]

**What Is an Asthma Attack**

An asthma attack may include coughing, chest tightness, wheezing, and trouble breathing. The attack happens in your body’s airways, which are the paths that carry air to your lungs. As the air moves through your lungs, the airways become smaller, like the branches of a tree are smaller than the tree trunk. During an asthma attack, the sides of the airways in your lungs swell and the airways shrink. Less air gets in and out of your lungs, and mucous that your body makes clogs up the airways even more.

You can control your asthma by knowing the warning signs of an asthma attack, staying away from things that cause an attack, and following your doctor’s advice. When you control your asthma:

- you won’t have symptoms such as wheezing or coughing,
- you’ll sleep better,
- you won’t miss work or school,
- you can take part in all physical activities, and
- you won’t have to go to the hospital.\[^4\]

**Types of Asthma:**

**Child-Onset Asthma**

Asthma that begins during childhood is called child-onset asthma. This type of asthma happens because a child becomes sensitized to common allergens in the environment - most likely due to genetic reasons. The child is atopic - a genetically determined state of hypersensitivity to environmental allergens.

Allergens are any substances that the body will treat as a foreign body, triggering an immune response. These vary widely between individuals and often include animal proteins, fungi, pollen, house-dust mites and some kind of dust. The airway cells are sensitive to particular materials making an asthmatic response more likely if the child is
exposed to a certain amount of an allergen. The identification and management of this group of patients remains of major importance. [16]

Adult-Onset Asthma

This term is used when a person develops asthma after reaching 20 years of age. Adult-onset asthma affects women more than men, and it is also much less common than child-onset asthma.

It can also be triggered by some allergic material or an allergy. It is estimated that up to perhaps 50% of adult-onset asthmas are linked to allergies. However, a substantial proportion of adult-onset asthma does not seem to be triggered by exposure to allergen(s); this is called non-allergic adult-onset asthma. This non-allergic type of adult-onset asthma is also known as intrinsic asthma. Exposure to a particle or chemical in certain plastics, metals, medications, or wood dust can also be a cause of adult-onset asthma.

Exercise-Induced Asthma

If you cough, wheeze or feel out of breath during or after exercise, you could be suffering from exercise-induced asthma. Obviously, your level of fitness is also a factor - a person who is unfit and runs fast for ten minutes is going to be out of breath. However, if your coughing, wheezing or panting does not make sense, this could be an indication of exercise-induced asthma.

As with other types of asthma, a person with exercise-induced asthma will experience difficulty in getting air in and out of the lungs because of inflammation of the bronchial tubes (airways) and extra mucus.

Cough-Induced Asthma

Cough-induced asthma is one of the most difficult asthmas to diagnose. The doctor has to eliminate other possibilities, such as chronic bronchitis, post nasal drip due to hay fever, or sinus disease. In this case the coughing can occur alone, without other asthma-type symptoms being present. The coughing can happen at any time of day or night.

Occupational Asthma

This type of asthma is triggered by something in the patient's place of work. Factors such as chemicals, vapors, gases, smoke, dust, fumes, or other particles can trigger asthma. It
can also be caused by a virus (flu), molds, animal products, pollen, humidity and temperature. Another trigger may be stress. Occupational asthma tends to occur soon after the patients starts a new job and disappears not long after leaving that job.

**Nocturnal Asthma**

Nocturnal asthma occurs between midnight and 8 AM. It is triggered by allergens in the home such as dust and pet dander or is caused by sinus conditions. Nocturnal or nighttime asthma may occur without any daytime symptoms recognized by the patient. The patient may have wheezing or short breath when lying down and may not notice these symptoms until awoken by them in the middle of the night - usually between 2 and 4 AM.

**Steroid-Resistant Asthma (Severe Asthma)**

While the majority of patients respond to regular inhaled glucocorticoid (steroid) therapy, some are steroid resistant. Airway inflammation and immune activation play an important role in chronic asthma. Current guidelines of asthma therapy have therefore focused on the use of anti-inflammatory therapy, particularly inhaled glucocorticoids (GCs). By reducing airway inflammation and immune activation, glucocorticoids are used to treat asthma. However, patients with steroid resistant asthma have higher levels of immune activation in their airways than do patients with steroid sensitive (SS) asthma.\[^7\]

**Causes of an Asthma Attack:**

An asthma attack can happen when you are exposed to “asthma triggers. Some of the most common triggers are:

- **Tobacco Smoke:**
  Tobacco smoke is unhealthy for everyone, especially people with asthma. If you have asthma and you smoke, quit smoking.

- **Dust Mites:**
  Dust mites are tiny bugs that are in almost every home. If you have asthma, dust mites can trigger an asthma attack. To prevent attacks, use mattress covers and pillowcase covers to make a barrier between dust mites and yourself.

- **Outdoor Air Pollution:**
  Outdoor air pollution can trigger an asthma attack. This pollution can come from factories, automobiles, and other sources.
Cockroach Allergen
Cockroaches and their droppings can trigger an asthma attack. Get rid of cockroaches in your home by removing as many water and food sources as you can.

Pets
Furry pets can trigger an asthma attack. If you think a furry pet may be causing attacks, you may want to find the pet another home. If you can’t or don’t want to find a new home for the pet, keep it out of the person with asthma’s bedroom.

Mold
Breathing in mold can trigger an asthma attack. Get rid of mold in your home to help control your attacks. Humidity, the amount of moisture in the air, can make mold grow.

Smoke From Burning Wood or Grass
Smoke from burning wood or other plants is made up of a mix of harmful gases and small particles. Breathing in too much of this smoke can cause an asthma attack. If you can, avoid burning wood in your home.[4]

Allergies
Almost all asthma sufferers have allergies. In fact, over 25% of people who have hay fever (allergic rhinitis) also develop asthma. Allergic reactions triggered by antibodies in the blood often lead to the airway inflammation that is associated with asthma. Common sources of indoor allergens include animal proteins (mostly cat and dog allergens), dust mites, cockroaches, and fungi. It is possible that the push towards energy-efficient homes has increased exposure to these causes of asthma.[3]

Obesity
Overweight adults - those with a body mass index (BMI) between 25 and 30 - are 38% more likely to have asthma compared to adults who are not overweight. Obese adults - those with a BMI of 30 or greater - have twice the risk of asthma. According to some researchers, the risk may be greater for nonallergic asthma than allergic asthma.

Pregnancy
The way you enter the world seems to impact your susceptibility to asthma. Babies born by Caesarean sections have a 20% increase in asthma prevalence compared to babies born by vaginal birth. It is possible that immune system-modifying infections from bacterial exposure during Cesarean sections are responsible for this difference.
When mothers smoke during pregnancy, their children have lower pulmonary function. This may pose additional asthma risks.

Epidemiological studies showed that bronchial asthma is one of the most common diseases which can complicate pregnancy (1–7%).\[14\]

Stress
People who undergo stress have higher asthma rates. Part of this may be explained by increases in asthma-related behaviors such as smoking that are encouraged by stress. However, recent research has suggested that the immune system is modified by stress as well.

Genes
It is possible that some 100 genes are linked to asthma - 25 of which have been associated with separate populations as of 2005.

Mom and Dad may be partially to blame for asthma, since three-fifths of all asthma cases are hereditary. The Centers for Disease Control (USA) say that having a parent with asthma increases a person's risk by three to six times.

Airway Hyperreactivity
Researchers are not sure why airway hyperreactivity is another risk factor for asthma, but allergens or cold air may trigger hyperreactive airways to become inflamed. Some people do not develop asthma from airway hyperreactivity, but hyperreactivity still appears to increase the risk of asthma.

Atopy
Atopy - such as eczema (atopic dermatitis), allergic rhinitis (hay fever), allergic conjunctivitis (an eye condition) - is a general class of allergic hypersensitivity that affects different parts of the body that do not come in contact with allergens. Atopy is a risk factor for developing asthma.

Some 40% to 50% of children with atopic dermatitis also develop asthma, and it is probable that children with atopic dermatitis have more severe and persistent asthma as adults.[24]

Other Triggers
Infections linked to influenza (flu), colds, and respiratory syncytial virus (RSV) can trigger an asthma attack. Sinus infections, allergies, breathing in some chemicals, and acid reflux can also trigger attacks.

Physical exercise; some medicines; bad weather, such as thunderstorms or high humidity; breathing in cold, dry air; and some foods, food additives, and fragrances can also trigger an asthma attack.

Strong emotions can lead to very fast breathing, called hyperventilation, that can also cause an asthma attack.⁴ ³⁰

PATHOPHYSIOLOGY

Hypoxemia, hypercapnia, lactic acidosis, and dynamic hyperinflation are relevant pathophysiological events. Smooth muscle bronchoconstriction, airway edema and inflammation result in airway occlusion. Mucus plugs form the pathologic basis of gas-exchange abnormalities and lead to the development of extensive intrapulmonary shunting. Inhomogeneous distribution of areas of premature airway closure and obstruction cause ventilation/perfusion mismatching, thus resulting in hypoxemia and acidosis. In patients with severe respiratory acidosis caused by hypercapnia, metabolic acidosis may coexist. It may be related to diaphragmatic fatigue or the excessive use of β2-agonists. Elevated negative intrapleural pressure causes increased ventricular afterload and favors transcapillary filtration of fluid into airspaces, which at last leads to ventilation/perfusion mismatching and a high risk for pulmonary edema. Right-ventricular afterload may increase as a result of the pulmonary hypertension caused by lung hyperinflation. In advanced stages, the absence of pulsus paradoxus indicates ventilatory muscle fatigue and impending respiratory failure.⁵

![Pathophysiology of Asthma](image-url)
Major Features of Asthma

There are three major features of asthma:

1. **Airway obstruction.** During normal breathing, the bands of muscle that surround the airways are relaxed, and air moves freely. But in people with asthma, allergy-causing substances and environmental triggers make the bands of muscle surrounding the airways tighten, and air cannot move freely. Less air causes a person to feel short of breath, and the air moving through the tightened airways causes a whistling sound known as wheezing.

2. **Inflammation.** People with asthma have red and swollen bronchial tubes. This inflammation is thought to contribute greatly to the long-term damage that asthma can cause to the lungs. And, therefore, treating this inflammation is key to managing asthma in the long run.

3. **Airway irritability.** The airways of people with asthma are extremely sensitive. The airways tend to overreact and narrow due to even the slightest triggers such as pollen, animal dander, dust, or fumes.[1]

Tests and diagnosis

Medical History

A detailed family history of asthma and allergies can help your doctor make an accurate asthma diagnosis. Information about asthma symptoms is also useful. Be prepared to divulge when and how often they occur and what factors seem to exacerbate or worsen symptoms. Many patients with breathlessness and chronic obstructive lung disease are diagnosed with either asthma, COPD, or frequently mixed disease.[20] Common symptoms and signs include:

- Wheezing
- Coughing
- Breathing difficulty
- Tightness in the chest
- Worsening symptoms at night
- Worsening symptoms due to cold air
- Symptoms while exercising
• Symptoms after exposure to allergens

It is also wise to make note of health conditions that can interfere with asthma management such as runny nose, sinus infections, acid reflux disease, psychological stress, and sleep apnea.

It is often somewhat harder to diagnose young children who may develop their first asthma symptoms before age 5. Symptoms are likely to be confused with those of other childhood conditions, but young children with wheezing episodes during colds or respiratory infections are likely to develop asthma after 6 years of age.\[3,25\]

The diagnosis of asthma is based on the recognition of characteristics pattern of symptoms and signs.\[11\]

Physical exam

To rule out other possible conditions — such as a respiratory infection or chronic obstructive pulmonary disease (COPD) — your doctor will do a physical exam and ask you questions about your signs and symptoms and about any other health problems.\[8\]

A physical examination will generally focus on the upper respiratory tract, chest, and skin. A doctor will use a stethoscope to listen for signs of asthma in your lungs as you breathe. The high-pitched whistling sound while you exhale - or wheezing - is a key sign of both an obstructed airway and asthma.\[23\]

Physicians will also check for a runny nose, swollen nasal passages, and nasal polyps.

Skin will be examined for conditions such as eczema and hives, which have been linked to asthma.

Physical symptoms are not always present in asthma sufferers, and it is possible to have asthma without presenting any physical maladies during an examination.\[3\]

Tests to measure lung function:

You may also be given lung (pulmonary) function tests to determine how much air moves in and out as you breathe. These tests may include:

**Spirometry:**

This test estimates the narrowing of your bronchial tubes by checking how much air you can exhale after a deep breath and how fast you can breathe out.

**Peak flow:**
A peak flow meter is a simple device that measures how hard you can breathe out. Lower than usual peak flow readings are a sign your lungs may not be working as well and that your asthma may be getting worse. Your doctor will give you instructions on how to track and deal with low peak flow readings.

Lung function tests often are done before and after taking a bronchodilator, such as albuterol, to open your airways. If your lung function improves with use of a bronchodilator, it's likely you have asthma.

Additional tests:
Other tests to diagnose asthma include:

Methacholine challenge:
Methacholine is a known asthma trigger that, when inhaled, will cause mild constriction of your airways. If you react to the methacholine, you likely have asthma. This test may be used even if your initial lung function test is normal.

Nitric oxide test:
This test, though not widely available, measures the amount of the gas, nitric oxide, that you have in your breath. When your airways are inflamed — a sign of asthma — you may have higher than normal nitric oxide levels.

Imaging test:
A chest X-ray and high-resolution computerized tomography (CT) scan of your lungs and nose cavities (sinuses) can identify any structural abnormalities or diseases (such as infection) that can cause or aggravate breathing problems.

Sputum eosinophils:
This test looks for certain white blood cells (eosinophils) in the mixture of saliva and mucus (sputum) you discharge during coughing. Eosinophils are present when symptoms develop and become visible when stained with a rose-colored dye (eosin).

Provocative testing for exercise and cold-induced asthma:
In these tests, your doctor measures your airway obstruction before and after you perform vigorous physical activity or take several breaths of cold air.\[8\]

How asthma is classified
GINA guidelines classify asthma severity into four steps: \[13,\, 17\]
Asthma classification | Signs and symptoms
--- | ---
Mild intermittent | Mild symptoms up to 2 days a week and up to 2 nights a month
Mild persistent | Symptoms more than twice a week, but no more than once in a single day
Moderate persistent | Symptoms once a day and more than 1 night a week
Severe persistent | Symptoms throughout the day on most days and frequently at night

Treatment

Follow an Asthma Action Plan
You can work with your doctor to create a personal asthma action plan. The plan will describe your daily treatments, such as which medicines to take and when to take them. The plan also will explain when to call your doctor or go to the emergency room.
If your child has asthma, all of the people who care for him or her should know about the child’s asthma action plan. This includes babysitters and workers at daycare centers, schools, and camps. These caretakers can help your child follow his or her action plan.

Avoid Things That Can Worsen Your Asthma
Many common things (called asthma triggers) can set off or worsen your asthma symptoms. Once you know what these things are, you can take steps to control many of them.
For example, exposure to pollens or air pollution might make your asthma worse. If so, try to limit time outdoors when the levels of these substances in the outdoor air are high.
If animal fur triggers your asthma symptoms, keep pets with fur out of your home or bedroom.
One possible asthma trigger you shouldn’t avoid is physical activity. Physical activity is an important part of a healthy lifestyle. Talk with your doctor about medicines that can help you stay active.
Several health conditions can make asthma harder to manage. These conditions include runny nose, sinus infections, reflux disease, psychological stress, and sleep apnea. Your doctor will treat these conditions as well. [9,28]
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. The drugs used most commonly in the treatment of asthma, β₂ 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.

The critical determinant of the delivery of any particulate matter to the lungs is the size of the particles. Particles larger than 10 mm 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. Unfortunately, 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.

Even under 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. 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.

β₂ Adrenergic Receptor Agonists
The second most commonly used drug was β2-agonists.\textsuperscript{[15,27]}

Mechanism of Action and Use in Asthma

The mechanism of the antiasthmatic action of β-adrenergic receptor agonists is undoubtedly 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 β2 adrenergic receptors. Stimulation of these receptors activates the $G_s$ adenylyl cyclase-cyclic AMP pathway with a consequent reduction of in smooth muscle tone. β2 Adrenergic receptor agonists also increase the conductance of large Ca$^{2+}$-sensitive 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 Ca$^{2+}$ entry by small G proteins.

There are β2 adrenergic receptors on cell types in the airways other than bronchial smooth muscle. Of particular interest, stimulation of β2 adrenergic receptors inhibits the function of numerous inflammatory cells, including mast cells, basophils, eosinophils, neutrophils, and lymphocytes. In general, stimulating β2 adrenergic receptors in these cell types increases intracellular cyclic AMP, activating a signaling cascade that inhibits the release of inflammatory mediators and cytokines.

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.

Long-Acting β Adrenergic Receptor Agonists
Salmeterol xinafoate (SEREVENT) and formoterol (FORADIL) are long-lasting adrenergic agents with very high selectivity for the $\beta_2$-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.

**Toxicity**

Owing to their $\beta_2$-receptor selectivity and topical delivery, inhaled $\beta$ adrenergic receptor agonists at recommended doses have relatively few side effects. 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 $\beta$ adrenergic receptor activation.

**Heliox**

Heliox is a 70:30 mixture of helium to oxygen and is less viscous than ambient air. It can reduce breathing or propel therapeutic aerosols more efficiently. Heliox-driven nebulization can be used in patients with lifethreatening attacks. It is most effective when used early in acute attacks. Heliox is used to relieve respiratory distress, decrease breathing, and improve gas exchange, but not to critical asthmatic patients. Heliox may be effective to relieve severe asthma attacks.\(^5\)

**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. These formulations greatly enhance the therapeutic index of the drugs, substantially diminishing the number and degree of side effects without sacrificing clinical utility. In a previous study, we noticed that these drug classes were frequently dispensed to asthma patients in primary care.\(^{18}\) There are currently five glucocorticoids available in the United States for inhalation therapy:
beclomethasone dipropionate (BECLOVENT, VANCERIL), 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.

**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.

**Leukotriene-Receptor Antagonists and Leukotriene-Synthesis Inhibitors**
Zafirlukast (ACCOLATE) and montelukast (SINGULAIR) are leukotriene-receptor antagonists. Zileuton (ZYFLO) is an inhibitor of 5-lipoxygenase, which catalyzes the formation of leukotrienes from arachidonic acid.

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

**Leukotriene-Receptor Antagonist:**
Cysteinyl leukotrienes (cys-LTs) include leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4). All the cys-LTs are potent constrictors of bronchial smooth muscle. On a molar basis, LTD4 is approximately 1000 times more potent than is histamine as a bronchoconstrictor. The receptor responsible for the bronchoconstrictor effect of leukotrienes is the cys-LT1 receptor. Although each of the cys-LTs is an agonist at the cys-LT1 receptor, Zafirlukast and montelukast are selective high-affinity competitive antagonists for the cys-LT1 receptor. Pranlukast is another cys-LT1-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-induced bronchial smooth muscle contraction likely is involved in the therapeutic effects of these agents to relieve the symptoms of asthma.

**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.[22,31]

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.

Mechanism of Action
The Fc region of IgE binds with high affinity to the Fc epsilon receptor I. It 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 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.

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. Suffice it to say that the mechanism of action of cromolyn and nedocromil in asthma is not known.

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-adrenergic receptor agonists, and leukotriene-modifying drugs has diminished theophylline use significantly,
and it has been relegated to a third- or fourth-line treatment in patients whose asthma is otherwise difficult to control.

**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. Theophylline and related methylxanthines are relatively nonselective in the PDE subtypes they inhibit.

**Anticholinergic Agents**

**Mechanism of Action** 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.

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).

**Pharmacogenetics and Variability of Response to Asthma Medications**

There is a wide degree of interindividual variability in the response of asthmatic subjects to pharmacotherapy. For example, some individuals benefit dramatically from treatment with leukotriene modifiers, whereas many others are essentially resistant to these treatments. Although more rare, the "steroid resistant" asthmatic receives relatively little benefit from treatment with inhaled corticosteroids. At present, it is impossible to predict who will benefit the most from a given treatment. This unpredictability of response largely reflects our limited understanding of the underlying pathophysiology of asthma.

Three functionally relevant mutations have been found in the promotor region of the gene encoding 5-lipoxygenase. These mutations lead to a small decrease in promotor activity and leukotriene synthesis. About 35% of the population has at least one of these mutations in at least one allele. In one placebo-controlled clinical trial it was noted that
individuals with mutations at both alleles responded less well to treatment with a 5-lipoxygenase inhibitor than did those with two wild-type alleles.\[26,29\]

There are several relatively rare genetic variants in the gene encoding the glucocorticoid receptor. Some of these variants produce receptors with a diminished affinity for glucocorticoid agonists. There is no evidence, however, that any glucocorticoid-receptor polymorphism is strongly associated with clinically relevant steroid resistance. Consequently, attention is shifting away from polymorphisms in the receptor per se toward the numerous other candidate genes in the functional pathway of glucocorticoids as potential explanations for the unresponsiveness of some individuals to steroid therapy. \[10, 21\]

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