Chapter 7

Anti-inflammatory and Antiasthmatic Agents

Objectives

Upon completion of this chapter, you will be able to

- Describe the inflammatory process as it relates to airway disease.
- List the chemical mediators involved in allergic reactions.
- Discuss the physiology of corticosteroids.
- Define *hypothalamic-pituitary-adrenal axis, suppression,* and *steroid dependency.*
- Be able to describe the pharmacotherapy of oral, parenteral, and inhalational corticosteroids.
- Be able to differentiate the anti-inflammatory and antiasthmatic classes of medications available to treat asthma according to their mechanisms of action and clinical uses.

Key Terms

antigen
bronchial hyperresponsiveness
chemical mediators
corticosteroid
exercise-induced bronchospasm
glucocorticoid
histamine
immunocompromised
leukotriene
mineralocorticoid
prostaglandin

Abbreviations

ACTH	adrenocorticotropic hormone
BHR	bronchial hyperresponsiveness
CAM	cellular adhesion molecule
CBC	complete blood count
CRF	corticotropin-releasing factor
EAR	early asthmatic reaction
EIB	exercise-induced bronchospasm
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
H_1	histamine 1
H_2	histamine 2
HPA	hypothalamic-pituitary-adrenal axis
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
LAR	late asthmatic reaction
MRI	mediator release inhibitor
PEF	peak expiratory flow
PG	prostaglandin
PGE_1	prostaglandin E_1
PGE_2	prostaglandin E_2
$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$

Learning Hint

Remember from Chapter 5 that bronchospasm is the contraction of the smooth muscle layer *within* the airway and is treated by a fast-acting bronchodilator to relax the smooth muscle layer. The inflammatory process produces pressure and swelling *around* the airway, which compresses or constricts the airway. Just relaxing the smooth muscle layer within an airway with a bronchodilator will not solve the problem; the inflammation and associated swelling compressing the airway must be relieved. That is where anti-inflammatory medications come into play.

In Chapter 5, we learned about the role of bronchodilators to treat bronchospasm within the smooth muscle layer of the airway. Bronchospasm can be the result of an immediate reaction to an airway irritant, but the story doesn't end there. What about the subsequent airway inflammation that can result from bronchospasm, disease processes such as asthma or chronic bronchitis, or mechanical lung trauma? In this chapter, we focus on the anti-inflammatory and antiasthmatic classes of medications, which are frequently used in association with bronchodilators to treat and/or lessen the subsequent pulmonary inflammation. To distinguish the roles of these classes of drugs, it is first important to review how the airway can be affected by inflammation and what the various pathways are that lead to the inflammatory response.

Lung inflammation can result from diseases, infections, inhalation of toxic substances, or trauma. The resulting mucosal edema, bronchoconstriction, and increased mucus production can be life threatening because of increases in airway resistance from swelling and decreasing ventilation leading to poor gas exchange.

Inflammation occurs in response to a stimulus that causes release of chemical mediators that travel to the site of injury. Several different pathways containing chemical mediators lead to inflammation in the lungs. Different drugs discussed in this chapter work on different mediator pathways. This is the rationale for using combinations of drugs: to attack the specific pathway(s) leading to the inflammatory response in each particular situation.

7.1 The Inflammatory Process

7.1a The Immune Response

The major function of the body's natural defense mechanism—the immune system—is to neutralize, destroy, and eliminate foreign materials called **antigens**. It accomplishes this through the ability of white blood cells (leukocytes) to produce specific antibodies to combat foreign invasion. Antigens stimulate both the immune and inflammatory processes. Some of these common antigens include:

- Dust mites
- Mold

- Smoke
- Viruses
- Animal dander
- Pollen
- Sulfites
- Bacteria

The *immune system* has two functional units: *humoral* (circulating) *immunity* and *cell-mediated immunity.* Either or both units can respond to an antigen and activate white blood cells such as lymphocytes and macrophages. Humoral immune response involves activation of *B lymphocytes* while cell-mediated immunity involves production of *T lymphocytes.*

B lymphocytes produce antigen-specific antibodies called *immunoglobulins* that act to remove or destroy the antigen. We currently know of five major classes of immunoglobulins that are found naturally in the body or produced by B lymphocytes in response to foreign objects. See Table 7–1 for a list of the classes of immunoglobulins. T lymphocytes remove or destroy antigens directly or may act indirectly with help from macrophages and neutrophils.

Table 7–1 Immunoglobulins

Type	Characteristics
IgG	Most common; 80% of total immunoglobulins in plasma; protects against childhood diseases
IgM	10% of total immunoglobulins; numbers increase in chronic infections
IgE	Hypersensitivity reactions, allergic rhinitis, allergic asthma; bound to mast cells
IgA	Mucous membranes in respiratory tract; salivary and bronchial secretions; transfer immunity to the child
IgD	Role unknown; potentially B cell maturation or plays a role in antigen-triggered lymphocyte differentiation

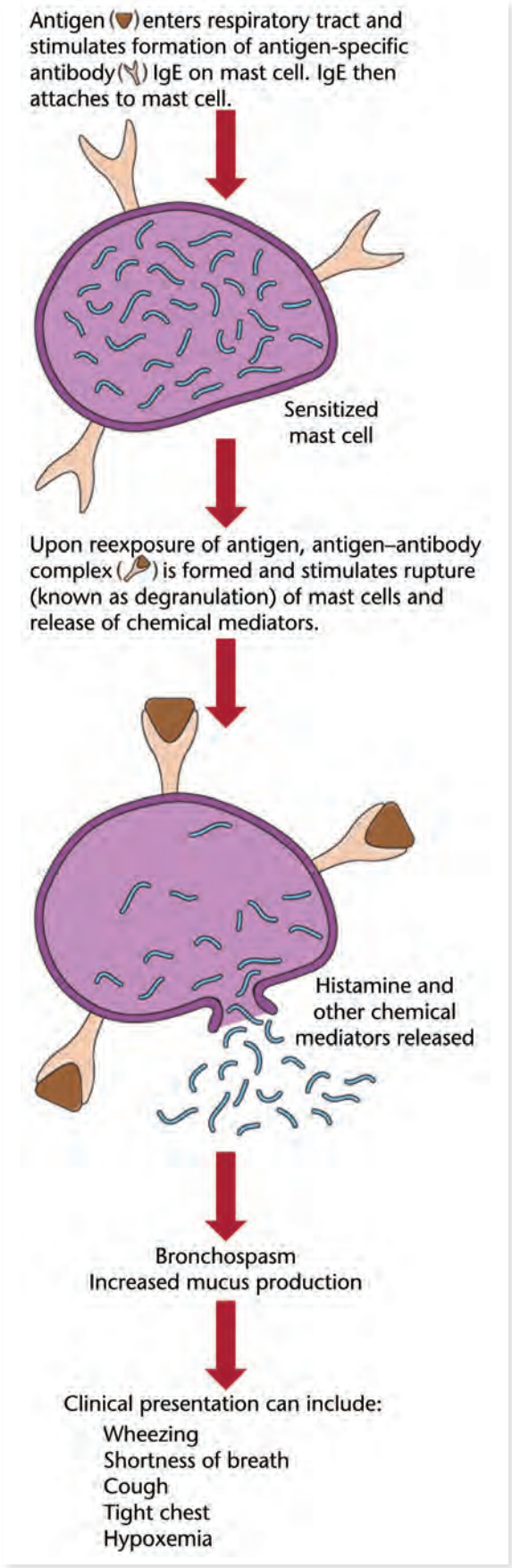
7.1b Mast Cell Chemical Mediator Release

The most common immune system–produced antibody involved in allergic asthma and rhinitis (runny/stuffy nose) is immunoglobulin E (IgE). Once IgE becomes exposed to an antigen, it fixes itself to the surface of a mast cell membrane. Mast cells can be found throughout the body, but for our discussion, we will focus on those found in the respiratory tract. In essence, once the antigen attaches to the mast cell, the mast cell becomes "sensitized" and awaits reexposure of the antigen, much like a police officer waiting to leap out and grab a known perpetrator that he's seen before. Upon reexposure, an antigen–antibody reaction occurs, which consists of a cascade of **chemical mediators** spilling out from the ruptured mast cell (degranulation). Mediators released include histamine, heparin, and other chemical factors.

Within the airway, these chemicals can immediately lead to bronchospasms. Eventually, these chemicals—and others produced as a result of the cleanup of the mast cell rupture (arachidonic acid metabolism producing leukotrienes and prostaglandins)—cause *inflammation*; the inflammatory reaction causes further airway smooth muscle contraction, mucosal edema, cellular infiltration, and mucus secretions with plugging. See Figure 7–1, which represents the initial mechanism that leads to mast cell rupture or degranulation.

Mast cells are found throughout the body. If the sensitized mast cell ruptures (degranulates) in the airway, bronchoconstriction may result. If sensitized mast cells in the eyes are exposed to an antigen, the eyes may water, become red, and swell. Likewise, mast cell degranulation in the nasal passages can lead to rhinitis and upper airway congestion.

Figure 7–1 Mast Cell Rupture or Degranulation in the Airways



7.1c Types of Asthma

Because asthma represents a disease of chronic inflammation, it can be used to illustrate the inflammatory response. Keep in mind that the inflammatory response is a needed body response; it is only *hyperactivation* of this response that can cause serious consequences. When treating inflammation, the goal is to decrease the inflammatory response enough to relieve the negative symptoms of hyperactivation inflammation, but not so much that the normal inflammatory response is compromised. It's a little like handling a hot cup of coffee. If it is too hot to drink, you may put an ice cube in it or blow on it to lower the temperature to a more desirable level. However, with conditions such as severe rheumatoid arthritis, treatment must exceed the threshold of desirability in order to be effective. Patients on medications that suppress the hyperactive inflammation and normal inflammation are considered to be **immunocompromised** and special considerations are taken in their future medical care, including preventative care like specific vaccine recommendations. Fortunately, asthma and other lung/airway related conditions can be treated effectively without causing clinically significant immunosuppression.

There are two main types of asthma: allergic asthma and nonallergic asthma. Most people have the allergic kind, caused by an external antigen such as pollen, dust, smoke, or pets. This is the kind that can lend itself to treatment with *immunotherapy,* commonly known as allergy shots, if we know the exact antigen that triggers the immune and inflammatory response. Allergy shots work because an allergic individual exposed to small doses of an antigen or allergen produces antibodies that are specific to that antigen. The antibodies are then sensitized and can recognize and fight the antigen when it returns. Although allergy shots may sound like the most logical treatment possible, they are usually used only if drug therapy is not effective for allergies. This is because immunotherapy treatment can be lengthy, with symptom relief not occurring until after at least 6 months of therapy. Also, there is always a risk of anaphylaxis in patients with severe asthma who receive allergy shots; some believe this is because too many mast cells become sensitized and the subsequent chemical mediator release can then be too great.

Nonallergic asthma is precipitated by infection, cold air, exercise, or stress, with no specific antigen identified. No immune response is involved, but mast cells still degranulate, which then can result in an acute asthma attack. Prophylactic antiasthmatic agents are used to lessen the frequency and severity of attacks, whether nonallergic or allergic; they stabilize or desensitize mast cells, preventing their rupture and chemical mediator release. This is why these agents are also known as *mast cell stabilizers*. These agents are discussed later in this chapter.

Allergic asthma is sometimes also called *atopic* or *extrinsic asthma* because it is known to be stimulated by a specific antigen source. Nonallergic asthma is referred to as *intrinsic* or *nonatopic asthma.*

7.1d Phases of the Inflammatory Response

Regardless of the type of asthma, the inflammatory response related to an asthmatic attack and mast cell degranulation can have two distinct phases: early and late. The *early-phase response* of any inflammatory reaction consists of local vasodilation and increased vascular permeability, redness, and wheal (local, usually itchy, swelling) or welt formation. The immediate inflammatory response in asthma results in bronchial contraction, with wheezing, cough, dyspnea, and hypoxemia resulting from mast cell degranulation and the subsequent release of histamine and other chemical mediator substances. Please see Figure 7–1 again, which illustrates the early phase of the inflammatory response.

Bronchodilators almost always reverse bronchospasm in the early phase; however, in more difficult cases of asthma, the episode launches a series of steps leading to a slow inflammatory process that develops 6–8 hours later. This is termed the *late-phase response* and is very difficult to resolve. The late-phase reaction can be serious, and treatment is aimed at stopping inflammatory progression before it occurs at this stage. White blood cells, including lymphocytes, and other chemical mediators contribute to late-phase inflammation. White blood cells infiltrate the asthmatic airways, as evidenced by an increase in eosinophils and neutrophils. Sloughing of airway cells and growth of goblet cells result in hypersecretion of mucus and mucosal swelling. Increased vascular permeability then occurs, causing further mucus secretion and mucosal swelling, which results in mucus plugging. In essence, a "traffic jam" of cellular debris and secretions piles up.

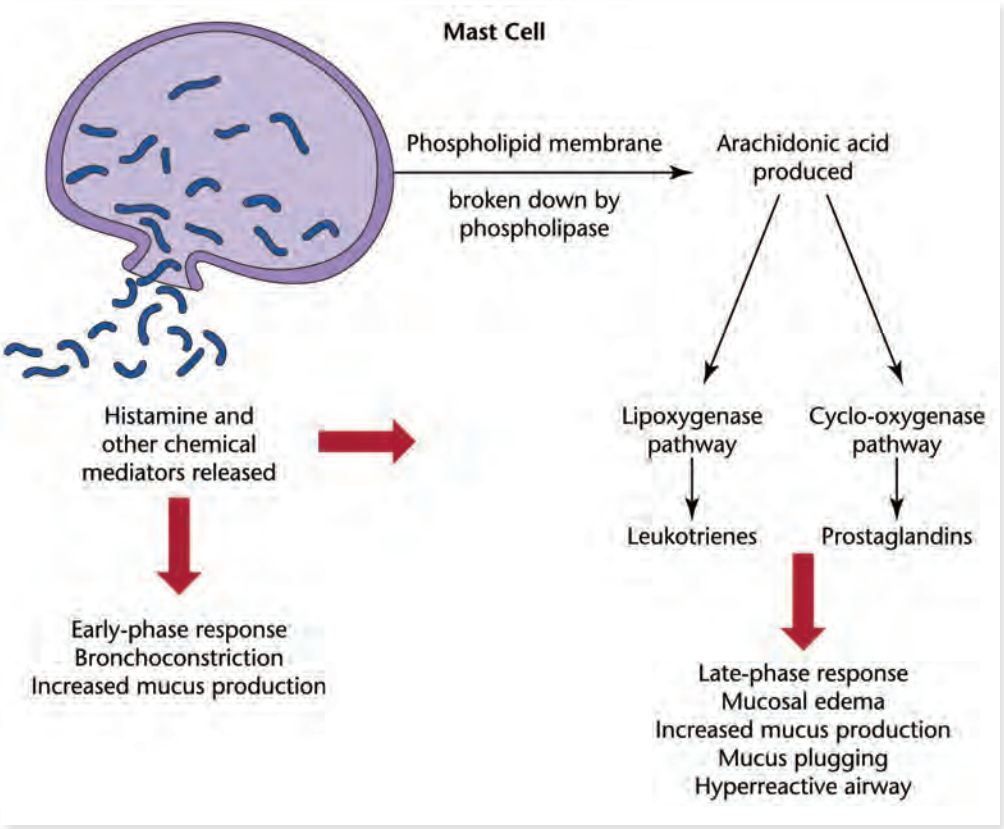
Learning Hint

On a complete blood count (CBC), the presence of increased eosinophils hints at the presence of an active allergic response.

In addition, the destruction of the phospholipid degranulated mast cell membrane and its subsequent breakdown by phospholipase produces the fatty acid arachidonic acid. Arachidonic acid then produces two pathways that contribute to the late-phase response. The lipoxygenase pathway consists mainly of **leukotriene** release, and the cyclo-oxygenase pathway primarily releases **prostaglandins**, all adding to the late-phase responses of submucosal edema, mucus production, and hyperreactive airways. See Figure 7–2, which shows the early- and late-phase inflammatory responses.

Figure 7–2 The Early- and Late-Phase Inflammatory Response in the Airways

Note: Increased neutrophils, monocytes, and eosinophils migrating to inflamed airways also contribute to late-phase response.



Time for Review

Contrast early- and late-phase responses; why do you think this is important for drug therapy?

Looking at Figure 7–2, logic tells us that the optimal blockage of the inflammatory response would be to stabilize the mast cell membrane and not allow it to begin the cascade of mediator release leading to both the early- and late-phase responses. This is the mechanism of action of the prophylactic anti-asthmatics discussed later in this chapter. In addition, this chapter discusses other categories of drugs that block specific inflammatory pathways, such as the leukotriene inhibitors, antihistamines, and prostaglandin inhibitors. For now, we will focus on **corticosteroids**, which have a broad spectrum of activity and work on several of the different mediator pathways in both the early- and late-phase inflammatory responses.

Clinical pearl

Other drugs currently being researched for their ability to inhibit airway inflammatory response include monoclonal antibodies to specific cytokines as well as cellular adhesion molecules (CAM-1). These drugs work by preventing proteins in the immune system from becoming activated, which is also an underlying cause of allergic asthma symptoms. The drug omalizumab (Xolair®) binds to IgE and prevents IgE from binding to cells and triggering an allergic reaction. This drug is given subcutaneously. For more information, see the discussion to follow later in this chapter.

7.2 Corticosteroids

7.2a Corticosteroid Physiology

Corticosteroids can block both the initial immune response and the subsequent inflammatory process and are therefore a mainstay of treatment for allergic asthma. Before we can talk about corticosteroids and how they work, though, we must review corticosteroid physiology.

Body functions are controlled by the nervous system and the endocrine system working together in an integrated fashion. The endocrine system produces hormones, which are chemical substances secreted into the bloodstream that then circulate and exert physiologic effects on body cells and tissues. The adrenal glands contain two endocrine organs: the adrenal medulla and the adrenal cortex. The adrenal medulla secretes catecholamines, norepinephrine, and epinephrine and is functionally related to the sympathetic component fight-or-flight of the autonomic nervous system, as discussed in Chapter 3. In this chapter, we focus on the adrenal cortex. Its role is secretion of steroid substances called adrenocortical hormones, or corticosteroids.

Clinical pearl

Spironolactone (Aldactone®) is a diuretic that works as an aldosterone antagonist.

Corticosteroids are classified into **mineralocorticoids** and **glucocorticoids**. Depending on the chemical structure of the corticosteroid hormone, drugs differ in their mineralocorticoid and glucocorticoid activities. Mineralocorticoids are corticosteroids with salt-retaining activity that are important for electrolyte balance and fluid volume. Aldosterone (produced by the adrenal gland) and fludrocortisone (synthetic) are examples of mineralocorticoids. Aldosterone and fludrocortisone cause increased sodium and water reabsorption by the kidney into the bloodstream, which decreases urine production and thereby causes volume expansion within the bloodstream.

Glucocorticoids affect carbohydrate, protein, and fat metabolism and are useful pharmacologically for anti-inflammatory activity and their ability to suppress immunologic activity. Synthetic corticosteroids have been developed to optimize anti-inflammatory activity (to be more glucocorticoid-like) and to minimize mineralocorticoid activity (not cause water retention). Although the

two classifications seem distinct, glucocorticoids also tend to have some mineralocorticoid activity (see Table 7–2).

Since glucocorticoids affect the metabolism of carbohydrates, diabetic patients should be aware that taking them can affect their blood sugar. If the patient is expected to be on glucocorticoids for an extended period of time, adjustments may need to be made to their diabetic treatment plan.

Table 7–2 Glucocorticoid and Mineralocorticoid Activity of Oral Corticosteroids

Corticosteroid	Glucocorticoid strength	Mineralocorticoid strength
hydrocortisone	1	1
cortisone	0.8	0.8
prednisone	2.5–3.5	0.8
prednisolone	3–4	0.8
methylprednisolone	4–5	0–0.8
dexamethasone	20–40	0

Time for Review

Immunosuppression using high doses of corticosteroids may be beneficial after organ transplantation, but this has implications for precautions you should take when treating transplant patients. Can you think of what precautions you should take and why?

Clinical pearl

Corticosteroids are secreted daily by the adrenal cortex at the rate of about 10–30 mg/day. This release does not occur steadily but occurs in response to surgery, stress, infection, and emotion on a 24-hour diurnal rhythm cycle. Serum concentrations peak at about 8 a.m. Night-shift workers have very different patterns, or diurnal rhythms, and dosing time of exogenous pharmacologic steroids may have to be reversed in their case.

Other corticosteroids that are not as pertinent to cardiorespiratory pharmacotherapy, and therefore are not discussed here, are sex hormones, which have androgenic, estrogenic, or progestenic activity. Some of these types of corticosteroids have been used by weightlifters or as sexual hormone–replacement therapy. The term *steroid* is frequently used instead of *corticosteroid* in these contexts. All steroids except the sex hormones are essential for survival. (One could, of course, argue that the sex hormones are also essential—for the survival of the species.)

Corticosteroids are used to treat many diseases, such as rheumatoid arthritis, cancers, and pulmonary diseases. In respiratory disease, they are used to treat acute and chronic asthma, although their use in COPD is controversial, as discussed in Chapter 13. Administration routes used are inhalation, oral, and parenteral.

Treatment with corticosteroids is usually short term and adjunctive, but it can also be long term. Corticosteroids make some patients feel euphoric, and patients frequently want to be on steroids. Unfortunately, therapeutic pharmacologic use can alter the balance of natural steroid production. This will be discussed shortly, since it relates to steroid dependence and adrenal suppression.

Controversy

Corticosteroids may provide significant benefits, but they also carry the risk of several side effects. The implications of their clinical use must be understood and jointly agreed to by both the patient and the health-care provider.

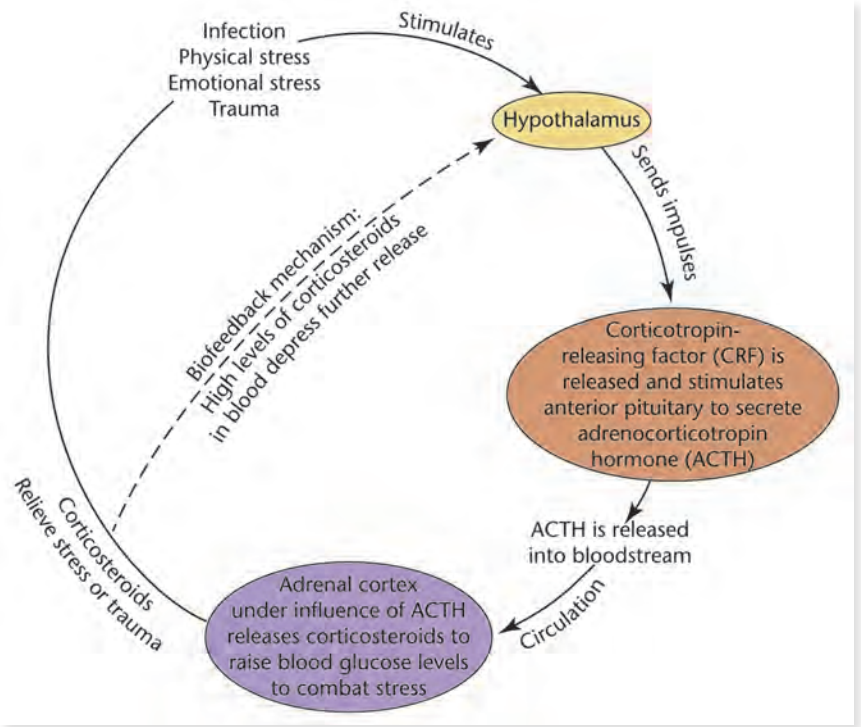
The main internally produced or endogenous glucocorticoid is hydrocortisone. It is important to understand the production and control of the body's endogenous corticosteroids and the hypothalamic-pituitary-adrenal axis. Only then can the concept of adrenal suppression and steroid dependence be understood.

7.2b Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal axis (HPA) controls corticosteroid release in the body. It is responsible for the normal diurnal variation in blood levels of steroids. For example, when we get up in the morning, the body must ready itself to face the day; hormone production begins and then peaks and troughs throughout the day according to our metabolic needs. One factor that influences corticosteroid release in the body is stress. In stressful situations, corticosteroids work to decrease the effects of stress. They do this by raising blood glucose levels so that vital tissues, such as the brain and heart, get the glucose needed in stressful situations.

When the hypothalamus is stimulated, it sends impulses that cause corticotropin-releasing factor (CRF) to be released in the anterior pituitary gland. The anterior pituitary gland, under the influence of CRF, then causes adrenocorticotropic hormone (ACTH) to be released into the bloodstream. ACTH then circulates within the bloodstream to the adrenal cortex, where it stimulates the secretion of corticosteroids. This is under normal biofeedback mechanism control, by which high levels of corticosteroids in the bloodstream inhibit further release of CRF and ACTH (see Figure 7–3).

Figure 7–3 HPA Mechanism for Release and Regulation of Corticosteroids



If exogenous pharmacologic corticosteroid drugs are used to treat diseases, adrenal or HPA suppression can occur, causing the adrenal glands to atrophy because they no longer have to work to produce these hormones. The body cannot tell the difference between the endogenous corticosteroids it has produced itself and those that have been administered pharmacologically. The body just knows it has a higher level of hormones and tells itself to turn off its own production. It then becomes dependent on the administered pharmacologic corticosteroids. This means that when exogenous pharmacologic corticosteroids are administered over the short term (up to 3 weeks), they can simply be stopped without a taper; but patients who have taken corticosteroids for longer periods or at higher doses must taper off slowly (generally a 10%–20% reduction every 1–2 weeks) to give the body time to pick up production and regain internal regulation. Some steroids are available in "dose packs" for acute conditions that make it easy for a patient to taper down as they execute the treatment plan.

7.2c Corticosteroid Mechanism of Action

It is well documented that corticosteroids, when used in conjunction with β_2-agonists, improve pulmonary functions such as forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEFs).

Corticosteroids have a variety of mechanisms of action all related to blocking or diminishing late-phase asthma responses by blocking the arachidonic acid cascade of metabolites (leukotrienes and prostaglandins). In addition, corticosteroids remove circulatory lymphocytes, monocytes, eosinophils, and basophils by moving them to lymph, bone marrow, and the spleen. Fewer cells then reach the site of inflammation; therefore, there is less congestion. Corticosteroids also inhibit macrophage and leukocyte processing of antigens, so the ability of cells to respond to antigens is decreased, thus suppressing the immune response.

Corticosteroids also decrease the production of eosinophils, basophils, and monocytes. They have shown an additional beneficial effect, enhancing the responsiveness of β_2-receptors by increasing the responsiveness of adenylyl cyclase in airway smooth muscle to catecholamines or β-agonists (see Chapter 5). Corticosteroids do not have a direct relaxing effect on bronchial muscle but do facilitate the effect of β-agonists, thereby enhancing the desired bronchodilation effects of β_2-adrenergic drugs given for the hyperreactive airways. Taking all these factors into account, corticosteroids clinically reduce airway inflammation, decrease airway obstruction, improve oxygenation, and increase the response to β-agonists.

The effects of corticosteroids are often time dependent. Although the cellular and biochemical effects of corticosteroids are immediate, clinical response takes longer. Increased responsiveness to β-agonists occurs within 2 hours, and β-receptor density increases within 4 hours. Seasonal **bronchial hyperresponsiveness** (BHR) requires at least a week of therapy to reverse. **Exercise-induced bronchospasm** (EIB) sensitivity decreases after 4 weeks of therapy.

7.2d Corticosteroid Use in Airway Remodeling

Learning Hint

While remodeling a house results in an improvement, remodeling the airway results in structural changes that impair proper airway function.

Corticosteroids prevent or suppress airway inflammation, which results in reduction of bronchial hyperresponsiveness and prevention and reduction of airway remodeling. Airway remodeling is important because it is a change in the composition of the airway wall that occurs in some asthmatics over time. Think of a ball being thrown against the same spot on a wall. The first couple of times it may not leave a mark, but after repeated throws, it will change the surface of the wall. The structural changes in the airway result from long-standing airway inflammation. One of the consequences is persistent airway obstruction that may not be responsive to treatment. Considering airway remodeling, use of corticosteroids as an early anti-inflammatory intervention makes sense.

Controversy

Should drug therapy of asthma be disease modifying and a primary prevention strategy, or should it simply produce symptom control?

7.2e Adverse Effects of Corticosteroids

Side effects of steroids can be short term or long term, depending on the duration of use and route of administration (systemic or topical). The most common side effects of short-term use include appetite stimulation, stomach irritation, headache, and mood changes. The mood changes may be a sense of well-being or steroid psychosis. Steroids can exacerbate acne and cause hypokalemia, hyperglycemia, and leukocytosis. The hyperglycemia causes what is called steroid diabetes. Once the steroids are discontinued, these side effects usually go away. As discussed earlier, steroids can worsen or affect the blood sugar of patients already diagnosed with diabetes.

Long-term side effects include osteoporosis or bone changes that could lead to fractures; immunosuppression, which can lead to increased risk of infection; and myopathy of skeletal muscles. See Table 7–3 for possible side effects of corticosteroids.

Table 7–3 Side Effects of Corticosteroids

Category	Side effect
Immunologic	Immunosuppression Increased susceptibility to infections
Cardiovascular	Edema Hypertension
CNS	Euphoria Insomnia
Dermatologic	Thin skin Impaired wound healing Bruising Altered fat distribution
Endocrinologic	Diabetes Cushingoid state
Metabolic	Electrolyte imbalance Negative nitrogen balance
Musculoskeletal	Muscle weakness Osteoporosis Growth suppression
Ophthalmic	Glaucoma

Life Span Considerations

Steroids and Growth

Controversy exists about the extent of effect that corticosteroids have on children's growth as a result of steroid-induced changes in bone growth and epiphyseal (growth-plate) maturation. Several studies actually show improved growth rates for children switched from oral steroids to inhaled steroids. This result could be due to better control of the asthma and less need for oral systemic steroids. The most recent data concerning the use of inhaled corticosteroids in children suggest no apparent effect on final adult height.

7.2f Oral and Parenteral Corticosteroid Administration

Sometimes oral steroids are given as pulse or burst doses—for example, 40 mg of prednisone per day orally for 3 days. At other times, they are given on an every-other-day regimen at 2–3 times the daily dose. Whatever the regimen, the lowest possible dose of steroid should be used to accomplish the therapeutic goal.

Corticosteroids often take days, not hours, to heal damaged airways. Although it is common to use parenteral administration, research results are ambivalent as to whether this route is faster acting than oral administration. Objective improvement takes a minimum of 6–12 hours, and maximum improvement may take longer than a week. Objective measures such as pulmonary function tests may show improvement 12 hours after administration. In the emergency room, corticosteroids are warranted for patients with a poor response to β-agonists over 1–2 hours. Because of the delayed onset, many clinicians initiate early corticosteroid use to lessen or prevent the late-phase inflammatory response.

Hydrocortisone (Cortef®) and methylprednisolone (Solu-Medrol®) are most commonly given by injection. Methylprednisolone's advantage is less fluid retention in patients with heart disease because of fewer mineralocorticoid effects (again, see Table 7–2). After hospitalized patients improve in 48–72 hours, the IV dose is tapered to an oral dose and the duration of treatment is based on clinical response. If the patient had been steroid dependent before hospitalization, tapering the dose to what it was before hospitalization is the goal.

7.2g Inhaled Corticosteroids

Clinical pearl

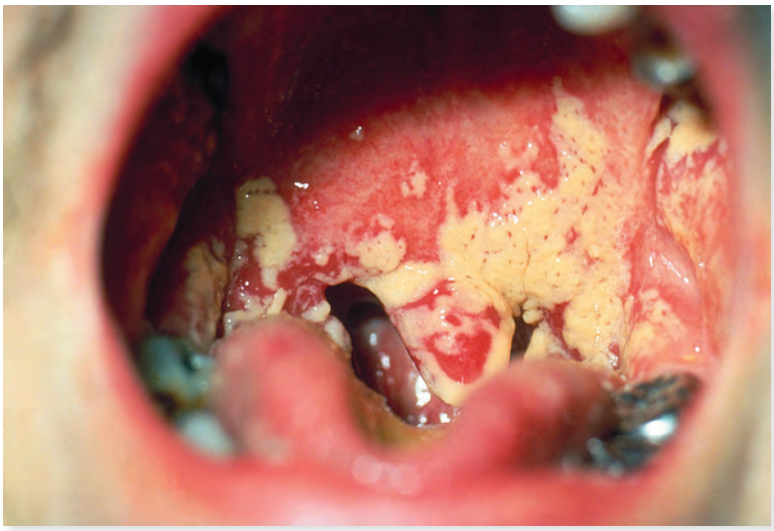
Thrush (candidiasis) is treatable with liquid antifungal antimicrobials that are swished in the mouth and swallowed. Using a spacer to reduce oropharyngeal deposition and rinsing the mouth with water or a mouthwash after taking a steroid MDI minimizes the occurrence of opportunistic fungal infections.

The aerosol corticosteroids are chemically altered to minimize systemic toxicity and are available in metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), and nebulizer solutions. Some newer DPIs have capabilities to capture inhaler usage data on an app via built-in sensors. This data can help patients and doctors better manage care. A small portion of all aerosol steroids is deposited in the mouth and pharynx and then swallowed. The portion that is swallowed is absorbed into the bloodstream and metabolized by the liver. Inhalational or topical corticosteroids have advantages over oral or parenteral administration in terms of lessened systemic adverse effects. The minimization of systemic side effects via the inhalational route makes it ideal for treating airway inflammation.

Typical side effects from aerosol administration include oropharyngeal fungal infections, with the most common being thrush (*Candida* yeast infection) (see Figure 7–4). Some patients may have changes in their voices and/or hoarseness (dysphonia) as a result of inhaled steroids. The incidence of dysphonia is usually

not reduced with the use of a spacer but may be lowered with dry-powder inhalers. See Table 7–4, which compares the characteristics of the aerosol and oral routes.

Figure 7–4 Oral Thrush Due to Inhaled Steroids



Source: Image courtesy of Centers for Disease Control and Prevention

Table 7–4 Comparison of Oral and Aerosol Corticosteroids

Characteristic of the drug	Oral	Aerosol
HPA suppression	Yes	No*
Cushing's syndrome	Yes	No**
Steroid dependence	High risk	Low risk
Local therapeutic effects	No	Yes
Risk to growth development in children	Yes	No
Easy to use	Yes	No
Cost	Inexpensive	Expensive
Local airway reaction	No	Yes

* HPA suppression has been reported, but the risk is small with recommended doses.
**Case reports of Cushing's syndrome have been reported. The risk is increased when high inhaled corticosteroid (ICS) doses are used with drugs that inhibit the metabolism of the ICS.

There is little advantage of one aerosol steroid over another when they are used at similar doses. Doses are usually classified as low, medium, or high. See Table 7–5 for comparative adult inhaled corticosteroid doses. Most inhaled steroids can be given twice daily. Doses should be adjusted to provide control with minimal side effects. Inhaled steroids have a different time course of response than oral steroids. Inhaled steroids produce symptom improvement in the first 1–2 weeks of therapy, with maximum improvement in 4–8 weeks. FEV_1 and PEF may take 3–6 weeks for maximum improvement. BHR improvement can take 1–3 months and continue over 1 year. See Figure 7–5 for images of selected inhaled corticosteroid drugs and devices.

Clinical pearl

The most important way to determine the right dose of an inhaled corticosteroid (ICS) for a patient is to carefully monitor the patient's response to therapy using clinical parameters, always attempting to find the lowest effective dose.

Table 7–5 Comparative Adult Inhaled Daily Corticosteroid Doses (Divided Doses, Twice Daily)

Drug	Low dose	Medium dose	High dose
beclometasone dipropionate HFA (Qvar Redihaler®) 40 or 80 mcg/dose	80–160 mcg/day	160–320 mcg/day	>320 mcg
budesonide DPI (Pulmicort®) 90 or 180 mcg/dose	180–600 mcg/day	600–1,200 mcg/day	>1,200 mcg/day
ciclesonide HFA (Alvesco®) 80 or 160 mcg/dose	80–160 mcg/day	160–320 mcg/day	>320 mcg/day
fluticasone propionate HFA (Flovent®) (MDI) 44, 110, 220 mcg/dose (DPI) 50, 100, 250 mcg/dose	88–264 mcg/day 100–300 mcg/day	264–440 mcg/day 300–500 mcg/day	>440 mcg/day >500 mcg/day
fluticasone propionate (ArmonAir Digihaler®) (DPI) 55, 113, 232 mcg/dose	110–220 mcg/day	226–452 mcg/day	>464 mcg day
mometasone furoate (Asmanex®) (DPI) 110 or 220 mcg/dose	110–220 mcg/day	>220–440 mcg/day	>440 mcg/day
fluticasone furoate (Arnuity Ellipta®) (DPI) 100 mcg or 200 mcg/dose	100 mcg/day	n/a	200 mcg/day

Figure 7–5 Selected Inhaled Corticosteroid Drugs

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Controversy

There is no doubt that inhaled corticosteroids have fewer systemic adverse effects than their oral or parenteral cousins. A patient's risk of systemic adverse effects may depend on the delivery system, cumulative dose, and the absorption of the drug from the lung or the gastrointestinal tract when the drug is swallowed. Patients should have regular eye exams and bone health should be maintained by regular exercise and adequate calcium and vitamin D intake. Bone density testing to detect osteoporosis should be obtained in patients on high-dose inhaled corticosteroids.

7.2h Benefits of Daily Corticosteroid Use

Corticosteroids are the most potent anti-inflammatory agents for asthma and are most effective when taken via inhalation for long-term control of persistent asthma (more specifics on this in Chapter 13). They not only affect improvement in bronchial hyperresponsiveness over time but also prevent and reverse airway remodeling. This has led some to think the drugs may improve long-term outcomes for asthma patients. Once corticosteroids are discontinued, however, lung function returns to pretreatment values over the course of a month or two. Because less drug is usually better in the long run, studies have looked at and determined that step-down dosing from oral corticosteroids to inhaled corticosteroids can be effective. There are many benefits of daily inhaled use. To summarize, there are many benefits of daily use of inhaled corticosteroids, including:

- Fewer symptoms
- Fewer severe exacerbations
- Reduced use of quick-relief β_2-agents
- Reduction in airway remodeling
- Improved lung function
- Reduced airway inflammation

Therapy with inhaled corticosteroids alone has been shown to be superior to long-acting beta-agonists (LABAs) alone. A combination of the long-acting bronchodilator salmeterol (Serevent®) and the corticosteroid fluticasone (Flovent®) is used in a DPI device called the Advair® Diskus® (Figure 7–6).

Learning Hint

Corticosteroid inhalational products are not equivalent per puff or per microgram. Comparative doses are estimated and rely on clinician judgment.

Figure 7–6 Advair® Drug Advertisement and Inhaler Device

The combination drug Advair® contains the bronchodilator drug salmeterol and the corticosteroid anti-inflammatory drug fluticasone. Notice the background magazine advertisement that points out that asthma has two main causes: airway constriction and inflammation. A combination drug such as Advair® treats both at the same time to prevent acute attacks.

Source: Copyright GSK. Used with permission.

Combinations of ICSs and LABAs are used in the treatment of COPD (emphysema and chronic bronchitis); you will learn more about this in Chapter 13. Please see Table 7–6, which lists some combination drugs and their trade names and dosages.

Table 7–6 Commercially Available Combinations of ICS and LABA

(Some combinations may also contain an anticholinergic component; see Chapter 5 for details on anticholinergic inhalations.)

Note: This is a representative list. Other doses may be available.

Generic Names	Trade Name	Dosage
budesonide 160 mcg and formoterol 4.5 mcg	Symbicort®	Two inhalations twice daily
fluticasone 250 mcg and salmeterol 50 mcg	Advair Diskus®	One inhalation twice daily
fluticasone 100 mcg and vilanterol 25 mcg	Breo Ellipta®	One inhalation once daily
fluticasone 250 mcg and salmeterol 50 mcg	Wixela® (DPI)	One inhalation twice daily
fluticasone 113 mcg and salmeterol 14 mcg	Airduo®	One inhalation twice daily
mometasone 50 mcg and formoterol 5 mcg	Dulera®	Two inhalations twice daily
budesonide 160 mcg and glycopyrrolate 9 mcg and formoterol 4.8 mcg	Breztri Aerosphere®	Two inhalations twice daily
fluticasone 100 mcg and umeclidinium 62.5 mcg and vilanterol 25 mcg	Trelegy Ellipta®	One inhalation once daily

Time for Review

Do you start early or wait until later to administer corticosteroids in persistent asthma? How do you decide what route to use? If using an inhaled bronchodilator in conjunction with an inhaled steroid, which do you give first and why?

7.2i Steroid Dependency

Steroid dependency can be classified into two forms. One is related to a psychological desire for the drug, and the other is related to physiological steroid suppression of the normal functions of the HPA. Psychological dependence can occur because of the sense of well-being induced by these drugs as well as the effective symptom relief they provide.

Withdrawing patients from steroids quickly can lead to physiological adrenal insufficiency symptoms from HPA suppression. Steroid withdrawal syndrome consists of anorexia, nausea, vomiting, lethargy, headache, and hypotension. Ways to avoid steroid dependence include alternate-day steroid administration and aerosol use.

Clinical pearl

Additional uses of corticosteroids include stimulation of lung maturation in the fetus, relief from rheumatoid arthritis, and prevention of organ transplant rejection.

7.3 Antiasthmatics

7.3a Cromolyn Sodium

Whereas corticosteroids are effective in treating an already established inflammatory process, mast cell membrane stabilizers can impair or prevent the inflammatory process from ever beginning by preventing rupture of mast cells. Cromolyn and nedocromil (Alocril®), a chemical derivative with similar pharmacology, are similar drugs whose main difference is potency. For this reason, we will talk about the two drugs concurrently. They are used for allergic and nonallergic intermittent asthma and also for prevention of allergic rhinitis and exercise-induced bronchospasm (EIB).

Cromolyn is *not* a bronchodilator or inhibitor of action of the chemical mediators already released. The effect of cromolyn is prophylactic, and the drug must be used as a pretreatment. It is theorized that calcium influx into the mast cell is needed for microfilament contraction that then expels the contents of (*degranulates*) the mast cell. Cromolyn works to inhibit calcium influx into the mast cell, and this prevents release of inflammatory mediators. This is why the drug is called a mast cell stabilizer or mediator release inhibitor (MRI). By inhibiting release of inflammatory mediators, it blunts early- and late-phase asthmatic reactions to antigens and inhibits mast cell degranulation produced by immunologic and nonimmunologic mechanisms.

These drugs inhibit immediate early asthmatic reaction (EAR). Even though the following effects have not been associated with mast cell mediator release, cromolyn has also been shown to inhibit bronchoconstriction produced by inhalation of cold air and ultrasonically nebulized water. These drugs also inhibit late

Clinical pearl

Cromolyn and nedocromil are not bronchodilators and must not be used for acute reversal of bronchospasm. They must be used regularly for maximum effectiveness, even during symptom-free periods.

asthmatic reactions (LAR) and prevent subsequent bronchial hyperresponsiveness (BHR). Long-term treatment can prevent the rise in BHR that is associated in some patients with pollen seasons. Even though they have not been directly compared to inhaled corticosteroids in a clinical trial, it is widely believed that these drugs are less effective clinically.

7.3b Dosage Forms

Cromolyn is poorly absorbed from the gastrointestinal tract, so it only works when it is deposited directly into the airways by aerosol administration and is not effective in oral forms. Cromolyn is available as a solution for nebulization. Response and duration are both dose related. Cromolyn nebulized solution is compatible with β-agonist solutions, so they can be administered together. The only way to know whether the drug will work is to try it for 4 to 6 weeks and check the response. A positive response is less frequency and/or severity of asthmatic episodes. Cromolyn may be an alternative for children who have side effects from theophylline.

7.3c Side Effects

Nedocromil and cromolyn are nontoxic drugs with no predilection for tolerance. Following inhalation, cough and wheeze have been reported as well as bad taste and headache. Significant adverse side effects occur in less than 1 in 10,000 patients.

7.4 Prostaglandins

7.4a Physiology

Some drugs inhibit prostaglandin (PG) synthesis in the body. These are commonly known as nonsteroidal anti-inflammatory agents and include common medications such as ibuprofen, aspirin, and naproxen, which will be mentioned in the discussion of pain medications. Their inhibitory effect has been related to the induction of bronchospasm when used in some patients with asthma. Aspirin-sensitive asthmatics may differ from nonsensitive asthmatics by having a reliance on the PG mechanism rather than the β-system to regulate airway tone.

While not currently used to treat airway disease, the bronchoactive properties of prostaglandins are worth discussing because they may have future potential use. Prostaglandins are present in almost all tissues, including the lungs. Prostaglandins are yet another group of chemical mediators that modulate airway function and pulmonary hemodynamics. Anything that promotes release of prostaglandins in the lung can alter ventilation perfusion disturbances. Some examples of these factors are:

- Pulmonary embolism
- Lung edema
- Hypoxia
- Bradykinin
- Histamine
- Antigen–antibody reaction

Prostaglandins are classified on the basis of their chemical structure and are categorized alphabetically. They are synthesized upon stimuli and are released, not stored, once they are made. In addition, they have very short half-lives (minutes). The type of prostaglandin that dominates depends on the tissue location. In the lung, $PGF_{2\alpha}$ is the most common prostaglandin, and when stimulated and produced, it causes bronchoconstriction and increased mucus production.

PGE_1 and PGE_2 are also considered important in airway muscle tone and can cause bronchodilation. Prostaglandins are mentioned here because they may have future applications for therapy. Table 7–7 lists pulmonary effects of prostaglandins $PGF_{2\alpha}$, PGE_1, and PGE_2 in the lung.

Table 7–7 Effects of Prostaglandins in the Lung

Prostaglandin	Airway	Blood vessels
$PGF_{2\alpha}$	Bronchoconstriction Increased mucus secretion	Contraction Increased vascular resistance
PGE_1	Bronchodilation	Relaxation Decreased vascular resistance
PGE_2	Bronchodilation	Contraction Increased vascular resistance

7.5 Leukotriene Modifiers

7.5a Physiology

Leukotriene modifiers are a group of oral medications available for asthma treatment; they inhibit the leukotriene mediator cascade from arachidonic acid metabolism that leads to airway inflammation. Leukotrienes are potent mediators of inflammation involved in the pathogenesis of asthma. Leukotrienes are derived from arachidonic acid by the 5-lipoxygenase pathway. This pathway forms leukotrienes that cause contraction of airway smooth muscle, vasodilation, increased vascular permeability, increased mucus secretion, and decreased mucociliary clearance when they activate receptors. The three agents available are zafirlukast (Accolate®), montelukast (Singulair®), and zileuton (Zyflo®). Zileuton is rarely used because it may cause injury to the liver and must be monitored closely for this potentially serious adverse effect. Zafirlukast and montelukast are leukotriene antagonists. They both work by preventing the harmful effects of leukotrienes.

At this time, these drugs are considered alternatives to low-dose inhaled steroids, cromolyn, or nedocromil in patients with mild to persistent asthma; they are used for long-term control, not acute treatment. They are a logical drug choice on the basis of the role of leukotrienes in inflammation as discussed previously.

Zafirlukast is effective for allergen-induced asthma and early and late allergen responses. For best effects, the drug should be taken on an empty stomach. The only clinically important drug interaction is with warfarin. Zafirlukast may increase the effects of warfarin, resulting in an increased prothrombin time. Side effects of zafirlukast include pharyngitis, headache, rhinitis, and gastritis. It may also decrease liver function.

Research results have shown that montelukast can decrease the number of puffs of β-agonists needed daily in children and increase their morning forced expiratory volume (FEV_1). It has also been shown to increase FEV_1 in adults. When it is used in combination with inhalational corticosteroids, montelukast decreases the dose of inhaled steroid needed. Side effects, however, include fatigue, fever, nasal congestion, cough, dizziness, and rash.

The clinical use of this drug class is primarily in patients with mild to moderate asthma. Some people with asthma respond better to leukotriene modifiers than others. This probably has to do with the relative importance of leukotriene production in a given patient with asthma. Therefore, patients are generally given a 1-month trial with this class of drugs; if they experience no improvement of symptoms during that time, they should be classified as leukotriene nonresponders and switched to another controller medication.

7.6 Antiasthmatic Monoclonal Antibody

7.6a Physiology

As mentioned previously, immunoglobulin E (IgE), when exposed to an antigen, fixes itself to the surface of a mast cell membrane. The mast cell becomes "sensitized" and awaits reexposure of the antigen. Upon reexposure, an antigen–antibody reaction occurs, which consists of a cascade of chemical mediators spilling out from the ruptured mast cell (degranulation). Mediators released include histamine, heparin, and other chemical factors. Omalizumab (Xolair®) is an immunoglobulin G (IgG) monoclonal antibody that works by inhibiting IgE binding to the IgE receptor on mast cells and basophils. This reduces the activation and release of mediators in the allergic response. Long-term treatment with omalizumab has shown a decrease in asthma exacerbations and corticosteroid use.

Omalizumab is administered to patients subcutaneously. The dose and frequency of administration are based on body weight and pretreatment total IgE levels. Its use should be considered in patients with moderate to severe allergic asthma uncontrolled with a combination of medium- to high-dose inhaled corticosteroids and a long-acting beta$_2$-agonist. Injection site reactions are the most common adverse drug events. Monitoring of patients using omalizumab should include baseline serum IgE levels, body weight, and pulmonary function tests.

Other medications in this class include mepolizumab (Nucala®), which is administered subcutaneously every 4 weeks and benralizumab (Fasenra®), which is administered subcutaneously every 4–8 weeks. Both of these medications block the binding of the IL-5 receptor, reducing the production and survival of eosinophils. IL-5 is the major cytokine responsible for the growth, differentiation, recruitment, activation, and survival of eosinophils. These medications are expensive and usually reserved for patients who fail to achieve adequate control with more traditional medications. It should be noted that an individual will only respond to a particular monoclonal antibody treatment, if that specific molecule pathway underlies their disease.

7.7 Treating Upper Airway Congestion

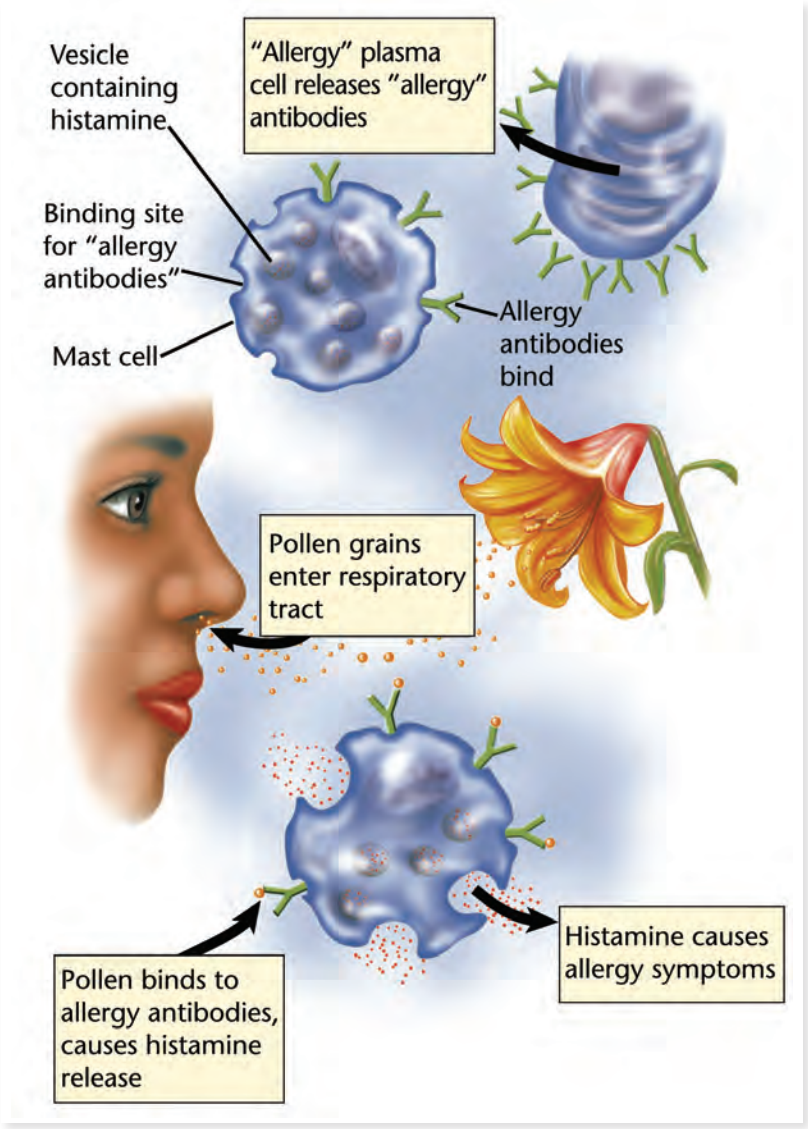
Any process that causes upper airway congestion will, of course, make it more difficult to breathe and therefore increase the work of breathing. In someone who does not have lung disease, the increased work of breathing may be barely noticeable and just an annoyance. However, in patients who have lung disease, it may be overwhelming and contribute to overall decreased alveolar ventilation. Therefore, treatment of the common "head cold" in these patients is no trivial matter.

Eye symptoms such as itching can also be a problem in allergic rhinitis. Ophthalmic corticosteroids or antihistamines are available for this indication.

7.7a Allergic Rhinitis

Allergic rhinitis (runny nose) can be seasonal or perennial. It is characterized by an immunologic response that causes symptoms such as sneezing, rhinorrhea, nasal congestion, and pruritus. In addition to increasing the work of breathing, any upper airway congestion will increase airway resistance and the likelihood of spreading infection throughout the respiratory system (see Figure 7–7). Because allergic rhinitis involves the degranulation of mast cells in the nasal passageways, one logical treatment is to stabilize the mast cells.

Figure 7–7 Allergic Rhinitis



7.7b Intranasal Medications

Intranasal mast cell stabilizers are used for allergic rhinitis and are administered before the onset of pollen season. Cromolyn is available intranasally (Nasalcrom®) without a prescription and is effective for sneezing, rhinorrhea, and itching but not for preexisting nasal congestion. It must be used 3–4 times a day, and it takes 2–4 weeks to show full benefits. It is used most commonly in children with mild symptoms whose parents wish to avoid intranasal corticosteroids.

Intranasal corticosteroids are also available. Intranasal corticosteroids inhibit cytokine release from nasal epithelial cells and inhibit leukotriene production. Intranasal corticosteroids also are beneficial in decreasing nasal congestion by decreasing function of mediators that affect vascular permeability. See Table 7–8 for common intranasal corticosteroids.

Clinical pearl

Intranasal cromolyn may be beneficial when visiting a friend with a cat or on other occasions of one-time exposure to a known allergen if used 15–30 minutes before exposure.

Merck Visual Communications

Nasonex®

Table 7–8 Intranasal Corticosteroids

Generic name	Brand name
beclometasone dipropionate	Beconase® AQ®
budesonide	Rhinocort®
ciclesonide	Omnaris®
fluticasone propionate	Flonase®
fluticasone furoate	Veramyst®
triamcinolone	Nasacort®
mometasone furoate	Nasonex®

Source: Merck Visual Communications

Intranasal corticosteroids can take 2–4 weeks to work fully, with 8 weeks being an adequate treatment trial for efficacy. Some of the newer products can begin to work within 3–12 hours. Maximum effects can take up to 6 months. Products differ in their side effects (but not their efficacy), which include burning, stinging, irritation, and dry nose.

Patient & Family Education

Intranasal Medication Delivery

Therapy with intranasal medications should be started with the maximal dose for the patient's age. Once symptoms are controlled, the dose should be reduced until the lowest effective dose is determined. If mucus crusting is present, it should be removed from the nose prior to use. Patients should position their head downward during administration to minimize drainage into the throat.

7.7c Antihistamines

Histamine is stored in tissue mast cells. In the lung, mast cells are located below the respiratory tract mucosa in connective tissue. Scientific efforts have been made to identify factors that cause release of histamine from mast cell storage sites. These efforts have shown that the autonomic nervous system is involved through cholinergic and β- and α-receptor sites on mast cells. Histamine production is influenced by nonspecific stimuli to tissue such as chemical stimuli, physical injury, or allergy. Examples of substances that can cause histamine release include:

- Antigen–antibody IgE reactions
- Mechanical tissue trauma
- Tissue hypoxia
- Drugs
- Dust
- Cigarette smoke

Clinical pearl

Histamine-2 receptors mediate the actions of histamine on gastric secretion. Antagonists of this histamine are called H_2-blockers, not antihistamines; drugs such as cimetidine (Tagamet®) are H_2-blockers, not antihistamines.

Histamine acts on two different receptors called histamine 1 (H_1) and histamine 2 (H_2). Histamine smooth muscle contraction is controlled by H_1 receptors. These receptors are activated by subepithelial irritant receptors, with a resultant increase in vagal activity. Drugs that antagonize H_1 receptors are called *antihistamines*.

Histamine release provokes airway obstruction. Airway obstruction can result from mucosal edema and inflammatory cell infiltration with eosinophils. This can be influenced by release of local mediators. See below for the pulmonary and systemic effects of histamine.

Pulmonary effect

- Increased airway resistance
- Decreased maximum expiratory flow rate
- Decreased diffusion capacity
- Increased total lung capacity
- Increased mucus production
- Promotion of mucosal edema

Systemic effect

- Vasodilation
- Stimulation of adenylyl cyclase in mast cells
- Release of catecholamines from adrenal medulla
- Increased vascular permeability

The mechanisms involved in the release of histamine and other mediators during allergic response are complex and consist of many steps. The antigen–antibody interaction triggers many of the steps. Therapy for histamine release has been directed toward prevention or inhibition of mediator release from storage sites and antagonism of airway response to mediators.

Drugs used to prevent the release of histamine from mast cells include β-agonists, methylxanthines, and cholinergic blockers, as discussed in Chapter 5. In addition, cromolyn and corticosteroids have a role in blocking histamine production, as discussed earlier in this chapter.

Antihistamines block the action of histamine at histamine 1 receptors. Here is the tricky part: They do this not by blocking the receptor but by inactivating the receptor. Sort of like when you "deactivate" by sitting down in front of the television after a long day of school or work. They do not prevent or block the release of histamine at histamine receptors in the GI system. They are not useful in acute asthma treatment because so many other mediators are released in acute asthma episodes as well. Antihistamines are used basically for allergic rhinitis. Antihistamines prevent the onset of symptoms better than they reverse symptoms already present.

Clinical pearl

Even some drugs can cause histamine release. The itching that is frequently associated with use of opioids such as morphine is due to histamine release, although this does not necessarily imply that the patient is allergic to the drug. The effects on histamine release by neuromuscular blocking drugs is one factor that influences the decision to use one drug instead of another.

Time for Review

For predictable seasonal allergies, when would be the best time to start taking an antihistamine?

Clinical pearl

A histamine provocation test or challenge is based on airway hyperactivity. This test can provide not only information about an individual's response to therapeutic drugs but also diagnostic information.

Side effects of antihistamines include dry mouth and throat, altered coordination, and sedation. One should not drive or operate dangerous machinery when under the influence of antihistamines (or anything else, for that matter). Some patients experience excitation rather than the expected sedation. Antihistamines can induce their own metabolism, which may present as what appears to be tolerance to the drug with chronic use.

Like cephalosporin antibiotics, there are first- and second-generation antihistamines. First-generation antihistamines are sedating, and second-generation are less so. Second-generation antihistamines have anti-allergic and anti-inflammatory effects. Second-generation antihistamines are now the preferred agents, since the first-generation drugs impair CNS function and individuals consuming these OTC medications are considered to be under the influence of drugs. Improvement in symptoms with first-generation antihistamines occurs within 1–2 hours of the first dose, but maximum effects are not seen for weeks.

Olopatadine and azelastine are antihistamine nasal sprays available by prescription. They may be useful in patients with mild or episodic symptoms (e.g., you are going to visit Uncle Charlie but are allergic to his dog). Azelastine can be administered as needed, since it has a rapid (15 minute) onset of action, but can be sedating if swallowed.

Tolerance to the sedation effects may develop in 2–3 weeks; see Table 7–9 for common antihistamines.

First-generation antihistamines are very effective for symptom relief. However, only about 30% of patients are satisfied with this treatment because of side effects, and therefore they are considered second-line agents.

Table 7–9 Common Antihistamines

Generation	Generic name	Brand name
First	chlorpheniramine diphenhydramine brompheniramine	Chlor-Trimeton® Benadryl® Dimetane
Second	loratadine cetirizine fexofenadine desloratadine levocetirizine	Claritin® Zyrtec® Allegra® Clarinex® Xyzal®

Life Span Considerations

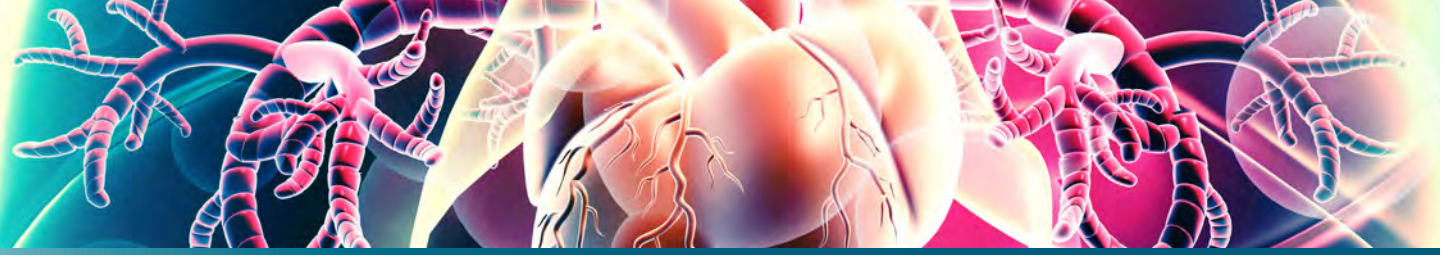
Antihistamines and Age Considerations

First-generation antihistamines should be avoided in children and the elderly. Impairment of CNS function is well documented. In children, the first-generation antihistamines are associated with impaired school performance. Older adults are more susceptible to their anticholinergic effects, such as blurred vision, confusion, and urinary hesitancy.

7.7d Decongestants

Nasal decongestants are α-adrenergic drugs with corresponding vasoconstrictive properties. It is the vasoconstriction that reduces the blood flow and therefore the swelling of the nasal passages in the inflammatory process. Due to increasing pseudoephedrine (Sudafed®) abuse (used to produce methamphetamine and as an athletic "performance enhancer"), phenylephrine has been used as a replacement in most OTC combination antihistamine/decongestant preparations. It is less effective in reducing rhinitis symptoms and should be used cautiously in patients with diabetes, heart disease, hyperthyroidism, or glaucoma. Owing to its vasoconstrictive properties, blood pressure should also be monitored. Topical decongestants such as nasal sprays can be used, but not for longer than 3 consecutive days, or rebound nasal congestion occurs. Topical decongestants may be helpful for increasing absorption of intranasal corticosteroids by opening up the nasal passageways first and then administering the corticosteroid.

Regulations prevent some competitive athletes from taking oral stimulants such as decongestants. The over-the-counter decongestant phenylpropanolamine is no longer available because of its side effects.



Summary

There are a variety of inflammatory pathways and mediators of inflammation. Anti-inflammatory drugs target these pathways to reduce the inflammatory response that leads to hyperactive airways, mucosal edema, and increased mucus production. Corticosteroids are among the mainstays of anti-inflammatory drugs. They vary in pharmacology and cardiorespiratory therapeutic applications. They have very important physiologic effects that must be balanced with their adverse effects. One method of achieving this balance is through careful attention to the route of administration and the dose and duration of use.

Antiasthmatic agents are used prophylactically to prevent the occurrence of the inflammatory response; their role is different than that of corticosteroids. Antiasthmatics include leukotriene modifiers, mast cell stabilizers, and omalizumab.

Drugs that treat upper respiratory congestion are frequently used in combination with antiasthmatic and anti-inflammatory agents.

Review Questions

1. The most common antibody involved in allergic asthma and rhinitis is
   (a) IgG
   (b) IgE
   (c) IgF
   (d) IgT
   (e) IgB

2. Corticosteroids can be classified as
   (a) mineralocorticoid
   (b) glucocorticoid
   (c) potassium sparing
   (d) glucose sparing
   (e) (a) and (b)

3. Routes used for corticosteroids include
   (a) inhalational
   (b) oral
   (c) intranasal
   (d) parenteral
   (e) all of the above

4. Check which indication would be appropriate for the following drugs.

prednisone	___	acute asthma treatment
	___	chronic asthma treatment
cromolyn	___	acute asthma treatment
	___	chronic asthma treatment
zileuton	___	acute asthma treatment
	___	chronic asthma treatment

5. Check which effect relates to each drug most closely.

β-agonists	___	block histamine release
	___	block histamine production
cromolyn	___	blocks histamine release
	___	blocks histamine production
corticosteroids	___	block histamine release
	___	block histamine production

6. Describe the early and late phases of inflammation and why they are important to pharmacotherapy.

7. Explain the role of the hypothalamic-pituitary-adrenal axis in terms the patient can understand.

8. List some factors that can influence mediator release from mast cells.
9. What are the important side effects of antihistamines?
10. A 57-year-old asthmatic presents with complaints of voice changes, hoarseness, white spots on his throat and tongue, and a "funny taste in his mouth." What type of medication and route do you suspect may be causing these complaints? What would the proposed treatment and follow-up education consist of?
11. A patient with a history of severe late-phase asthma response is prescribed an inhaled short-acting bronchodilator, corticosteroid, and mast cell stabilizer. Explain in lay terms when each of these drugs is indicated and highlight any special considerations concerning sequence, side effects, and what to expect as positive outcomes.

Case Study 7–1

A 24-year-old woman

A 24-year-old woman with persistent mild asthma has noticed that she is having more acute episodes, especially during the fall season. Her peak flows often drop to 50% of predicted during this period, and she has to use her quick-acting rescue bronchodilator frequently. This is the only respiratory medication she is taking. List other categories of respiratory medications that may help reduce the number and severity of her episodes. How and when would you suggest administering them?

Case Study 7–2

A 40-year-old man

A 40-year-old man has recently changed his profession and is now working outside frequently at a lumberyard. He operates a large crane that is used to move logs from one area to another. He has never had significant seasonal allergies, but this spring he began to experience severe allergy symptoms. He states in the morning he is fine, but by lunchtime he develops nasal congestion and itchiness, as well as watery red eyes that affect his work. What type of medication can he take to relieve his allergy symptoms? When should he take it? What should he be cautioned of, given his job?