Management of Chronic Asthma in Adults

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KEYWORDS

• Chronic airway inflammation • Allergic • Non-allergic • Adult-onset
• Chronic asthma • Chronic management • Asthma in pregnancy • COVID-19

KEY POINTS

- Asthma can be diagnosed in childhood, or late-onset as an adult. Respiratory symptoms can present before 5 years of age, but it is often difficult to diagnose asthma in infants or toddlers.
- Respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough vary over time and in intensity.
- Diagnosis is a combination of the history of symptoms along with bronchodilator reversibility testing.

INTRODUCTION

As defined by 2022 Global Initiative for Asthma (GINA): "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation".[1]

Often, airway hyperresponsiveness, bronchoconstriction, and airway edema cause the reversible airway obstruction that is characteristic of asthma. One of the key drivers of asthma is acute and chronic inflammation.[2]

Asthma is a chronic respiratory disease that affects 1% to 18% of populations in varying countries.[1] As of 2017, asthma affects 25 million people, including 6 million children under the age of 18.[3] Although symptoms may resolve spontaneously, exacerbations can often be life-threatening and carry significant financial burdens to patients and the communities in which they live.

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In the United States, asthma has a prevalence of 7.5% in children and 7.7% in adults.[4] In adults, women are more likely to die from asthma than men, whereas, in children, boys are more likely to die than girls.[5] This reversal of trends may be because of the effects of testosterone on the lungs; testosterone has been found to decrease the swelling of airways in asthma, as suggested by some studies.[6] As of 2020, adults with asthma are five times more likely to die than children.[5] In the United States, black people are almost three times more likely to die from asthma than white people.[5] Deaths due to asthma were on the rise for the first time in over two decades in 2020; it is estimated that 11 people die in the United States from asthma every day.[5]

The annual economic cost of asthma, including medical costs and loss of work or school, was estimated to be over $81.9 billion; over $50.3 billion were due to medical costs.[7]

Clinical Presentation

- Asthmatics, particularly adults, will experience symptoms such as coughing, chest tightness, wheezing, or shortness of breath[1]
  - Often worse at night or early morning, and can vary in intensity and over time
  - Triggered by viral infections, exercise, allergen exposure, or changes in weather[8] (**Table 1**)

Risk factors for exacerbations of chronic asthma

- Poor asthma control[8–12]
- Poor adherence to chronic medications
- Incorrect use of inhaler/incorrect technique
- History of chronic sinusitis
- Chronic smoking

Diagnosing: criteria for asthma in adults

- There is no gold standard testing that is set for the diagnosis of asthma. Instead, diagnosis can be made by history, clinical findings, and observation of clinical

Table 1
Expected symptoms

Respiratory Symptoms (Wheezing, Shortness of Breath, Cough, Chest Tightness) Typical of Asthma:	Symptoms Unlikely Due to Asthma:
Worse at night or when waking up	Isolated cough
Varies in intensity and time	Chronic sputum production
Symptoms triggered/worsened by viral infections, exercise, changes in weather, exercise	Chest pain
Symptoms can be worsened by laughter or strong smells (eg, perfume, incense, smoke, floral smells, car exhaust)	Exercise-induced dyspnea with noisy inspiration
	Shortness of breath along with paresthesia or light-headedness

Data from Levy ML, Fletcher M, Price DB, Hausend T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPCRG) guidelines: Diagnosis of respiratory diseases in primary care. Primary Care Respiratory Journal. 2006;15(1):20-34.

course over time by a primary care provider, often a family physician. Objective measures, such as pulmonary function tests, can aid in the diagnosis, if this is available to the patient. Refer to **Table 2**.

- Pulmonary function may reveal expiratory airflow limitations and excessive variability in lung function.[1,13]
  - When the forced expiratory volume in the first second (FEV1) is reduced, confirm FEV1/forced vital capacity (FVC) is reduced.
    - Lower limit of normal:
      - Adults >0.75 to 0.80
      - Children >0.90[14]
  - Diagnosis is better confirmed with greater variations in the variability of lung function testing, ie, if initial testing is normal, can consider repeating during the onset of symptoms or early in the morning
- Partial (10%) reversibility of airflow obstruction on spirometry after beta2-agonist administration[2,15]
- When a clinical diagnosis is not clear, perform a broncho-provocative challenge test with methacholine. A positive test is when the FEV1 decrease is more than 20% at 8 mg/mL.[2,16,17]
- Monitoring test: peak flow meter[18]

Table 2
Asthma categories of severity

Intermittent	• Daytime symptoms ≤2 per week • ≤2 nocturnal awakenings per month • SABA to relieve symptoms ≤2 days per week • FEV1 measurements between exacerbations within normal range (≥80% of predicted) • FEV1/FVC ratio between exacerbations is normal (based on age-adjusted values) • ≤1 exacerbation requiring oral glucocorticoids per year
Mild persistent	• Symptoms >2 times weekly • Three to four nocturnal awakenings per month (fewer than every week) • SABA use for symptom relief >2 days out of the week (not daily) • Minor interference with normal activities • FEV1 measurements within normal range (≥80% of predicted)
Moderate persistent	• Daily symptoms • Nocturnal awakenings as often as once per week • Daily SABA for symptom relief. • Limitation in normal activity • FEV1 ≥60% and <80% of predicted and FEV1/FVC below normal
Severe persistent (defined by National Asthma Education and Prevention Program—NAEPP)	• Symptoms throughout the day • Nightly nocturnal awakening • Reliever medication needed for symptoms several times per day • Extreme limitations to daily activity

Abbreviation: SABA, short-acting beta-agonist.
Data from Refs.[19–22]

Chronic Management and Maintenance

- Main goals: optimize control of asthma symptoms and reduce risk of asthma exacerbations[1]
  - Avoid allergens, air pollution, and other environmental triggers
  - Weight reduction
  - Smoking cessation
- Four essential components of management:
  - Patient education
  - Controlling asthma triggers
  - Monitoring for changes in symptoms or lung function
  - Pharmacologic therapy
- Patient–health care provider partnership[1]:
  - Effective management should be a partnership between patient and health care provider[23]; shared decision-making has been shown to have improved outcomes[24,25]
  - Education on self-management reduces morbidity in adults[23]

Treatment

- Treatment of asthma in the United States is guided by the Asthma Management Guidelines 2020, a report from the NAEPP Coordinating Committee Expert Panel Working Group by the National Heart, Lung, and Blood Institute (NHLBI) (**Fig. 1**).
- Treatment of asthma in Europe is guided by the GINA2022 (**Fig. 2**).
- With an initial diagnosis of asthma, it is important to initiate inhaled medications (see **Fig. 1**).
- Short-acting beta-agonists (SABA) for mild intermittent and persistent disease[20] (see **Fig. 1**).
  - Intensity of treatment depends on the severity of symptoms
    - Intermittent asthma: typical use is every 4 to 6 hours, as needed
    - As prophylaxis: advise the patient to use 15 to 30 minutes before participating in physical activity
    - In severe exacerbations, as typically seen in the emergency room or in acute office visits: can use up to three treatments in 20-minute intervals as needed
    - Using SABA >2 times a week for relief of symptoms indicates poor control and requires treatment step up
- Inhaled maintenance therapies for persistent disease[20] (see **Fig. 1**)
  - Inhaled maintenance therapies are the mainstay of management for mild persistent, moderate to severe, and uncontrolled persistent asthmatics.
- Biologics for severe persistent disease
  - Anti-IgE: consider in allergic-driven disease
    - Omalizumab injections every 2 to 4 weeks: consider when serum IgE levels are between 30 and 700.
    - Mechanism of action: binds to third constant domain of IgE heavy chains and forms complexes with free IgE, preventing interaction with these receptors on mast cells and basophils
    - Minimum of 12 weeks of treatment to determine the efficacy
    - Adverse effects: hypersensitivity including anaphylaxis, urticaria, and injection site reactions
  - Anti-IL5: consider when there are high serum eosinophils
    - Mepolizumab injections once every 4 weeks: consider: when eosinophil levels >150.

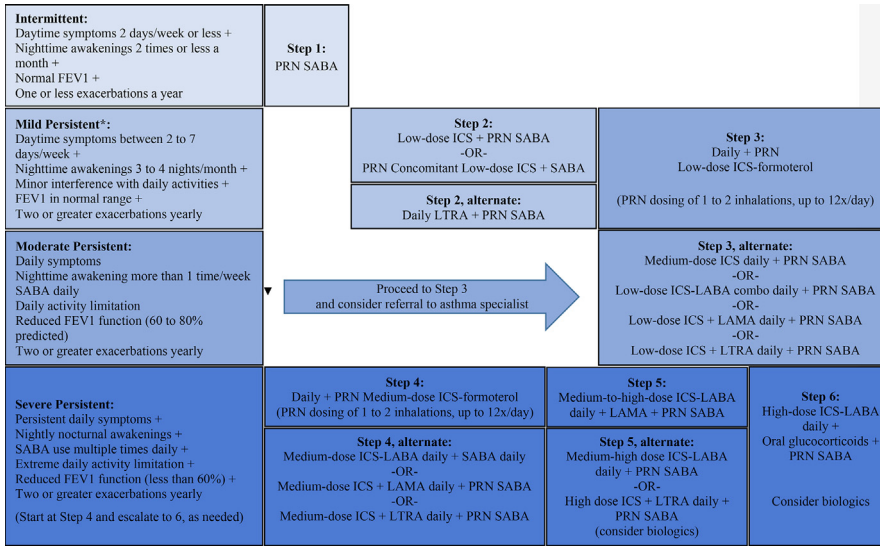

Fig. 1. Assessment and treatment of asthma in ages 12 years and older as defined by the National Asthma Education and Prevention Program: Expert Panel Working Group 2020. ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting beta-agonist. [a]If poorly controlled Mild Persistent Asthma, proceed to Step 3. (*Adapted from* Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC); Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, Dixon AE, Elward KS, Hartert T, Krishnan JA, Lemanske RF Jr, Ouellette DR, Pace WD, Schatz M, Skolnik NS, Stout JW, Teach SJ, Umscheid CA, Walsh CG. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270. https://doi.org/10.1016/j.jaci.2020.10.003. Erratum in: J Allergy Clin Immunol. 2021 Apr;147(4):1528-1530. PMID: 33280709; PMCID: PMC7924476.)

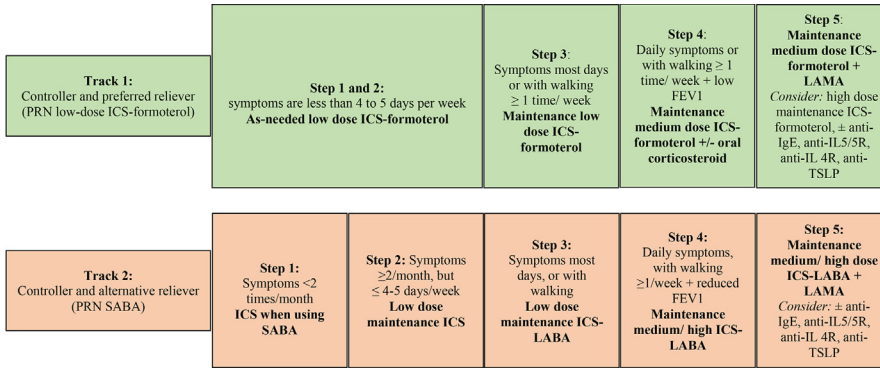

Fig. 2. Assessment and treatment of asthma as defined by GINA 2022. PRN, as needed; TSLP, thymic stromal lymphopoietin. (*Data from* Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma. Updated 2022. Accessed July 1, 2022. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-02-WMS.pdf (1) (1) (1).)

Mechanism of action: inhibits IL-5 signaling and reduces the production of eosinophils
Adverse effects: injection site reactions, headache, and hypersensitivity reactions
- Reslizumab infusions over 20 to 50 minutes, 3 mg/kg every 4 to 6 months; consider in severe asthmatics >18 years of age and have an eosinophilic phenotype
- Benralizumab given subcutaneously every 4 weeks for the first three doses, then every 8 weeks for severe asthmatics >12 years and older with an eosinophilic predominance

- Anti-IL4/IL13: consider in moderate to severe eosinophilic or oral glucocorticoid dependent
  - Dupilumab subcutaneous injections once (loading dose) and then every other week
    - Mechanism of action: binds to IL-4 receptor and modifies signaling of IL-4 and IL-13 pathway
    - Adverse effects: urticaria, angioedema, injection site rash, erythema multiforme, serum sickness-like reaction, conjunctivitis, blepharitis, keratitis, eye pruritis, xerophthalmia

- Consider consulting an asthma specialist if the patient is experiencing uncontrolled moderate persistent asthma, or if the patient is requiring Step 3 of treatment. If the patient has severe persistent asthma, that is, requiring Step 4 of treatment, consult an asthma specialist (see **Fig. 1**).
- Control assessment:
  - First check: Adherence, correct inhaler technique, environmental factors, comorbid conditions
  - Escalate treatment if not controlled; can reassess in 2 to 6 weeks
  - Deescalate treatment if asthma has been well controlled for at least 3 months consecutively
- Vitamin D: In patients who require systemic corticosteroids, vitamin D supplementation may reduce the rate of exacerbation in patients with baseline 25(OH)D of less than 25 to 30 nmol/L.[26,27] Overall, current studies are not of good quality, and more studies are needed for clear recommendations.[1]

Vaccine Recommendations

- Annual influenza vaccine[1,28]
- Although children and the elderly who have asthma are more at risk of pneumococcal disease,[29] there is insufficient evidence for routine pneumococcal vaccination[30]
- If requiring biologic therapy, the first dose of biologic therapy and COVID-19 vaccine should not be given on the same day[1]
- COVID-19 vaccine and influenza vaccine can be given on the same day[1]

Adult Asthma Considerations with Comorbid Conditions

- COVID-19: Current studies indicate that well-controlled asthmatics are not at increased risk of COVID-19-related death; There is an increased risk of COVID-19 death in asthmatics who recently needed oral corticosteroids or were hospitalized for severe asthma.[1]
- Obesity: Body mass index (BMI) should be documented for all asthma patients, as it is more difficult to control symptoms in obese patients.[31–34] ICS are a key treatment of asthma in obese patients. However, the clinical response to

glucocorticoid-containing regimens is reduced in asthmatics who are overweight or obese.[34] Improved quality of life and control of asthma symptoms are seen with 5% to 10% weight reduction.[35]

- Gastroesophageal reflux disease (GERD): Symptoms are more common in asthmatics than in the general population.[36] Treatment with proton pump inhibitors (PPI) in patients who have both asthma and GERD has a small benefit for lung function; PPI therapy in adult asthmatics yields a small improvement in morning peak expiratory flow.[37,38] However, there is still limited data that are statistically significant to recommend empirical PPI use in the routine treatment of asthma.[37]

Asthma in Pregnancy

- Exacerbations are common and typically occur in the second trimester.[39]
- Poorly controlled asthma can result in worse outcomes for the baby (pre-term delivery, low birth weight) and the mother (pre-eclampsia). Well-controlled asthma during pregnancy has little or no increased risk of adverse maternal or fetal complications.[40]
- ICS, beta2-agonists, montelukast, or theophylline are not associated with increased incidence of fetal abnormalities[41]
  - Use of ICS reduces the risk of having asthma exacerbations during pregnancy[11,40,42]
- Important to aggressively treat acute exacerbations of asthma with SABA, oxygen, and administration of systemic corticosteroids to prevent fetal hypoxia[1]
- During labor and delivery: continue usual controller medications and add reliever when needed. If acute exacerbation during delivery, manage with SABA.[1]
  - If high doses of beta-agonist are given within 48 hours before delivery, neonatal hypoglycemia should be monitored with blood glucose checks for the first 24 hours.[43,44]

DISCUSSION

In the United States, asthma is a common disease affecting approximately 25 million people, of which 20 million are adults aged 18 and older.[2] As of 2018, asthma accounted for 1.6 million emergency department visits, 178,530 inpatient hospitalizations,[45,46] and 5.8 million office visits.[4] Although treatment is widely available, and the ability to diagnose asthma by clinical judgment and testing has improved drastically, deaths caused by asthma or asthma exacerbations remain prominent. For the first time in 20 years, deaths due to asthma were on the rise, with 4,145 people dying from complications from asthma; proper treatment and care could have prevented nearly all these deaths.[5] Although ICS may control symptoms, it alone does not change the underlying disease process or progression of asthma.[47] Thus, it is important to provide appropriate medications to manage and control chronic asthma and to identify and treat immediate exacerbations. Medications containing ICS are considered controller medications and are used to reduce airway inflammation, control asthma symptoms, and reduce asthma exacerbations.[48]

Although long-term studies of COVID-19 are currently limited, studies to date suggest that well-controlled asthmatics are not at risk of COVID-19-related deaths.[49,50] However, in severe asthmatics requiring hospitalization[51] and asthmatics requiring oral corticosteroids to control acute exacerbations,[49,52] the risk of COVID-19-related death was increased.

Since 2007, the NHLBI has made substantial changes in recommendations in the most recent 2020 guidelines, to include changes regarding allergen mitigation, ICS

use, and immunotherapy. Regarding treatment in asthmatics ages 12 and older with mild persistent asthma, a conditional recommendation of treatment now includes concomitant as-needed ICS and SABA use versus daily low-dose ICS and SABA as needed for quick relief. A strong recommendation in the 2020 guidelines for asthmatics ages 4 years and older with moderate to severe persistent asthma includes starting treatment with ICS-formoterol in a single inhaler as both a daily controller and reliever therapy.[20] SMART therapy, or "single maintenance and reliever therapy," is perhaps the most impactful recommendation from the 2020 guideline. The NHLBI recommends the daily use of ICS–LABA combinations that contain formoterol be initiated in moderate persistent asthma. With proper use, SMART therapy was found to significantly reduce asthma exacerbations, emergency room visits, hospitalizations, as well as significantly lower the need for systemic corticosteroids.[20,53–56]

Although treatment is often aimed at symptom control, severe asthmatics can often remain uncontrolled despite the use and adherence to high-dose controller therapy. Over the last few decades, biologic drugs have been developed to target specific causative mechanisms that have allowed asthma treatment to be personalized.[57,58] Approval by the United States Food and Drug Administration for biologics, beginning with omalizumab in 2003, has allowed for substantial clinical studies to evaluate the efficacy of treatment in uncontrolled severe asthmatics. Biologics that are currently available, including omalizumab, mepolizumab, reslizumab, and benralizumab have been shown to be effective in reduction of asthma exacerbations, systemic corticosteroid treatment, and overall improvement of lung function and quality of life in severe asthmatics.[59,60]

As per the 2022 GINA guidelines, two types of reliever medications can be prescribed to asthmatics: an as-needed low-dose ICS-formoterol or an as-needed SABA, refer to **Fig. 2**. When considering between the rescue medications, the use of SABA daily increases the risk of asthma exacerbations, and therefore, ICS budesonide-formoterol is the preferred rescue medication.[61,62] An important goal in asthma management is reducing and eventually eliminating the need for SABA relievers.[1] Although the GINA guidelines are used in Europe, they are not followed in the United States.

Primary care physicians are often the first providers to recognize, diagnose, and treat patients with asthma. It is evident that physicians must communicate with patients the importance of taking their prescribed asthma medications, avoidance of triggers, as well as supporting and encouraging patients to take ownership of their chronic regimen. It is important to treat asthmatics by prescribing the correct medications and inhalers to control chronic asthma. It is also crucial for physicians to recognize and immediately treat acute exacerbations to prevent avoidable complications, including hospitalizations, missed days at work or school, or even death. Primary care physicians must be able to recognize when asthma symptoms are not well controlled and require higher care, particularly when requiring the addition of biologics. It is at this step in management that referral to an asthma specialist, a pulmonologist, or an allergist, is crucial for appropriate care. The ability to do this will aid in the reduction of the general economic burden, but perhaps more importantly, it ultimately reduces the economic and physical burden on patients.

CLINICS CARE POINTS

- When evaluating adolescent asthmatics, do it in private without a parent or guardian to obtain accurate information to adequately diagnose the severity and correct treatment.

- In pregnant asthmatics, continue controller medications and add reliever medications during labor and delivery. Although rare, if there is an acute exacerbation during delivery, administer SABA.
- Well-controlled asthmatics are not at an increased risk of COVID-19-related deaths.
- There is insufficient evidence for routine pneumococcal vaccination in asthmatics who are young or elderly.

DISCLOSURE

The authors have no financial conflicts of interest to disclose.

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