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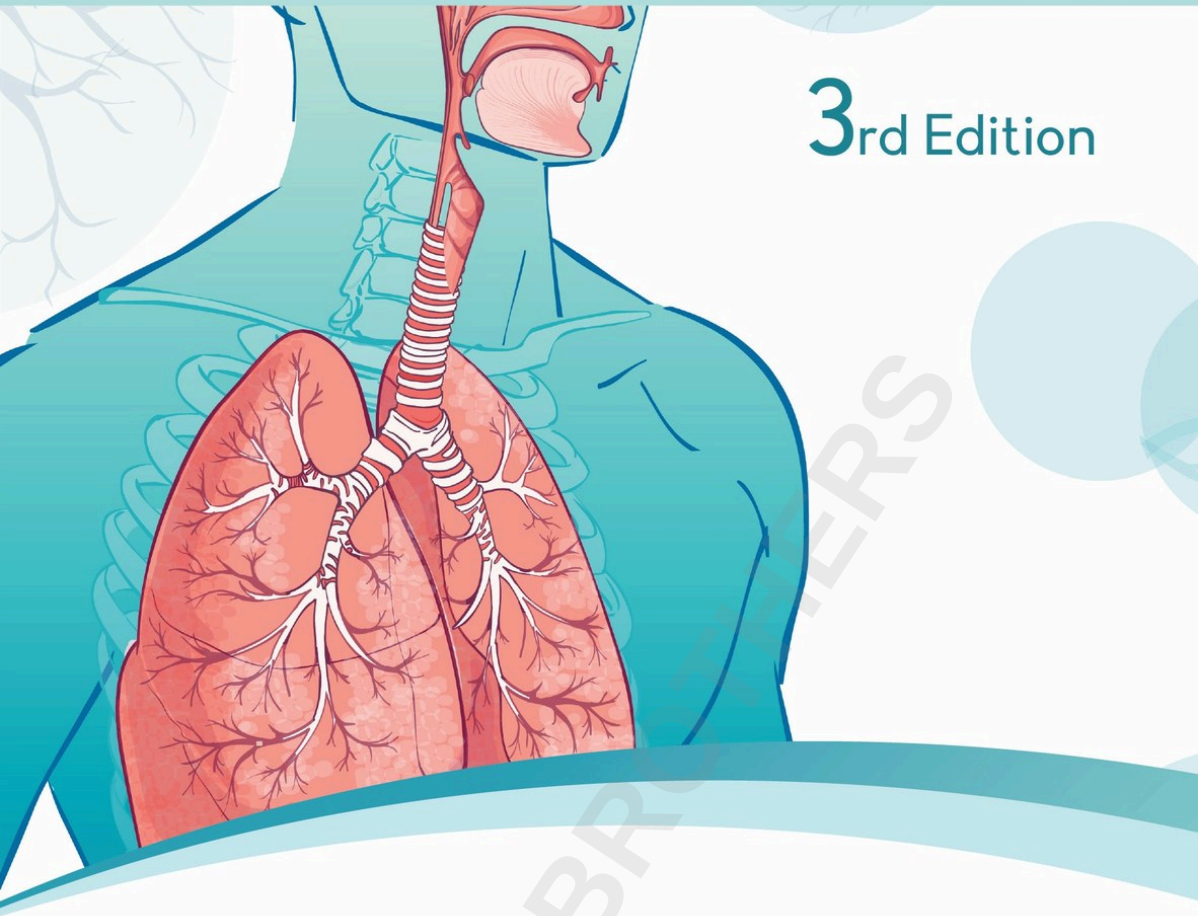

3rd Edition

Handbook of Pulmonary & Critical Care Medicine

Editor-in-Chief
SK Jindal

JAYPEE

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CHAPTER 28

Control and Management of Stable Asthma

Sidney S Braman, Katherine E Hodgin

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INTRODUCTION

Treatment protocols for the management of stable asthma have undergone considerable change over the past 60 years. There is a growing consensus that asthma is not a single disease but rather an umbrella term for multiple diseases with different phenotypes (i.e., observable characteristics) and different endotypes that have unique mechanisms of inflammation. National and international asthma guidelines and asthma treatment protocols have provided a roadmap for asthma care. The optimal management of asthma depends on a careful assessment of a patient's symptoms, including the use of objective measures of asthma control with questionnaires and physiologic testing. The treatment of asthma is tailored to the patient's needs in a step-up and step-down manner.

ESSENTIAL COMPONENTS OF ASTHMA CARE

Avoidance

Allergens, environmental irritants, and occupational factors are considered to be the most important triggers of asthma. For successful long-term management of asthma, these triggers must be identified and prevention of exposures should be the first line of defense. Tailored allergen intervention strategies are recommended for those who are exposed to specific allergens that result in asthma symptoms and for whom allergy testing [skin testing or specific immunoglobulin E (IgE)] is positive.

Both outdoor and indoor pollutants contribute to worsening asthma symptoms. Indoor pollutants include cooking and heating fuel exhausts as well as insulating products, paints, and varnishes. Clinicians should advise patients to be aware of the potential irritating effects of newly installed furnishings and finishes which can arise from new linoleum flooring, synthetic carpeting, particleboard, wall coverings, furniture, and fresh paint. Also, fumes from wood-burning appliances or fireplaces, commonly used for heating and cooking in poor, underserved regions of the world, can precipitate symptoms in persons

who have asthma. Sprays and strong odors, particularly perfumes, can also irritate the lungs and precipitate asthma symptoms. The use of high-efficiency particulate air (HEPA) cleaners in homes may increase symptom-free days but does not demonstrate significant differences for acute asthma healthcare events or symptom-free nights.

Monitoring Asthma: Use Objective Measures of Asthma

Objective measurements of pulmonary function are important in patients with asthma to confirm the diagnosis and to assess disease control at various time intervals. While there is a poor correlation between the airway inflammation and lung function, physiologic measurements are extremely important in the management of asthma. Physiologic testing can demonstrate the major diagnostic features of asthma: (1) Airflow obstruction, (2) reversibility of airflow obstruction, and (3) bronchial hyperresponsiveness—and can therefore be useful in confirming or excluding the diagnosis.

Pulmonary function tests are extremely useful for establishing the diagnosis of asthma and/or following the clinical course of the patient once the diagnosis has been made. They include spirometry, peak expiratory flow rate (PEFR) measurements, and bronchoprovocation testing. In addition, various biomarkers have been developed that lead to a better classification of distinct phenotypes (clinical presentation) or endotypes (functional or pathophysiologic mechanism) and may lead to more personalized treatment. They include measurements of sputum and blood eosinophil counts, fraction of exhaled nitric acid levels, and serum IgE levels.

TREATMENT OF STABLE ASTHMA

Asthma Pharmacotherapeutic Agents

Choices for medication use will depend on the health system, cost, and availability of the treatment. Inhaled therapy is preferred; oral bronchodilator therapy is discouraged because of its higher side-effect profile and slower onset of action. Nebulized medication with face mask may be necessary in very small children and pressurized metered dose inhalers used, if tolerated. The available treatments include both reliever (giving as needed relief of breakthrough symptoms) and controller medications (medications that are taken daily on a long-term basis to achieve and maintain control of persistent asthma and reduce the risk of exacerbations). Another newer approach for acute symptomatic relief is maintenance and reliever therapy (MART) that combines an inhaled corticosteroid (ICS) for its anti-inflammatory mechanism, and a long-acting beta agonist (LABA), formoterol, for both immediate symptom relief and long-acting bronchodilatation.

Beta-2-adrenoceptor Agonists

Selective inhaled beta-2-adrenoceptor agonists have been the main bronchodilating agents for the treatment of asthma, through their rapid and potent effects

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in relaxing airway smooth muscle. They are classified based on the duration of action into short and long acting. They produce bronchodilation by direct stimulation of the airway smooth muscle leading to relaxation via the activation of the adenylate cyclase pathway.

- *Short-acting beta agonists (SABAs)*, such as salbutamol, are widely used due to their acute (4–6 hours) bronchodilator effects and for the ability to protect against various triggers such as cold air, exercise, and allergen. They are generally well tolerated, even with frequent use.
- *Long-acting beta agonists*, such as salmeterol and formoterol, are considered "controller therapy" and provide bronchodilation and improve bronchial responsiveness for up to 12 hours and in the case of vilanterol or indacaterol for up to 24 hours. Like SABAs, they inhibit the acute early allergic response with the addition of inhibition of the late-phase response and airway hyperresponsiveness lasting up to 24 hours after allergen challenge. The use of LABAs as monotherapy should be avoided in the stable asthmatic.

Anticholinergic Agents

In poorly controlled asthmatics, a long-acting once-a-day anticholinergic to a low-to-medium dose of ICS is as effective as adding salbutamol or doubling the dose of the ICS on top of ICS/LABA combination in moderate-to-severe asthmatic patients. Anticholinergic agents such as tiotropium, glycopyrrolate, aclidinium bromide, and revefenacin should be considered for patients with uncontrolled asthma before any biologic or systemic corticosteroid treatment is initiated.

Inhaled Corticosteroids

Inhaled corticosteroids have become the mainstay of treatment in persistent asthma. This is because of their proven efficacy, superior to other classes of asthma therapy, and their lower potential for systemic side effects compared to oral glucocorticosteroids. They exert their anti-inflammatory activity via the glucocorticoid receptor complex that regulates gene transcription of proteins that inhibit proinflammatory cytokines. Clinically, they improve airway inflammation, hyperresponsiveness, airflow obstruction, and symptoms in asthmatics.

Theophylline

Theophylline has a weak bronchodilator effect and also anti-inflammatory and immunomodulatory effects. The guidelines recommend that theophylline may be considered for use as add-on therapy in patients not well controlled on low-dose ICS but recommend LABAs as more effective with fewer adverse events. Side effects are especially pronounced in the elderly where polypharmacy and potential drug-to-drug interactions are becoming more frequent. Theophylline has a rather narrow therapeutic window, and unwanted effects are usually seen at plasma levels above 20 mg/dL. To avoid untoward effects, it is advisable to monitor blood theophylline levels. The recommended therapeutic range for theophylline is 5–15 mg/dL.

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Leukotriene Pathway Modifiers

Available antagonists against cysteinyl leukotriene receptor antagonists (LTRAs) include montelukast, pranlukast, and zafirlukast. These medications serve to inhibit many important pharmacologic actions that contribute to airflow obstruction in asthma such as airway smooth-muscle contraction, edema formation, and mucus secretion. The anti-leukotrienes (LTs) may be used as first-line therapy when anti-inflammatory therapy is needed but they are generally less effective than ICS. There are certain phenotypes of adult asthma that have shown more favorable responses including aspirin-exacerbated respiratory disease, elderly asthma, and asthma associated with smoking, obesity, and allergic rhinitis. The LT modifiers may have an additive effect to ICS and inhaled β2 agonist in the moderate persistent asthmatic when step-up care is needed.

Oral Corticosteroids

Systemic administration of corticosteroids is generally reserved for patients with severe asthma or is used as a trial of therapy to attempt to optimize lung function in patients with a component of fixed airflow obstruction despite conventional asthma therapies. Because of the side effects, systemic corticosteroids, even at lower doses, should be avoided in the routine treatment of chronic stable asthma.

Other Approaches to Asthma Treatment

Antibiotics

Atypical bacterial infections such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are thought to be responsible for only a minority of exacerbations of asthma. Antibiotics should be reserved for cases in which clear signs, symptoms, or laboratory test results are suggestive of bacterial infection.

There is evidence to suggest that macrolides may be more beneficial in subgroups of patients with noneosinophilic (i.e., neutrophil predominant) asthma.

Biologic Therapies

Biologic therapies are used in difficult-to-control asthmatics who do not respond to conventional therapy and suffering asthma exacerbations despite the use of high-dose ICSs or oral steroids.

Allergen Immunotherapy

Allergen-specific immunotherapy to common allergen sources such as pollens and house dust mites is the practice of administering gradual quantities of an allergen extract to a patient to ameliorate symptoms from subsequent exposures. Clinical evidence suggests that immunotherapy is effective to treat seasonal or perennial allergic rhinitis as well as asthma. This modality should be considered when conventional pharmacotherapy is not able to control asthma symptoms in an atopic individual or medication side effects prove to be intolerable. It has been

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shown to reduce symptoms, medication needs, and to improve overall asthma control, often without concomitant changes in lung function.

Antifungal Therapy

Airborne exposure to fungi is a common phenomenon worldwide. Fungal sensitization is seen in some asthmatics and can greatly affect the course of their disease. Caused by sensitization to *Aspergillus fumigatus*, the syndrome of allergic bronchopulmonary aspergillosis (ABPA), or allergic bronchopulmonary mycosis (ABPM) if it is caused by another mycosis, is associated with severe difficult-to-treat asthma.

Diet and Asthma

Recommendations to increase the consumption of fruits, vegetables, grains, and legumes, while decreasing saturated fat and dairy intake, might reduce the risk of asthma development and exacerbations. High fat intake and low fiber intake have been associated with airway inflammation and worsened lung function in asthmatic patients, while high consumption of fruits and vegetables has been found to be associated with a reduced risk of developing asthma.

While there is an epidemiological association between low serum levels of vitamin D and the development of asthma, asthma severity, and recurrent exacerbations, prospective clinical trials do not support that improving the vitamin D status of asthmatic children improves asthma control. There is an association between obesity and risk for the development of asthma in adults and children. There is also evidence that asthma might contribute to the onset of obesity, especially in those who have required systemic corticosteroids. Children with obesity who have asthma have greater severity and poorer control of their asthma symptoms. Weight loss has been shown to improve asthma control and overall quality of life.

TREATMENT PROTOCOLS FOR ASTHMA

Treatment protocols use a step-care pharmacologic approach based on the intensity of the asthma symptoms over time. As symptoms and lung function worsen, step-up or add-on therapy is given based on the clinical findings **(Fig. 1)**. As symptoms improve, therapy can be stepped down until a long-term maintenance program is established.

Lung function was often used as the primary endpoint, but because of the poor correlation between lung function, patient symptoms, and overall outcomes, a composite of measures was suggested by international asthma guidelines. The asthma severity scale reflects the intensity of the disease and can be used when a patient is not receiving long-term control therapy. The components of impairment include daily symptoms more than twice a week, any nighttime awakenings, need of quick relief rescue therapy more than two times a week, and asthma interference with normal daily activities. Validated assessment tools such as the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) are helpful to monitor and control asthma objectively for the clinician.

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When the patient's asthma is either partly or poorly controlled or the FEV_1 is <80% of predicted, regular treatment with anti-inflammatory therapy is recommended and the patient is considered to have "persistent" asthma. There are a number of causes of uncontrolled asthma **(Fig. 2)**. The response to therapy, which is defined as how the manifestations of asthma have been reduced or eliminated, is referred to as the degree of asthma control. Asthma control has another component which is the reduction in the risk of future adverse events including exacerbations, loss of lung function, and side effects of the medical therapy. The presence of high eosinophil counts (>300 cells/μL) and a high fractional exhaled nitric oxide (FeNO) should be recognized as risk factors for the development of future exacerbations.

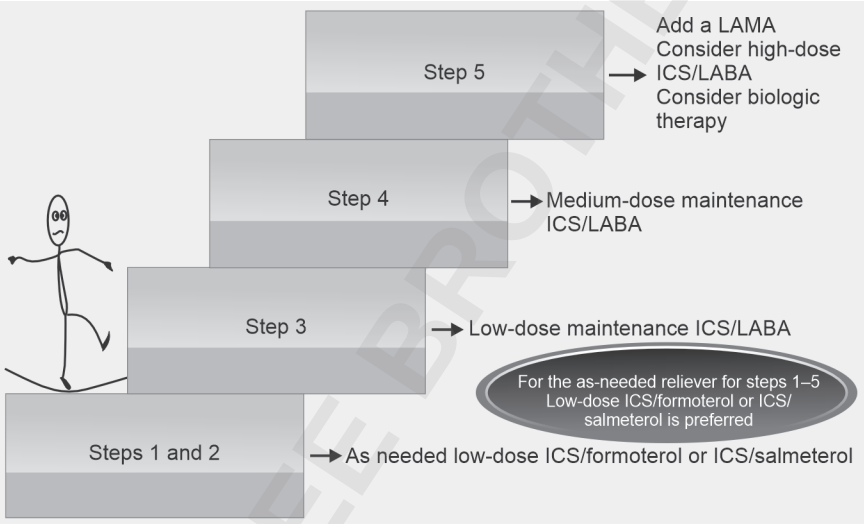

FIG. 1: Preferred treatment step-up care for adults and teenagers.
(ICS: inhaled corticosteroid; LABA: long-acting beta agonist)
Source: Adapted from GINA Guidelines (2023).

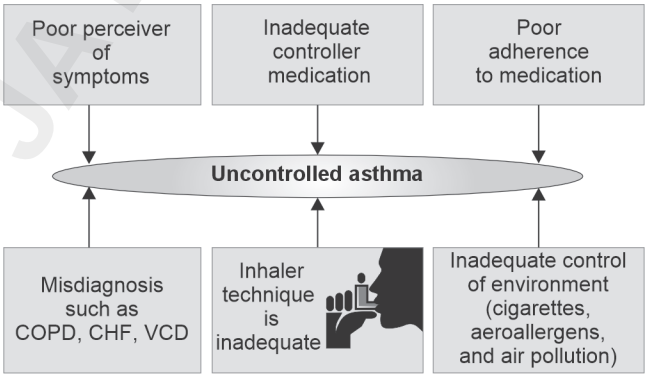

FIG. 2: Common causes of uncontrolled asthma.
(CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; VCD: vocal cord dysfunction)

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At each visit, the patient should be assessed for the level of asthma control, adherence to the recommended treatment, and for potential side effects from the drugs used. Step-up therapy is advised for patients not well controlled according to guideline recommendations. There are no hard and fast rules on stepping down asthma care, but at least 3 months of stability is recommended before a reduction in medication is attempted. The lowest dose of medication to maintain stability should be offered at all points. At each step, reliever medication with a SABA or SMART treatment is used for breakthrough symptoms, but increased use implies poor control and the need for additional measures.

CONCLUSION

A step-up approach has been advocated beginning with newer recommendations for combined MART using a LABA plus corticosteroid for infrequent symptoms or if available, a single inhaler SABA ICS. Persistent symptoms require continuous ICSs as first-line therapy. Monitoring with objective measures of disease activity, including pulmonary function tests and symptom questionnaires, has been advised and patient education programs can lead to self-reliance, better adherence to therapy, and improved outcomes.

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Handbook of Pulmonary & Critical Care Medicine

Salient Features

- The "*Handbook of Pulmonary and Critical Care Medicine*" is an abbreviated version of the two-volume Textbook of Pulmonary and Critical Care Medicine (3rd edition) by the same authors. For the purpose of the brevity, some of the finer details and reference citations from the larger version have been excluded without the loss of the essential clinical components.
- The handbook includes basic up-to-date information on core pulmonary diseases, critical care medicine, and sleep medicine among several other important topics.
- It includes chapters by over 100 expert authors from different parts of India and other countries.
- It provides easy-to-read important information on primary diseases of the lungs and pulmonary manifestations of systemic illnesses. It serves as a quick referral book for pulmonologists and students of sister-specialties.

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