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In the Clinic®

Care of the Patient With Asthma

Nearly 8% of the U.S. population is diagnosed with asthma, leading to more than 5 million office visits and 1 million emergency department visits annually. Both outpatient and inpatient internal medicine clinicians treat asthma frequently, but nuances in diagnosis and management have emerged. This article highlights many of these developments.

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

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Diagnosis

What is the epidemiology of asthma?

Asthma defines a diverse group of inflammatory airway diseases characterized by wheezing, dyspnea, chest tightness, and cough. These symptoms, which often include variable expiratory airflow limitation, can fluctuate in severity and frequency (1). Asthma affects more than 300 million people globally and causes around 1000 deaths each day, mostly in low- and middle-income countries (2). In the United States, 7.7% (25 million) of the general population currently has asthma. The prevalence is greater in women; people identifying as Black, Native American, or Puerto Rican; and those living below the poverty level. Annually, asthma is associated with 5 million office visits, 1 million emergency department (ED) encounters, and a mortality rate of 10.6 deaths per 1 million persons (3). Although mortality is decreasing in the United States, women, Black-identifying people, and older adults have increased rates of severe asthma and asthma mortality (4–6).

What drives the development and pathogenesis of asthma?

Although hereditary factors largely determine asthma susceptibility, exposure to environmental triggers is needed for disease development (7). While some overlap exists, viral and environmental allergies play a critical role in early-onset asthma, whereas air pollution, tobacco smoke, obesity, and metabolic dysregulation are important risk factors for people with disease onset after puberty (8). Repetitive exposures, duration of airway inflammation, and lack of adequate treatment can worsen disease progression, promoting development of chronic airway remodeling and loss of lung function (9).

What is the role of spirometry in suspected asthma?

The Global Initiative for Asthma (GINA) (10), the National Asthma Education and Prevention Program (11), and the American Thoracic Society (ATS) and European Respiratory Society (ERS) (12) recommend that patients older than 6 years undergo spirometry with bronchodilator testing when asthma is suspected. Spirometry can confirm the diagnosis, provide information on the degree of airflow obstruction at presentation (which is useful to correlate with symptom burden), and suggest alternative diagnoses. In addition, serial spirometry measurements can aid in assessment of treatment response and patient symptoms at the time of office visits.

There are 3 important measures on spirometry: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and the ratio of FEV_1 to FVC. In obstructive lung disease, FEV_1 reflects airflow limitation. Normal values are above 80% of predicted or above the lower limit of normal (LLN), calculated using patient sex, age, and height. The inclusion of race in percentage predicted measurements is controversial; many pulmonary function laboratories use race-neutral calculations, as recent data suggest no difference in disease diagnosis but a potential detriment in occupational eligibility and disability (13). An FEV_1–FVC ratio below 70% or below the LLN indicates airway obstruction is present. A positive bronchodilator test result is a predicted increase in FEV_1 or FVC of at least 200 mL and at least 10% (14). Spirometry is effort-dependent and should therefore be administered by trained personnel (14).

Does a normal spirometry result rule out asthma?

A normal spirometry result and a lack of bronchodilator response do not rule out asthma. Asthma is, by definition, intermittent and reversible airflow limitation (14); thus, many patients have obstruction and bronchodilator reversibility only under specific conditions (such as exercise or acute illness).

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Table 1. **Clinical Asthma Phenotypes and Key Differences in Management**

Phenotype	*Clinical Features*	*Keys to Management*
Allergic/T2 high	Markers of T2 high inflammation: elevated eosinophil count, IgE, FeNO Common comorbidities: allergic rhinitis, atopic dermatitis, food allergy	Typically responds well to guideline-directed management with ICS–formoterol regimens Responds well to asthma biologics when appropriate
Nonallergic/T2 low	More common among people with adult-onset asthma, women, and people with obesity	Can be less responsive to ICS Only available biologic is tezepelumab
Cough variant	Common cause (24%–32%) of chronic cough in nonsmoking adults	No difference in effectiveness among budesonide–formoterol, montelukast, or both
Irritant-induced asthma	Development of asthma symptoms <24 h after high-intensity, single inhaled exposure	ICS with tapering pending symptom and spirometry trajectory Consider short ICS trial for moderate to severe symptoms LTRA may be helpful
Occupational asthma	Sensitization to a workplace agent leading to IgE production Symptoms typically are worse toward the end of a workday and improve on weekends Early identification and removal of exposure are important, although many patients have persistent symptoms	Removal from occupational exposures if possible Consider referral to occupational medicine specialist
Exercise-induced asthma	Present in people with T2 high and low asthma Can be difficult to diagnose even with provocative testing	Exercise before treatment with ICS–SABA or ICS–formoterol Variable evidence for LTRA
Aspirin-exacerbated respiratory disease	Characterized by chronic rhinosinusitis with nasal polyposis, T2 high asthma, and symptoms after COX inhibitors	LTRA Refer to allergist for consideration of aspirin therapy after aspirin desensitization Omalizumab, mepolizumab, and dupilumab may be helpful
Obesity-associated asthma	Obesity can drive the development of T2 low asthma and can worsen preexisting asthma Obesity is associated with common comorbidities that worsen asthma control, including GERD and OSA	Weight loss Emerging data on potential role of GLP-1RAs ICS may be less effective Biologic therapies seem to work, if indicated
Asthma with persistent airflow limitation/ACO	Heterogeneous group of diseases with predominant features of either COPD or asthma History is important in determining predominant asthma or COPD	Avoid long-acting bronchodilator monotherapy among patients with asthma features Avoid ICS monotherapy among patients with COPD features

ACO = asthma and chronic obstructive pulmonary disease overlap; COPD = chronic obstructive pulmonary disease; COX = cyclooxygenase; FeNO = fraction of exhaled nitric oxide; GERD = gastroesophageal reflux disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist; OSA = obstructive sleep apnea; SABA = short-acting β_2-agonist; T2 = type 2 inflammation.

When should clinicians consider provocative pulmonary testing?

There is no gold standard for the diagnosis of asthma. However, in patients with normal spirometry results and atypical response to initial asthma therapies, direct bronchoprovocation with methacholine can be helpful. Although considered safe, this challenge is not recommended in patients with an FEV_1 less than 60% of predicted; those who cannot consistently perform spirometry; or those with recent myocardial infarction, aortic aneurysm, or poorly controlled hypertension (15, 16). A methacholine challenge is considered positive for airway hyperresponsiveness if FEV_1 decreases by 20% or more from baseline with a provocative dose below 200 mcg or a provocative concentration below 8 $mg*mL^{-1}$, particularly if symptoms have been present in the days leading up to testing (16, 17).

What are common asthma phenotypes, and how do they affect clinical management?

Asthma has several clinical phenotypes, and recognition of the appropriate phenotype is important for accurate diagnosis and optimal treatment (Table 1). The most common division between phenotypes is high versus low

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Table 2. **Common Differential Diagnosis for Patients Presenting With Asthma**

Diagnosis	*Key Features on History*	*Additional Diagnostic Testing*
Inducible laryngeal obstruction	Inspiratory wheeze Sudden onset of symptoms Poor response to rescue inhalers	Truncation of inspiratory limb Laryngoscopy
Chronic obstructive pulmonary disease	Tobacco use or strong family history Often older age at onset	Fixed airflow obstruction on spirometry
Allergic bronchopulmonary aspergillosis	Severe asthma symptoms, often with recurrent exacerbations Mucus plugs common in sputum	IgE level >1000 IU/mL and blood eosinophil count >0.500 × 10^9 cells/L Elevated IgE level specific to *Aspergillus* Precipitating IgG to *Aspergillus* CT can show bronchiectasis, signs of mucoid impaction ("glove finger sign"), centrilobular nodules, tree-in-bud opacities
Eosinophilic granulomatosis with polyangiitis	Typically has 3 phases: Prodromal: Adult-onset asthma, rhinitis, sinusitis, with or without polyps Eosinophilic: Elevated peripheral eosinophilia and eosinophilic infiltration of affected organs Vasculitic phase: Small to medium vessel vasculitis can affect many organs, typically with mononeuritis multiplex	High blood eosinophilia, typically >1.0 × 10^9 cells/L Can be positive for myeloperoxidase antineutrophil cytoplasmic antibody; negative result does not rule out Eosinophilic with or without vasculitis on biopsy CT chest scan with ground glass and consolidative opacities; can have intralobular septal thickening, bronchial wall thickening
Heart failure	Lower-extremity edema, orthopnea, paroxysmal nocturnal dyspnea Can have hypoxia	Echocardiogram
Cystic fibrosis	Although uncommon, cystic fibrosis can be diagnosed in adulthood Significant mucus production Sinonasal disease Recurrent sinus and pulmonary infections, particularly with *Pseudomonas* colonization	Sweat chloride testing CFTR genetic testing CT chest scan with bronchiectasis
Non–cystic fibrosis bronchiectasis	Chronic cough with significant sputum production Recurrent pulmonary infections	Bronchiectasis on CT chest scan Check immunoglobin levels, α1-antitrypsin, rheumatoid arthritis and Sjögren autoantibodies Allergic bronchopulmonary aspergillosis testing, culture sputum for nontuberculous mycobacteria, and testing for aspiration often indicated
Subglottic stenosis	May have dyspnea and wheeze May have history of trauma, recent intubation, caustic or thermal inhalational exposure, or foreign body aspiration	Truncation of the expiratory limb or both inspiratory and expiratory limb on flow-volume loop

CT = computed tomography.

type 2 (T2) inflammation, which is characterized by elevated blood eosinophil count (≥0.300 × 10^9 cells/L), IgE, and fraction of exhaled nitric oxide (FeNO; ≥30 ppb). Patients with T2 high asthma are more likely to have childhood-onset asthma, comorbid allergic rhinitis, atopic dermatitis, and/or food allergy (18). T2 low asthma more commonly develops in adults, particularly women and those with obesity (19, 20). Current treatment guidelines recommend the same approaches for both phenotypes, apart from biologic therapies.

Other phenotypes are worth noting as these patients may present with atypical asthma symptoms or histories. These include cough-variant asthma (21), exercise-induced bronchospasm or asthma, aspirin exacerbation respiratory disease (AERD) (22), asthma with persistent airflow limitation, and asthma and chronic obstructive pulmonary disease (COPD) overlap (23, 24). Clinical features and keys to management for these are presented in Table 1.

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What diagnoses can present similarly to asthma, and how can they be differentiated?

The differential diagnosis of asthma is broad (Table 2). Clinicians should consider an alternative diagnosis when spirometry does not support an asthma diagnosis, asthma is difficult to control, or the patient has atypical signs and symptoms. In patients who do not respond to asthma therapies or have atypical symptoms, a careful review of the history may lead to the correct diagnosis or inform additional testing. For example, fixed obstruction in spirometry with no bronchodilator response in a patient with a history of tobacco use is more suggestive of COPD than asthma. Imaging, often with computed tomography (CT) of the chest, can help to identify bronchiectasis (25, 26) or patterns consistent with allergic bronchopulmonary aspergillosis (ABPA) (27). The flow-volume loop of spirometry can also indicate inducible laryngeal obstruction (ILO) (28) or subglottic stenosis (29). Finally, asthma does not cause hypoxia except in severe exacerbations. Therefore, in a patient with respiratory symptoms and hypoxia, full pulmonary function testing, CT chest imaging, and echocardiography are warranted.

When should clinicians consider referral to a specialist?

Referral to a pulmonologist should be considered when the patient has atypical symptoms, recurrent exacerbations (≥2 in 12 months), hospitalization for asthma exacerbation, an abnormal chest radiograph, pulmonary function test results that suggest both obstruction and restriction, unusual manifestations of the disease, or a suboptimal response to therapy (10). If a patient reports seasonal variation in symptom severity or sensitivity to specific environmental exposures, referral to an allergist may be appropriate (Box: Clinical Scenarios That Should Prompt Referral to a Specialist).

Clinical Scenarios That Should Prompt Referral to a Specialist

- Severe persistent asthma requiring GINA step 5 therapy
- History of severe or life-threatening exacerbations
- Atypical signs and symptoms
- Need for daily oral corticosteroids, >2 courses of oral steroids in a 1-year period, or lack of asthma control with high-dose inhaled corticosteroids
- Comorbidities that complicate asthma diagnosis or treatment
- Problems with adherence or allergen avoidance
- Occupational or other exposures
- Asthma-associated conditions requiring specialized treatment, including eosinophilic granulomatosis with polyangiitis, ABPA, and AERD

Diagnosis... A careful history focusing on the nature and timing of symptoms (wheezing, dyspnea, cough, chest tightness) and potential triggers is essential for diagnosing asthma. Moderate-quality evidence supports the use of spirometry in the assessment of all adult patients and older children suspected of having asthma. However, normal spirometry results and lack of bronchodilator response do not rule out asthma. Clinicians should consider referral to a specialist for patients with characteristic symptoms of asthma but normal spirometry results who have an atypical response to first-line asthma therapies.

CLINICAL BOTTOM LINE

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Treatment

How should clinicians assess asthma?

The annual GINA report provides up-to-date guidelines for assessing and managing asthma (2). Current guidelines emphasize the importance of monitoring symptoms during each visit by using the Asthma Control Test or the Asthma Control Questionnaire. Asthma is considered well controlled when patients experience few or no symptoms, have no activity limitations, and require little or no rescue medication. Nocturnal symptoms such as wheezing and dyspnea, even when infrequent, are important because they may indicate worsening airway inflammation and the potential for greater loss of control (**Table 3**). In patients with well-controlled asthma, step-down of therapy should be considered. In patients who do not respond to therapy, assessment of difficult-to-treat asthma (discussed later) should be pursued.

How should clinicians select from among available asthma medications?

The goals of asthma treatment are to control symptoms, maintain patient activity levels, prevent exacerbations and loss of lung function, and limit medication adverse effects. Medications are stepped up or down based on symptoms, exacerbations, and response to therapies (**Figure 1**).

Anti-inflammatory reliever therapy

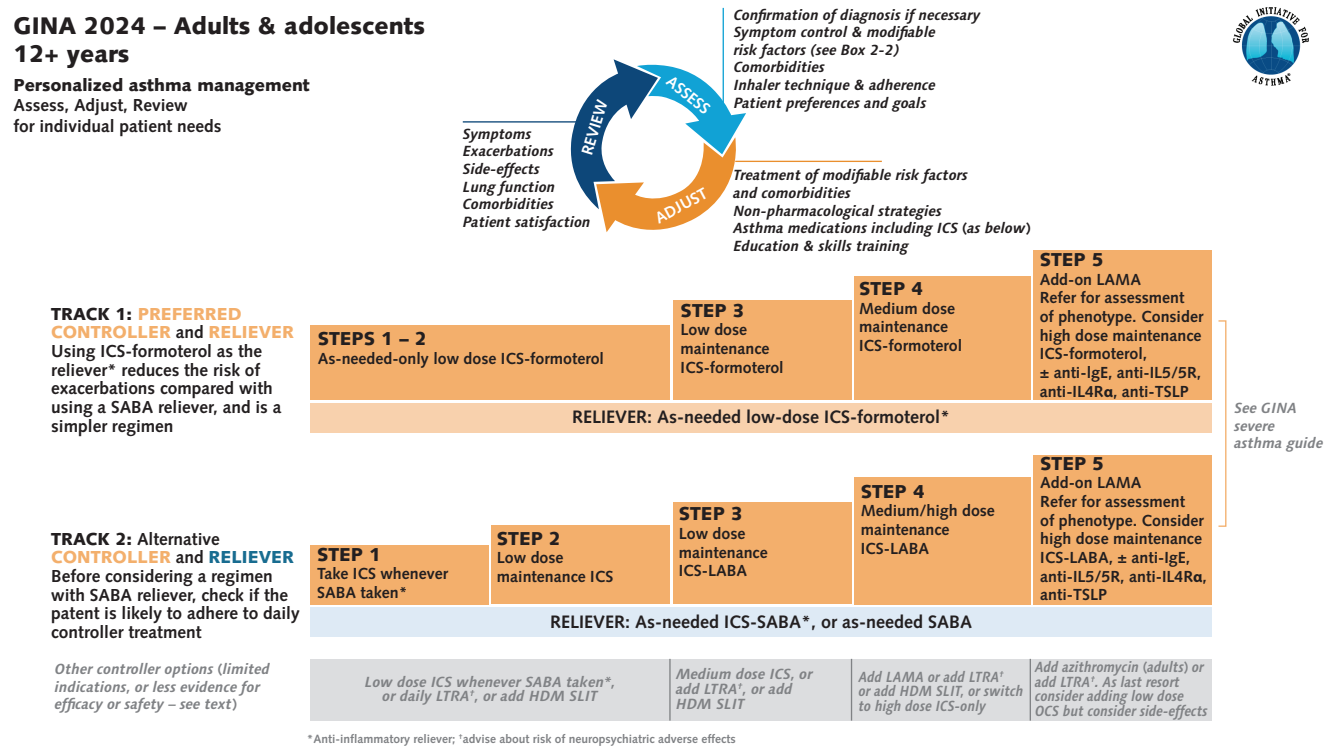
The 2019 GINA guidelines recommend use of inhaled corticosteroids (ICS) with bronchodilators in adolescents and adults as rescue therapy—a significant change in asthma management (30). For patients older than 12 years, current GINA guidelines (**Figure 1**) recommend as-needed ICS and formoterol, a rapid-onset, long-acting β-agonist (LABA), to control asthma symptoms in GINA steps 1 and 2. This dual therapeutic approach, known as anti-inflammatory reliever (AIR) therapy, provides pharmacologic synergy and reduces overall steroid exposure. AIR therapy reduces exacerbations while minimizing ICS use because it delivers anti-inflammatory therapy at symptom onset. In mild asthma, AIR therapy without maintenance inhalers showed the

Table 3. **Asthma Assessment**

Component	*Comments*
Symptoms	The patient's asthma is controlled when: Symptoms occur <2 d/wk Nighttime awakenings occur <2 times/mo Interference with normal activities does not occur Rescue inhaler use for symptom control occurs <2 d/wk Asthma Control Test score is >20 Asthma Control Questionnaire score is >0.75
Spirometry	Serial spirometry can help assess response to therapy and can be used to correlate symptoms with lung function
Risk for exacerbations and severe asthma	There is risk for exacerbations and adverse outcomes when the patient: Uses SABA for symptom control ≥2 d/wk Does not use an ICS or uses it incorrectly Has an FEV_1 <60% of the predicted value or fixed obstruction Is unable to avoid asthma triggers Is exposed to tobacco or environmental smoke Is sensitive to allergens, including food allergens Has uncontrolled comorbidities, including obesity, chronic rhinosinusitis, gastroesophageal reflux, or obstructive sleep apnea Is pregnant Was ever intubated or in intensive care because of asthma Had ≥1 severe exacerbation during the previous 12 mo

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist.

Figure 1. **GINA 2024 treatment guidelines.**



GINA = Global Initiative for Asthma; HDM = house dust mite; ICS = inhaled corticosteroid; IL = interleukin; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β2-agonist; SLIT = sublingual immunotherapy; TSLP = thymic stromal lymphopoietin. (GINA ©2024 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org.)

same reduction in exacerbations as in patients using maintenance ICS (31–33).

Maintenance and reliever therapy

Patients with persistent or frequent symptoms with AIR therapy alone require addition of a maintenance inhaler regimen (**Figure 1** [GINA step 3]). This combines AIR therapy with a low-dose ICS–LABA. If symptoms remain poorly controlled, GINA steps 4 and 5 recommend escalation to a medium- to high-dose ICS–LABA in addition to AIR rescue. To simplify this regimen, ICS–formoterol inhalers can be used as maintenance and reliever therapy (MART), which has been shown to reduce severe exacerbations by 32% and 23% compared with the same dose or low-dose daily ICS plus LABA (34). AIR therapy refers to the use of ICS with a short-acting β_2-agonist (SABA) or formoterol as rescue therapy, whereas MART refers to the use of ICS–formoterol as MART. GINA guidelines recommend that all patients be prescribed an ICS–SABA or ICS–formoterol regardless of maintenance therapy.

What are practical considerations when prescribing AIR and MART regimens?

There are important practical considerations with either AIR or MART (35). First, patients do not need to space out use of rescue medications to every 4 or 6 hours as recommended for SABAs, although the maximum total number of ICS–formoterol inhalations should not exceed 12 per day based on safety of the total formoterol dosage (35). Second, combining as-needed ICS–formoterol with maintenance therapy with other ICS–LABAs has not been studied for safety or efficacy, and there is concern about patients being confused about which inhaler to use for rescue

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(35). Third, MART preferentially benefits patients with frequent exacerbations. Standard rescue SABA with daily ICS or ICS–LABA controller regimens are adequate for patients who adhere well to treatment. Fourth, the effectiveness of AIR in reducing exercise-induced bronchospasm is not well documented, particularly when it is used before exertion. However, among 66 patients with known exercise-induced asthma, regular use of AIR during 6 weeks was noninferior to daily ICS and superior to SABA-only therapy in reducing bronchospasm during an exercise challenge test (36). Finally, mouth rinsing is required after maintenance doses but is unnecessary after as-needed doses.

An additional concern for U.S.-based prescribers is that ICS–formoterol inhalers are not approved by the U.S. Food and Drug Administration (FDA) for rescue use. In patients requiring 2 puffs of maintenance ICS–formoterol twice daily, use of this inhaler for rescue will result in early refill requests, which are often denied by insurers. In these patients, use of ICS–SABA as rescue (AIR) with a maintenance ICS–LABA is recommended to ensure adequate access to maintenance and rescue inhalers.

Additional long-term controller therapies

Leukotriene receptor antagonists (LTRAs), such as montelukast, have a modest bronchodilatory effect and can occasionally be used to treat patients with mild exercise-induced asthma. These drugs have additional indications in allergic rhinitis and AERD. Montelukast carries a black box warning from the FDA for possible neuropsychiatric effects (37). Although patients should be informed of this, systematic reviews have found that montelukast is not associated with suicide or depression in asthma, although there are possible associations with anxiety and insomnia in adult populations (37).

Long-acting muscarinic antagonists (LAMAs), such as tiotropium, improve lung function and reduce exacerbations when added to combination therapy with an inhaled glucocorticoid and a LABA in patients whose symptoms are not adequately controlled (38). Based on these results, the ERS/ATS guidelines recommend the addition of tiotropium for patients whose symptoms remain uncontrolled despite GINA step 4 to 5 therapy (38). The combination of a LAMA, a LABA, and an ICS in a single inhaler significantly simplifies therapy and is available in a once-daily FDA-approved formulation (39).

Long-term macrolide therapy

In addition to their antimicrobial effect, macrolides have pleiotropic anti-inflammatory effects and can reduce airway neutrophilia (40). In a randomized clinical trial, azithromycin reduced the number of combined moderate and severe exacerbations and time to the first exacerbation compared with placebo in a cohort of patients with asthma. This clinical improvement was similar in T2 high and T2 low phenotypes, although it did not achieve minimal clinically important differences in lung function or asthma control (41). Therefore, the ERS/ATS guidelines only recommended a trial of macrolide treatment to reduce exacerbations in adults using GINA step 5 therapy whose symptoms persist or remain uncontrolled. Patients using this therapy did not experience more episodes of pneumonia, prolonged QTc duration, or hearing impairment (41). Of note, in the asthma clinical trial and COPD trials, people with baseline long QTc (≥450 ms) were excluded, although no significant QT prolongation was noted on therapy (42). Similarly, those with baseline hearing loss were excluded from trials. In a COPD trial, there was a small but statistically significant increased risk for hearing impairment with long-term azithromycin therapy, although this was not seen in the asthma trial (41, 42). However, the safety of this therapy beyond 1 year remains unknown.

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Monoclonal antibodies

There are 6 FDA-approved monoclonal antibodies recommended for GINA step 5 patients with severe asthma whose symptoms remain poorly controlled or who continue to experience 2 or more exacerbations annually (**Appendix Table**, available at Annals.org). Five of these target T2 inflammatory pathways, including IgE (omalizumab [43]) and eosinophil-related cytokines (mepolizumab [44], reslizumab [45], benralizumab [46, 47], and dupilumab [48, 49]). Tezepelumab, the most recently approved biologic, is the only one approved for patients with T2 low inflammation (50, 51).

These biologics significantly reduce exacerbation rates, improve lung function, and reduce the need for daily systemic corticosteroids among patients with steroid-dependent asthma, but their effects on asthma control and quality of life do not reach minimal clinically important differences. Use of these agents is best directed by a pulmonary or allergy specialist.

What is asthma remission, and how should clinicians adjust medications in remission?

Biologic therapy with monoclonal antibodies has made asthma remission achievable. An expert consensus framework defined remission as 12 months with absence of significant symptoms by a validated instrument, optimization or stabilization of lung function, agreement between the patient and the clinician about remission, and no use of systemic corticosteroids (52). Although remission is the goal for all patients, approximately 30% to 38% who receive biologics achieve it (53). Some of the factors identified in achieving this level of remission include shorter disease duration and lower body mass index (BMI) (54).

What should clinicians consider if a patient does not respond to therapy?

Although some difficult-to-treat asthma may represent severe disease, many patients with difficult-to-treat asthma have other factors contributing to their lack of treatment response (**Figure 2**). If a patient does not respond to standard therapy, clinicians should follow a stepwise, systematic approach before increasing the intensity of the asthma medication regimen (10, 55) (**Figure 3**).

In patients with asthma that is not well controlled with standard therapy, the first recommended step is to confirm the diagnosis. If confirmed, the next step is assessment of inhaler technique. Inappropriate or ineffective inhaler technique is common across inhaler types (56) and is a common cause of change or increase in asthma therapy (57, 58). In addition to inhaler technique, spacers should be used with all metered-dose inhalers (MDIs). Medication and inhaler

Figure 2. **Overview of difficult-to-treat and severe asthma.**

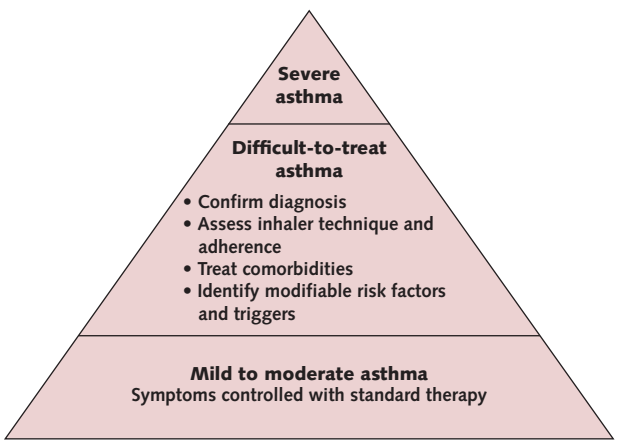

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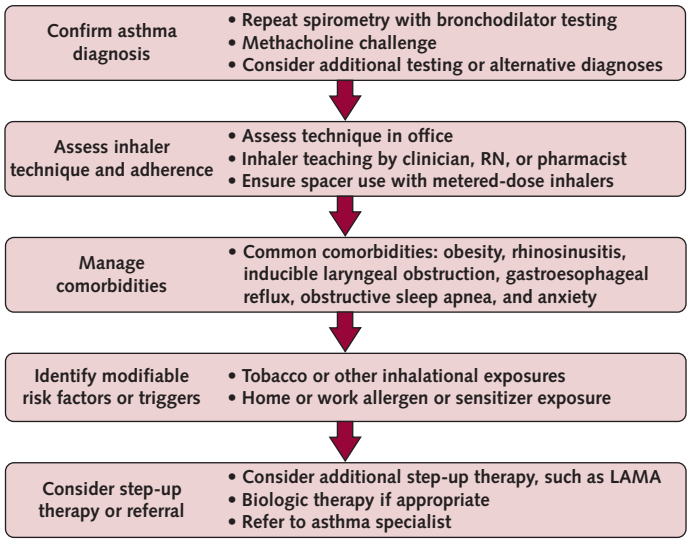
Figure 3. **Stepwise approach to evaluating difficult-to-treat asthma.**



LAMA = long-acting muscarinic antagonist; RN = registered nurse.

adherence should also be assessed to ensure that persistent symptoms are not due to lack of use of prescribed inhalers.

Comorbidities such as obesity, ILO, rhinosinusitis, gastroesophageal reflux disease (GERD), and obstructive sleep apnea (OSA) may worsen asthma control (59–61). Assessment for each of these and optimization of their control (for example, weight loss or referral to a speech language pathologist) can markedly improve asthma without changes in asthma-specific therapies.

After assessment of comorbidities, clinicians should assess for modifiable risk factors, including personal or environmental exposure to tobacco smoke, allergens, pet dander or sensitizers in the home or workplace, indoor air pollutants, and nonsteroidal anti-inflammatory drugs (10, 55).

What are common comorbidities that affect asthma control?

Addressing common comorbidities can improve asthma control and quality of life and decrease exacerbations.

Obesity

Patients with comorbid obesity and asthma have worse asthma outcomes, and obesity is common among those with difficult-to-treat asthma. Although weight loss is challenging, losing 10% of body weight is associated with improvement in asthma control (59). Increasing physical activity among people with obesity and asthma has been shown to improve asthma control independent of weight loss (62). Novel therapies and potential anti-inflammatory benefits of existing therapies, such as glucagon-like peptide-1 receptor agonists, are being actively investigated (63).

Rhinosinusitis

Chronic rhinosinusitis (CRS) with or without nasal polyps is believed to have some of the same T2 inflammatory pathways that drive disease development in T2 high asthma, making these common comorbid diseases (64). Patients with CRS and asthma have more severe asthma, and CRS is an independent cause of cough. Intranasal steroids and saline nasal rinses are first-line management (65). In severe disease or CRS with nasal polyps, referral to an otolaryngologist for discussion of endoscopic surgery and biologic therapy is appropriate.

Gastroesophageal reflux disease

An estimated 50% of patients with asthma have comorbid GERD, a higher prevalence than in the nonasthma

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population (59, 66). Patients with asthma and GERD have worse asthma control and quality of life and more frequent exacerbations (67). Empirical therapy with proton-pump inhibitors is first-line treatment. Data on improvement of asthma outcomes with treatment of GERD are variable, with some studies finding improvement in asthma control and lung function and others finding no difference compared with placebo (59, 67).

Obstructive sleep apnea

OSA occurs in an estimated 49.5% of patients with asthma (95% CI, 36.4% to 62.6%), and the odds of comorbid OSA among patients with preexisting asthma are higher than among those without asthma (68). OSA is associated with increased asthma exacerbations and ED visits and decreased asthma control and quality of life (59, 69). In observational studies, treatment of OSA with continuous positive airway pressure (CPAP) during sleep is associated with improved asthma control and quality of life and smaller decreases in FEV_1, independent of BMI (59). In a randomized controlled trial, CPAP use was associated with improved asthma quality of life but no difference in control or lung function (70).

Inducible laryngeal obstruction

Previously called vocal cord dysfunction, ILO is a common comorbidity in asthma. ILO occurs with paradoxical adduction of the vocal cords during inspiration, leading to acute onset of inspiratory wheeze and, often, severe dyspnea that does not improve with bronchodilators. The diagnosis is confirmed via laryngoscopy, although clinical history and truncation of the inspiratory limb of the flow-volume loop are suggestive. First-line treatment is respiratory retraining therapy with a specialized speech language pathologist (71).

Anxiety and depression

Approximately 24% to 38% of patients with asthma have anxiety, and 10% to 25% have depression (66). These are associated with worse asthma control and quality of life and increased exacerbations (66, 72). Cognitive behavioral therapy and lifestyle changes show potential benefit in asthma control and quality of life (73). The effects of pharmacologic interventions on depression and anxiety are largely inconclusive (73).

What are risk factors for and signs of asthma exacerbation?

Signs of an exacerbation are increase in coughing, wheezing, and dyspnea above baseline; increase in nocturnal symptoms; and increase in rescue inhaler use. Moderate exacerbations are defined as an increase in symptoms that warrants an increase in rescue inhaler use and a temporary increase in a maintenance medication regimen, whereas severe exacerbations warrant use of systemic corticosteroids for at least 3 days or an ED visit or hospitalization (74).

Vital sign measurement and physical examination are helpful in determining severity of an exacerbation. Patients with severe to life-threatening exacerbations speak in words or short sentences, often sit forward or hunched, are unable to lie down, use accessory respiratory muscles, and appear anxious. Acute encephalopathy or somnolence is a sign of impending respiratory failure and a life-threatening exacerbation. On pulmonary auscultation, breath sounds may be inaudible in life-threatening exacerbations, or expiratory wheezes may be heard throughout. Tachypnea, tachycardia, and hypoxia with Spo_2 below 90% are signs of severe exacerbation and warrant hospitalization for treatment (75). Arterial blood gas typically shows hypoxia and hypocapnia from hyperventilation. Subsequent normalization of the partial pressure of carbon dioxide is a sign of fatigue and impending respiratory failure. In life-threatening exacerbations, hypercapnia from severe bronchospasm and air trapping can occur (76).

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Risk Factors for Poor Outcomes During Exacerbations

- Prior intubation or life-threatening exacerbation
- Multiple exacerbations
- Overuse of short-acting β_2-agonists
- Lack of ICS-containing regimen or SABA-only regimen
- ED visits or hospitalization for asthma in the previous year
- Recent or current use of oral corticosteroids
- History of depression or anxiety
- Obesity
- Current use of tobacco or inhaled substance

How are asthma exacerbations managed in the outpatient setting?

Patients with moderate and some severe exacerbations can be managed in the outpatient setting with appropriate escalation of therapy. For those with moderate exacerbations, an increase in ICS-containing rescue therapy has been shown to prevent exacerbations requiring systemic corticosteroids (32). If symptoms remain inadequately controlled after 24 to 48 hours, a course of oral corticosteroids should be prescribed for severe exacerbations. The most common regimen is prednisone, 40 mg daily for 5 days; however, patients with severe asthma or a history of severe or difficult-to-treat exacerbations may require a burst and taper of prednisone (60 mg for 3 days followed by 40 mg for 3 days and then 20 mg for 3 days). It should be noted that there are few data to drive dose and duration of oral corticosteroids in this population. Patients should continue using their rescue inhaler as needed throughout the exacerbation, with maximum use of ICS–formoterol rescue of 12 puffs in 24 hours. Patients should also be instructed to immediately seek medical attention if symptoms persist or worsen or if rescue inhalers are required more frequently than every 4 hours.

What therapies should clinicians use for patients hospitalized with severe asthma exacerbations?

All patients admitted with a severe exacerbation should receive high-dose corticosteroids and short-acting bronchodilators. Although short-acting bronchodilators are an essential component of exacerbation management, the optimal dosing and frequency are debated (75). Use of an MDI has been shown to be as efficacious as nebulized therapies (77), although patients with severe dyspnea may struggle to maintain MDI technique, leading to use of nebulized therapies in the ED and inpatient settings. SABAs with or without ipratropium can be administered continuously at first, and clinical response should be addressed and used to determine ongoing frequency. Supplemental oxygen should be delivered to maintain Spo_2 of 90% to 92%, ideally.

The optimal duration and dose of systemic corticosteroids for acute exacerbations are not well defined. However, a course of at least 5 days in adults has been shown to prevent relapse or incomplete treatment of exacerbation (78). The optimal dose of oral corticosteroids is unknown; typically, the equivalent of 1 mg of prednisone per kilogram of body weight is given initially, followed by a 5-day course or a longer taper course of prednisone, 40 mg daily, based on clinical response. There is no difference in effectiveness between intravenous or oral corticosteroids in treating acute exacerbations, although in presentations with respiratory distress, intravenous methylprednisolone is often used as patients are kept nil per os.

Intravenous magnesium sulfate has been shown to reduce hospitalizations in pediatric populations (79) but has not been well studied in adults. In a meta-analysis in adult populations, intravenous magnesium did not decrease hospitalizations and had variable improvement in FEV_1 and peak flow (80). Finally, antibiotics should be given only if there is concern about

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bacterial pneumonia, as routine antibiotics have not been shown to improve asthma exacerbation outcomes (78, 81).

How should clinicians care for patients with asthma in the intensive care unit?

In patients admitted to the intensive care unit with severe and life-threatening exacerbations, additional ventilatory support is often required. Noninvasive ventilation (NIV), either as CPAP or bilevel airway pressure, can be used in patients with signs of increased work of breathing and hypercapnia (82). Prospective and randomized trials studying NIV in asthma are lacking, but retrospective data have shown that these treatments decrease the need for invasive mechanical ventilation (IMV) and in-hospital mortality (83). If NIV is used in asthma, the expiratory positive airway pressure should be titrated to improvement in work of breathing. These patients must be closely monitored, as endotracheal intubation may be required if they do not improve.

How does pregnancy affect asthma?

Approximately 40% to 45% of pregnant women with asthma have worsening of their symptoms or have an exacerbation requiring treatment during pregnancy (84–86). Asthma exacerbations in pregnancy are associated with preeclampsia, preterm birth, and low birthweight (85). Diagnosis of asthma in pregnancy does not differ from the nonpregnant state; however, it should be noted that pregnancy itself can cause dyspnea; increased reflux; and, in certain clinical contexts, pulmonary embolism, all of which can mimic asthma symptoms. Asthma medications should be continued or, when appropriate, started in pregnancy. Self-discontinuation of medications is common due to fear or misinformation that these medications could harm the fetus; however, poorly controlled asthma and exacerbations lead to greater adverse outcomes (85). Although prospective data on the safety of asthma medications in pregnancy are limited, retrospective and population-based studies support their safety in pregnancy (86). Similarly, observational data show that biologics do not seem to cause adverse maternal or fetal outcomes and are highly effective at preventing exacerbations (87). In the event of an exacerbation, systemic corticosteroids should be used.

Treatment... Asthma control should be regularly assessed using standardized metrics based on GINA guidelines. AIR therapy using ICS–formoterol or ICS–SABA is recommended as first-line reliever therapy. In patients requiring maintenance therapy, ICS–formoterol is recommended as MART. Patients with 2 or more exacerbations per year may benefit from monoclonal antibodies or long-term macrolide therapy, and referral to a specialist is recommended. If a patient does not respond to therapy, a stepwise approach ensuring appropriate use of asthma medications, confirmation of the diagnosis, and management of relevant comorbidities is recommended. Oral corticosteroids are recommended for severe exacerbations that do not improve with increased use of ICS-containing rescue inhalers. Patients with severe exacerbations requiring hospitalization should receive short-acting bronchodilators and high-dose systemic corticosteroids. NIV may prevent the need for IMV in some patients, although they require close monitoring.

CLINICAL BOTTOM LINE

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Do U.S. stakeholders consider asthma care when evaluating the quality of care a physician delivers?

The Centers for Medicare & Medicaid Services (CMS) has established several specific quality metrics to monitor asthma care (88). These include metrics on optimal outpatient asthma control based on the Asthma Control Test and exacerbations and medication prescription for those with persistent asthma. CMS has also developed metrics on hospitalizations for asthma or COPD as a reflection of quality of outpatient asthma care.

How is climate change affecting asthma morbidity in the United States, and what advice should clinicians give to patients?

Climate change is playing a role in increased asthma exacerbations. Increased air pollutants, including ground-level ozone and particulate matter smaller than 2.5 μm ($PM_{2.5}$), are linked to development of asthma, exacerbations, and asthma mortality (89). Climate change is leading to increased forest fires, extended and expanding pollen seasons, and dust and thunderstorms that worsen asthma severity, increase exacerbations, and drive asthma and atopic disease development (89, 90). These changes in air quality and exposures disproportionately affect communities with health disparities. Patients with asthma should be instructed to monitor their local Air Quality Index and pollen counts. For those with allergic asthma, staying indoors on particularly high-pollen days may help avoid triggers. In addition, understanding drivers of indoor air pollution and use of indoor air filters may help in personal mitigation of $PM_{2.5}$ and other air pollutants; however, this is an evolving area of research (91).

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In the Clinic
Tool Kit

Care of the Patient With Asthma

Patient Information

https://medlineplus.gov/asthma.html
https://medlineplus.gov/languages/asthma.html
Information on asthma in English and other languages from the National Institutes of Health's MedlinePlus.

www.nhlbi.nih.gov/health/asthma
www.nhlbi.nih.gov/es/salud/asma
Information on asthma in English and Spanish from the National Heart, Lung, and Blood Institute.

www.cdc.gov/asthma
Information on asthma from the Centers for Disease Control and Prevention.

Information for Health Professionals

https://ginasthma.org/2024-report
Global strategy for asthma management and prevention from the Global Initiative for Asthma.

www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
Asthma management guidelines from the Expert Panel Working Group of the National Heart, Lung, and Blood Institute.

https://publications.ersnet.org/content/erj/55/1/1900588
European Respiratory Society/American Thoracic Society guideline on the management of severe asthma.

WHAT YOU SHOULD KNOW ABOUT ASTHMA

What Is Asthma?

Asthma is an illness that affects the airways in your lungs and makes it hard to breathe. When you have asthma, tubes that bring air to the lungs become swollen. Things that irritate your lungs, like smoke, dust, or respiratory infections, can trigger a reaction called an asthma attack.

What Are the Symptoms?

Symptoms of asthma include:

- Coughing
- Wheezing
- Tightness in your chest
- Shortness of breath
- Cough that wakes you from sleep

You may experience worsening symptoms from:

- Exercising
- Respiratory infections, particularly viral infections
- Breathing irritants, such as smoke, pollen, or animal dander
- Breathing irritants at work, such as dust or fumes
- Taking aspirin and other medications

How Is It Diagnosed?

- Your clinician will ask you questions about your medical history and your symptoms and do a physical examination.
- You may have spirometry, which is a breathing test that measures how much and how fast you can breathe air out before and after using an inhaled medication called albuterol.
- If you have unusual symptoms or your asthma is difficult to control with standard treatment, your clinician might refer you to a specialist.

How Is It Treated?

You can usually control your asthma with medication and by reducing exposure to triggers. Your clinician may prescribe several types of medicine, such as:

- An inhaled medicine that can quickly relieve symptoms during an asthma attack
- An inhaled medicine you can take once or twice daily to prevent asthma attacks
- A steroid pill, which you may need to take for about a week if you have severe asthma attacks
- A specialized injectable medication, which might be an option if you have many asthma attacks or severe symptoms

Ask your clinician to watch you use your inhaled medications and provide feedback on your technique. More than half of patients do not take their inhaled medications correctly, and many types of inhalers need to be used with a spacer device to ensure medication is delivered to your lungs.

Nonmedical treatment of asthma includes identifying and reducing environmental triggers.

- Stop smoking, vaping, and using inhaled cannabis, and avoid all secondhand smoke.
- Use air conditioners and dehumidifiers to reduce moisture in your home.
- Remove carpets and limit fabric household items.
- Avoid pets if you are allergic or they trigger your asthma. If you have a cat or dog that triggers asthma, make sure it is not allowed to sleep in your bed. Removing pets from the home may be needed.
- If you have overweight or obesity, weight loss can help with asthma control. Physical activity, regardless of weight loss, can also improve asthma symptoms.
- Work with your clinician to treat chronic sinus issues as these can worsen asthma control.
- Many people with asthma also have intermittent abnormal movement of their vocal cords, which can mimic asthma symptoms. Your clinician may refer you to an otolaryngologist (ear, nose, and throat specialist) or a speech therapist to help with this condition.

Develop a written action plan with your clinician to help you understand how to keep your asthma under control, when and how to take your medicine, and when to get emergency help. This plan may include when and how to increase certain inhaler doses and frequencies. It will also help your clinician make decisions about your treatment and inform how to adjust your medications.

Questions for My Doctor

- What tests should I have to diagnose asthma?
- How can I prevent an asthma attack?
- Do I need an inhaler? Does my inhaler need a spacer device? Would you show me how to use it?
- Do I need a daily inhaler to control my asthma?
- What should I do if I have an asthma attack?
- When should I get emergency help?

For More Information

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Leading Internal Medicine, Improving Lives

National Heart, Lung, and Blood Institute
www.nhlbi.nih.gov/health-topics/asthma

MedlinePlus
https://medlineplus.gov/asthma.html

A tutorial on proper use of a metered-dose inhaler
https://youtu.be/9ipqxF-4p5g

Patient Information

Appendix Table. **Biologic Therapies for Severe Asthma**

Drug	*Dosing*	*Mechanism*	*Asthma Indications*	*Adverse Effects*	*Additional FDA-Approved Indications*
Omalizumab	75–375 mg by subcutaneous injection every 2 or 4 wk Determine dose and dosing frequency by serum total IgE, measured before the start of treatment, and by body weight in kilograms	Anti-IgE Binds the Fc receptor	IgE level of 30–1300 IU/mL and ≥1 positive aeroallergen skin test result or elevated specific aeroallergen IgE level	Black box warning (risk for anaphylaxis)	Chronic rhinosinusitis with nasal polyposis, IgE-mediated food allergy, chronic spontaneous urticaria
Mepolizumab	100 mg by subcutaneous injection every 4 wk	Anti–IL-5 Binds the IL-5 ligand	AEC ≥0.300 × 10^9 cells/L	Causes anaphylaxis rarely	Chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome
Reslizumab	3 mg/kg by intravenous infusion every 4 wk	Anti–IL-5 Binds the IL-5 ligand	AEC ≥0.400 × 10^9 cells/L	–	–
Benralizumab	300 mg subcutaneously in 3 monthly doses, then every 8 wk	Anti–IL-5R Binds the IL-5 receptor	AEC ≥0.300 × 10^9 cells/L	–	Eosinophilic granulomatosis with polyangiitis
Dupilumab	Initial dose of 400 or 600 mg subcutaneously followed by 300 or 200 mg subcutaneously every 2 wk	Anti–IL-4 and anti–IL-13 Binds the IL-4 receptor	AEC ≥0.150 × 10^9 cells/L	–	Chronic rhinosinusitis with nasal polyposis, atopic dermatitis, eosinophilic esophagitis, eosinophilic COPD, prurigo nodularis
Tezepelumab	210 mg subcutaneously every 4 wk	Binds to TSLP blocking interaction with receptor	No AEC cutoff	–	–

AEC = absolute eosinophil count; COPD = chronic obstructive pulmonary disease; FDA = U.S. Food and Drug Administration; IL = interleukin; TSLP = thymic stromal lymphopoietin.