Chapter 78: Asthma

INTRODUCTION

- *Asthma* is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

PATHOPHYSIOLOGY

- There is a variable degree of airflow obstruction (related to smooth muscle bronchospasm, edema, and mucus hypersecretion), bronchial hyperresponsiveness (BHR), and airway inflammation.
- In acute inflammation, inhaled allergens in allergic patients cause early-phase allergic reaction with activation of cells bearing allergen-specific immunoglobulin E (IgE) antibodies. After rapid activation, airway mast cells and macrophages release proinflammatory mediators such as histamine and eicosanoids that induce contraction of airway smooth muscle, mucus secretion, edema, and exudation of plasma in the airways. Plasma protein leakage induces a thickened, engorged, edematous airway wall and narrowing of lumen with reduced mucus clearance.
- Late-phase inflammatory reaction occurs 6–9 hours after allergen provocation and involves recruitment and activation of eosinophils, T lymphocytes, basophils, neutrophils, and macrophages. Eosinophils migrate to airways and release inflammatory mediators.
- T-lymphocyte activation leads to release of cytokines from type 2 T-helper (TH_2) cells that mediate allergic inflammation (interleukin [IL]-4, IL-5, and IL-13). Conversely, type 1 T-helper (TH_1) cells produce IL-2 and interferon-γ that are essential for cellular defense mechanisms. Allergic asthmatic inflammation may result from imbalance between TH_1 and TH_2 cells.
- Mast cell degranulation results in release of mediators such as histamine; eosinophil and neutrophil chemotactic factors; leukotrienes C_4, D_4, and E_4; prostaglandins; and platelet-activating factor (PAF). Histamine can induce smooth muscle constriction and bronchospasm and may contribute to mucosal edema and mucus secretion.
- Alveolar macrophages release inflammatory mediators, including proinflammatory and anti-inflammatory cytokines, reactive oxygen species, and eicosanoids. Production of neutrophil chemotactic factor and eosinophil chemotactic factor furthers the inflammatory process. Neutrophils also release mediators (PAFs, prostaglandins, thromboxanes, and leukotrienes) that contribute to BHR and airway inflammation. Leukotrienes C_4, D_4, and E_4 are released during inflammatory processes in the lung and produce bronchospasm, mucus secretion, microvascular permeability, and airway edema.
- Bronchial epithelial cells participate in inflammation by releasing eicosanoids, peptidases, matrix proteins, cytokines, and nitric oxide. Epithelial shedding results in heightened airway responsiveness, altered permeability of airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading inflammatory neuropeptides. The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. Bronchial glands increase in size, and goblet cells increase in size and number.
- The airway is innervated by parasympathetic, sympathetic, and nonadrenergic inhibitory nerves. Normal resting tone of airway smooth muscle is maintained by vagal efferent activity, and bronchoconstriction can be mediated by vagal stimulation in small bronchi. Airway smooth muscle contains noninnervated β_2-adrenergic receptors that produce bronchodilation. The nonadrenergic, noncholinergic (NANC) nervous system in the trachea and bronchi may amplify inflammation by releasing nitric oxide.

CLINICAL PRESENTATION

Chronic Asthma

- Symptoms include episodes of shortness of breath, chest tightness, coughing (particularly at night), wheezing, or a whistling sound when breathing. These often occur with exercise but may occur spontaneously or in association with known allergens.
- Signs include expiratory wheezing (rhonchi) on auscultation; dry, hacking cough; and atopy (eg, allergic rhinitis or atopic dermatitis).
- Asthma can vary from chronic daily symptoms to only intermittent symptoms. Intervals between symptoms may be days, weeks, months, or years.
- Severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. Patients can present with mild intermittent symptoms that require no medications or only occasional short-acting inhaled β_2-agonists (SABAs) to severe chronic symptoms despite multiple medications.

Acute Severe Asthma

- Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm result in profound airway narrowing that is poorly responsive to bronchodilator therapy.
- Patients may be anxious in acute distress and complain of severe dyspnea, shortness of breath, chest tightness, or burning. They may be able to say only a few words with each breath. Symptoms are unresponsive to usual measures (ie, SABAs).
- Signs include expiratory and inspiratory wheezing on auscultation; dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis; and hyperinflated chest with intercostal and supraclavicular retractions. Breath sounds may be diminished with severe obstruction.

DIAGNOSIS

Chronic Asthma

- Diagnosis is made primarily by history of recurrent episodes of coughing, wheezing, chest tightness, or shortness of breath and confirmatory spirometry.
- Patients may have family history of allergy or asthma or symptoms of allergic rhinitis or atopic dermatitis. History of exercise or cold air precipitating dyspnea or increased symptoms during specific allergen seasons suggests asthma. Patient may have excessive variability in twice-daily peak expiratory flows (PEF) over 2 weeks.
- Spirometry demonstrates obstruction (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <80%) with reversibility after inhaled β_2-agonist administration (at least 12% and 200 mL increase in FEV_1). If baseline spirometry is normal, challenge testing with exercise, methacholine, or mannitol can be used to elicit BHR.

Acute Severe Asthma

- PEF and FEV1 are <40% of normal predicted values. Pulse oximetry reveals decreased arterial oxygen and O_2 saturations.
- Arterial blood gases may reveal metabolic acidosis and low partial pressure of oxygen (Pao_2).
- Obtain the history and physical examination while initial therapy is provided, assessing for onset and causes of the exacerbation; severity of symptoms and if associated with anaphylaxis; medication use, adherence, and response to current therapy; and risk factors for asthma-related death (history of near-fatal asthma requiring intubation and mechanical ventilation, hospitalization or emergency care in the past year, recent use of oral corticosteroids, no current use of inhaled corticosteroids [ICS], overuse of SABA therapy [more than 1 canister/month], history of psychiatric disease or psychosocial problems, poor medication adherence, lack of a written asthma action plan, and food allergy). During the

physical exam, assess vital signs and identify any complicating factors (eg, pneumonia, anaphylaxis) and comorbid conditions that could be causing acute shortness of breath such as inhaled foreign body, heart failure, pulmonary infection, and pulmonary embolism.

- Measure lung function testing by PEF or FEV_1 before treatment if possible, 1 hour after start of treatment, and then periodically until response is achieved or no further improvement is evident. Monitor oxygen saturation closely, preferably by pulse oximetry.
- Arterial blood gases are typically reserved for patients who are poorly responsive to initial treatment or deteriorating.
- Obtain a complete blood count if there are signs of infection (fever and purulent sputum).

TREATMENT

- Goals of Treatment: The GINA long-term goals for asthma management include (1) achieve good control of symptoms and maintain normal activity levels, and (2) minimize future risk of exacerbations, fixed airflow limitation, and side effects. For acute severe asthma, the primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and early intervention.

Nonpharmacologic Therapy

- Patient education is mandatory to improve medication adherence, self-management skills, and use of healthcare services.
- Short-term (approximately 2 weeks) home PEF monitoring can be used to assess treatment response. However, routine PEF monitoring is generally recommended only for patients with severe asthma or poor symptom perception.
- Avoidance of known allergenic triggers can improve symptoms, reduce medication use, and decrease BHR. Environmental triggers (eg, animals) should be avoided in sensitive patients, and smokers should be encouraged to quit.
- In acute asthma exacerbations, initiate oxygen therapy to achieve an arterial oxygen saturation of 93%–95% in adolescents and adults and 94%–98% in school-aged children and pregnant women or those with cardiac disease.
- Correct dehydration if present; urine specific gravity may help guide therapy in children when assessment of hydration status is difficult.

Pharmacotherapy

General Approach

- **Table 78-1** summarizes GINA recommendations for initial controller treatment in adults and adolescents with persistent asthma. Regardless of the long-term therapy, all patients must have an inhaled SABA available for quick relief of acute symptoms.
- **Table 78-2** depicts the GINA stepwise approach for control-based management, which emphasizes three components: (1) ASSESS symptom control and risk factors, (2) ADJUST therapy and treat modifiable risk factors, and (3) REVIEW RESPONSE and optimize control about every 3 months. Step-down of controller treatment may be considered if symptoms have been well controlled and lung function has been stable for 3 months or longer. While engaging the patient in this effort, monitor symptoms and PEF and schedule follow-up. Stepping down ICS doses by 25%–50% at 3-month intervals is feasible and safe for most patients.
- The primary therapy of acute exacerbations includes inhaled SABAs and (depending on severity) systemic corticosteroids, inhaled ipratropium, intravenous (IV) magnesium sulfate, and oxygen. Treatments are typically administered concurrently to facilitate rapid improvement. Measure initial response 1 hour after the first three inhaled bronchodilator treatments.
- **Figure 78-1** outlines strategies for self-management of worsening asthma.
- **Figure 78-2** is an algorithm for management of acute asthma exacerbations in acute care facilities (eg, emergency departments).

FIGURE 78-1

Self-management of worsening asthma in adults and adolescents with a written asthma action plan. (*Adapted from Global initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available from: www.ginasthma.org.*)

image

FIGURE 78-2

Management of asthma exacerbations in acute care facilities (eg, emergency departments).

image

TABLE 78-1

GINA Recommendations for Initial Controller Treatment in Adults and Adolescents

Symptom Presentation	Preferred Treatment (Evidence Level)
Symptoms or need for SABA less than 2×/mo; no waking due to asthma in last month; and no risk factors for exacerbations, including in prior year	No controller (D)
Infrequent symptoms, but patient has one or more risk factors for exacerbation (eg, low lung function, use of OCS in prior year, intensive care treatment for asthma ever)	Low-dose ICS (D)
Symptoms or need for SABA between 2×/mo and 2×/week, or patient wakes due to asthma more than once/mo	Low-dose ICS (D)
Symptoms or need for SABA >2×/week	Low-dose ICS[a] (A)
Troublesome symptoms most days or waking ≥1 ×/week, esp. if any risk factors exist	Medium/high-dose ICS or low-dose ICS/LABA[b] (A)
Symptoms consistent with severely uncontrolled asthma, or with an acute exacerbation	OCS short course AND start of high-dose ICS or moderate-dose ICS/LABA[b] (D)

[a]Less effective options are LTRA or theophylline.

[b]Not recommended for initial controller treatment in children ages 6–11 years.

(A), (B), (C), (D) = grade of evidence with A as the highest grade and D as the lowest grade.

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β_2-agonist.

TABLE 78-2

GINA Stepwise Approach to Control Symptoms and Minimize Future Risk

Step	Preferred Option (Evidence Level)	Other Recommended Options (Evidence Level)
1	As-needed SABA (A)	Consider low-dose ICS, in addition to as-needed SABA, for patients at risk for exacerbations (B)
2	Low-dose ICS plus as-needed SABA (A)	LTRA (A) Low-dose ICS/LABA (A) ICS started with symptoms of allergic asthma, for seasonal treatment only (D)
3	Low-dose ICS/LABA, plus as-needed SABA for adults/adolescents OR low-dose ICS/formoterol as both maintenance and reliever (A) For children 6–11 years of age, moderate-dose ICS, plus as-needed SABA	Medium-dose ICS for adults/adolescents (A) Low-dose ICS plus LTRA (A) or low-dose, sustained-release theophylline (B)
4	Medium-dose ICS/LABA, plus as-needed SABA for adults/adolescents (B) OR medium-dose ICS/formoterol as both maintenance and reliever (A) For children 6–11 years of age, refer child to asthma specialist	Add-on therapy with tiotropium for adults with exacerbation history (A) Sublingual allergen immunotherapy in adults with allergic rhinitis and house dust mite sensitization if FEV_1 is >70% predicted
5	Referral to specialist and consideration of add-on treatment if asthma remains uncontrolled	Add-on anticholinergic (B): tiotropium if ≥12 years of age Add-on anti-IgE (A): omalizumab (subcutaneous) for moderate-to-severe allergic asthma if ≥6 years of age Add-on anti-interleukin-5 therapy (A): mepolizumab if ≥12 years (subcutaneous); reslizumab if ≥18 years) (intravenous) Add-on anti-interleukin 5 receptor (A): benralizumab if ≥12 years (subcutaneous) Sputum-guided treatment adjusted by eosinophilia >3% (0.03) (A) Bronchial thermoplasty in some adults with severe asthma (B) Add-on low-dose OCS (≤7.5 mg/day prednisone equivalent) (B)

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting β_2-agonist.

β_2-Agonists

- SABAs are the most effective bronchodilators. Aerosol administration enhances bronchoselectivity and provides more rapid response and greater protection against provocations (eg, exercise, allergen challenges) than systemic administration. In adults, administration as either continuous or intermittent (every 20 minutes for 3 doses) administration over 1 hour results in equivalent improvement. In acute severe asthma, continuous

nebulization of a SABA (eg, albuterol) is recommended for patients having unsatisfactory response after three doses (every 20 minutes) of aerosolized β_2-agonists and potentially for patients presenting initially with PEF or FEV_1 values <30% of predicted normal.

- **Albuterol** and other inhaled SABAs are indicated for intermittent episodes of bronchospasm and are the treatment of choice for acute severe asthma and EIB. Regular treatment (four times daily) does not improve symptom control over as-needed use and is not indicated. Nonprescription inhaled **epinephrine** as Primatene Mist metered-dose inhaler is less effective than prescription SABAs and is only to be used for temporary relief of mild symptoms of intermittent asthma in patients ≥12 years old; patients should see a physician immediately if improvement is not seen within 20 minutes, symptoms become worse, or require more than 8 inhalations in a 24-hour period, or there are more than two episodes in a week.
- Two long-acting β_2-agonists (LABAs), **formoterol** (Foradil) and **salmeterol** (Serevent), provide bronchodilation for 12 hours or longer. The LABAs are preferred adjunctive therapy with ICS in adults and children ≥12 years old for step 3 and for children 6–11 years of age for steps 4 and 5. Combination treatment with ICS/LABA provides greater asthma control than increasing the dose of ICS alone while reducing the frequency of mild and severe exacerbations. A SABA should be continued for acute exacerbations.
- Three ultra-LABAs (**indacaterol** [Arcapta Neohaler], **olodaterol** [Striverdi Respimat], and **vilanterol**) have a 24-hour bronchodilator duration of effect. Vilanterol is available only in combination with fluticasone furoate (Breo Ellipta) for once-daily dosing for asthma in adults ≥18 years old in the United States and for children and adults ≥12 years old in Europe. Products containing indacaterol and olodaterol are currently only indicated for COPD but are being evaluated for asthma.
- **Table 78-3** contains dosing guidelines for acute severe asthma exacerbations.

TABLE 78-3

Drug Doses for Treatment of Acute Severe Exacerbations of Asthma

	Dosages		
Medications	**≥12 Years Old**	**<12 Years Old**	**Comments**
Inhaled β-agonists			
Albuterol nebulizer solution (5 mg/mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL)	2.5–5 mg every 20 minutes for three doses, and then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hr continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses, and then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hr by continuous nebulization	Only selective β_2-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 4 mL at gas flow of 6–8 L/min. Use face mask if <4 years of age
Albuterol MDI (90 mcg/puff)	4–8 puffs every 30 minutes up to 4 hours, and then every 1–4 hours as needed	4–8 puffs every 20 minutes for three doses, and then every 1–4 hours as needed	In patients in severe distress, nebulization is preferred; use VHC-type spacer with face mask if <4 years old
Levalbuterol nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 2.5 mg/1 mL, 1.25 mg/3 mL)	Give at one-half the milligram dose of albuterol above	Give at one-half the milligram dose of albuterol above	The single isomer of albuterol is twice as potent on a milligram basis Not recommended
Levalbuterol MDI (45 mcg/puff)	See albuterol MDI dose	See albuterol MDI dose above	See albuterol MDI dose; one-half as potent as albuterol on a microgram basis Not recommended
Anticholinergics			
Ipratropium bromide nebulizer solution (0.25 mg/mL)	500 mcg every 30 minutes for three doses, and then every 2–4 hours as needed	250 mcg every 20 minutes for three doses, and then 250 mcg every 2–4 hours	May mix in same nebulizer with albuterol; only add to β_2-agonist therapy
Ipratropium bromide MDI (18 mcg/puff)	8 puffs every 20 minutes as needed for up to 3 hours	4–8 puffs as needed every 2–4 hours	Not to be continued once hospitalized
Corticosteroids			
Prednisone, methylprednisolone, prednisolone	50 mg in one or two divided doses (prednisone equivalent)	1 mg/kg (maximum 40 mg/day) in two divided doses (prednisone equivalent)	For outpatient "burst" use 1–2 mg/kg/day, maximum 60 mg, for 3–5 days in children and 40–60 mg/day in one or two divided doses for 5–7 days in adults

Note: No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for IV administration over oral therapy. The usual regimen is to continue the oral corticosteroid for the duration of hospitalization. The final duration of therapy following a hospitalization or emergency department visit may be from 3 to 10 days. If patients are then started on an ICS, there is no need to taper the systemic corticosteroid dose. An ICS can be started at any time during the exacerbation.

Corticosteroids

- ICS are the preferred long-term control therapy for persistent asthma because of potency and consistent effectiveness; they are the only therapy shown to reduce risk of dying from asthma. See **Table 78-4** for comparative ICS doses; all agents are approved for once- or twice-daily dosing. Most patients with moderate disease can be controlled with twice-daily dosing of most ICS. In milder asthma, once-daily dosing is often sufficient to maintain control. More severe patients may require multiple daily dosing; after asthma is controlled, many patients can reduce the ICS dose and maintain control.
- Response to ICS is delayed; symptoms improve in most patients within the first 1–2 weeks and reach maximum improvement in 4–8 weeks. Maximum improvement in FEV_1 and PEF rates may require 3–6 weeks.
- Systemic toxicity of ICS is minimal with low-to-moderate doses, but risk of systemic effects increases with high doses (eg, growth suppression in children, osteoporosis, cataracts, dermal thinning, adrenal insufficiency). Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, which can be reduced by using a spacer device.
- Systemic corticosteroids (**Table 78-5**) are indicated in all patients with acute severe asthma not responding completely to initial inhaled β_2-agonist administration (every 20 minutes for 3 doses) and should be administered within 1 hour of presentation. IV therapy offers no advantage over oral administration except in patients unable to take oral medications. Adults are treated effectively with 5–7 days of oral prednisone (or equivalent), but children may require only 3–5 days. Dexamethasone for 1–2 days is an option for children and has the benefit of less vomiting. Continue full doses until the PEF reaches 70% of predicted normal or personal best. Tapering the dose after discharge is unnecessary if patients are prescribed an ICS for outpatient therapy.
- Because short-term (1–2 weeks), high-dose corticosteroids (1–2 mg/kg/day of oral prednisone) do not produce serious toxicities, the ideal strategy is to use systemic corticosteroids in a short “burst” and then maintain the patient on appropriate long-term control therapy with ICS.

TABLE 78-4

Available Inhaled Corticosteroid Products, Lung Delivery, and Comparative Daily Dosages

ICS	Product	Lung Delivery[a]
Beclomethasone dipropionate (BDP)	40 and 80 mcg/actuation HFA MDI	50%–60%
Budesonide (BUD)	90 or 180 mcg/dose DPI, Flexhaler	15%–30%
	200 and 500 mcg ampules, 1 mg	5%–8%
Ciclesonide (CIC)	80 or 160 mcg/actuation HFA MDI	50%
Flunisolide (FLU)	80 mcg/actuation HFA MDI	68%
Fluticasone furoate (FF)	100, 200 mcg/actuation DPI, Ellipta	80%–85%
Fluticasone propionate (FP)	44, 110, and 220 mcg/actuation HFA MDI	20%
	50, 100, and 250 mcg/dose DPI, Diskus	15%
Mometasone furoate (MF)	110 and 220 mcg/dose DPI, Twisthaler; 100 mcg and 200 mcg/actuation HFA MDI	11%

	Comparative Daily Dosages (mcg) of Inhaled Corticosteroids		
	Low Daily Dose Child[a]/Adult	Medium Daily Dose Child[a]/Adult	High Daily Dose Child[a]/Adult
BDP			
HFA MDI	80–160/80–240	>160–320/>240–480	>320/>480
BUD			
DPI	180–360/180–540	>360–720/>540–1080	>720/>1080
Nebules	500/UK	1000/UK	2000/UK
CIC HFA MDI	80–160/160–320	>160–320/>320–640	>320/>640
FLU			
HFA MDI	160/320	320/320–640	≥640/>640
FF DPI		UK/100	UK/200
FP			
HFA MDI	88–176/88–264	176–352/264–440	>352/>440
DPI	100–200/100–300	200–400/300–500	>400/>500
MF, DPI	110/110–220	220–440/>220–440	>440/>440

[a]5–11 years of age, except for BUD Nebules, which is 2–11 years of age. UK, unknown.

TABLE 78-5

Comparison of Systemic Corticosteroids

Systemic	Anti-Inflammatory Potency	Mineralocorticoid Potency	Duration of Biologic Activity (Hours)	Elimination Half-Life (Hours)
Hydrocortisone	1	1	8–12	1.5–2
Prednisone	4	0.8	12–36	2.5–3.5
Methylprednisolone	5	0.5	12–36	3.3
Dexamethasone	25	0	36–72	3.4–4

Anticholinergics

- **Ipratropium bromide** (Atrovent HFA) and **tiotropium bromide** (Spiriva) produce bronchodilation only in cholinergic-mediated bronchoconstriction. Anticholinergics are effective bronchodilators but are not as effective as β_2-agonists. They attenuate but do not block allergen- or exercise-induced asthma in a dose-dependent fashion. Ipratropium bromide is approved by the US Food and Drug Administration (FDA) for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) but is not currently approved for treatment of asthma. Tiotropium bromide is also approved for once-daily maintenance treatment of COPD and is also indicated for the long-term, once-daily, maintenance treatment of asthma in patients ≥6 years of age.

- Time to reach maximum bronchodilation from aerosolized ipratropium is longer than from aerosolized SABAs (30–60 minutes vs. 5–10 minutes). However, some bronchodilation is seen within 30 seconds, and 50% of maximum response occurs within 3 minutes. Ipratropium bromide has a duration of action of 4–8 hours; tiotropium bromide has a duration of 24 hours.

- In acute asthma exacerbations, inhaled ipratropium bromide produces a further improvement in lung function of 10%–15% over inhaled β_2-agonists alone. When added to initial asthma therapy, ipratropium bromide reduces the hospitalization rate in patients with moderate-to-severe exacerbations.

- Inhaled ipratropium bromide should only be considered as adjunctive therapy in acute severe asthma not completely responsive to β_2-agonists alone.

- Tiotropium may be considered as add-on therapy in patients whose asthma is not well controlled with a medium-to-high dose of ICS and LABA combination therapy. Addition of tiotropium only modestly improves lung function, but it increases the time to severe exacerbation requiring oral corticosteroid treatment.

Leukotriene Modifiers

- **Zafirlukast** (Accolate) and **montelukast** (Singulair) are oral leukotriene receptor antagonists (LTRA) that reduce the proinflammatory and bronchoconstriction effects of leukotriene D_4. In persistent asthma, they improve pulmonary function tests, decrease nocturnal awakenings and β_2-agonist use, and improve symptoms. However, they are less effective than low-dose ICS, and they are less effective than LABAs when added to ICS for moderate persistent asthma. They are not used to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods. The adult zafirlukast dose is 20 mg twice daily, taken at least 1 hour before or 2 hours after meals; the dose for children ages 5–11 years is 10 mg twice daily. The adult montelukast dose is 10 mg once daily, taken in the evening without regard to food; the dose for children ages 6–14 years is one 5 mg chewable tablet daily in the evening.

- In general, the LTRA are well tolerated. An idiosyncratic syndrome similar to the Churg–Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported rarely; a direct causal association has not been established. Because of reports of adverse neuropsychiatric events especially within a few weeks of starting therapy, monitor patients for signs of irritability, aggressiveness, and sleep disturbances; suicidality has also been reported rarely. There have been reports of fatal hepatic failure associated with zafirlukast.

- **Zileuton** (Zyflo) is a 5-lipoxygenase inhibitor; its use is limited due to potential for elevated hepatic enzymes, especially in the first 3 months of therapy, and inhibition of metabolism of drugs metabolized by CYP3A4 (eg, theophylline, warfarin). The dose of zileuton tablets is 600 mg four times daily with meals and at bedtime. The dose of zileuton extended-release tablets is two 600 mg tablets twice daily, within 1 hour after the morning and evening meals (total daily dose 2400 mg).

Biologic Agents

- These agents target the IgE pathway (relevant to allergic asthma) or IL-4, IL-13, and IL-5 pathways (relevant to the Th2 pathway and eosinophilic disorders) and are indicated for patients with moderate or severe asthma (depending upon the drug) along with other biomarkers or clinical indicators associated with treatment response. They are typically reserved for patients with moderate-to-severe persistent asthma who have been treated with dual therapy with ICS/LABA or triple therapy such as with ICS/LABA+ long-acting muscarinic antagonist (LAMA) and remain poorly controlled.

- **Omalizumab** (Xolair) is an anti-IgE antibody approved for treatment of allergic asthma not well controlled by oral or ICS. Dosage is determined by baseline total serum IgE (international units/mL [kIU/L]) and body weight (kg). Doses range from 150 to 375 mg subcutaneously (SC) at either 2- or 4-week intervals. Omalizumab is recommended for treating patients >6 years of age with moderate-to-severe asthma not adequately controlled by ICS, ICS/LABA, and in some cases, oral corticosteroids. Elevated levels of the fraction of exhaled nitric oxide (FeNO) at ≥19.5 ppb are predictive of an exacerbation rate reduction of ~50%. Because of a 0.2% incidence of anaphylaxis, observe patients for a reasonable period after injection because 70% of reactions occur within 2 hours. Some reactions have occurred up to 24 hours after injection.

- **Mepolizumab** (Nucala) and **reslizumab** (Cinqair) are monoclonal antibodies directed against IL-5 to block activation of the IL-5 receptor on eosinophils. **Benralizumab** (Fasenra) binds to the alpha subunit of the IL-5 receptor of eosinophils and prevents binding of IL-5, thus mitigating downstream eosinophilic inflammation. Mepolizumab and benralizumab are approved for patients ≥12 years old with severe asthma and are administered SC; reslizumab is approved for severe asthma in patients ≥18 years old and is administered IV. Mepolizumab and reslizumab are dosed every 4 weeks; benralizumab is dosed every 4 weeks for 3 months then every 8 weeks. Doses are to be administered in a healthcare setting by professionals who are prepared to manage anaphylaxis. Each of these drugs is indicated for patients with an "eosinophilic phenotype" (which has not been formally defined). However, a reduction in exacerbation rate of ~50% is observed when patients have a certain minimum peripheral blood eosinophil count that varies by drug.

- **Dupilumab** (Dupixent) targets the IL-4α receptor, thus blocking signaling of IL4 and IL-13, which are cytokines that promote IgE synthesis and inflammatory cell recruitment. Dupilumab is approved for patients with moderate-to-severe asthma age ≥12 years old with an eosinophilic phenotype and is administered SC every 2 weeks. Unlike mepolizumab, reslizumab, and benralizumab, FeNO levels >25 ppb in addition to blood eosinophil levels ≥150 cells/μL (0.15×10^9/L) is predictive of a response in reducing the asthma exacerbation rate by ~50%.

Magnesium Sulfate

- Magnesium sulfate is a moderately potent bronchodilator, producing relaxation of smooth muscle by blocking calcium ion influx into smooth muscles; it may also have anti-inflammatory effects.

- For patients with severe asthma exacerbations, a single 2 g IV infusion may reduce hospital admissions in adults who have an FEV_1 <25%–30% predicted upon arrival in the emergency department, children and adults who have persistent hypoxemia after standard treatment, and children whose FEV_1 remains <60% predicted after 1 hour of standard treatment. Adverse effects include hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, and CNS and respiratory depression.

Methylxanthines

- Methylxanthines are rarely used today because of the high risk of severe life-threatening toxicity, numerous drug interactions, and decreased efficacy compared with ICS, LABAs, and biologics. **Theophylline** is a moderately potent bronchodilator with mild anti-inflammatory properties and is available for oral and IV administration. Theophylline dosing requires monitoring of serum concentrations for both efficacy and toxicity, including seizures and death. In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP P450 microsomal enzymes (primarily CYP1A2 and CYP3A4), and drug interactions affecting metabolism significantly affect blood concentrations.

EVALUATION OF THERAPEUTIC OUTCOMES

- Focus the initial encounters on the patient's concerns, expectations, and goals of treatment. Basic education should include discussion of asthma as a chronic lung disease, the types of medications, and how they are to be used. Teach inhaler technique, advise the patient about when to seek medical advice, and provide written action plans. Both peak flow-based or symptom-based self-monitoring can be effective, if taught and followed correctly.

- At the first follow-up visit, reinforce the educational messages from the first visit and review of the patient's current medications, adherence, and any difficulties related to therapy.

- The two key components of effective asthma control are "symptom control" and "future risk of adverse outcomes." Assess symptom control by frequency of daytime and nighttime asthma symptoms, reliever medication use, and activity limitations; poor symptom control is also an indicator

of future risk for exacerbations.

- Future risk of adverse outcomes includes assessment of risks for future exacerbations, fixed airflow limitation (and thus diminished response to therapy), and medication adverse effects. To assess the risk for future exacerbations, measure lung function before the start of treatment and then 2 months later when maximum response to controller medications is likely attained.
- During ongoing care, measure spirometry yearly but reserve long-term PEF monitoring for patients with severe asthma.
- Validated questionnaires can be administered regularly, such as the Asthma Control Test, Asthma Therapy Assessment Questionnaire, and Asthma Control Questionnaire.
- Ask patients about exercise tolerance because perceived good exercise tolerance may be biased by a sedentary lifestyle adapted to the frequency of bothersome symptoms.
- All patients on inhaled drugs should have their inhalation technique evaluated monthly initially and then every 3–6 months.
- After initiation of anti-inflammatory therapy or increase in dosage, most patients should experience decreased symptoms within 1–2 weeks and achieve maximum improvement within 4–8 weeks. Improvement in baseline FEV_1 or PEF should follow a similar time course, but decrease in BHR as measured by morning PEF, PEF variability, and exercise tolerance may take longer and improve over 1–3 months.

See Chapter 43, Asthma, authored by Kathryn V. Blake and Jason E. Lang, for a more detailed discussion of this topic.