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Asthma, a Comprehensive Clinical Review

Andrew Weinstein, MD

INTRODUCTION

It has been estimated that globally 300 million people have asthma.[1] In the United States approximately 24 million individuals have asthma.[2] This is 7.4 percent of adults and 8.6 percent of children. Asthma has been increasing since the early 1980s in all age, sex and racial groups.[3] Asthma causes almost 2 million emergency room visits each year.[4] Each year, asthma causes more than 14 million doctor visits and 439,000 hospital stays.[5] In 2014, 3,651 people died from asthma. Many of these deaths are avoidable with proper treatment and care.[5] The annual cost of asthma in the U.S is about $56 billion.[6] Direct costs were nearly $50.1 billion. Hospital stays were the largest part of these costs. Indirect costs, like lost pay from illness or death, were $5.9 billion.[7] Ethnic differences in asthma frequency, illness and death are highly connected with poverty, city air quality, indoor allergens, not enough patient education and poor health care.[6] African American children have recently seen the greatest rise in asthma. Sixteen percent of African American children have asthma. Eight percent of white children have asthma.[4] Women are more likely to have asthma than men.[6] In 2011, 8 million women had an asthma attack. Only 5.1 million men had asthma attacks.[4] Women have almost 65% of asthma deaths overall.[7] Children have the greatest incidence of asthma. An average of 1 out of every 10 school-aged children have asthma.[6] Asthma is the third-leading cause of hospital stays in children.[6]

DEFINITION

The sources of information that clinicians in specialist settings use to diagnose asthma are: a history of the characteristic symptoms such as cough, particularly when awakened at night; wheeze, breathlessness (particularly in young children), and objective evidence of a spontaneously variable or reversible airflow obstruction measured using spirometry; a bronchoconstrictor response to histamine, methacholine, or mannitol; or daily or diurnal variability in peak expiratory flow rates. In primary care, the symptoms of wheeze and cough are often used to determine whether a patient has suspected asthma, and a recording of clinician-diagnosed asthma is made if a patient responds to a bronchodilator (airways reversibility) or an inhaled corticosteroid.[8]

ASTHMA PHENOTYPES

As yet, there is no universally agreed upon asthma phenotype.[9] The currently recognized phenotypes include early-onset, preadolescence asthma, which is mostly allergic in nature and driven by T-helper type 2 (Th2) processes. The later-onset eosinophilic phenotype is more common in women and adults older than 20 years and is pathologically associated with a thickening of the basement membrane zone and characterized by the presence of eosinophilia as determined by sputum, bronchoscopy, or blood analysis.

Other phenotypes include: (1) exercise-induced asthma, a non-Th2 asthma where reactive bronchoconstriction occurs in response to sustained exercise, often found in individuals with mild asthma; (2) obesity-related asthma; and (3) neutrophilic asthma, in which neutrophils are

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prominent in airway secretions during acute, severe asthma exacerbations and patients are relatively corticosteroid resistant.[10]

Other asthma phenotypes include aspirin intolerance, asthma related to chronic or persistent respiratory infections and steroid-resistant asthma, which has several subtypes and is thought to be characterized by the genetic background of the individual.[11] The key clinical features of asthma include:

1. Variable airway obstruction. Airway obstruction in asthma, as measured by spirometry, may vary spontaneously from none to severe in the course of minutes to hours, and improves after suitable therapy. Breathlessness, impaired exercise tolerance and a feeling of tightness of the chest, which may be perceived as wheeze.
2. Nonspecific bronchial hyper reactivity. Nonspecific bronchial hyper reactivity refers to the tendency of the smooth muscle cells of asthmatic airways to constrict in response to a very wide variety of nonspecific (i.e., nonimmunological) environmental as well as pharmacological stimuli (including, for example, cold air, smoke, exercise, aerosol sprays, and dust) that do not cause clinically significant bronchoconstriction in nonasthmatics. The mechanism of this remarkable phenomenon remains obscure. It is further exacerbated by excessive mucus production and edema of the airway mucosa, both of which further narrow the internal airway lumen, increasing the degree of obstruction produced by a given degree of smooth muscle constriction.[12]

HISTOPATHOLOGY

Asthma is invariably characterized by inflammatory changes throughout the submucosa of the airways, but not the alveoli or the lung parenchyma. This has naturally led to the assumption that this inflammation is primarily responsible for the clinical features of the disease, although the evidence to support this assertion remains largely circumstantial.[12,13]

Immunopathogenesis

The first principal characteristic of asthmatic inflammation is mucosal infiltration with inflammatory cells, particularly mononuclear cells (macrophages and cluster of differentiation 4 [CD4+] T lymphocytes) and granulocytes (eosinophils and neutrophils).

Some severe asthmatics appear, in addition, to have elevated numbers of mucosal mast cells, but this is not universal.[14]

The second principal characteristic of asthmatic airway inflammation is the variable presence of structural changes in the airways, collectively termed remodeling.[15] These include hypertrophy and hyperplasia of the airway smooth muscle cells, increased numbers of mucous goblet cells in the airway epithelium, deposition of extracellular matrix proteins (including collagen, fibronectin, and tenascin) beneath the epithelial basement membrane and in the submucosa, and neovascularization resulting in a proliferation of the vascular capillary beds within the submucosa. Some of these changes are not specific for asthma; for example, many chronic inflammatory processes involving the bronchial mucosa (asthma, COPD, bronchiectasis) are associated with mucous hypertrophy. Smooth muscle hypertrophy, hyperplasia and extracellular matrix protein deposited within the mucosa of the airways appear to be more asthma specific.[16]

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Despite these observations, there are still many doubts about the cause and effect relationship between inflammation and remodeling largely because it is so difficult to characterize the natural progression of these two phenomena. Role of Immunoglobulin (IgE)-Mediated Mechanisms IgE-mediated mechanisms, and in particular the IgE- mediated degranulation of mast cells and basophils by cross-linking surface-bound, allergen-specific IgE leading to the release of histamine and other mediators, have been traditionally considered the central contributing factor.[16]

Role of Leukotrienes

More recently, T-helper type 2 (th2) T lymphocytes and associated inflammatory pathway involvement of CD4+ Th2 T lymphocytes with their capacity to secrete a wide variety of cytokines and chemokines, have also risen to prominence.[17]

They are not only able to promulgate the inflammatory granulocyte infiltrate which characterizes asthma, including mast cell, eosinophilic and basophilic inflammation, but also B cell switching to IgE synthesis and a range of asthma-associated remodeling changes in the airway mucosa.[16] Many, but not all of the key cytokines implicated so far in the pathophysiology of asthma include those encoded in the IL-4 cluster on chromosome 5q31: IL-3, IL-4, IL- 5, IL-9, IL-13, and granulocyte/macrophage colony- stimulating factor (GM-CSF).[16] The role of leukotriene IL-5 in the pathogenesis of asthma with eosinophilia has been confirmed with treatment by mepolizumab.[18] This agent blunts eosinophil-related inflammation and improves severe asthma with high eosinophilia refractory to oral glucocorticoid steroids.

Genetics and Asthma

Since the beginning of genome-wide studies in asthma, several genes/chromosomal regions have been consistently associated with asthma susceptibility in multiple ethnic groups: ORMDL3/GSDMB, IL- 33, IL-1RL1, RAD50/IL-13, HLA-DR/DQ, TSLP, and SMAD3.19, 20 In most cases, the effect of each individual genetic variant is relatively small, suggesting that the additive effect of multiple risk variants should be evaluated.

GUIDELINES

Following a review of 59 evaluations that met rigorous scientific criteria, Grimshaw and Russell concluded that almost all of the guidelines on various conditions including asthma were associated with an improvement in medical practice, while the size of the improvements in performance varied from one intervention to another.[19] Wide variations have been observed in the translation of current guidelines into care, particularly primary care, and various care gaps persist.[20] The translation of recommendations into care by practitioners is influenced by their level of knowledge and their attitudes, skills, beliefs, and values.[21] Content of current asthma guidelines is voluminous and is beyond the scope of this chapter. We will stress some general principles and commonalities of the current guidelines.

Environmental Triggers/Control Causing Asthma Exacerbation

Allergy sensitivity can be diagnosed by prick skin tests and serum-specific IgE tests.

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Pollen and Mold

Detailed descriptions of the complexities involved in pollen and mold species are beyond the scope of this chapter. However, pollen and mold spore exposures can trigger asthma exacerbations or worsen the symptoms in sensitized individuals. In most parts of the United States, trees pollinate in the spring, grass pollinates from late spring to early summer, and weeds pollinate in late summer through fall.[22] Fungal spores are responsible for both seasonal and perennial allergy symptoms.[23] Outdoor spores peak in mid- summer and diminish with the first hard frost in regions that experience cold winter seasons. Dry-air spores, including Alternaria, Cladosporium, and Epicoccum, peak in the afternoon hours under low humidity.

Wet-air spores peak during the predawn hours with high humidity and include ascospores and basidiospores (mushrooms, puffballs). Alternaria is the most prevalent mold in dry, warm climates

Dust mite, pets, cockroaches

Dust mite exposure leads to sensitization and asthma.[24] There are several approaches to house-dust mite remediation and experts agree that a comprehensive strategy is best. This would include the use of dust mite encasings for mattresses and pillows,[10] washing linens weekly in hot water greater than 130°F, the removal of carpeting especially in the bedroom, keeping humidity levels in the home to less than 50%, and using a high-efficiency particulate air (HEPA) filter vacuum on a weekly basis.

Exposure to cockroach may lead to sensitization and asthma.[25] It is important to perform a careful inspection to detect insect hiding places and travel routes, and to identify food sources (grease, cooking debris). Remove sources of food and household food wastes (do not keep garbage cans inside, avoid exposed pet food and snack food containers). Apply insecticides using gels or baits, in selected areas including the kitchen.

Pets: Exposure to dog, cat mouse and other pets leads to sensitization and asthma.[26]

While the best way to eliminate a pet allergen is to remove the pet from the home, this is often difficult for families. If the pet remains, it is generally recommended to remove the pet from the bedroom and confine it to one area of the home as much as possible. Other effective strategies include the removal of all carpeting, the use of allergen-proof encasings for mattresses and pillows, and the use of HEPA filters.

Environmental Pollutants

Epidemiological evidence from the last two decades has shown that environmental pollutants such as ozone, particulate matter, diesel exhaust, and biological/microbial agents contribute significantly to the morbidity associated with asthma, including increasing exacerbation frequency.[27] More recently, some pollutants, such as ozone, are now being implicated as causal agents in the development of new-onset asthma. Moreover, studies have now focused on certain exposure locations, such as living near busy roadways or high traffic areas, as places of particularly high risk to suffer the deleterious effects of air pollution.[28] Public health measures need to be implemented to reduce these environmental pollution exposures.

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Viral Triggers

Respiratory viruses cause asthma exacerbations and are associated with an increased risk of developing asthma. Common respiratory viruses such as HRV and RSV are most frequently implicated, but many additional respiratory viruses have recently been identified using newer molecular virus detection methods.[29] Exercise-Induced Bronchoconstriction EIB is defined as a transient narrowing of the lower airway with an associated increase in airway resistance, during or following exercise.[30] There are two forms of EIB: EIB in patients who do not have evidence of chronic asthma (called EIB alone); and EIB in patients who also have chronic asthma (called EIB with asthma). The more common condition, EIB with asthma, is seen in as many as 90% of asthmatic patients.[1–3] The more severe the EIB is, the more poorly controlled the chronic asthma will be.[31] A history of respiratory symptoms alone, during or following exercise, is not reliable for the diagnosis of EIB. EIB is identified by establishing objective evidence for a fall in post exercise FEV1 of at least 10% from its pre-exercise value, after 8 min of strenuous aerobic exercise.[30]

Treatment for EIB

Beta-agonists, either inhaled short-acting beta-agonists (SABAs) or long-acting beta-agonists (LABAs) can be administered 15–30 min prior to exercise on an intermit- tent basis in the majority of individuals.[32] Anticholinergic agents, such as ipratropium bromide, have been inconsistent in attenuating EIB; Leukotriene receptor antagonists (LTRAs) such as montelukast and zafirlukast and 5-lipoxygenase inhibitors such as zileuton provide approximately 60% protection against EIB.

Rhinitis and Asthma

Rhinitis and asthma frequently occur as comorbid conditions in adults and children as manifestations of the same inflammatory disease continuum. Rhinitis is a predictor of future asthma. It impacts negatively on asthma, leading to more severe disease, worse asthma control, and impaired quality of life, despite adherence to asthma treatment. Good treatment of rhinitis is likely to improve asthma control and outcomes.[33] Patients with asthma and rhinitis should be treated for both conditions. Relevant allergens and triggers should be sought and excluded. The combination of intranasal and inhaled corticosteroids for persistent rhinitis and asthma should be considered, with the addition of other drugs including anti- histamines, cromones, and LTRAs as appropriate.[34]

PHARMACOTHERAPY

The following is a summary of the individual asthma therapies.

Short-acting beta2-adrenergic agonists (SABAs)

Beta2-agonists stimulate beta-adrenergic receptors and increase cyclic adenosine monophosphate (CAMP), causing a relaxation of the airway smooth muscles and thus reversing bronchoconstriction.[35] Albuterol, salbutamol, levalbuterol, and pirbuterol are all drugs of choice for the immediate relief of symptoms. SABAs should only be used as rescue medications and not continuously for disease control. Higher frequency usage is a warning sign for loss of disease control and an increased risk for an exacerbation.

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Long-acting beta2-adrenergic agonists (LABAs)

LABAs have an increased lipophilic nature and thus have prolonged retention in the lung tissue with a duration of action of up to 12 h.[36] Salmeterol has a slower onset of action than formoterol, which some studies support using as a rescue inhaler when combined with ICS. Side effects include tachycardia, a prolonged QTC interval, and hypokalemia. LABAs should not be used as monotherapy, and when used with ICS there is an improvement in both the impairment and risk domains.[37]

Corticosteroids

Corticosteroids have multiple mechanisms of action: suppressing cytokine release, decreasing the recruitment of air- way eosinophils, and inhibiting the release of inflammatory mediators. They help diminish airway hyper responsiveness and decrease lung inflammation.[38]

Corticosteroids can be administered via different routes: inhaled, oral, intramuscular, or intravenous. Inhaled corticosteroids are the mainstay of asthma therapy and may be combined with LABAs for patients with more severe asthma (they generally improve lung function and airway responsiveness, reduce and prevent asthma symptoms, and prevent exacerbations).[39]

Oral candidiasis and dysphonia can be controlled by washing the mouth after each use and by using a spacer.[40] Severe and difficult-to-control asthma warrants the possibility of using oral corticosteroids for long-term symptom control but side effects must be considered. Systemic side effects, seen more commonly with the prolonged use of oral corticosteroids, include Cushingoid features associated with adrenal gland suppression, hypertension, uncontrolled blood sugars, cataracts, a fatty liver, and proximal muscle weakness.[40]

Leukotriene Modifiers

Montelukast and zafirlukast block the effects of the CysLT1 receptor (approved for use in childhood asthma) and zileuton inhibits the 5-lipoxygenase pathway. The use of zileuton requires close monitoring of liver function tests. Leukotriene modifiers can be used in mild persistent asthma as a mono- therapy and in addition to ICS for more severe disease.[41] Certain phenotypes show a better response, including patients with a smoking history, obesity, aspirin-exacerbated disease, and ICS insensitivity.

Methylxanthines

Sustained-release theophylline is a mild to moderate bronchodilator that can be used for mild asthma or in addition to ICS in more severe disease. It is essential to monitor the serum levels of theophylline because of its narrow therapeutic range and side effects, including arrhythmias and seizures.[42] Theophylline levels between 8 and 13 μg/mL are considered therapeutically effective and safe.

Omalizumab

Omalizumab is a recombinant IgG humanized monoclonal antibody to the FC3 portion of the IgE antibody. It decreases the binding of IgE to the surface of mast cells, leading to a decrease in the release of mediators, in response to exposure to any allergen. It is recommended as an adjunctive therapy for patients with perennial allergies and those who have moderate to severe persistent asthma. There is a small but significant improvement in lung function (approximately

6%), a decrease in the number of exacerbations, and in the capacity to decrease the dose of oral corticosteroids.[43]

Anticholinergic agents

Ipratropium bromide inhibits muscarinic cholinergic receptors and reduces the intrinsic vagal tone of airways. This is a quick-relief medication used either as an additive to SABA or as an alternative to SABA in patients who cannot tolerate SABAs. Recently, long- acting muscarinic antagonists (tiotropium) have shown benefits equivalent to LABAs in patients on ICS.[17,18] The addition of tiotropium to a combination therapy with ICS plus LABA has shown improved FEV1 values.[44]

Cromolyn Sodium and Nedocromil

Here, the mechanism of action is through blocking chloride channels and modulating the release of mast cell mediators and eosinophil recruitment. Both agents inhibit broncho- spasm caused by exercise or cold air and prophylactically prevent allergen-induced asthma worsening. Their safety profile is very good and they can be used as a maintenance therapy especially in childhood asthma.[45] However, they are no longer available in the United States.

Allergy Immunotherapy

Both subcutaneous and sublingual immunotherapy have been shown to decrease asthma-related symptoms and improve lung function and bronchial hyper-reactivity.

However, anaphylactic reactions (primarily in subcutaneous immunotherapy) can occur and therefore immunotherapy should only be used in patients whose asthma is controlled and who have an FEV1 of >70% predicted normal. Studies in children have shown a decrease in the incidence of asthma exacerbations with immunotherapy and the ability to prevent new sensitizations and the progression to newly diagnosed asthma in patients with allergic rhinitis.[46]

Bronchial Thermoplasty

A novel approach to treating severe asthma is through bronchial thermoplasty, which involves a bronchoscopy and administering thermal energy to the airways. It is believed to work by reducing the airway smooth muscle mass. While there has been no decrease in airway hyper-responsiveness or an improvement in FEV1, there has been a significant improvement in patients' quality of life.[47]

EMERGENCY MANAGEMENT

A severe attack may be suggested by the patient's difficulty in completing sentences and diaphoresis. Respiratory distress at rest can present with using the accessory muscles of respiration, an increased respiratory rate of >28, tachycardia, and alternating abdominal and ribcage breathing. Indications for admission include: FEV1 of 30% of predicted values; Arterial blood gas PaO2<60 mmHG; increasing PaCO2 secondary to fatigue. Management consists of intensive bronchodilator therapy, oxygen, and systemic corticosteroids. Even though there are several complications associated with mechanical ventilation, such as barotrauma, hypotension, and infections, it can be lifesaving in patients with severe exacerbations. Identifying the

precipitating cause of the exacerbation is the next step after stabilizing the patient, in order to dictate the most appropriate immediate and prophylactic therapies.[48]

Inhaler Devices

Pressure MDI (pMDI), Dry powder (DPI), Breath activated (BA pMDI), and Soft mist (SMI).

pMDI is a portable multi-dose device that utilizes a propellant under pressure to generate a metered dose of an aerosol through an atomization nozzle. CFC propellants have, in most cases, been replaced by hydrofluoroalkane (HFA) propellants that do not have ozone- depleting properties. Despite numerous advantages of pMDIs, many patients have difficulty coordinating actuation with inhalation.[49] Spacers can assist the patient to inhale without coordination concerns. Breath-activated MDIs and Dry Powder MDIs overcome coordination issues. Dry Powder MDIs require patients to inhale quickly and forcefully.

Dry Powder Inhalers

Generally, DPIs have many advantages over pMDIs. DPIs are actuated and driven by the patient's inspiratory flow; consequently, DPIs do not require propellants to generate the aerosol, removing the need to coordinate inhaler actuation with inhalation. However, a forceful and deep inhalation through the DPI is needed to de- aggregate the powder formulation into respirable-sized particles as efficiently as possible and, consequently, to ensure that the drug is delivered to the lungs.[50] Soft Mist MDI use liquid formulations similar to those in nebulizers, but they are generally multidose devices. Individual doses are delivered via a precisely engineered nozzle system as a slow-moving aerosol cloud (hence the term soft mist).[51]

ASTHMA EDUCATION

There is unequivocal evidence to support asthma self-management education and its ability to improve the morbidity of this disease in both children and adults; as such, asthma self-management education is fundamental to optimal asthma management.[52] Self- management support is defined as "the systematic provision of education and supportive interventions by health care staff to increase patients' skills and confidence in man- aging their health problems, including regular assessment of progress and problems, goal setting, and problem-solving support. Self- management is defined as the tasks that individuals must undertake to live well with one or more chronic conditions. These tasks include having the confidence to deal with medical management, role management, and emotional management of their conditions."[53]

The most effective programs include the transfer of information, skills training, regular medical follow-up, the delivery of written asthma action plans (WAAPs), and regular monitoring of symptoms or lung function by the patient. These are achieved through effective therapeutic patient–clinician partnerships using a person- centered approach. Adequate skill in the use of inhaler devices is integral to achieving good asthma outcomes.[54]

Self-Monitoring

Self-monitoring is the regular self-recording of symptoms and/or peak expiratory flow (PEF) measurements that patients perform in their home and work or school environment. WAAPs are developed by a medical practitioner or an accredited nurse practitioner to provide patients with

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written instructions, either in the form of text or as pictorial information, about their maintenance treatment and instructions for the escalation of treatment during both moderate and severe asthma exacerbations.[54]

ADHERENCE

It is well known that adherence in chronic disease can be poor, and this is particularly true in chronic respiratory conditions. In a meta-analysis of 569 studies, adherence to therapy in respiratory diseases ranked poorly, with a mean adherence rate of 68.8%, which was fifteenth out of seventeen different diseases.[55]

A prospective study of asthma found that 24% of severe exacerbations were attributable to nonadherence.[56] There are two distinct patterns of behavior associated with non-adherence, which are referred to as intentional and unintentional nonadherence.[57] Understanding the behavior pattern of non-adherence in individuals will guide their education and help develop adherence-aiding strategies.[58]

Intentional non-adherence occurs when patients make purposeful decisions to take and perform treatments in a way other than that prescribed. This often refers to the self-adjustment or titration of treatment according to the patient's symptoms or beliefs, or the cessation of treatment earlier than prescribed.[57] Intentional non-adherence usually results when the patient weighs the risks against the benefits of taking medication and makes a decision based on his or her reasoning. While intentional non-adherence may result from a balance of reasoning, the decision could result from poor knowledge about the treatment, or an erroneous understanding regarding the nature or consequence of the problem, the prescribed therapy, and the potential benefit of treatment. Therefore, this form of non- adherence can often be addressed through strategies that improve patients' knowledge and influence their health beliefs and concerns.[58]

Unintentional non-adherence occurs when patients do not adhere to treatment advice due to reasons out of their control.[57] These are often related to cognitive impairments, language barriers, and physical disabilities. In the case of an older person with asthma, this could relate to impaired vision or musculoskeletal problems affecting his or her ability to use inhaled medications.

Further unintentional non-adherence could also result from ineffective communication or inaccurate recollection of the prescribed treatment prescription.[58]

Studies of how well patients retain health information suggest that less than 50% of the information conveyed by the physician is recalled immediately after an office visit.[57] Recognizing non-adherence, establishing the reasons for non-adherence, and working with patients to improve their adherence are essential elements of asthma education.[59]

Monitoring of Asthma

Often, asthma control is poorly assessed, which can lead to under treatment and an increased risk of severe events. This is often due to the poor use of control criteria and objective measures that assess airflow obstruction. Spirometry should be regularly measured, ideally at each visit and at least once a year.[60] If spirometry is not available, PEF measurements with devices such as the Mini-Wright peak flow meter should be utilized. Measures of airway inflammation (i.e., induced sputum and exhaled nitric oxide) have been pro- posed, particularly for moderate to severe asthma, to titrate the treatment, and these measures have resulted in the reduction of exacerbations.[61,62]

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Management of Exacerbations: The Asthma Action Plan Since the late 1980s, consensus reports recognize that asthma is a chronic disease whose seriousness can fluctuate on a daily basis and that asthmatics should know how to modify their treatment accordingly.

Written action plans are recommended for all asthmatic patients, indicating when and how to intensify their anti-inflammatory therapy according to asthma control criteria, when to introduce oral corticosteroids, and when to seek medical advice. Action plans based on symptoms are as effective as those that are based on PEF monitoring. Although much remains to be evaluated in regard to the optimal action plan, the most important strategies to include in action plans have recently been formally evaluated.[63] Clinicians may need to consider other factors that may aggravate asthma include rhinosinusitis[64]; obesity[65]; gastroesophageal reflux[66]; or other associated respiratory conditions such as smoking-induced COPD[67] and obstructive sleep apnea.[68]

Diagnosis of asthma in preschool age children

The diagnosis of asthma in childhood is primarily based on the frequency, quality, variability, and severity of the symptoms in addition to a family history and other allergic comorbidities (see Figure 1). The Asthma Predictive Index (API) was developed uses a combination of clinical and easily available laboratory data to help identify preschool-age children at risk for developing persistent asthma.[7] The index requires recurrent wheezing in the first 3 years, plus one major (parental history of asthma or physician-diagnosed atopic dermatitis) or two of three minor (eosinophilia [2:4%], wheezing unrelated to a viral URI, and/or allergic rhinitis) risk factors. Children with a positive API were up to10 times more likely to have active asthma at some time during grade school compared with those with a negative API. In addition, both the negative predictive value and the specificity for the API were greater than 80%, indicating that the vast majority of preschool-age children with recurrent wheeze and a negative API will not have asthma at school age.[69]

The response to therapy can be especially helpful in younger children where pulmonary function testing may not be feasible. The differential diagnosis of recurrent wheezing is large especially in younger children and testing to rule out other conditions should be performed in a thoughtful manner.[70]

Figure 1. Classifying Asthma Severity and Initiating Treatment in Children 0-4 and 5-11 Years of Age

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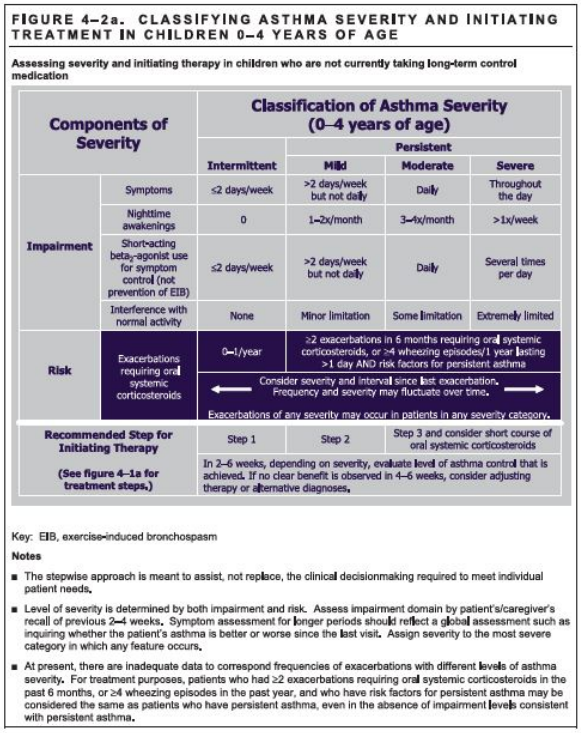

FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. →			
		Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy (See figure 4–1a for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

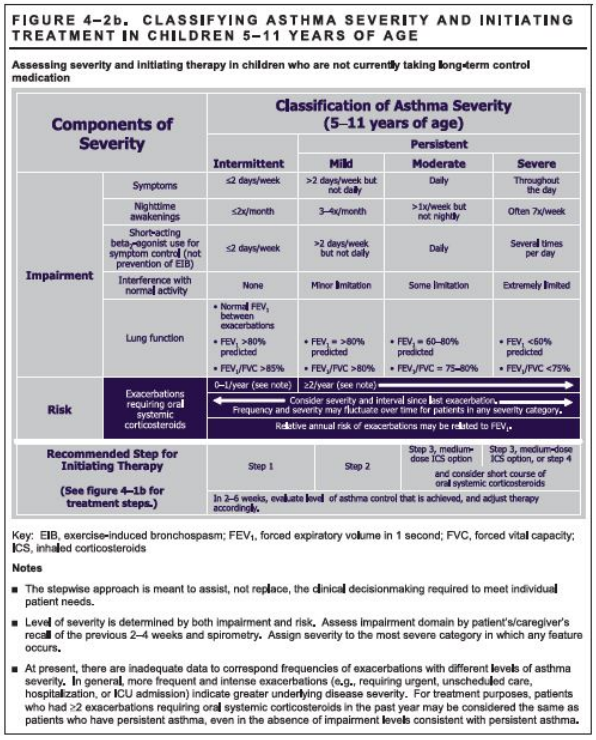

FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy (See figure 4–1b for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Diagnosis of Asthma in Older Children and Adults

The diagnosis of asthma in older children and adults is made by the presence of symptoms consistent with asthma and the demonstration of variable airflow obstruction. The presence of the characteristic symptoms alone is not sufficient for an accurate diagnosis, as these are not specific for asthma. Variable airflow obstruction is usually documented by demonstrating changes in spirometry, particularly FEV1 and VC, and the ratio of these numbers. The currently accepted definition of an improvement in FEV1 that is consistent with asthma is >12% and >200 mL.[71]

In some instances, however, an improvement in FEV1 is only demonstrated after a more prolonged period of treatment with inhaled or oral corticosteroids (as in the case presentation). In patients with mild asthma, or those on an effective treatment, spirometry can be normal. In these situations, measurements of PEF over several weeks, or the documentation of airway bronchoconstriction after exercise or inhaled mannitol, can establish the diagnosis.

Making the diagnosis of asthma can be challenging in patients who cannot reproducibly perform spirometry, and in adults with a smoking history and in whom there is fixed airflow obstruction (not reversible even after optimal treatment has been administered for a period of time) (see Figure 2). The presence of fixed airflow obstruction suggests a diagnosis of COPD, but this should be confirmed with ancillary testing such as lung diffusion capacity. See table for differential diagnosis for asthma.[72]

Figure 2. Classifying Asthma Severity and Initiating Treatment in Youths ≥ 12 Years of Age and Adults

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FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

— Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

—

Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Assessing and Monitoring Asthma Severity, Control, and Responsiveness in Managing Asthma

Asthma control is defined as the extent to which the effects of the disease are reduced or removed by treatment. Since the disease is inherently variable over time, an assessment of asthma control should address both the current state of a person's asthma as well as accounting for the risk of problems in the future. Hence, the terms current control and future risk have been advocated.[73,74]

Future risk refers to the risk of adverse outcomes in the future, including exacerbations, the risk of accelerated lung function decline, or even the risk of side effects from medications. Poorly controlled asthma is a known risk factor for future exacerbations. In particular, nighttime symptoms and more frequent short-acting beta-agonist (SABA) use are strongly associated with an increased risk for a future exacerbation.

The current emphasis on asthma control in clinical management differs from the earlier emphasis on asthma severity. Asthma severity was previously defined in terms of its clinical features before any treatment; this was thought to reflect the intrinsic qualities of the disease.[74] However, this definition was impractical once patients started regular treatment.

To appreciate the importance of assessing asthma control one must understand the impact of asthma on the patient; to predict the risk of future adverse outcomes; to guide treatment and monitor treatment response; and to facilitate patient–doctor communication about asthma

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management. The impact on quality of life may include: missed work or school from asthma; reduction in usual activities; disturbance of sleep.[75] Instruments that measure asthma control include: Asthma Control Questionnaire[76] and the Asthma Control Test.[77]

The concepts of severity and control are used as follows for managing asthma[78]:

- During a patient's initial presentation, if the patient is not currently taking long-term control medication, asthma severity is assessed to guide clinical decisions on the appropriate medication and other therapeutic interventions.
- Once therapy is initiated, the emphasis thereafter for clinical management is changed to the assessment of asthma control. The level of asthma control will guide decisions either to maintain or adjust therapy.
- For population-based evaluations, clinical research, or subsequent characterization of the patient's overall severity, asthma severity can be inferred after optimal therapy is established by correlating levels of severity with the lowest level of treatment required to maintain control. For clinical management, however, the emphasis is on assessing asthma severity for initiating therapy and assessing control for monitoring and adjusting therapy.

NHLBI Expert Panel Report 3 has determined guidelines for the management of asthma in different age categories. These are provided in Figure 3 through 6. These include a step-wise approach to manage; classify severity and initiating treatment; assessing control and adjusting therapy.[78]

Figure 3. Stepwise Approach for Managing Asthma in Children 5-11 Years of Age.

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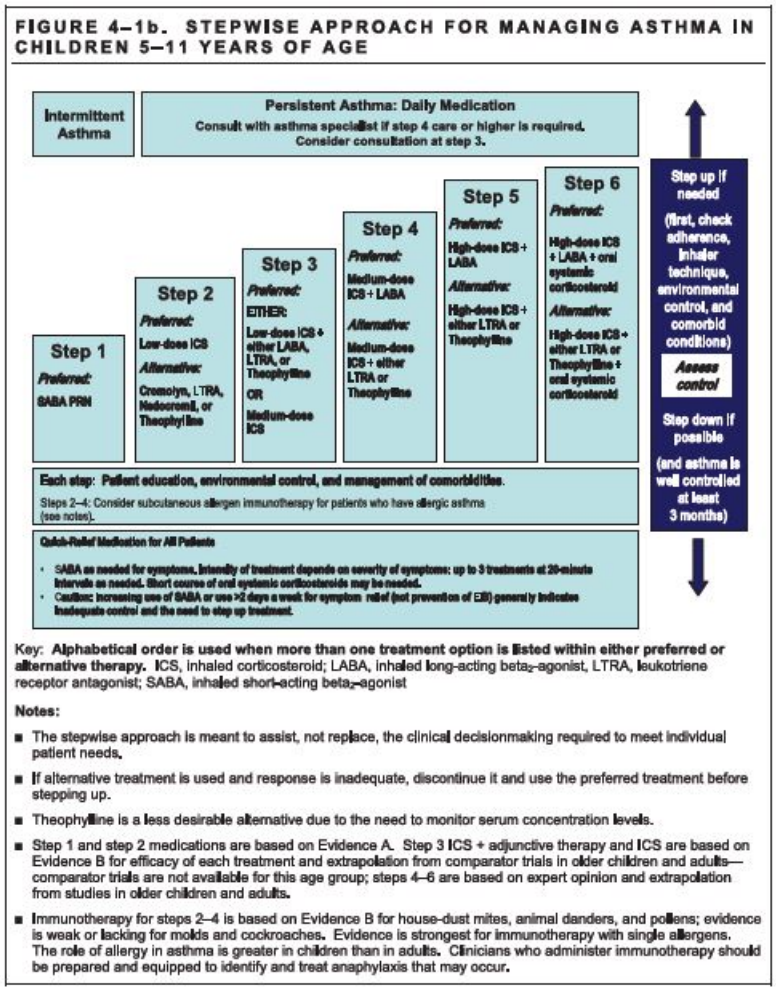

Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

Figure 4. Assessing Asthma Control and Adjusting Therapy in Children 0-4 and 5-11 Years of Age.

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FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE

Components of Control		Classification of Asthma Control (0–4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1a for treatment steps.)		• Maintain current treatment. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up (1 step) and • Reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, and environmental control.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function • FEV_1 or peak flow • FEV_1/FVC	 >80% predicted/ personal best >80%	 60–80% predicted/ personal best 75–80%	 <60% predicted/ personal best <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	>2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1b for treatment steps.)		• Maintain current step. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects: consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

Figure 5. Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults

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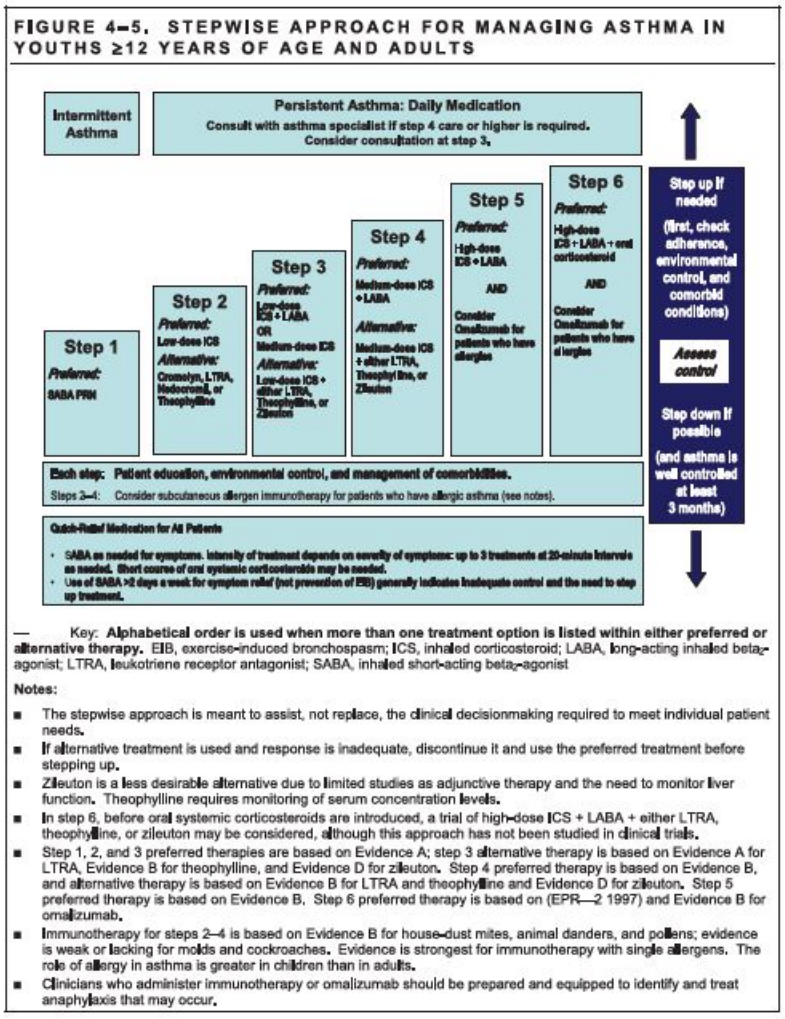

— Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

Figure 6. Assessing Asthma Control and Adjusting Therapy in Youths ≥ 12 Years of Age and Adults

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FIGURE 4–7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16–19	≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see figure 4–5 for treatment steps)		• Maintain current step. • Regular followups every 2–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.
Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Validated Questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain)
  - ATAQ = Asthma Therapy Assessment Questionnaire© (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
  - ACQ = Asthma Control Questionnaire© (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
  - ACT = Asthma Control Test™ (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
  - Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.
- Before step up in therapy:
  - Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
  - If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

REFERRAL FOR SPECIALIST INVESTIGATIONS

The majority of patients with asthma have mild to moderate disease and can be managed in primary care. However, some patients benefit from referral to a respiratory specialist for assessment and management. Specifically, patients should be referred if they experience recurrent exacerbations, significant limitation of activity due to asthma, frequent symptoms despite normal lung function, or frequent symptoms despite treatment with ICS/LABA after confirming that their inhaler technique and adherence are adequate. Patients with more severe or difficult-to-treat asthma may benefit from more detailed lung function testing to optimally assess their asthma control and guide treatment strategies. Studies may include: allergy testing to identify causes for symptoms[79]; high- resolution computed tomography chest scans[80]; bronchial provocation testing breath testing for exhaled nitric oxide[81,82]; and sputum induction for inflammatory cell count.[83]

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