Asthma

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Introduction

- Asthma has been known since antiquity, yet it is a disease that still defies precise definition.
- The word asthma is of Greek origin and means “panting.”
- More than 2000 years ago, Hippocrates used the word asthma to describe episodic shortness of breath; however, the first detailed clinical description of the asthmatic patient was made by Aretaeus in the second century.
Definition

• Asthma is defined as a chronic inflammatory disorder of the airways.
• Many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells.
• The inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.
• These episodes associated with widespread airflow obstruction that is often reversible either spontaneously or with treatment.
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• 5 million children affected in US. Over the past two decades

• Prevalence of asthma has increased by 75% in US, whereas the rate in children younger than age 5 has increased 160%.

• It accounts for 1.6% of all ambulatory care visits (13.7 million) and results in more than 470,000 hospitalizations and 2 million emergency department visits per year.
• Children have the highest prevalence of asthma, at 68.6 per 1000 population younger than 18 years of age.
• Asthma accounts for more than 10 million missed school days per year.
• In young children (0 to 10 years of age), the risk of asthma is greater in boys than in girls, becomes about equal during puberty, and then is greater in women than in men.
• Ethnic African-Americans and Hispanics have a higher prevalence than whites, but this appears to be a result of urbanization and not race or socioeconomic
Etiology

- Asthma is at least a partially heritable complex syndrome that requires a gene-by-environment interaction.
- Environmental risk factors for the development of asthma include: socioeconomic status, family size, exposure to secondhand tobacco smoke in infancy and in utero, allergen exposure, urbanization, and decreased exposure to common childhood infectious agents.
• Risk factors for early (<3 years of age) recurrent wheezing associated with viral infections include low birth weight, male gender, and parental smoking.
• Atopy is the predominant risk factor for children to have continued asthma.
• Asthma can occur in adults later in life.
• Occupational asthma in previously healthy individuals emphasizes the effect of environment on the development of asthma.
Environmental exposures are the most important precipitants of severe asthma exacerbations.

Epidemics of severe asthma in cities have followed exposures to high concentrations of aeroallergens.

Viral respiratory tract infections remain the single most significant precipitant of severe asthma in children and are an important trigger in adults as well.
Agents and Events Triggering Asthma

- Respiratory infection: Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, Mycoplasma pneumonia
- Allergens: Airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores
- Environment: Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke, wood smoke
- Emotions: Anxiety, stress, laughter
- Exercise: Particularly in cold, dry climate
- Drugs/preservatives: Aspirin, NSAIDs (cyclooxygenase inhibitors), sulfites, benzalkonium chloride, β-blockers
- Occupational stimuli: Bakers (flour dust); farmers (hay mold); spice and enzyme workers; printers (arabic gum); chemical workers; plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)
Pathophysiology

• The major characteristics of asthma include a variable degree of airflow obstruction (related to bronchospasm, edema, and hypersecretion), BHR, and airways inflammation.
Acute Inflammation

• Inhaled allergen contribute to acute inflammation in asthma.
• Inhaled allergen leads to an early-phase allergic reaction that, in some cases, may be followed by a late-phase reaction.
• The activation IgE initiates the early-phase reaction.
• It is characterized primarily by the rapid activation of airway mast cells and macrophages.
• The activated cells rapidly release proinflammatory mediators such as histamine, eicosanoids, and reactive oxygen species that induce contraction of airway smooth muscle, mucus secretion, and vasodilatation.

• The late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation.

• It involves the recruitment and activation of eosinophils, CD4+ T cells, basophils, neutrophils, and macrophages.
• The activation of T cells leads to the release of T-helper cell type 2 (Th2)–like cytokines that may be a key mechanism of the late-phase response.

• The release of preformed cytokines by mast cells is the likely initial trigger for the early recruitment of cells.

• The enhancement of nonspecific BHR usually can be demonstrated after the late-phase reaction but not after the early-phase reaction following allergen or occupational challenge.
Chronic Inflammation

- Airways inflammation has been demonstrated in all forms of asthma.
- In asthma, all cells of the airways are involved and become activated “eosinophils, T cells, mast cells, macrophages, epithelial cells, fibroblasts, and bronchial smooth muscle cells”.
- These cells also regulate airway inflammation and initiate the process of remodeling by the release of cytokines and growth factors.
Clinical Consequences Of Chronic Inflammation

• Chronic inflammation is associated with nonspecific BHR and induces asthma exacerbations.
• Exacerbations are characterized by symptoms or worsening of asthma over a period of days or even weeks.
• Corticosteroids remain the most potent anti-inflammatory drugs for use in the treatment of asthma.
Cont’d

- Patients with mild symptoms or in remission demonstrate lower levels of responsiveness, although still greater than the normal population.
Remodeling of The Airways

- Acute inflammation is a beneficial, nonspecific response of tissues to injury and generally leads to repair and restoration of the normal structure and function.
- In contrast, asthma represents a chronic inflammatory process of the airways followed by healing.
- The end result may be an altered structure referred to as a remodeling of the airways.
Cont’d

• Repair involves replacement of injured tissue by parenchymal cells of the same type and replacement by connective tissue and its maturation into scar tissue.

• Airways remodeling is of concern because it may represent an irreversible process that can have more serious sequelae such as the development of COPD.
Clinical Presentation

• Asthma is a disease of exacerbation and remission, so the patient may not have any signs or symptoms at the time of exam.

• Symptoms include episodes of dyspnea, chest tightness, coughing (particularly at night), wheezing, or a whistling sound when breathing.

• These often occur in association with exercise, but also occur spontaneously or in association with known allergens.
• Signs may include expiratory wheezing on auscultation, dry hacking cough, or signs of atopy (allergic rhinitis and/or eczema) may occur.

• On lab spirometry demonstrates obstruction (FEV1/FVC less than 80%) with reversibility following inhaled β2-agonist administration (at least a 12% improvement in FEV1).

• Other diagnostic tests represent a fall in FEV1 of at least 20% following 6 minutes of near maximal exercise.
• Elevated eosinophil count and IgE concentration in blood.
• Elevated Fraction of Exhaled Nitric Oxide (FeNO) greater than 12 ppb.
• Positive methacholine challenge (PC20 FEV1 less than 12.5 mg/mL).
Chronic Asthma

- Classic asthma is characterized by episodic dyspnea associated with wheezing.
- Wheezing is the characteristic symptom of asthma.
- Patients may present with a chronic persistent cough as their only symptom.
- There is no single test that can diagnose asthma.
- The diagnosis is based primarily on a good history.
• The patient may have a family history of allergy or asthma or have symptoms of allergic rhinitis.

• Reversibility of airways obstruction following administration of an inhaled short-acting $\beta_2$-agonist provides confirmation but is not by itself diagnostic.

• Patients with normal values of spirometry can be challenged by exercise or substances that produce bronchoconstriction, such as methacholine.
Sputum eosinophil counts and (FeNO) are consistent with asthma but not diagnostic of asthma.

The intervals between symptoms can be days, weeks, months, or years.

Asthma also can vary as to its severity.

The severity is determined by lung function and symptoms prior to therapy, as well as by the amount of medication required to control the patient’s symptoms.
Sample Questions for the Diagnosis

• Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), or shortness of breath?
• Have you had colds that “go to the chest” or take more than 10 days to get over?
• Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year?
• Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (e.g., animals, tobacco smoke, perfumes)?
• Have you used any medications that help you breathe better? How often?
• Are the symptoms relieved when the medications are used?
• In the past 4 weeks, have you had coughing, wheezing, or shortness of breath
  1. At night that has awakened you?
  2. In the early morning?
  3. After running, moderate exercise, or other physical activity?
## Classification of Asthma Severity

<table>
<thead>
<tr>
<th>Step</th>
<th>Symptoms</th>
<th>Lung Fun.</th>
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</thead>
<tbody>
<tr>
<td>Step 1: Mild Intermittent</td>
<td>Daytime $\leq$ 2 times/wk</td>
<td>FEV1 or PEF $\geq$ 80%</td>
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<tr>
<td></td>
<td>Asymptomatic between exacerbations</td>
<td>PEF variability $&lt; 20%$</td>
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<tr>
<td></td>
<td>Exacerbations brief (from a few hours to a few days); intensity may vary</td>
<td></td>
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<td></td>
<td>Nocturnal $\leq$ 2 times/mo</td>
<td></td>
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<tr>
<td>Step 2: Mild Persistent</td>
<td>Daytime $&gt;$ 2 times/wk but $&lt; 1$ time/day</td>
<td>FEV1 or PEF $\geq$ 80%</td>
</tr>
<tr>
<td></td>
<td>Exacerbations may affect activity</td>
<td>PEF variability 20%-30%</td>
</tr>
<tr>
<td></td>
<td>Nocturnal $&gt;$ 2 times/mo</td>
<td></td>
</tr>
<tr>
<td>Step 3: Moderate Persistent</td>
<td>Daily symptoms</td>
<td>FEV1 or PEF $&gt; 60%$ to $&lt; 80%$</td>
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<tr>
<td></td>
<td>Daily use of inhaled, short-acting beta 2-agonists</td>
<td>PEF variability &gt; 30%</td>
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<tr>
<td></td>
<td>Exacerbations affect activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations $\geq$ 2 times/wk; may last days</td>
<td></td>
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<tr>
<td></td>
<td>Nocturnal $&gt; 1$ time/wk</td>
<td></td>
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<tr>
<td>Step 4: Severe Persistent</td>
<td>Continual symptoms</td>
<td>FEV1 or PEF $\leq$ 60%</td>
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<tr>
<td></td>
<td>Limited physical activity</td>
<td>PEF variability &gt; 30%</td>
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<tr>
<td></td>
<td>Frequent exacerbations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nocturnal frequent</td>
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Severe Acute Asthma

- Uncontrolled asthma can progress to an acute state where inflammation, airways edema, excessive accumulation of mucus, and severe bronchospasm result in a profound airways narrowing that is poorly responsive to usual bronchodilator therapy.

- Hyperacute attacks are associated with neutrophilic as opposed to eosinophilic infiltration and resolve rapidly with bronchodilator therapy.
Cont’d

• An episode can progress over several days or hours (usual scenario) or progresses rapidly over 1 to 2 hours.
• The patient is anxious in acute distress and complains of severe dyspnea, shortness of breath, chest tightness, or burning.
• The patient is only able to say a few words with each breath.
• Symptoms are unresponsive to usual measures (inhaled β2-agonist administration).
Cont’d

• Signs include expiratory and inspiratory wheezing on auscultation (breath sounds may be diminished with very severe obstruction), dry hacking cough, tachypnea, tachycardia, pale or cyanotic skin, hyperinflated chest with intercostal and supraclavicular retractions, hypoxic seizures if very severe, normal or slightly elevated temperature.
Cont’d

• PEF and/or FEV1 less than 50% of normal predicted values.

• Decreased PaO2, and O2 saturations by pulse oximetry (SaO2 less than 90% on room air is moderate to severe).

• Decreased arterial or capillary CO2 if mild, but in the normal range or increased in moderate to severe obstruction.
Cont’d

• Blood gases to assess metabolic acidosis (lactic acidosis) in severe obstruction.
• Complete blood count if there are signs of infection.
• Serum electrolytes as therapy with β2-agonist and corticosteroids can lower serum K and Mg and increase glucose.
• Chest radiograph if signs of consolidation on auscultation.
Exercise Induced Bronchospasm (EIB)

- During vigorous exercise, pulmonary functions (FEV1 and peak expiratory flow [PEF]) in asthmatic patients increase during the first few minutes but then begin to decrease after 6 to 8 minutes.
- EIB is defined as a drop in FEV1 of greater than 15% to 20% of baseline (pre-exercise value).
- Heat loss and/or water loss from the central airways appears to play an important role.
Cont’d

• EIB is provoked more easily in cold, dry air, and warm, humid air can blunt or block it.
• A refractory period following EIB lasts up to 3 hours after exercise.
• During this period, repeat exercise of the same intensity produces either no decrease in pulmonary function or a drop of less than 50% of the initial response.
• The refractory period is thought to be caused by an acute depletion of mast cell mediators and time required for their repletion.
Nocturnal Asthma

• Worsening of asthma during sleep is referred to as nocturnal asthma.
• Patients with nocturnal asthma exhibit significant falls in pulmonary function between bedtime and awakening.
• Typically, their lung function reaches a nadir at 3 to 4 A.M.
• It has been associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine.
• Nocturnal asthma includes increased circulating histamine and activated eosinophils and leukotriene excretion at night associated with increased hyperresponsiveness to methacholine.
• Numerous other factors that may affect nocturnal worsening of asthma, including allergies and improper environmental control, gastroesophageal reflux, and sinusitis, also must be considered when evaluating these patients.
Factors Contributing To Asthma Severity

- Viral infections are primarily responsible for exacerbations of asthma "rhinovirus, RSV, parainfluenza virus, coronavirus, and influenza viruses"
- Ozone and sulfur dioxide, common components of air pollution
- Asthma produced by repeated prolonged exposure to industrial inhalants
- Emotions and stress rarely can precipitate attacks of asthma but more commonly worsen an attack in progress.
• Upper respiratory tract, particularly sinusitis and rhinitis, have been linked with asthma.
• GERD has been associated with asthma.
• Nocturnal asthma may be associated with nighttime reflux.
• Premenstrual worsening of asthma has been reported in as many as 30% to 40% of women.
• In general, bronchial responsiveness and symptoms improve in asthmatics during pregnancy.
Cont’d

- Additives specifically sulfites used as preservatives, can trigger life-threatening asthma exacerbations.
- Beer, wine, dried fruit, and open salad bars in particular have high concentrations of metabisulfites.
- Aspirin and other NSAIDs can precipitate an attack in up to 20% of adults with asthma. The mechanism is related to cyclooxygenase inhibition.
Treatment
Severe Acute Asthma

• The primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and early intervention.

• Goals of treatment include:
  1. Correction of significant hypoxemia
  2. Rapid reversal of airflow obstruction
  3. Reduction of the likelihood of recurrence of severe airflow obstruction
  4. Development of a written action plan in case of a further exacerbation
These goals are best achieved by early initiation of treatment and close monitoring of objective measures of oxygenation and lung function.

Early response to treatment as measured by the improvement in FEV1 at 30 minutes following inhaled β2-agonists is the best predictor of outcome.

Oxygen supplementation to maintain oxygen (O2) saturations above 90% (or above 95% in pregnant women) is essential.
• In children younger than 6 years of age, in whom lung function measures are difficult to obtain, a combination of objective (e.g., oxygen saturation, capillary CO2, respiratory rate, and heart rate) and subjective measures may be used to assess severity.

• The primary therapy of acute exacerbations is pharmacologic, which includes inhaled short-acting β2-agonists and, depending on the severity, systemic corticosteroids and O2.

• It is important that therapy not be delayed, so the initial history and physical examination should be obtained while initial therapy is being provided.
Patients at risk for life-threatening exacerbations require special attention. Risk factors include a history of previous severe asthma exacerbations (e.g., hospitalizations, intubations, or hypoxic seizures), complicating illnesses (e.g., cardiac disease, diabetes, illicit drug use, or psychosis), use of more than two canisters per month of short-acting inhaled β2-agonists, and current intake of oral corticosteroids or recent withdrawal from oral corticosteroids.
• A complete blood count may be appropriate for patients with fever or purulent sputum, but many patients will have a leukocytosis from a viral infection or secondary to corticosteroid administration.

• Routine chest radiographs have not been shown to be of value unless physical findings suggestive of consolidations or pneumothoraces are present.
• Serum electrolytes should be monitored if high dose continuous inhaled or systemic β2-agonists are to be used because they can produce transient decreases in potassium, magnesium, and phosphate.

• The combination of high-dose β2-agonists and systemic corticosteroids occasionally may result in excessive elevations of glucose.

• Initial response should be achieved within minutes, and most patients experience significant improvement within the first 30 to 60 minutes of therapy, with most patients doubling their FEV1 or PEF.
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• Hypoxemia, primarily a result of ventilation-perfusion mismatch, is immediately correctable by low-flow oxygen.
• While reversal of lung function into the normal range may take 12 to 24 hours, complete restoration takes much longer—up to 3 to 7 days.
• A strategy to prevent recurrence such as systemic corticosteroids and PEF monitoring should be used.
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- It is essential to provide the patient with a self-management plan that includes a written action plan for dealing with exacerbations.
- Patients at risk for severe exacerbations should be taught how to use a peak-flow meter and monitor morning peak flows at home.
- In young children, an increased respiratory rate, increased heart rate, and inability to speak more than one or two words between breaths are signs of severe obstruction.
Cont’d

• Oxygen saturations by pulse oximetry and peak flows should be measured in all patients not completely responding to initial intensive inhaled β2-agonist therapy.

• Initially, on admission, the peak flows or clinical symptoms should be monitored every 2 to 4 hours.
Cont’d

- Systemic corticosteroids and aggressive use of inhaled $\beta_2$-agonists continue to be the cornerstones of therapy for acute severe asthma exacerbations.
Non Pharmacologic Therapy

- Unless dehydration has occurred, increased fluid therapy is not indicated in acute asthma management because the capillary leak from cytokines and increased negative intrathoracic pressures may promote edema in the airways.
- Correction of significant dehydration is always indicated.
- Chest physical therapy and mucolytics are not indicated in acute asthma.
• Sedatives should not be given because anxiety may be a sign of hypoxemia.
• Antibiotics also are not indicated routinely because viral respiratory tract infections are the primary cause of asthma exacerbations.
• Antibiotics should be reserved for patients who have signs and symptoms of pneumonia (e.g., fever, pulmonary consolidation, and purulent sputum from polymorphonuclear leukocytes).
• Mycoplasma and Chlamydia are infrequent causes of severe asthma exacerbations but should be considered in patients with high oxygen requirements.

• Respiratory failure or impending respiratory failure as measured by rising PaCO2 (>45 mm Hg) or failure to correct hypoxemia with supplemental oxygen therapy is treated with intubation and mechanical ventilation.
Pharmacologic Therapy
\textbf{β2-Agonists}

- They are the most effective bronchodilators and the treatment of choice for the management of severe acute asthma.
- Up to 66% of adults presenting to an emergency department require only three doses of 2.5 mg nebulized albuterol to be discharged.
- Systemic adverse effects, hypokalemia, hyperglycemia, tachycardia, and cardiac dysrhythmias are more pronounced in patients receiving systemic $\beta_2$-agonist therapy.
• Children younger than 2 years of age achieve clinically significant responses from nebulized albuterol.

• Effective doses of aerosolized β2-agonists can be delivered successfully through mechanical ventilator circuits to infants, children, and adults in respiratory failure secondary to severe airways obstruction.
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• Frequent administration of inhaled \( \beta_2 \)-agonists (every 20 minutes or continuous nebulization) has been found to be superior to the same dosage administered at 1-hour intervals.

• In severely obstructed patients, continuous nebulization decreases the hospital admission rate, provides greater improvement in the FEV1 and PEF, and reduces duration of hospitalization when compared with intermittent (hourly) nebulized albuterol in the same total dose.
Continuous nebulization is recommended for patients having an unsatisfactory response (achieving less than 50% of normal FEV1 or PEF) following the initial three doses (every 20 minutes) of aerosolized β2-agonists and potentially for patients presenting initially with PEF or FEV1 values of less than 30% of predicted normal.
• The nebulizer dose of inhaled β2-agonists for children often is given on a weight basis (mg per kg).
• Fixed minimal dose (2.5 mg albuterol or equivalent), as opposed to a weight-adjusted dose, is more appropriate in younger children because children younger than 5 years of age receive a lower lung dose.
• Adults dosed on a weight basis demonstrate excessive cardiac stimulation, so they have fixed maximal doses.
• Initial doses of inhaled β2-agonists can produce vasodilation, worsening ventilation-perfusion mismatch, slightly lowering oxygen saturation or PaO2.

• High-doses of inhaled β2-agonists can produce a hypokalemia, tachycardia, and hyperglycemia.

• Temporary elevation of heart rate is not an indication to use lower doses or to avoid using inhaled β2-agonists.
Cont’d

• Administration of β2-agonists does not reduce BHR, confirming a lack of significant anti-inflammatory activity.

• β2-Adrenergic stimulation also activates Na+,K+-ATPase, produces gluconeogenesis, and enhances insulin secretion, resulting in a mild to moderate decrease in serum potassium concentration by driving potassium intracellularly.
(R)-Albuterol is metabolized more rapidly than (S)-albuterol, which could lead to accumulation of (S)-albuterol with continued dosing. This accumulation is more exaggerated with oral dosing, as would be expected from a drug with a high first-pass effect. On the other hand, (S)-terbutaline is eliminated more rapidly than (R)-terbutaline. Both the intensity and duration of response are dose-dependent, and more important, the dose-response relationship is dynamic.
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• Chronic administration of β2-agonists leads to downregulation (decreased number of β2 receptors) and a decreased binding affinity for these receptors.

• Systemic corticosteroid therapy can both prevent and partially reverse this phenomenon.

• The inhaled short-acting selective β2-agonists are indicated for the treatment of intermittent episodes of bronchospasm.
They are the first treatment of choice for acute severe asthma and exercise-induced bronchospasm.

They inhibit EIB and provide complete protection for a 2-hour period following inhalation with varying levels of patient-dependent protection over 4 hours.

Although the regular administration of β2-agonists slightly decreases the effect, two inhalations prior to exercise still essentially blocks exercise-induced bronchospasm completely (1% versus 5% drop in FEV1).
Corticosteroids

- Systemic corticosteroids are indicated in all patients with acute severe asthma not responding completely to initial inhaled \( \beta_2 \)-agonist administration.
- This therapy usually is continued until hospital discharge.
- Tapering the dose in acute asthma following discharge from the hospital appears unnecessary, provided that patients are prescribed inhaled corticosteroids for outpatient therapy.
Most patients achieve 70% of predicted normal FEV1 within 48 hours and 80% of predicted by 6 days after plateauing by day 3.

Maintaining systemic corticosteroid courses for 10 to 14 days may be unnecessarily long in some patients.

It is recommended that a full dose of the corticosteroid be continued until the patient’s PEF reaches 80% of predicted normal or personal best.
Multiple daily dosing of systemic corticosteroids for the initial therapy of acute asthma exacerbations appears warranted because receptor-binding affinities of lung corticosteroid receptors are decreased in the face of airway inflammation.

Patients with less severe exacerbations may be treated adequately with once daily administration.
Cont’d

• High-dose and very-high-pulse-dose corticosteroid regimens have not been shown to enhance the outcomes in severe acute asthma but are associated with a higher likelihood of side effects.

• A recommended practice is to increase or double the dose of inhaled corticosteroids in patients who are experiencing a deterioration of their asthma control to prevent an exacerbation that requires emergency care.
Anticholinergics

- Inhaled ipratropium bromide generally produces a further improvement in lung function of 10% to 15% over inhaled \( \beta_2 \)-agonists alone.
- In children and adults, multiple-dose ipratropium bromide added to initial therapy also produced a reduced hospitalization rate in the subset of patients with an FEV1 of less than 30% of predicted at baseline.
- Ipratropium bromide, a quaternary amine, is poorly absorbed and produces minimal or no systemic effects.
• Care should be used when administering ipratropium bromide by nebulizer.
• If a tight mask or mouthpiece is not used, the ipratropium bromide that deposits in the eyes may produce pupillary dilatation and difficulty in accommodation.
• Ipratropium bromide is not a vasodilator, so unlike \( \beta_2 \)-agonists it will not worsen ventilation-perfusion mismatch.
• Anticholinergics are effective bronchodilators but not as effective as $\beta_2$-agonists.
• Ipratropium bromide is a nonselective muscarinic receptor blocker, and blockade of inhibitory muscarinic receptors theoretically could result in an increased release of acetylcholine and overcome the block on the smooth muscle receptors.
• Only the quaternary ammonium derivatives such as ipratropium bromide should be used because they have the advantage of poor absorption across mucosae and the blood-brain barrier.
• This results in negligible systemic effects with a prolonged local effect (i.e., bronchodilation).
• In addition, the quaternary compounds do not appear to produce a decrease in mucociliary clearance.
• Ipratropium bromide has a duration of action of 4 to 8 hours.
• Both intensity and duration of action are dose-dependent.
• Time to reach maximum bronchodilation is considerably slower than from aerosolized short-acting β2-agonists (2 hours versus 30 minutes).
Ipratropium bromide is only indicated as adjunctive therapy in severe acute asthma not completely responsive to $\beta_2$-agonists alone because it does not improve outcomes in chronic asthma.
Alternative Therapies

• The use of aminophylline for acute asthma has not been recommended for a number of years.

• Clinical trials of aminophylline in adults and children hospitalized with acute asthma have not reported sufficient evidence of efficacy (improvement in lung function and reduced hospital stay) but have reported an increased risk of adverse effects.

• Two studies of aminophylline in children with severe disease suggested a possible small benefit in reducing ICU admissions.
Adverse effects of theophylline include nausea and vomiting and potentiation of the cardiac effects of the inhaled β2-agonists.

Magnesium sulfate is a moderately potent bronchodilator that is similar to aminophylline, producing relaxation of smooth muscle and central nervous system depression.

The use of I.V. magnesium sulfate in patients presenting to the emergency department is controversial.
The adverse effects of magnesium sulfate include hypotension, facial flushing, sweating, nausea, loss of deep tendon reflexes, and respiratory depression.

Patients have required dopamine to treat the hypotension.

The inhalational anesthetics halothane, isoflurane, and enflurane all have been reported to have a positive effect in children and adults with severe asthma that is unresponsive to standard medical therapy.
• The proposed mechanisms for inhalational anesthetics include direct action on bronchial smooth muscle, inhibition of airway reflexes, attenuation of histamine-induced bronchospasm, and interaction with β2-adrenergic receptors.

• Potential adverse effects include myocardial depression, vasodilation, arrhythmias, and depression of mucociliary function.
Ketamine has been recommended for rapid induction of anesthesia in patients with asthma who require intubation and mechanical ventilation.

Ketamine is thought to produce bronchodilation from a combination of an increase in circulating catecholamines, direct smooth muscle relaxation, and inhibition of vagal flow.
• Ketamine has several significant adverse effects, including the anesthesia emergence reaction, which can alter mood and cause delirium.

• Other risks include an increase in heart rate, arterial blood pressure, and cerebral blood flow because of its sympathetic effects.
Special Populations

- Infants and children younger than 4 years of age may be at greater risk of respiratory failure than older children and adults.
- Although treated with the same drugs, these younger children require the use of a facemask for delivery of aerosolized medication.
- Use of the facemask reduces delivery of drug to the lung by one-half so that a minimal dose is recommended as opposed to a weight-adjusted dose.
The facemask should be sized appropriately and should fit snugly over the nose and mouth.
Chronic Asthma

• The diagnosis of chronic asthma is made primarily by history and confirmatory spirometry.

• In the older child and adult patient in whom spirometric evaluations can be performed, failure of pulmonary functions to improve acutely does not necessarily rule out asthma.

• If baseline spirometry is normal, challenge testing with exercise, histamine, or methacholine can be used to elicit BHR.
• Patients with significant symptoms and/or an FEV1 of less than 65% of predicted normal should not be challenged.

• Studies for atopy such as serum IgE and sputum and blood eosinophil determinations are not necessary to make the diagnosis of asthma, but they may help differentiate asthma from chronic bronchitis in adults.

• Skin testing is of no value in diagnosing asthma but is useful in identifying triggers.
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• In small infants unable to perform spirometry
• They may demonstrate hyperinflation on the chest roentgenogram.
• Radiologic examination is helpful in ruling out other causes of wheezing
• Parents should record symptoms and precipitating events.
Goals Of Management

1. Maintain normal activity levels (including exercise and other physical activity).
2. Maintain (near) normal pulmonary functions.
3. Prevent chronic and troublesome symptoms.
4. Prevent recurrent exacerbations of asthma, and minimize the need for emergency department visits or hospitalizations.
5. Provide optimal pharmacotherapy with minimal or no adverse effects.
6. Meet patients’ and families’ expectations of satisfaction with asthma care.
Nonpharmacologic Therapy

- Although the mainstay of the management of asthma is pharmacologic therapy
- It is important to note that the nonpharmacologic aspects of therapy are incorporated into the steps.
- It includes instruction to patient regarding her or his medications and disease.
Educational Messages for Patients

• Basic facts about asthma
  1. The contrast between asthmatic and normal airways
  2. What happens to the airways in an asthma attack

• Roles of medications
  1. How medications work
  2. Long-term control: medications that prevent symptoms, often by reducing inflammation
  3. Quick relief: short-acting bronchodilator relaxes muscles around airways
  4. Stress importance of long-term-control medications and not to expect quick relief from them

• Skills
  1. Inhaler use (patient demonstrate)
  2. Spacer and holding chamber use
  3. Symptom monitoring, peak flow monitoring, and recognizing early signs of deterioration

• Environmental control measures
  1. Identifying and avoiding environmental precipitants or exposures

• When and how to take rescue actions
  1. Responding to changes in asthma severity (daily self-management plan and action plan)
Pharmacologic Therapy

- All patients need to have quick-relief medication in the form of short-acting inhaled β2-agonists available for acute symptoms.
- The inhaled corticosteroids are considered the preferred long-term control therapy for persistent asthma in all patients.
- Low- to medium-dose inhaled corticosteroids reduce BHR, improve lung function, and reduce severe exacerbations leading to emergency department visits and hospitalizations.
• They are more effective than either cromolyn, nedocromil, theophylline, or the leukotriene antagonists.
• In addition, the inhaled corticosteroids are the only therapy that reduces the risk of dying from asthma.
• The principal adverse effect at low to medium doses is delayed growth in children that appears to be about 1 to 2 cm in the first year of therapy and does not appear to prevent attainment of predicted adult height.
• The inhaled corticosteroids do not appear to increase the risk of osteoporosis in the elderly or glaucoma and cataracts except at high doses

• Alternative long-term control therapies (e.g., cromolyn, leukotriene antagonists, nedocromil, and theophylline) demonstrate improvement in symptoms, lung function, and as-needed short-acting inhaled β2-agonist use, they do not reduce BHR.
Special Populations

- In children 5 years of age and younger, studies of inhaled corticosteroids are supportive.
- The nebulized formulation of budesonide gained FDA approval from three pivotal efficacy and safety trials.
- FDA approval for montelukast in children younger than age 6 was based on safety and pharmacokinetic studies establishing doses but not on efficacy trials.
- Not all trials of cromolyn in this younger group have demonstrated efficacy.
Theophylline has not been evaluated adequately, except for pharmacokinetics.

Owing to the increased risk of osteoporosis in the elderly, patients requiring high doses of inhaled corticosteroids should have their bone mineral density determinations followed and appropriate therapies for osteoporosis instituted if necessary.
• It is safer for pregnant women with asthma to be treated with asthma medications than for them to have asthma exacerbations.

• Proper monitoring and control of asthma should enable a woman with asthma to maintain a normal pregnancy with little or no risk to her or her fetus.

• A stepwise approach include low-dose inhaled corticosteroids as preferred treatment for step 2 and the addition of long-acting β-agonists added in step 3 and step 4
• Budesonide is considered the preferred inhaled corticosteroid to initiate because it has the greatest safety.
• Albuterol is considered the preferred rescue therapy.
Inhaled Corticosteroids

• Inhaled corticosteroids (ICS) have high topical potency to reduce inflammation in the lung and low systemic activity.
• They have high anti-inflammatory potency, approximately 1000-fold greater than endogenous cortisol.
• Delivery method can make a significant difference in the relative comparable dose.
• Local adverse effects include oropharyngeal candidiasis and dysphonia that are dose-dependent.

• Systemic adverse effects can occur with high dose.

• Long-term adverse effects of greatest concern include growth suppression in children, osteoporosis, cataracts, and adrenal insufficiency and crisis.
Long-Acting Inhaled $\beta_2$-Agonist

- The two long-acting $\beta_2$-agonists, formoterol and salmeterol, provide long-lasting bronchodilation (12 or more hours) when administered as aerosols.
- They are lipid-soluble.
- Salmeterol is more $\beta_2$-selective than albuterol and more bronchoselective.
- Both formoterol and salmeterol will produce dose-dependent systemic $\beta_2$-agonist effects.
• The differences between formoterol and salmeterol is that formoterol has a more rapid onset of action (similar to that of albuterol), and formoterol is a full agonist, whereas salmeterol is a partial agonist.

• They are available singly and as fixed-dose combinations with ICSs.

• Patients should be warned that salmeterol is ineffective for acute severe asthma because it can take up to 20 minutes for onset and 1 to 4 hours for maximum bronchodilation following inhalation.
• Patients need to continue their short-acting inhaled \( \beta_2 \)-agonists for acute exacerbations while receiving the long-acting inhaled \( \beta_2 \)-agonists.

• Tolerance is produced with chronic administration.
Methylxanthines

- Their use has declined due to the high risk of severe life-threatening toxicity and numerous drug interactions, as well as decreased efficacy compared with ICSs and long-acting inhaled β2-agonists.
- Theophylline is a moderately potent bronchodilator with mild anti-inflammatory properties.
- Methylxanthines are functional antagonists of bronchospasm.
- Theophylline SR is the preferred oral form and aminophylline is the preferred injectable form.
Cont’d

- Theophylline produces bronchodilation effect through nonselective phosphodiesterase inhibition.
- Theophylline has a log-linear dose response.
- Significant bronchodilation will be obtained when serum concentration reaches 5 mcg/mL, and most patients will have no toxic symptom with serum concentrations of less than 15 mcg/mL.
Cont’d

• Adults and children > 1 y old: 10 mg/kg/day up to 300 mg/day,
• Infants < 1 y old: Dose mg/kg = (0.2) (age in weeks) + 5.0
• If tolerated after 3 days increase dose to:
  • Adults: 400 mg/day, Children < 45 kg: 16 mg/kg/day up to 400 mg/day
  • Check serum concentration: 4–6 h after morning dose of q 12 h SRT; 8 h after q 24 h SRT preparation (5–15 mcg/mL)
• Further dosage adjustments based on patient symptoms and serum concentrations
Cromolyn Sodium And Nedocromil Sodium

- Cromolyn sodium and nedocromil sodium are pharmacologically similar.
- They are classified as mast cell stabilizers, and the principal difference appears to be potency, with 4 mg nedocromil by MDI equivalent to 10 mg cromolyn.
- No apparent difference in the clinical efficacy between these two drugs.
- They inhibit the early and late asthmatic response to allergen challenge, as well inhibit exercise-induced bronchospasm.
Cont’d

• Treatment prevents the usual rise in bronchial hyperresponsiveness with specific pollen seasons, but long-term treatment produces minimal to no change in baseline bronchial hyperresponsiveness.

• Both are effective by inhalation.

• Higher doses produce greater and more prolonged protection.

• Both drugs are remarkably safe.
• Cough and wheeze have been reported following inhalation of each, and bad taste and headache following nedocromil are reported.
• They are no more or less effective than theophylline or the leukotriene antagonists for persistent asthma but not as effective as ICS
• Most patients will experience an improvement in 1 to 2 weeks.
Cont’d

• It may take longer to achieve maximum benefit.

• Patients initially should receive cromolyn or nedocromil four times daily, and then only after stabilization of symptoms may the frequency be reduced to two times daily for nedocromil and three times daily for cromolyn.
Leukotriene Modifiers

- Two clinically distinct leukotriene receptor antagonists (zafirlukast and montelukast) and one inhibitor of leukotriene synthesis (zileuton)
- They reduce allergen-, exercise-, cold-air hyperventilation-, irritant-, and aspirin-induced asthma.
- These drugs improve pulmonary function tests (FEV1 and PEF), decrease nocturnal awakenings and β2-agonist use, and improve asthma symptoms.
Advantage is that they are effective orally, administered once or twice a day, and contribute to patient adherence and satisfaction with therapy.

They are less effective in asthma than low doses of ICSs, although some patients (even those with severe disease) may have useful clinical improvement.
• They are well tolerated and do not appear to have serious class-specific effects. In the early
• Postmarketing surveillance reports include elevations in serum aminotransferase concentrations and clinical hepatitis
• An idiosyncratic syndrome similar to the Churg-Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported of patients treated with zafirlukast or montelukast.
• The majority of these patients had been receiving high-dose inhaled or oral corticosteroids and were able to reduce the dose as a consequence of the LTD4 receptor antagonists.
Anti-ige

- Omalizumab is the first anti-IgE antibody approved for the treatment of asthma not well controlled on high doses of ICSs.
- It is a composite of 95% human and 5% antihuman murine IgE sequences.
- The mouse protein becomes part of the receptor complex and thus is shielded from exposure to the immune system and presents a low risk for an anaphylactic response.
- It is administered SQ and has a slow absorption rate;
- Peak serum concentration is achieved in 3 to 14 days.
It is eliminated primarily through the reticuloendothelial system and has an elimination half-life of 17 to 22 days; serum free IgE levels return to baseline in about 3 weeks.

The dosage of omalizumab is determined by the patient’s baseline total serum IgE level (international units per milliliter) and body weigh (kilograms).

Doses range from 150 to 375 mg and are given at either 2- or 4-week intervals.
• No further adjustments for variations in total serum IgE are required, and patients receive a consistent dose for the duration of treatment.
• It has been studied in patients aged 12 to 74 years and appears to be safe and efficacious.
• It is only indicated for corticosteroid-dependent atopic patients requiring oral corticosteroids or on high-dose ICSs with continued symptoms and high IgE levels.
Methotrexate

- Low-dose methotrexate (15 mg/week) used for inflammatory diseases to reduce the systemic steroid dose in patients with severe steroid-dependent asthma.
- The mechanism is unknown but may be anti-inflammatory or immunomodulatory effects.
- Low-dose weekly methotrexate is not without hazard.
- Hepatotoxicity and pulmonary fibrosis have been reported.
Steps for Using Your Inhaler

Please demonstrate your inhaler technique at every visit.

1. Remove the cap and hold inhaler upright.
2. Shake the inhaler.
3. Tilt your head back slightly and breathe out slowly.
4. Position the inhaler in one of the following ways (A or B is optimal, but C is acceptable for those who have difficulty with A or B. C is required for breath-activated inhalers):

   A Open mouth with inhaler 1 to 2 inches away.
   B Use spacer/holding chamber (that is recommended especially for young children and for people using corticosteroids).
   C In the mouth. Do not use for corticosteroids.

   D NOTE: Inhaled dry powder capsules require a different inhalation technique. To use a dry powder inhaler, it is important to close the mouth tightly around the mouthpiece of the inhaler and to inhale rapidly.

5. Press down on the inhaler to release medication as you start to breathe in slowly.
6. Breathe in slowly (3 to 5 seconds).
7. Hold your breath for 10 seconds to allow the medicine to reach deeply into your lungs.
8. Repeat puff as directed. Waiting 1 minute between puffs may permit second puff to penetrate your lungs better.
9. Spacers/holding chambers are useful for all patients. They are particularly recommended for young children and older adults and for use with corticosteroids.

Avoid common inhaler mistakes. Follow these inhaler tips:
• Breathe out before pressing your inhaler.
• Inhale slowly.
• Breathe in through your mouth, not your nose.
• Press down on your inhaler at the start of inhalation (or within the first second of inhalation).
• Keep inhaling as you press down on inhaler.
• Press your inhaler only once while you are inhaling (one breath for each puff).
• Make sure you breathe in evenly and deeply.

NOTE: Other inhalers are becoming available in addition to those illustrated above. Different types of inhalers require different techniques.


one-quarter of the dose.26 The Aerolizer and the Diskus deliver about 15% of the dose to the airways, and this appears to be similar at both 30 and 60 L/min inspiratory flows; both have been approved for children aged 5 and 4 years, respectively.7,26

TREATMENT: Severe Acute Asthma

The primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and early intervention. As such, the principal goals of treatment include:

• Correction of significant hypoxemia
• Rapid reversal of airflow obstruction
• Reduction of the likelihood of recurrence of severe airflow obstruction
• Development of a written action plan in case of a further exacerbation

These goals are best achieved by early initiation of treatment and close monitoring of objective measures of oxygenation and lung function.2 Early response to treatment as measured by the improvement in FEV1 at 30 minutes following inhaled β2-agonists is the best predictor of outcome.27 Providing adequate oxygen supplementation to maintain oxygen (O2) saturations above 90% (or above 95% in pregnant women) is essential. In children younger than 6 years of age, in whom lung function measures are difficult to obtain, a combination of objective (e.g., oxygen saturation, capillary CO2, respiratory rate, and heart rate) and subjective measures may be used to assess severity.2,10

The primary therapy of acute exacerbations is pharmacologic, which includes inhaled short-acting β2-agonists and, depending on the severity, systemic corticosteroids and O2 (Figs. 26–6 and 26–7). It is important that therapy not be delayed, so the initial history and physical examination should be obtained while initial therapy is being provided. Patients at risk for life-threatening exacerbations require special attention. Risk factors include a history of previous severe asthma exacerbations (e.g., hospitalizations, intubations, or hypoxic seizures), complicating illnesses (e.g., cardiac disease, diabetes, illicit drug use, or psychosis), use of more than two canisters per month of short-acting inhaled β2-agonists, and current intake of oral corticosteroids or recent withdrawal from oral corticosteroids.10

A complete blood count may be appropriate for patients with fever or purulent sputum, but many patients will have a leukocytosis.
from a viral infection or secondary to corticosteroid administration. Routine chest radiographs have not been shown to be of value unless physical findings suggestive of consolidations or pneumothoraces are present. Serum electrolytes should be monitored if high-dose continuous inhaled or systemic β₂-agonists are to be used because they can produce transient decreases in potassium, magnesium, and phosphate. The combination of high-dose β₂-agonists and systemic corticosteroids occasionally may result in excessive elevations of glucose.

Initial response should be achieved within minutes, and most patients experience significant improvement within the first 30 to 60 minutes of therapy, with most patients doubling their FEV₁ or PEF. In patients ultimately admitted to the hospital, only a 10% to 20% predicted improvement is seen within the first 2 hours. Hypoxemia, primarily a result of ventilation-perfusion mismatch, is immediately correctable by low-flow oxygen. While reversal of lung function into the normal range may take 12 to 24 hours, complete restoration takes much longer—up to 3 to 7 days. A strategy to prevent recurrence such as systemic corticosteroids and PEF monitoring should be used. It is essential to provide the patient with a self-management plan that includes a written action plan for dealing with exacerbations. Patients at risk for severe exacerbations should be taught how to use a peak-flow meter and monitor morning peak flows at home. In young children, an increased respiratory rate, increased heart rate, and inability to speak more than one or two words between breaths are signs of severe obstruction. Oxygen saturations by pulse oximetry and peak flows should be measured in all patients not completely responding to initial intensive inhaled β₂-agonist therapy. Initially, on admission, the peak flows or clinical symptoms should be monitored every 2 to 4 hours. Prior to discharge from the emergency department or hospital, the patient should be given a sufficient supply of prednisone, taught the purpose of the medications and proper inhaler technique, and given an appointment for a follow-up visit.

Early recognition of deterioration and aggressive treatment are the keys to successful treatment of acute asthma exacerbations. Thus patient and/or parent education teaching self-management skills and written action plans for early institution of therapy for acute exacerbations improve outcomes. For more moderate to severe patients, this therapeutic plan also may include the availability of oral prednisone to begin at home. Easy access by telephone to health care providers is also needed. Because of the rapid progression to severe asthma that can occur, patients and parents should be encouraged to communicate promptly with their asthma care provider during an exacerbation. Systemic corticosteroids and aggressive use of inhaled β₂-agonists continue to be the cornerstones of therapy for acute severe asthma exacerbations.

Figures 26–6 and 26–7 illustrate the recommended therapies for the treatment of acute asthma exacerbations in home and emergency department/hospital settings, respectively. The dosages of the drugs for acute severe asthma are provided in Table 26–6. Institutions should strongly consider developing critical-pathways/treatment algorithms for their emergency departments because their implementation has been shown to improve outcomes and decrease the cost of care.
**FIGURE 26–7.** Emergency department and hospital care of acute asthma exacerbations. (From ref. 2.)

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**NONPHARMACOLOGIC THERAPY**

Infants and young children may be mildly dehydrated owing to increased insensible loss, vomiting, and decreased intake. Unless dehydration has occurred, increased fluid therapy is not indicated in acute asthma management because the capillary leak from cytokines and increased negative intrathoracic pressures may promote edema in the airways. Correction of significant dehydration is always indicated, and the urine specific gravity may help to guide therapy in young children, in whom the state of hydration may be difficult to determine. Chest physical therapy and mucolytics are not indicated in the...
therapy of acute asthma. Sedatives should not be given because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants. Antibiotics also are not indicated routinely because viral respiratory tract infections are the primary cause of asthma exacerbations.2 Antibiotics should be reserved for patients who have signs and symptoms of pneumonia (e.g., fever, pulmonary consolidation, and purulent sputum from polymorphonuclear leukocytes). Mycoplasma and Chlamydia are infrequent causes of severe asthma exacerbations but should be considered in patients with high oxygen requirements.7

Respiratory failure or impending respiratory failure as measured by rising PaCO2 (> 45 mm Hg) or failure to correct hypoxemia with supplemental oxygen therapy is treated with intubation and mechanical ventilation. In order to prevent barotrauma and pneumothoraces from excess positive pressure, it is recommended that controlled hypoventilation or permissive hypercapnia be used (correcting the hypoxemia, PaO2 > 60 mm Hg, but allowing the PaCO2 to rise to the high 60 mm Hg range).

### PHARMACOTHERAPY

#### β2-AGONISTS

The short-acting inhaled β2-agonists are the most effective bronchodilators and the treatment of first choice for the management of severe acute asthma.2 Up to 66% of adults presenting to an emergency department require only three doses of 2.5 mg nebulized albuterol to be discharged.28 Most well-controlled clinical trials have demonstrated equal to greater efficacy and greater safety of aerosolized β2-agonists over systemic administration regardless of the severity of obstruction.27 Systemic adverse effects, hypokalemia, hyperglycemia, tachycardia, and cardiac dysrhythmias are more pronounced in patients receiving systemic β2-agonist therapy. Children younger than 2 years of age achieve clinically significant responses from nebulized albuterol.27 Effective doses of aerosolized β2-agonists can be delivered successfully through mechanical ventilator circuits to infants, children,

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dosages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled β-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol nebulizer soln. (5 mg/mL)</td>
<td>2.5–5 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously</td>
<td>0.15 mg/kg (minimum dose 2.5 mg) every 20 min for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed, or 0.5 mg/kg/h by continuous nebulization</td>
</tr>
<tr>
<td>Albuterol MDI (90 mcg/puff)</td>
<td>4–8 puffs every 30 min up to 4 h, then every 1–4 h as needed</td>
<td>4–8 puffs every 20 min for 3 doses, then every 1–4 h as needed</td>
</tr>
<tr>
<td>Levalbuterol nebulizer soln. (2 mg/mL)</td>
<td>Give at one-half the mg dose of albuterol above</td>
<td>Give at one-half the mg dose of albuterol above</td>
</tr>
<tr>
<td>Bitolterol nebulizer soln.</td>
<td>See albuterol dose</td>
<td>See albuterol dose</td>
</tr>
<tr>
<td>Pirbuterol MDI (200 mcg/puff)</td>
<td>See albuterol dose</td>
<td>See albuterol dose; one-half as potent as albuterol on a microgram basis</td>
</tr>
<tr>
<td><strong>Systemic β-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine 1:1000 (1 mg/mL)</td>
<td>0.3–0.5 mg every 20 min for 3 doses SQ</td>
<td>0.01 mg/kg up to 0.5 mg every 20 min for 3 doses SQ</td>
</tr>
<tr>
<td>Terbutaline (1 mg/mL)</td>
<td>0.25 mg every 20 min for 3 doses SQ</td>
<td>0.01 mg/kg every 20 min for 3 doses, then every 2–6 h as needed SQ</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium Br. nebulizer soln. (0.25 mg/mL)</td>
<td>500 mcg every 30 min for 3 doses, then every 2–4 h as needed</td>
<td>250 mcg every 20 min for 3 doses, then 250 mcg every 2–4 h</td>
</tr>
<tr>
<td>Ipratropium Br. MDI (18 mcg/puff)</td>
<td>4–8 puffs as needed every 2–4 h</td>
<td>4–8 puffs as needed every 2–4 h</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone, methylprednisolone, prednisolone</td>
<td>60–80 mg in 3 or 4 divided doses for 48 h, then 30–40 mg/day until PEFR reaches 70% of personal best</td>
<td>1 mg/kg every 6 h for 48 h, then 1–2 mg/kg/day in 2 divided doses until PEFR is 70% of normal predicted</td>
</tr>
</tbody>
</table>

Note: No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for intravenous administration over oral therapy. The usual regimen is to continue the frequent multiple daily dosing until the patient achieves an FEV1 or PEF of 50% of personal best or normal predicted value and then lower the dose to twice-daily dosing. This usually occurs within 48 hours. The final duration of therapy following a hospitalization or emergency department visit may be from 7 to 14 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic steroid dose. If the follow-up therapy is to be given once daily, studies indicate there may be an advantage to giving the single daily dose in the afternoon at around 3 PM.
is no rationale for using non-\(\beta_2\)-selective agonists in the treatment of asthma.\(^{25}\)

Table 26–8 compares the various \(\beta\)-adrenergic agonists used in asthma in terms of selectivity, potency, oral activity, and duration of action. The \(\beta_2\)-agonists are functional or physiologic antagonists in that they relax airway smooth muscle regardless of the mechanism for constriction.\(^{30}\) When administered in equipotent doses, all the short-acting drugs produce the same intensity of response; the only differences are in duration of action and cardiac toxicity.\(^{2,25}\) The catecholamine derivatives all have the disadvantage of rapid inactivation of their 3,4-hydroxyl catechol group from catechol-O-methyltransferase found in the gastrointestinal tract, rendering them orally inactive. In addition, catecholamines are taken up rapidly into tissues by secondary uptake mechanisms that limit their receptor occupancy and thus have a shorter duration of action.\(^{25}\) All the \(\beta_2\)-agonists are more bronchoselective when administered by the aerosol route.\(^{25}\) Aerosol administration of the short-acting \(\beta_2\)-agonists provides more rapid response and greater protection against provocations that induce bronchospasm such as exercise and allergen challenges than does systemic administration.\(^{25}\) Differences in myocardial effects are discernible between selective and nonselective agents even when administered as aerosols, particularly at the higher doses used for severe acute asthma. The \(\beta_2\)-agonists also differ in efficacy or ability to activate the \(\beta_2\)-adrenergic receptors. Full agonists include the catecholamines, metaproterenol, and formoterol.\(^{30}\) Partial agonists include albuterol, terbutaline, pirbuterol, and salmeterol.\(^{30}\) The principal differences between full and partial agonists is that full agonists require a lower fraction of receptor occupancy to produce their maximum effect and more easily produce receptor desensitization.\(^{30}\)

All synthetic \(\beta_2\)-agonists are 1:1 racemic mixtures of two mirror images (enantiomers) owing to an asymmetric or chiral carbon.\(^{30,38}\) Since most physiologic functions (receptor occupancy and activation and enzymatic metabolism) are stereoselective, the \(R\)-enantiomers of the \(\beta_2\)-agonists are the most pharmacologically active isomer.\(^{37}\) While it was felt initially that the \((S)\)-enantiomers were essentially inactive owing to the 1000-fold potency difference between the enantiomers, studies in animal models and isolated in vitro tissue preparations have suggested that the \((S)\)-enantiomers may be proinflammatory and could induce BHR.\(^{39}\) However, evidence that this occurs consistently in humans or is clinically relevant is lacking (see below).\(^{38}\) The pharmacokinetics are stereoselective as well, although not as predictable. \((R)\)-Albuterol is metabolized more rapidly than \((S)\)-albuterol, which could lead to accumulation of \((S)\)-albuterol with continued dosing.\(^{38}\) This accumulation is more exaggerated with oral dosing, as would be expected from a drug with a high first-pass effect.\(^{30}\) On the other hand, \((S)\)-terbutaline is eliminated more rapidly than \((R)\)-terbutaline.\(^{30}\)

Both the intensity and duration of response are dose-dependent, and more important, the dose-response relationship is dynamic.\(^{25}\) At increasing levels of baseline bronchoconstriction (irrespective of the stimulus), the dose-response curve is shifted to the right, and the duration of bronchodilation is decreased.\(^{30}\) This shift is reflected in the need for higher, more frequent doses in acute asthma exacerbations; the duration of protection against significant provocation is much less than the duration of bronchodilation in chronic stable asthma\(^{25}\) (see Table 26–8).

Chronic administration of \(\beta_2\)-agonists leads to downregulation (decreased number of \(\beta_2\) receptors) and a decreased binding affinity for these receptors.\(^{25,30}\) Systemic corticosteroid therapy can both prevent and partially reverse this phenomenon.\(^{2,25}\) However, the use of inhaled corticosteroids appears to have minimal ability to prevent tolerance to \(\beta_2\)-agonists.\(^{30}\) The homozgyous Gly-16 form of the receptor downregulates to a much greater extent compared with the homozgyous Arg-16 form of the receptor.\(^{37}\) The heterozygous Arg-16/Gly-16 is intermediate desensitized compared with the homozygous Gly-16 form. On the other hand, glutamate substitution at codon 27 (Glu-27) protects against downregulation compared with the glutamine form (Gln-27) of the receptor.\(^{37}\) However, the Gly-16 overcomes any protective effect of Glu-27.\(^{37}\) Tolerance primarily reduces duration of bronchodilation as opposed to peak response. A significantly greater tolerance develops in other tissues (e.g., lymphocytes and cardiac and skeletal muscle) compared with the lung primarily as a result of the surplus \(\beta_2\) receptors found in respiratory smooth muscle.\(^{25}\) Tolerance to the extrapulmonary effects (cardiac stimulation and hypokalemia) may account for a lack of significant cardiac effects with retention of the bronchodilator response despite chronic inhaled \(\beta_2\)-agonist therapy, whereas tolerance to mast cell stabilization may be a drawback to chronic use.\(^{25}\) Thus chronic \(\beta_2\)-agonist administration produces a tolerance of minimal clinical significance that is overcome easily by increasing the dose or by administering corticosteroids.\(^{2,25}\) Most of the tolerance occurs within a week of regular administration and does not worsen with continued administration. As would be expected from a receptor phenomenon, tolerance is a cross-tolerance to all \(\beta_2\)-agonists.\(^{25,30}\) Whether or not regular use of short-acting inhaled \(\beta_2\)-agonists produces worsening of asthma in a subset of patients remains controversial (see below), but it does not appear to occur in the entire population.\(^{40}\) However, regular treatment (four times daily) does not improve symptom control over as-needed use.\(^{41}\)

### TABLE 26–8. Relative Selectivity, Potency, and Duration of Action of the \(\beta\)-Adrenergic Agonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>(\beta_1) Selectivity</th>
<th>(\beta_2) Selectivity</th>
<th>Potency, (\beta_2^{*})</th>
<th>Duration of Action &lt;sup&gt;1&lt;/sup&gt;</th>
<th>Oral activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>++</td>
<td>+++</td>
<td>2</td>
<td>4–8</td>
<td>Yes</td>
</tr>
<tr>
<td>Bitolterol</td>
<td>+</td>
<td>+++</td>
<td>5</td>
<td>4–8</td>
<td>No</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>+</td>
<td>+++</td>
<td>5</td>
<td>4–8</td>
<td>Yes</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>+</td>
<td>+++</td>
<td>4</td>
<td>4–8</td>
<td>Yes</td>
</tr>
<tr>
<td>Formoterol</td>
<td>+</td>
<td>+++</td>
<td>0.24</td>
<td>≥12</td>
<td>Yes</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>+</td>
<td>+++</td>
<td>0.5</td>
<td>≥12</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>1</sup>Relative molar potency to isoproterenol: 15 = lowest potency.

<sup>2</sup>Median durations with the highest value after a single dose and lowest after chronic administration.

<sup>3</sup>Protection refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.
The corticosteroids are the most effective anti-inflammatories that prevent the action of proinflammatory cytokines on the cell.44 This leads to specific mRNA production, resulting in increased production of anti-inflammatory mediators; suppression of several proinflammatory cytokines such as IL-1, GM-CSF, IL-3, IL-4, IL-5, IL-6, and IL-8, reducing inflammatory cell activation, recruitment, and infiltration; and decreasing vascular permeability.44 In addition, the activated glucocorticoid receptor complex can act directly with cytoplasmic transcription factors, nuclear factor κB, and activating protein 1 to prevent the action of proinflammatory cytokines on the cell.44

Owing to the mechanism that modifies gene expression, the time required to see the particular effect depends on the time required for new protein synthesis, decreased formation of the particular mediator, and resolution of the inflammatory response.44 Generally, the cellular and biochemical effects are immediate, but varying amounts of time are required to produce a clinical response. β2-Receptor density increases within 4 hours of corticosteroid administration.44 Improved responsiveness to β2-agonists occurs within 2 hours.25 In severe acute asthma, 4 to 12 hours may be required before any clinical response is noted.25 Reversal of seasonally increased BHR requires at least 1 week of therapy.44 The chronic use of corticosteroids does not induce a state of corticosteroid dependence. Nor is there evidence of tolerance produced by chronic administration.

The corticosteroids used in asthma are compared in Table 26–9.45 Besides acute severe asthma, systemic corticosteroids are also recommended for the treatment of impending episodes of severe asthma unresponsive to bronchodilator therapy.2,10 The effects of corticosteroids in asthma are dose- and duration-dependent. This pattern is true for the adverse effects as well (Table 26–10). The clinician must balance the toxicity of chronic systemic corticosteroid therapy continually with control of asthma symptoms. Because short-term (1 to 2 weeks) high-dose corticosteroids (1 to 2 mg/kg per day of prednisone) do not produce serious toxicities, the ideal use is to administer the systemic corticosteroids in a short “burst” and then to maintain the patient on appropriate long-term control therapy with inhaled corticosteroids (discussed below).2,10 In general, therapy for more than 5 days at doses that exceed the usual physiologic endogenous cortisol

### TABLE 26–9. Pharmacodynamic/Pharmacokinetic Comparison of the Corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Systemic Potency</th>
<th>Mineralocorticoid Potency</th>
<th>Duration of Biologic Activity (h)</th>
<th>Elimination Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1.0</td>
<td>12</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>12–36</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>12–36</td>
<td>3.3</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>36–54</td>
<td>3.4–4.0</td>
</tr>
</tbody>
</table>

Note: Receptor binding affinities and topical skin blanching are relative to dexamethasone equal to 1. UK = unknown.

*MF studied in a different receptor system. Value estimated from relative values of BDP, TAA, and FP in that system.

**TABLE 26–10. Adverse Effects of Chronic Systemic Glucocorticoid Administration**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Hypothalamic–pituitary-adrenal suppression</th>
<th>Growth retardation</th>
<th>Skeletal muscle myopathy</th>
<th>Osteoporosis/fractures</th>
<th>Aseptic necrosis of bone</th>
<th>Pancreatitis</th>
<th>Pseudotumor cerebri</th>
<th>Psychiatric disturbances</th>
<th>Sodium and water retention</th>
<th>Hypokalemia/hyperglycemia</th>
</tr>
</thead>
</table>
### Classify Severity: Clinical Features Before Treatment or Adequate Control

<table>
<thead>
<tr>
<th>Symptoms/Day</th>
<th>PEF or FEV₁</th>
<th>Medications Required to Maintain Long-Term Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Continual</td>
<td>≤60%</td>
</tr>
<tr>
<td>Persistent</td>
<td>Frequent</td>
<td>&gt;30%</td>
</tr>
<tr>
<td><strong>STEP 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Daily</td>
<td>&gt;60% – &lt;80%</td>
</tr>
<tr>
<td>Persistent</td>
<td>&gt;1 night/week</td>
<td>&gt;30%</td>
</tr>
<tr>
<td><strong>STEP 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;2/week but &lt; 1x/day</td>
<td>≥80%</td>
</tr>
<tr>
<td>Persistent</td>
<td>&gt;2 nights/month</td>
<td>20–30%</td>
</tr>
<tr>
<td><strong>STEP 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>≤2 days/week</td>
<td>≥80%</td>
</tr>
<tr>
<td>Intermittent</td>
<td>≤2 nights/month</td>
<td>&lt;20%</td>
</tr>
</tbody>
</table>

#### Quick Relief

- **All Patients**
  - Short-acting bronchodilator: 2–4 puffs short-acting inhaled β₂-agonists as needed for symptoms.
  - Intensity of treatment will depend on severity of exacerbation: up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed.
  - Use of short-acting β₂-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

#### Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled β₂-agonist
- Minimal or no adverse effects from medications

#### Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV₁ is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled β₂-agonists. Over reliance on short-acting inhaled β₂-agonists (e.g., use of short-acting inhaled β₂-agonist everyday, increasing use or lack of expected effect, or use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

### FIGURE 26–8. Stepwise approach for managing asthma in adults and children older than 5 years of age. (From ref. 2.)
Although the addition of a third controller medication is often used clinically in patients requiring step 4 therapy, there are few studies evaluating this practice. Leukotriene antagonists added to high-dose inhaled corticosteroids and long-acting inhaled β₂-agonists do not improve outcomes. None of the other long-term controllers has been evaluated in this scenario. Omalizumab or anti-IgE has received FDA approval for use in corticosteroid-dependent, severe asthma. Thus patients with severe asthma and atopy with an elevated IgE concentration would be candidates for omalizumab.

### SPECIAL POPULATIONS

Children 5 years of age and younger have not been studied adequately. Thus many of the recommendations in this age group are based on extrapolation of data from older children and adults. The few studies of inhaled corticosteroids in this younger group are supportive. The nebulized formulation of budesonide gained FDA approval from three pivotal efficacy and safety trials. The FDA approval for montelukast in children younger than age 6 was based on safety and pharmacokinetic studies establishing doses but not on efficacy trials. Not all trials of cromolyn in this younger group have demonstrated efficacy. Theophylline has not been evaluated adequately, except for pharmacokinetics. Combination therapy of any kind has not been studied except for a small number of patients down to 4 years of age on inhaled corticosteroids plus long-acting inhaled β₂-agonists. The FDA approval of the Advair Diskus 100/50 in patients 4 to 11 years of age was based on extrapolation of efficacy data from patients older than 12 years of age and by safety and efficacy data from a study of the Advair Diskus 100/50 in children with asthma aged 4 to 11 years.

The recommendations for children 5 years of age and younger differ slightly from the recommendations for older children and adults. For step 3 therapy, both medium-dose inhaled corticosteroids as monotherapy and the combination of inhaled corticosteroids plus long-acting inhaled β₂-agonists are considered preferred. However, there is no more evidence for a significant dose-response to the inhaled corticosteroids in this age group than there is for combination therapy. Owing to the increased risk of osteoporosis in the elderly, patients requiring high doses of inhaled corticosteroids should have their bone mineral density determinations followed and appropriate therapies for osteoporosis instituted if necessary.

A systematic review of the evidence on the safety of asthma medications has been conducted by drug class. This review concluded that it is safer for pregnant women with asthma to be treated with asthma medications than for them to have asthma exacerbations. Proper monitoring and control of asthma should enable a woman with asthma to maintain a normal pregnancy with little or no risk to her or her fetus.

A stepwise approach to managing asthma during pregnancy and lactation has been published, with low-dose inhaled corticosteroids recommended as preferred treatment for step 2 and the addition of long-acting β₂-agonists added in step 3 and step 4. Budesonide is considered the preferred inhaled corticosteroid to initiate because it has the greatest safety data from the Swedish Birth Registry. Albuterol is considered the preferred rescue therapy.