The Saudi Initiative for Asthma - 2019 Update: Guidelines for the diagnosis and management of asthma in adults and children

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Abstract:

This is the fourth version of the updated guidelines for the diagnosis and management of asthma, developed by the Saudi Initiative for Asthma (SINA) group, a subsidiary of the Saudi Thoracic Society. The main objective of the SINA is to have guidelines that are up to date, simple to understand, and easy to use by healthcare workers dealing with asthma patients. To facilitate achieving the goals of asthma management, the SINA panel approach is mainly based on the assessment of symptom control and risk for both adults and children. The approach to asthma management is now more aligned for different age groups. The guidelines have focused more on personalized approaches reflecting better understanding of disease heterogeneity with integration of recommendations related to biologic agents, evidence-based updates on treatment, and role of immunotherapy in management. The medication appendix has also been updated with the addition of recent evidence, new indications for existing medication, and new medications. The guidelines are constructed based on the available evidence, local literature, and current situation at national and regional levels. There is also an emphasis on patient–doctor partnership in the management that also includes a self-management plan.

Keywords:

Asthma, asthma-control test, guidelines, Saudi Arabia

Introduction

Asthma is a common heterogeneous inflammatory chronic disorder of the airways. 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 often with variable expiratory airflow limitation can be demonstrated."[1,2] Asthma is one of the most common chronic diseases in Saudi Arabia, with increasing prevalence.[3] It has significant impact on patients, their families, and the community as a whole in terms of lost work and school days, poor quality of life, frequent emergency department (ED) visits, hospitalizations, and deaths.[4-10]

As part of the commitment of the Saudi Thoracic Society (STS) toward a long-term enhancement plan for promoting best practice in the field of respiratory diseases, the Saudi Initiative for Asthma (SINA) was launched in 2008 with special attention to nonasthma specialists, including primary

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care and general practice physicians.[11-14] Sections related to asthma in children represent the views of a panel from the Saudi Pediatric Pulmonology Association, another subsidiary of the STS. The Saudi Allergy Asthma and Immunology Society has also contributed to this update. The SINA guidelines received a comprehensive update from the previous 2016 version with an emphasis on personalized approaches, reflecting better understanding of disease heterogeneity, with integration of recommendations related to biologic agents, evidence-based updates on treatment, and role of immunotherapy in management. The medication appendix was also updated with the addition of recent evidence, namely new indications for existing medication and new medications.

The SINA panel is a group of Saudi experts with well-respected academic backgrounds and experience in the field of asthma. Since the SINA aims to have updated guidelines, which are simple to understand and easy to use, the SINA expert panel realized the need to update the current guidelines with the available new evidence, new medications, new indications for existing medications, and changes in current practices. To streamline recommendations, the SINA expert panel has stratified the guidelines based on the following age groups: adults: age above 18 years; adolescents: age ≥13–18 years; and children who were stratified into two groups: 5–12 years and <5 years.

Methods

The SINA guidelines document was initially based on the Global Initiative for Asthma strategies with reference to related major international guidelines.[1,2] The SINA is supplemented by the available local literature and the current setting in Saudi Arabia. Consensus among the SINA panel was followed whenever there was lack of evidence.[15] The following criteria are used to grade the evidence:

- Evidence Category A: Randomized controlled trials with rich body of data
- Evidence Category B: Randomized controlled trials with limited body of data
- Evidence Category C: Nonrandomized trials and observational studies
- Evidence Category D: SINA panel consensus judgment. This category is only used in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories.

For this update, the same approach used in previous updates has been employed, whereby each section has been internally reviewed by at least two other members. The SINA panel conducted frequent round-table discussions and online discussions. A panel of international experts reviewed that the guidelines and their recommendations were thoughtfully considered.

Epidemiology

Asthma is one of the most common chronic illnesses in Saudi Arabia and local reports suggest that the prevalence of asthma is increasing.[16-19] Inadequate knowledge, unfamiliarity with new drugs, and lack of awareness of the importance of disease control are common among primary care physicians who care for asthma patients in Saudi Arabia.[16,20] In addition to these key factors, there are other attributes to the magnitude of disease burden, such as socioeconomic status, number of siblings, knowledge of caregivers, and income.[21-26] Consequently, many asthma patients are uncontrolled and continue to be under-diagnosed, under-treated, and at risk of acute attacks, resulting in missed work or school, increased use of expensive acute healthcare services, and reduced quality of life.[16,27] This was also observed among pregnant women with asthma as one study from Saudi Arabia showed that almost half of pregnant women had the intention to stop asthma medications during pregnancy.[28]

A meta-analysis on the variation in prevalence of asthma in different regions in Saudi Arabia showed a rise in the asthma prevalence from 1990 to 2000 with stabilization in the prevalence of asthma since 2000.[29] The pooled weighted prevalence rate of asthma was 14.3%, lifetime wheeze was 16.5%, and rhinitis was 21.4%. The overall prevalence of asthma in children from Saudi Arabia has been reported to range from 8% to 25%, based on studies conducted over the past three decades. The increasing prevalence of asthma in the past three decades may be attributed to rapid lifestyle changes related to the modernization of Saudi society, changes in dietary habits, and exposure to environmental factors, such as indoor allergens, dust, sand storms, and tobacco. In addition, this high prevalence of asthma could be attributed to an increase in asthma awareness in the general population and among healthcare workers, allowing more individuals to be diagnosed. Other explanations have attributed the increased prevalence to the hygiene hypothesis, which proposes that there is a lack of sufficient microbial exposure early in life due to pharmacological manipulations and vaccines.[30]

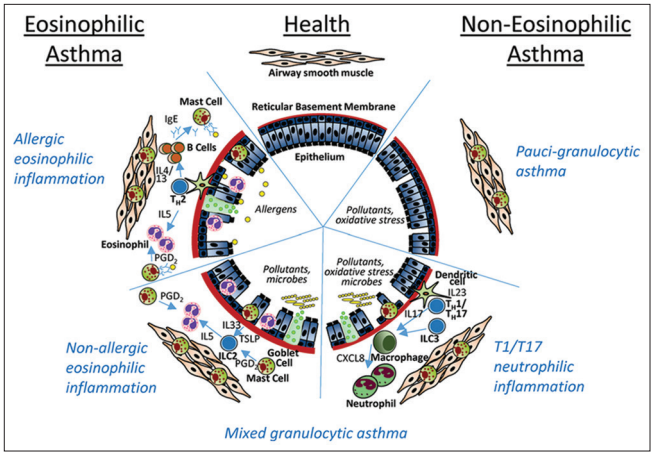
Most of the studies investigating the prevalence of asthma in various countries have focused on children age below 15 years or adults aged above 18 years. A study conducted by the STS investigated the prevalence of asthma and its associated symptoms in 16–18 years adolescents attending high schools in the

city of Riyadh. This study utilized the International Study of Asthma and Allergies in Children (ISAAC) questionnaire tool. Of 3073 students, the prevalence of lifetime wheeze, wheeze during the past 12 months, and physician-diagnosed asthma was 25.3%, 18.5%, and 19.6%, respectively. The prevalence of exercise-induced wheezing and night coughing in the previous 12 months was 20.2% and 25.7%, respectively. The prevalence of rhinitis symptoms in students with lifetime wheeze, physician-diagnosed asthma, and exercise-induced wheeze was 61.1%, 59.9%, and 57.4%, respectively. Rhinitis symptoms were significantly associated with lifetime wheeze, physician-diagnosed asthma, and exercise-induced wheeze.[31] By utilizing the ISAAC questionnaire method, another study conducted among 5188 primary schoolchildren in Madinah showed that the prevalence of asthma was 23.6%, while 41.7% had symptoms suggestive of at least one allergic disorder.[32] A national Saudi household survey was conducted in 2013 estimated that the self-reported clinical diagnosis of asthma to be 4.05%.[33] Another survey using the European Community Respiratory Health Survey questionnaire conducted in Riyadh among a total of 2405 Saudi nationals aged 20–44 years showed that the prevalence of wheezing in the last 12 months was 18.2% and physician-diagnosed asthma reported was 11.3%. There were no significant differences between asthmatic and nonasthmatic patients with respect to living area, level of education, and vaping history.[3]

Inadequate knowledge, lack of familiarity with new drugs, and lack of awareness of the importance of disease control are common among primary care physicians who care for asthma patients in Saudi Arabia.[16,20] In addition to these key factors, there are other attributes to the magnitude of disease burden, such as socioeconomic status, number of siblings, knowledge of caregivers, and income.[21-26] Consequently, many asthma patients are uncontrolled and continue to be under-diagnosed, under-treated, and at risk of acute attacks resulting in missed work or school, increased use of expensive acute healthcare services, and reduced quality of life.[16,27] This was also observed among pregnant women with asthma as one study from Saudi Arabia showed that almost half of pregnant women had the intention to stop asthma medications during pregnancy.[28]

Pathophsiology of Asthma

Asthma is a chronic inflammatory airway disease that results in narrow airway lumen. The airway narrowing is caused by increased mucus secretion as well as bronchial wall thickening due to edema, smooth muscle hypertrophy, and subepithelial fibrosis. The pathophysiological mechanisms that underlie these changes are diverse and heterogeneous Box 2.1. They



Box 2.1: Immunopathology of asthma*. Adapted from Russell *et al*.[48] with permission from the author

are driven by a variety of cell types including immune cells; mainly T-helper cells (Th2, Th17, Th1), mast cells, eosinophils, and neutrophils; as well as structural bronchial cells such as epithelial cells, myofibroblasts, and smooth muscle cells.[34] These mechanisms are broadly classified into four categories:

- Type 2 eosinophilic inflammation: This is the most common type and includes at least 60% of all asthma patients. It is defined by sputum eosinophilia of ≥2% of leukocytes in a sample. Patients frequently have blood eosinophilia of ≥300/μl. Eosinophils secrete mediators such as major basic protein and eosinophil cationic protein that can cause bronchial epithelial damage and fibrosis. Those patients usually respond well to inhaled corticosteroids (ICS), especially if they have mild or moderate disease. It is further subdivided into two types:
  - Early-onset allergic eosinophilic airway inflammation (extrinsic asthma): This type usually starts in childhood and can be triggered by allergen exposure. Allergens are taken up by dendritic cells and presented to naive T-cells that develop into Th2 cells characterized by the secretion of type 2 cytokines: interleukin (IL)-4, IL-5, and IL-13. IL-4 and IL-13 are necessary for specific B-cell activation and switching into immunoglobulin E (IgE)-producing cells. IgE binds to its high affinity receptor on mast cells. Subsequent cross-linking of IgE molecules by the allergen will lead to mast cell degranulation and release of mediators, such as histamine and tryptase as well as type 2 cytokines. In addition, IL-13 causes smooth muscle and goblet cell hyperplasia. On the other hand, IL-5 is essential for eosinophil development and maturation and contributes with certain other chemokines to their recruitment to the bronchial airways[35,36]
  - Late-onset nonallergic eosinophilic airway inflammation (intrinsic asthma): This type usually

starts during adulthood. Patients typically have no allergies but usually more severe airway limitation and airway hyperresponsiveness (AHR). It is triggered by microbes (bacteria and viruses), pollutants, and irritants. Bronchial epithelial cells will subsequently release IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) that will stimulate innate lymphoid cells type 2 to release IL-5 and IL-13.[37]

- Neutrophilic inflammation: It variably defined as neutrophils of ≥40%–60% of leukocytes in an induced sputum sample. It is less clearly characterized and involves release of Th1-and Th17-related cytokines and IL8 and Granulocyte-macrophage colony-stimulating factor (GM-CSF) that attracts neutrophils to the airways. It is triggered by infections, irritants, and tobacco smoke and may be a manifestation of the use of steroids in patients with eosinophilic inflammation. Those patients are mostly adults and do not respond to ICS as well[38]
- Mixed inflammation: This type has features of both eosinophilic and neutrophilic inflammation, including their cytokines profile. It is less common than the two previous types and tends to be more severe and more difficult to treat[39]
- Paucigranulocytic phenotype: In this form, there is not as much inflammation. The airway limitation is supposedly driven by other mechanisms. It is the least common and patients usually have milder disease.[40]

Airway hyperresponsiveness

This is a major feature of all asthma phenotypes. Its mechanisms and mediators are poorly understood. It worsens during and immediately after asthma attacks. It is usually worse in patients with severe asthma. However, it does not correlate well with markers of inflammation. Smooth muscle hypertrophy and neurohumoral factors may play a role in determining AHR.[41]

Airway remodeling

This is a major feature of asthma that starts early in the disease and causes incomplete reversibility by bronchodilator. It is characterized by bronchial epithelial damage, thickening of the basement membrane, and muscle hypertrophy.[42,43] It is influenced by ongoing airway inflammation and recurrent bronchoconstriction.[44]

Acute asthma

The pathophysiology of acute asthma is less clear due to the limited information. This is because of the difficulty in studying disease pathology and obtaining samples during the attack. The pathological manifestations generally depend on the trigger. At least 80% of cases of moderate-to-severe acute asthma are triggered not only by viruses, most commonly rhinovirus, but also by respiratory syncytial and influenza viruses.[45] Viral infections can cause significant epithelial damage, and symptoms tend to be more severe and last longer. On the other hand, allergen- or irritant-triggered attacks tend to be milder and resolve more quickly. Recurrent attacks may lead to progressive decline in lung function and increasing baseline asthma severity.[46-48]

Diagnosis of Asthma in Adults and Adolescents

The diagnosis of asthma is based on clinical assessment by a detailed history and physical examination supported by spirometry with reversibility testing.

History

The symptoms of wheezing, cough, shortness of breath, and chest tightness are not specific for asthma and can be seen with other pulmonary diseases. However, the combination of these symptoms increases the probability of asthma. The pattern of symptoms is usually varying over time and the patient may be entirely asymptomatic between attacks.[49,50] Symptoms are usually worse at night, particularly in children, and can be provoked by exercise or other triggering factors, such as viral infections and/or smoke. Asthma diagnosis can be supported by taking detailed history including patient's occupation, family history of asthma, other allergic disorders, and smoking and vaping. Box 3.1 lists the relevant questions that are commonly considered when taking a history where the diagnosis of asthma is under consideration. Asthma control may be worsened by coexisting symptomatic gastroesophageal reflux disease (GERD), rhinosinusitis, obesity, sleep disorders, or the use of some medications, such as beta-blockers and nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (ASA).[51,52] Asthma and rhinosinusitis commonly coexist.[53,54]

Physical examination

It is important to note that the examination of the chest may be normal in stable and controlled asthma, but the presence

Box 3.1: Relevant questions in the diagnosis of asthma

Does the patient or his/her family have a history of asthma or other atopic conditions, such as eczema or allergic rhinitis?
Does the patient have recurrent attacks of wheezing?
Does the patient have a troublesome cough at night?
Does the patient wheeze or cough after exercise?
Does the patient experience wheezing, chest tightness, or cough after exposure to pollens, dust, feathered or furry animals, exercise, viral infection, or environmental smoke (cigarettes, burning incense "Bukhoor," or wood?
Does the patient experience worsening of symptoms after taking aspirin/nonsteroidal anti-inflammatory medication or use of beta-blockers?
Does the patient's colds "go to the chest" or take >10 days to clear up?
Are symptoms improved by appropriate asthma treatment?
Are there any features suggestive of occupational asthma?

of bilateral expiratory widespread, high-pitched, variable musical wheezing is a characteristic feature of asthma. This may be accompanied by shortness of breath or diminished oxygen saturation. Examination of the upper airways is important to look for evidence of allergic rhinitis, such as mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis, also support the diagnosis of allergic asthma.[49,55] The presence of a localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.[56,57] Therefore, a careful consideration of any alternative diagnoses before commencing asthma treatment by a physician should be made.

Investigations

Spirometry is necessary to confirm airflow obstruction and demonstrates significant reversibility by performing a spirometry. The degree of significant reversibility is defined as an improvement in forced expiratory volume in the 1st s (FEV_1) ≥12% and ≥200 ml from the prebronchodilator value.[58] It may also help identify other alternative diagnoses such as upper airway obstruction. However, normal spirometry or failure to show reversibility does not rule out the diagnosis of asthma as it can be normal with the patient still being symptomatic.[59] Serial peak expiratory flow rate (PEFR) measurements may be helpful in the diagnosis of asthma by showing the characteristic increased variability and for follow-up after starting treatment. Bronchoprovocation testing is another tool to rule out asthma with atypical presentation and normal spirometry, but it is not routinely required. A diagnostic therapeutic trial with an ICS and a bronchodilator combination may be useful in confirming a diagnosis when it shows a favorable response.[60]

Chest X-ray (CXR) is not routinely recommended unless the diagnosis is in doubt, when symptoms are not typical or suggest alternative diagnoses. Peripheral eosinophilia and elevated IgE level are supportive of the diagnosis but are not routinely recommended unless dealing with moderate-to-severe asthma. Exhaled nitric oxide is an alternative method for detecting airway inflammation in eosinophilic asthma, but it is not widely available and can be suppressed with the use of ICS and in smokers.[61] Skin prick testing and radioallergosorbent test (RAST) may be helpful in identifying allergens to which the patient has been sensitized and in developing a strategy for avoiding allergen exposure.[62]

Clinical Assessment in Adults and Adolescents

Principles of asthma assessment

The principles of optimal asthma management should initially consist of an assessment of asthma control.[63,64] Before commencing a patient on treatment, the SINA expert panel recommends ensuring the following:

- Assessment of asthma control bring Box 4.1
- Performance of pulmonary function testing with spirometry and/or PEFR to assess for airflow limitations and postbronchodilator reversibility
- Documentation of current treatment and any related issues such as side effects, adherence, and inhaler technique
- Utilization of a written asthma action plan
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, anxiety, and exercise-induced laryngeal obstruction[65]
- Close monitoring for patients with severe asthma and history of asthma attacks
- The use of expectorated sputum eosinophilia and exhaled nitric oxide analysis in the assessment of asthma control are not recommended in routine practice.

Asthma-control test

Asthma severity was historically used as the entry point to determine the management strategy. This trend was replaced by the concept of asthma control.[66] Asthma control is a reflection of the adequacy of management by describing the clinical status of a patient as controlled, partially controlled, or uncontrolled. The control status may vary markedly over time and is recommended to entail short-term assessment of current asthma status, asthma burden, and medical management.[67] Focusing

Box 4.1: Assessing asthma control in adults

Component of control	Classification of asthma control		
	Controlled	Partial control	Uncontrolled
Symptoms and/or use of rapid-onset β2-agonist for symptoms relief	None or less than twice a week	More than twice a week	Throughout the day
Night time awakenings	None or once a month	Two or more attacks a month	Two or more attacks a week
Effect on daily activities	None	Some limitations	Extremely limited
FEV_1 or peak flow	>80% of predicted/personal best	60%-80% of predicted/personal best	<60% of predicted/personal best
Asthma control test score	≥20	16-19	<16
Attacks that require oral steroids or hospitalization	0	One attack per year	Two or more attack per year

Adapted with modification from the Global Initiative for Asthma.[2] FEV_1=Forced expiratory volume in the 1st s

on asthma control may improve patient perceptions and expectations that improve symptoms reporting and subsequently treatment decisions by clinicians.[67]

The SINA expert panel recommends the utilization of asthma-control test (ACT) to initiate asthma treatment in adults and adjust it at follow-up.[68-70] The ACT is a commonly used tool to assess asthma control. It is a short, validated, self-administered questionnaire to assess asthma control Bring Box 4.2. It consists of five items including limitation of activity, shortness of breath, frequency of night symptoms, use of rescue medication, and rating of overall control of the disease over the past 4 weeks.[71] The score of ACT is the sum of the five questions where each is scored from 1 (worst) to 5 (best), leading to a maximum best score of 25. The clinically important significant change in ACT score is considered to be ≥3 units.[72] The level of asthma control is categorized into:[70,71,73]

- Controlled: An ACT score of ≥20
- Partially controlled: An ACT score of 16–19
- Uncontrolled: An ACT score of <16.

Assessment when control is not achieved

If asthma control is not achieved at any step during therapy, the SINA expert panel recommends assessing the following:

- Medications and doses currently used
- Patient's adherence and correct technique in using devices
- Selection of the appropriate device and appropriate prescription of spacer with metered-dose inhaler (MDI) device
- Obstacles taking prescribed the medications (e.g., cost, time, patients' concerns lack of perceived need)
- Environmental exposure to allergens
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, and anxiety
- Future risk of attacks and fixed airflow obstruction.

Assessment of risk factors for future asthma attacks

The future risk of adverse outcomes should be assessed. This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effect of medications. The SINA expert panel recommends assessment of risk factors for poor asthma outcomes, especially in patients experiencing attacks.[2] The presence of one or more of the following risk factors increases the risk of attack despite controlled asthma status:

- High usage of relievers medication[2]
- ICS use[2]
- Low FEV_1[2]
- Previous intensive care unit (ICU) admission[2]
- Severe asthma attack in the previous 12 months[2]
- Major psychological disorders or reduced socioeconomic status[2]
- Continuous exposure to allergens[2]
- Presence of comorbidities
- Active smoking and vaping
- Frequent use of oral steroids
- Persistently elevated sputum or blood eosinophilia[2]
- Pregnancy.[2]

Asthma severity assessment in clinical practice

There is a trend in clinical practice to retrospectively assess asthma severity based on the step of treatment required to control symptoms and attacks.[74-77] Before classifying asthma severity, it is essential to ensure that control is achieved and maintained while using the minimal level of medications over a few months. Since

Box 4.2: Asthma control test*

Asthma control test items				Score
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school, or at home?				
All of the time	Most of the time	Some of the time	A little of the time	None of the time
□ 1	□ 2	□ 3	□ 4	□ 5
2. During the past 4 weeks, how often have you had SOB?				
More than once a day	Once a day	3-6 times a week	Once or twice a week	Not at all
□ 1	□ 2	□ 3	□ 4	□ 5
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, SOB, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?				
4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all
□ 1	□ 2	□ 3	□ 4	□ 5
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as salbutamol?				
3 or more times per day	1 or 2 times per day	2 or 3 time per week	Once a week or less	Not at all
□ 1	□ 2	□ 3	□ 4	□ 5
5- How would you rate your asthma control during the past 4 weeks?				
Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled
□ 1	□ 2	□ 3	□ 4	□ 5
				Total score

*Adapted from Nathan *et al*.[71] SOB=Shortness of breath

asthma severity level could change over years or months, therefore, asthma level of severity can be as classified as follows:

- Mild asthma: Controlled asthma at step 1 or 2
- Moderate asthma: Controlled asthma at step 3
- Severe asthma: Asthma that requires treatment step 4 or 5.

Non-pharmacological Management

The long-term goal of asthma therapy is to achieve and maintain asthma control by utilizing pharmacological and nonpharmacological measures [Box 5.1]. Appropriate implementation of nonpharmacological measures is expected to lead to utilization of the least possible doses of medications to minimize the risk of their side effects, if any.

Developing a partnership with the patient

The development of a partnership between patients and healthcare professionals leads to enhancement of knowledge, skills, and attitude that lead toward better understanding of asthma and its management. Based on agreed goals of management, a written self-management action plan should be offered to patients. A wide variety of plans are available which vary from patient-based to physician-based plans. This is expected to be reflected positively on patient adherence, which is a major issue in the management. Factors leading to nonadherence may be related to poor inhaler technique, a regimen with multiple drugs or devices, concern regarding side effects from the drugs, or the cost of medications.[78-80] Other factors include lack of knowledge about asthma, lack of partnership in its management, inappropriate expectations, underestimation of asthma symptoms, use of unconventional therapy, and cultural issues.[81,82]

Asthma education

The goal of asthma education is to provide patients with asthma (or the parents of a child with asthma) adequate training to enhance their knowledge and skills to be able to adjust treatment according to guided self-management.[64,83-87] To enhance the level of knowledge and skills among asthma patients, education is recommended to include knowledge about asthma and skills related to prescribed inhaler devices as there may be misperceptions about the use of inhalers and the safety of ICS [Box 5.2].[88-91] Asthma education is recommended to be conducted by a well-trained healthcare worker, who has good communication skills and is able to create an interactive dialog in a friendly environment. With the availability of appropriate information, patients will be encouraged to continue on the management plan and reassured about the control of their asthma.[92] It is essential to get the feedback from the patient to maintain a bidirectional rapport and an optimum environment. It has been documented that a well-structured asthma education program improves quality of life, reduces cost, and decreases the utilization of healthcare resources.[93-96] Asthma should be structured based on the available resources.

Identify and reduce exposure to risk factors

Measures to prevent or reduce exposures to risk factors should be implemented wherever possible. There are different triggers leading to acute asthma attacks, which may include allergens, viral infections, pollutants, drugs, and occupational agents. These factors can be classified as indoor or outdoor allergens and occupational sensitizers.

- Indoor allergens and air pollutants: There is a wide spectrum of indoor allergens that include dust

Box 5.1: Long-term goals of asthma management

Control asthma symptoms (cough, wheezing, or SOB)
Infrequent and minimal use (≤2 days a week) of reliever therapy
Maintain (near) normal pulmonary function
Maintain normal exercise and physical activity levels
Prevent recurrent of asthma flare-ups, and minimize the need for emergency department visits or hospitalizations
Optimize asthma control with the minimal dose of medications
Reduce mortality
Optimize quality of life and reduce risk of adverse outcomes

SOB=Shortness of breath

Box 5.2: Outcomes of asthma education program

Creation of patient-healthcare worker partnership
Understanding of clinical presentation of asthma and methods of diagnosis
Ability to differentiate between “reliever” and “controller” medications and their appropriate indications
Recognition of potential side effects of medications and the appropriate action to minimize them
The ability to use inhaler devices correctly
Identification of symptoms and signs that suggest worsening of asthma control and the appropriate action to be taken
Understanding the approach for monitoring asthma control
Recognition of the situations that need urgent medical attention
Ability to use a written self-management plan

mites, animals (mainly cats), cockroaches, and fungi (e.g., *Alternaria* and *Aspergillous*). Single allergen interventions are likely to fail. However, multifaceted, tailored, and intensive interventions most likely will help in improving asthma control. There are still several gaps in the literature in this area. It will take a few months for the allergen level to become significantly lower from the implementation of the control measures.[97] The most important indoor air pollutant is related to tobacco exposure. Measures to avoid tobacco exposure will lead to better asthma control and avoidance of long-term lung function impairment

- Outdoor allergens and dust: Outdoor allergens such as pollens and molds are impossible to avoid completely; exposure may be reduced by closing windows and doors and using air conditioning if possible. It is recommended to avoid outdoor strenuous physical activities in cold weather, low humidity, or high air pollution. Sand storms do not usually lead to asthma attacks, but mild symptoms may worsen. It is advisable to avoid going out in the storm if possible, especially for those with uncontrolled asthma[98]
- Occupational exposures: Whenever an occupational sensitizer is identified, it is advisable to keep the affected person away from that environment. The earlier the removal of this sensitizer takes place, the higher the chance of complete recovery from occupational asthma
- Food and drugs: Food and food additives are uncommon triggers of asthma. Avoidance cannot be recommended until it is documented by a specialist. However, certain drugs that could worsen asthma symptoms should be avoided (e.g., beta-blockers) if possible
- Vaccination: Annual influenza vaccination is advised for individuals with asthma, especially those with severe asthma.[99-101] It usually becomes available early on the fall season. It is advisable to get it as soon as it is available. Pneumococcal vaccination is also recommended as per local guidelines.[10]

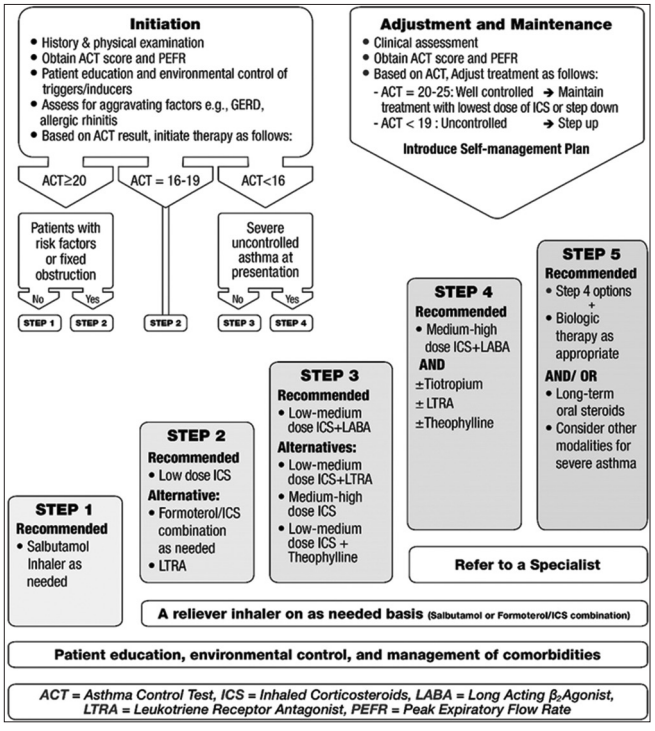
Pharmacological Management in Adults and Adolescent

The SINA expert panel recommends asthma treatment to be based on the following phases:

- Initiation of treatment
- Adjustment of treatment
- Maintenance of treatment.

At each phase, the patient is recommended to have a clinical assessment that includes symptoms assessment by ACT, a physiological measurement with PEFR or spirometry, review of current medications and patients' adherence and inhaler technique, a risk for attacks, and the response to treatment. Based on clinical and physiological assessment, the patient is placed on the appropriate treatment step [Box 6.1]. Appendix 1 contains more information about medications used in asthma treatment. The SINA expert panel recommends the following strategies for asthma treatment:

- A daily controller medication is the preferred recommendation for all steps, except for step 1. ICS is considered the most effective controller and the cornerstone of asthma treatment (Evidence A).[102,103] Uncontrolled patients may require the addition of other controller medications
- Relievers or rescue medications must be available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of worsening of asthma control (Evidence A).[104] The available relievers are:
  - A short acting bronchodilator agent (SABA) such as salbutamol that is recommended to be taken on "as-needed basis" to relieve symptoms
  - Formoterol/ICS combination could be used as a reliever therapy on "as needed basis" as per physician prescription. Formoterol is an Long acting bronchodilator agent (LABA) with fast-acting bronchodilator effect (Evidence B).[105-107]
- Regular assessment of adequate doses of treatment, proper technique, and adherence
- Regular assessment for independent risk factors for attacks, especially severe attacks in the past 12 months or prior history of admission to an intensive care setting; especially if intubated.[108,109] Other modifiable



Box 6.1: Outpatient asthma treatment for adults and adolescent

risk factors are recommended to be assessed, such as low initial FEV_1, pregnancy, inadequate ICS, smoking and vaping, comorbidities, and major psychological conditions
- Regular assessment of risk factors for fixed airway obstruction that include inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV_1, or sputum/blood eosinophilia[75,110]
- Management of comorbidities with a special attention to concomitant rhinosinusitis. As this condition affects asthma control, its treatment is expected to improve asthma (Evidence A).[111-116] Treatment includes nasal saline washes and/or steroids, leukotriene receptor antagonists (LTRAs), and antihistamines. Coexisting rhinosinusitis is recommended to be treated appropriately as well.

Initiation of treatment

Patients with asthma often underestimate the presence of symptoms and tend to assume that their asthma is controlled even when this is not the case. Therefore, the consensus among the SINA expert panel is to simplify the approach and supplement the initiation of asthma therapy by utilizing an objective measurement with the ACT questionnaire [Box 4.2]. The following initial steps are recommended for naive patients based on ACT score:
- ACT score ≥20
  - Step 1: SABA (such as salbutamol) on "as-needed basis" for patients with mild and infrequent symptoms that occurs once or twice a week[1,2]
  - Step 2: Low-dose ICS for patient with symptoms more than twice a week, the aforementioned risk factors for attack or fixed airway obstruction, low-dose ICS is recommended (Evidence B).[70,102,117,118] Early introduction of ICS leads to greater improvement of FEV_1 and lower the future doses of ICS[118]
  - Step 2: Patients with seasonal asthma who are symptomatic during the season are recommended to start low-dose ICS during the season and to be treated at step 1 for the rest of the year if their ACT score is ≥20 (Evidence D).
- ACT score 16–19
  - Step 2: Low-dose ICS for patients with an ACT score of 16–19 (Evidence B).[70] Alternative options may be considered as described in the adjustment section includes starting formoterol/ICS combination on "as-needed basis" or leukotrienes modifiers.
- ACT score <16
  - Step 3: A combination of regular low-dose ICS and LABA as maintenance treatment for patients with an ACT score of <16 (Evidence B)[70]
  - Step 4: For patients who have poorly uncontrolled asthma at presentation, initiation of asthma treatment with a combination of medium-dose ICS and LABA as regular maintenance treatment (Evidence D). However, for patients with early signs of attack at presentation, an initial short course of oral steroids may be required together with the prescription of the maintenance therapy.

Adjustment of treatment

After initiation of asthma treatment, it is recommended to assess the patient at 1–3-month intervals (Evidence D). The SINA expert panel recommends the utilization of stepwise approach of therapy to achieve asthma control. The stepwise approach consists of five steps as shown in Box 6.1. On follow-up, it is recommended to either maintain treatment until patients have achieved control, to step up for those who did not achieve control, or to step down for those who have maintained control for an extended period. Relievers or rescue medications must be made available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of asthma worsening (Evidence A).[104] The available relievers are detailed above.

The SINA panel recommends that the stepwise approach is not meant to be compartmental; it is rather a continuum of care based on patient engagement and close monitoring of the disease (Evidence D).[119] The following paragraphs will describe in detail each step.

Treatment at step 1

- Recommended option: A reliever therapy on "as-needed basis" (described earlier in the section). Symptoms are usually mild and infrequent with an ACT score of ≥20[104]
- Some patients may be recommended for low-dose ICS if they are controlled at the time of assessment (an ACT score of ≥20) but have risk factors for attacks or fixed airway obstruction.[119,120]

Treatment at step 2

- Recommended option: A daily low-dose ICS (<500 mcg of beclomethasone or equivalent/day) with a reliever therapy on "as-needed basis" (Evidence A)[102,121]
- Alternative options
  - Recent studies showed that the combination of budesonide/formoterol on "as-needed basis" is an alternative option (Evidence B).[106,107] When compared to regular maintenance with low-dose ICS alone, it was found to be inferior with respect to controlling symptoms and noninferior with respect to the rate of severe asthma attacks and time to first attack. Of note, the combination of budesonide/formoterol on "as-needed basis" achieved the outcome with substantially lower ICS dose equivalent to 17%–25% of the maintenance dose of ICS

- LTRA (montelukast) is another alternative option, especially for those patients who are reluctant to use ICS or continue to have side effects (such as voice hoarseness) despite preventive measures (Evidence A).[122] It should be noted that LTRA is less effective than ICS in achieving asthma control and in reducing the risk of attacks.

- Patients with mild and infrequent symptoms and an ACT score of ≥20 with risk factors for attack or fixed obstruction are recommended for low-dose ICS between asthma attacks (Evidence B)[102,117]
- Patients with seasonal asthma who are symptomatic during the season are recommended to be treated with low-dose ICS before the beginning of the season; otherwise, it is recommended to be maintained at step 1 for the rest of the year (Evidence D).

Treatment at step 3

- Recommended option: Adding an LABA to a low-medium-dose ICS in a combination device improves asthma control for patient whose asthma is not controlled at step 2 (Evidence A).[117,123,124] The patient is recommended to continue on reliever treatment on "as-needed basis" (Evidence A)
- ICSs in the form of beclomethasone dipropionate, budesonide, mometasone furoate, or fluticasone propionate are currently combined with either salmeterol or formoterol. These are normally prescribed twice daily. Once a day combination of ICS and LABA is also available [Appendix 1]
- If a formoterol/ICS combination is selected, patient may be advised to use this combination for both maintenance and rescue using extra puffs from the same inhaler (Evidence A).[105] The recommended dose is 1–2 puffs twice daily plus extra puffs that should not exceed 12 puffs per day. Those patients who require such high doses for 2–3 days should seek medical advice to step up maintenance therapy, and they may require the use of a short course of oral prednisolone (Evidence A)
- If salmeterol/ICS combination is selected, an escalation of the regular daily doses to maximum dosing achieves well-controlled asthma status in a majority of patients on steps 2 and 3 (Evidence A).[125] Salmeterol has a slow onset of action; therefore, it should only be used as a maintenance treatment
- The once a day combination of ICS/LABA can be prescribed based on availability. The approved product in the Saudi market is fluticasone furoate/vilanterol (Relvar) that can be prescribed for adults and children above 12 years at a dose of 100/25 μg (Evidence A).[126,127] Vilanterol has the advantage of an onset of action within 15 min and a long half-life; therefore, patient can use it only as a maintenance treatment
- Inhaled LABA should not be used alone in asthma management.[128] Asthma patients taking inhaled LABA without inhaled ICS are at an increased risk of asthma attacks, hospitalizations, and death.[129] Based on this evidence, the Saudi Food and Drug Administration withdrew all LABA monotherapy medications from the Saudi market by the end of 2010.[130] Therefore, the SINA panel has limited the use of relievers to SABA or to formoterol when combined with ICS
- Alternative and generally less effective strategies include the continuation of ICS as a monotherapy by increasing the dose to the medium-high-dose range (Evidence A),[129,131] or the addition of LTRA to a low-medium-dose ICS (Evidence A),[132,133] especially in patients with concomitant rhinitis.[134] The addition of sustained release theophylline to a low-medium dose ICS is a possible but less favorable choice (Evidence B)[135]
- Tiotropium is a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease (COPD).[136-138] Evidence has shown that when tiotropium is added to an ICS, it improves symptoms, reduces risk of attack, and improves the lung function in patients with inadequately controlled asthma. Its effect appears to be at least equivalent to LABA (Evidence A).[139-142] This evidence supports that tiotropium can be used as an alternative to LABA when added to ICS
- Consultation with an asthma specialist is recommended for patients whenever there is a difficulty in achieving control at step 3 (Evidence D).

Treatment at step 4

- Recommended option: Escalation of treatment by combining medium-high-dose ICS with LABA (Evidence A)[92,131,133,143]
- In addition to the currently available combinations of ICS/LABA mentioned in step 3 section, the once a day combination of fluticasone furoate/vilanterol (Relvar) can be prescribed for adults and children above 12 years at a dose of 200/25 μg dose[126,127]
- If symptom control is not achieved, adding tiotropium to the combination of ICS and LABA is a recommended option as it significantly improves lung function in uncontrolled cases (Evidence A)[136,144,145]
- Adding LTRA to the combination of high-dose ICS and LABA is also recommended, but the evidence is less robust (Evidence B).[142,146,147]
- Adding theophylline to the combination of high-dose ICS and LABA is another less favorable alternative (Evidence B)[147,148]
- If a patient is uncontrolled at step 4 despite adequate treatment and control of comorbid conditions, biologic therapy is recommended as described in step 5. Early consideration may save the patient from frequent or chronic use of oral corticosteroids
- Consultation with an asthma specialist is recommended for patients who require this step of therapy (Evidence D).[149]

Treatment at step 5

- Consultation with an asthma specialist is strongly recommended for patients requiring treatment at step 5 (Evidence D)
- To avoid frequent use of oral steroids, biologic therapy should be considered based on appropriate indications and availability
- Anti-IgE therapy (omalizumab) may be considered for those patients uncontrolled on maximum treatment at step 4 despite modification of any triggers and who have allergic asthma as determined by an IgE level in the appropriate therapeutic range, and positive skin test or RAST study (Evidence A), or a history of documented atopy (Evidence D).[131,132,143] If this treatment does not control asthma after 16 weeks of therapy, it should be stopped[150-152]
- Anti-IL-5 therapy can be considered for uncontrolled eosinophilic asthma at step 4 with frequent attacks [Appendix 1, medications section]. There are no data to determine the duration before deciding on treatment ineffectiveness. However, till this evidence is available, the treatment may be continued for up to 6–12 months before the decision of stopping treatment (Evidence D).[153] The available options are:
  - Mepolizumab, an anti-IL-5 therapy that is indicated when eosinophil level is ≥150 cells/μL at treatment initiation or ≥300 cells/μL at any time in the prior 12 months. The recommended dose is 100 mg subcutaneously every 4 weeks
  - Benralizumab, an anti-IL-5 receptor that is indicated when blood eosinophil level is ≥300 cells/μl at initiation of treatment. The recommended dose is 30 mg subcutaneously every 4 weeks for the first 3 months and then every 8 weeks thereafter
- There is no available evidence that compares anti-IgE therapy to any of the anti-IL-5 therapies or directly comparing different anti-IL-5 agents
- For patients with evidence of both atopy and high blood eosinophils, to date, there is no available evidence to favor either anti-IgE therapy versus anti-IL-5 agents. Omalizumab led to more reduction of asthma attacks in a category of asthma patients who showed >50% reduction in blood eosinophils during therapy.[154,155] A recent study showed that anti-IL-5 receptor therapy (benralizumab) reduced attacks by 46% and improved lung function in patients with severe, uncontrolled eosinophilic asthma, regardless of the serum IgE concentrations and atopy status.[156] When choosing a biologic, several factors should be considered including the frequency of administration, cost, side effect profile, age at onset of asthma, presence of comorbid conditions such as nasal polyps, previous response, and physician experience with the treatment
- If the patient does not have atopy, high blood eosinophils, or biologic therapy is not available or not adequately controlling the disease; the alternative approach is to use the lowest possible dose of long-term oral corticosteroids (Evidence D).[157] Other alternative are mentioned in the severe asthma section such as thermoplasty and long-term macrolides
- For patients who require long-term systemic corticosteroids, the following are recommended to be considered:
  - Use the lowest possible dose to maintain control
  - Closely monitor the development of corticosteroid-related side effects
  - When asthma control is achieved, attempts to reduce the dose of systemic corticosteroids, preferably to every other day frequency. Maintaining high-dose ICS therapy may help reduce the dose of systemic corticosteroid
  - Upward adjustment of the corticosteroid dose at the time of stress (e.g., infection, asthma attacks, surgery) is essential
  - Strongly consider concurrent treatments with calcium supplements, Vitamin D, and bone-sparing medications (e.g., bisphosphonates) in patients who have risk factors for osteoporosis or low bone mineral density (Evidence C).

Maintaining asthma control

Regular follow-up by a healthcare worker is essential. Depending on the level of asthma control, it is recommended to have a follow-up at 1–3-month intervals (Evidence D).[92,158] Follow-up should include monitoring and reviewing the patient's written asthma action plan, medication adherence and inhaler technique, patient's behaviors, comorbidities, and possible side effects of the medications. Once asthma is well controlled and the control is maintained for at least 3 months, a step-down in pharmacologic therapy is recommended at the minimum level that can maintain the good control and minimize the side effects (Evidence D). The following are the general recommendations:

- Reduction in therapy is recommended to be gradual and closely monitored based on clinical judgment of the individual patient's response to therapy and ACT score (Evidence D)
- If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25% every 3–6 months to the lowest dose possible that is required to maintain control (Evidence B)[85,159,160] and then changed to a single daily dose (Evidence A).[161] It is recommended to be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued[162]
- If the patient is on combination of ICS/LABA at step 3 or 4, abrupt discontinuation of LABA is not recommended as it may lead to deterioration of the control[163]
- If the patient is on a combination of ICS and LABA, LTRA, or other controllers, then start by tapering ICS to the lowest possible dose (Evidence B).[164,165]

If control is achieved, LTRA may be discontinued (Evidence D)[164]
- For significant side effects, consider a change in therapy, reduction in the dose, or frequency of ICS (if possible), advise vigorous mouth washing after inhalation, use of spacer (concomitant with MDI devices), and/or use of appropriate local antifungal therapy for severe oral thrush[166]
- Patients should be informed that asthma control may deteriorate if treatment is completely discontinued.

Referral to an asthma specialist

Situations that require referral to an asthma specialist for consultation or comanagement include:
- Uncertainty regarding the diagnosis
- Difficulty achieving or maintaining asthma control
- Immunotherapy or biologic therapy is being considered
- Difficulty to achieve asthma control at step 3 or higher
- Acute asthma attack requiring hospitalization
- Request of a patient for second opinion or further advice.

Allergen immunotherapy

The allergen immunotherapy (AIT) is a treatment modality to desensitize patients to specific allergens. It is considered for those with stable asthma and evidence of clinically relevant allergic sensitization at which the immunotherapy can be directed, especially if they have coexisting allergic rhinitis. Patients with poorly controlled asthma should not be started on immunotherapy.[167,168] Although there are insufficient data on the impact of AIT on asthma attacks and quality of life scores, it has specifically been shown to:
- Improve asthma symptoms and stepping down asthma treatment (Evidence A)[169]
- Improve AHR (Evidence B)[170]
- Decrease the progression of allergic rhinitis to asthma (Evidence B)[171]
- Decrease the chance of development of new sensitizations (Evidence B).[167]

AIT is likely to be cost-effective when appropriately used.[168] There are currently two types of AIT in clinical practice, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Most studies that compared SCIT to SLIT showed a better clinical efficacy of SCIT. However, SLIT has a better safety profile than SCIT as SCIT may rarely cause anaphylaxis.[169] Patients at risk are mainly those with asthma, especially if uncontrolled. High level of caution should be taken in patients using beta-blockers due to the risk of more serious anaphylaxis that is resistant to treatment with epinephrine.[167] Data are limited in pediatrics, but AIT has been used safely in children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV_1.[172] Although beneficial effects may be observed a few months from starting AIT, treatment with AIT needs patient's commitment for at least 3 years to have sustained desensitization after stopping the treatment. Furthermore, AIT can be continued, but not initiated, during pregnancy. Most studied that allergen-specific immunotherapy is dust mites, *Alternaria*, grass pollens, ragweed, and cat. Omalizumab could improve tolerability to AIT in patients with moderate-to-severe asthma.[173] If the patient is considered a candidate for AIT, referral to an allergist is recommended to explore this option further.

Severe asthma

Severe asthma carries several names; each point to an aspect of the disease. Chronic severe asthma, steroid-dependent asthma, difficult-to-treat asthma, and refractory asthma are some of these terminologies.[174] Severe asthma is defined by the "requirement of asthma treatment with high-dose inhaled ICS and a second controller or oral prednisolone, which remains uncontrolled despite this therapy, or to prevent it from becoming "uncontrolled."[77] Severe asthma probably accounts for 5%–10% of adult asthma, but the health cost is disproportionally high.[175] Morbidity and mortality are also higher compared to regular asthma patients because of increased side effects of treatment and much more frequent attacks and/or hospitalizations.[176,177] Before a diagnosis of severe asthma is considered, patients must undergo a systematic assessment where the diagnosis of asthma is confirmed, and comorbidities are identified and treated.[52] Patients in whom poor asthma control is related to other factors, such as poor adherence or due to the presence of other diseases, are to be termed "difficult-to-treat asthma." There are common comorbidities that need to be assessed in severe asthma such as allergic rhinoconjunctivitis (in 70% of cases), rhinosinusitis/nasal polyps (in 50%), COPD (in 20%), vocal cord dysfunction (in 32%–50%), anxiety/depression (in 4%–17%), obstructive sleep apnea (in 31%), GERD (in 17%–74%), bronchiectasis (in 25%–40%), and allergic bronchopulmonary aspergillosis (in 1%–2%).[178] The following steps are recommended for the assessment of patients with severe asthma:[179-184]

- Ensure that the patient is adherent to all medications with a good inhalation technique
- Be aware of possible misdiagnosis where the problem is not bronchial asthma to start with but another respiratory pathology that is mimicking asthma symptoms and not appropriately addressed, e.g., bronchiectasis, endobronchial tumors, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, or Churg–Strauss syndrome[182,185]
- Assess for the existence of comorbidities that can worsen bronchial asthma and make it difficult to manage (e.g., chronic rhinosinusitis, GERD, sleep apnea syndrome, Allergic bronchopulmonary aspergillosis

(ABPA), obesity, and congestive heart failure [CHF])[186]
- Medications over use or side effects
- Managing any psychosocial contributing factors
- Identify confounding factors (e.g., presence of allergens at home or work, active or passive smoking and vaping, or psychosocial problems).[182]

Asthma phenotyping

Phenotyping plays a major role in predicting the response to treatment of severe asthma. Inflammatory phenotyping is based on the type of and the extent of inflammatory reaction, while clinical phenotyping is based on combining clinical characteristics, physiological abnormalities, and inflammatory markers. Inflammatory phenotypes are based on the result of inflammatory cells identified in an induced sputum sample. There are four groups: neutrophilic asthma, eosinophilic asthma, mixed granulocytic asthma, and paucigranulocytic asthma.[178] Clinical phenotyping is based on age at onset, IgE-mediated allergy, eosinophilia or increased fractional exhaled nitric oxide, fixed airflow obstruction, and obesity. Clinical phenotypes can be recognized as an early-onset allergic phenotype, a later-onset obese phenotype, or a later-onset eosinophilic phenotype.

Selection of which biological agent is most appropriate for a particular patient can be achieved by clinical phenotyping. History of allergy, airflow obstruction, and attacks may predict a better effect of anti-IgE therapy. Eosinophilia combined with attacks may predict better effects of anti-IL5 therapy. However, patients with irreversible airflow limitation and frequent attacks may benefit from tiotropium.[187] Details of biological agents and their indications are discussed in detail in earlier sections.

As it may be difficult to achieve full control in many patients with severe asthma, the aim of treatment in this situation is to reach the best possible control.[187] After dealing with all comorbidities and other confounding factors that could have made asthma difficult to control, maximum therapy is recommended at step 5, which may include combination therapy of high-dose ICS/LABA, LTRA, long-acting antimuscarinic (cholinergic) agents (LAMA), and addition of one of the available biological therapies as appropriate.[152,188,189]

A significant percentage of patients with severe asthma do not respond adequately to high-dose ICS and other controller therapy; thus, they need frequent or continuous oral steroid therapy to achieve a reasonable response.[190] Such control may be lost when oral steroid is discontinued. Patients may differ in the degree of their responsiveness to oral steroids.[191] Some patients may fail to improve their FEV_1 by >15% following treatment with oral prednisolone for 2 weeks, a condition called "corticosteroids-resistant asthma."[192,193] If oral steroids are necessary, then it is recommended to use the lowest possible dose and to shorten the duration as much as possible.[194] In this situation, osteoporosis prophylaxis is recommended.

For patients with severe asthma that do not qualify or respond to biologic therapy, other modalities of treatment of severe asthma are recommended for consideration that includes:
- Macrolides: Due to their role in reducing neutrophilic airway inflammation, they were shown to have a role in the management of severe asthma. A recent study has assessed the benefit of azithromycin at a dose of 250–500 mg 3 days/week as add-on therapy for 48 weeks for patient with persistent symptomatic asthma.[195] Azithromycin significantly reduced the experience of at "least one asthma attack" from 61% to 44%. It has significantly improved asthma-related quality of life measures, and responses in eosinophilic asthma were greater than in those without eosinophils
- Bronchial thermoplasty (BT): Utilizing radiofrequency energy to alter the smooth muscles of the airways and possibly bronchial wall innervation, BT has been shown to reduce the risk of asthma attacks in clinical trial setting.[196] In well-selected patients with moderate-to-severe asthma, it may improve various aspects of asthma, including FEV_1, quality of life, asthma control, attacks, and use of rescue medications.[197-199] Until solid evidence is available, it is recommended to perform it in the setting of clinical trials and approval of an independent, institutional review board.[77] Contraindications to BT include moderate and severe bronchiectasis, very high sputum production, and fixed airflow obstruction with FEV_1 levels below 50% of predicted.

Management of Acute Asthma in Adults and Adolescents

Acute asthma attack is a challenging clinical scenario that requires a systemic approach to rapidly diagnose the condition, evaluate its severity, and initiate therapy. The first step of managing acute asthma is the early recognition to prevent the occurrence of attacks. Asthma in general has a low mortality rate compared with other lung diseases.[45] Nevertheless, asthma may lead to mortality, especially among patients with poorly controlled asthma whose condition deteriorates over a period of days before the final fatal event.[108,200-203] It has been shown that over 80% of such attacks developed over >48 h, allowing enough time for effective action to reduce the number of attacks requiring hospitalization.[204-207] The most specific marker associated with increased asthma mortality is a history of repeated

hospital admissions, particularly if patients required intensive care treatment or ventilatory assistance.[203,208] The characteristics of patients admitted with near-fatal asthma in Saudi Arabia were found to be younger and predominantly males and used less ICS/LABA combination.[209] Furthermore, it has been shown that a subgroup of patients who present with near-fatal asthma have blunted perception of dyspnea and have a history of frequent ED visits, hospitalizations, and near-fatal asthma events.[210] This section includes assessment of patient with acute asthma, initial management, and follow-up after initial management. More information about medications used in acute asthma can be found in Appendix 1.

Clinical assessment of acute asthma

The initial clinical assessment should rapidly determine whether the patient's presenting symptoms are related to an acute asthma attack or not. Of note, it is necessary to recognize that acute asthma is different from mild-to-moderate asthma attack secondary to poor asthma control that simply requires a step-up in the chronic asthma therapy. Although most acute asthma attacks develop over a period of days, patients with brittle asthma may present with a much more dramatic deterioration [Box 7.1]. It is important to realize that most patients who die from acute asthma attack had chronically uncontrolled asthma, had received inadequate treatment with ICS, and had inadequate monitoring of their asthma.[211-215] Management of acute asthma in adults is the extreme spectrum of uncontrolled asthma and represents the failure to reach adequate asthma control. The presence of the following features should be sought:

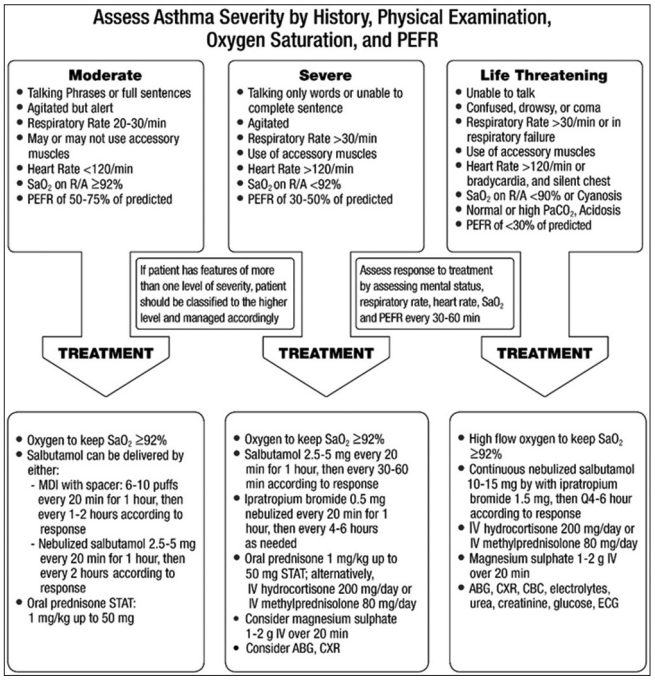
- Previous history of near-fatal asthma
- Whether the patient is taking three or more medications
- Heavy use of SABA
- Repeated visits to the ED
- Brittle asthma.

On presentation, a patient should be carefully assessed to determine the severity of the attacks [Box 7.2] and the type of treatment required.[216,217] PEFR and pulse oximetry measurements are complementary to history-taking and physical examination. Major causes linked with asthma-related deaths are cardiac arrhythmia and asphyxia. The risk of cardiac arrhythmia is theoretically increased by hypokalemia and QTc interval prolongation related to the use of high-dose SABA or intravenous (IV) aminophylline.[52,218-220] However, in a series of patients with near-fatal attacks, only a few arrhythmias other than sinus tachycardia and bradycardia were reported.[108,221] Hence, a more likely cause for death is probably related to asphyxia due to severe airflow obstruction and hypoxemia. This is supported by the pathologic evidence

Box 7.1: Levels of severity of acute asthma in adults

Level	Characteristics
Moderate asthma attacks	Increasing symptoms
	PEFR >50-75% best or predicted
	No features of acute severe asthma
Acute severe asthma	Any one of
	PEF 30-50% best or predicted
	Respiratory rate ≥25/min
	Heart rate ≥120/min
	Inability to complete sentences in one breath
Life-threatening asthma	Any one of the followings in a patient with severe asthma
	SpO_2<92% (PaO_2<60 mmHg) on high-flow FIO_2
	PEF<30% best or predicted
	Bradycardia
	Dysrhythmia
	Cyanosis
	Hypotension
	Normal or high $PaCO_2$
	Exhaustion
	Confusion
	Silent chest
	Coma
	Weak respiratory effort
Near-fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation
Brittle asthma	Type 1: Wide PEF variability (>40% diurnal variation for >50% of the time over a period >3-6 months) despite intense therapy
	Type 2: Sudden severe attacks on a background of apparently well-controlled asthma

PEF=Peak expiratory flow



Box 7.2: Initial management of acute asthma for adults and adolescents

of extensive airway obstruction, mucous plugging, and dynamic hyperinflation found at autopsy in patients who died of acute severe asthma.[222] Treatment of acute asthma attacks requires a systematic approach similar to chronic asthma management. Acute asthma management is recommended to follow these steps:

1. *Assess* severity of the attack
2. *Initiate* treatment to rapidly control the attack
3. *Evaluate* continuously the response to treatment.

The following levels of acute asthma severity should be quickly identified as approach to management and prognosis varies significantly [Box 7.2].

Assessment of acute asthma severity

- Mild acute asthma: Patients presenting with mild asthma attack are usually treated in an outpatient setting by stepping up in asthma management, including increasing the dose of ICS.[223] However, some cases may require short course of oral steroids
- Moderate acute asthma: Patients with moderate asthma attack are clinically stable. They are usually alert and oriented but may be agitated. They can communicate and talk in full sentences. They are tachypneic and may be using their respiratory accessory muscles. Heart rate is usually <120/min and blood pressure is normal. A prolonged expiratory wheeze is usually heard clearly over the lung fields, but examination of the chest may be relatively normal. Oxygen saturation is usually normal secondary to hyperventilation. The PEFR is usually in the range of 50%–75% of predicted or previously documented best. Measurement of arterial blood gases (ABGs) are not routinely required in this category; however, if done, it shows widened alveolar–arterial oxygen gradient and low $PaCO_2$, secondary to increased ventilation–perfusion mismatch and hyperventilation, respectively. CXR is not usually required for moderate asthma attacks, unless pneumonia is suspected
- Severe acute asthma: Patients are usually agitated and unable to complete full sentences. Their respiratory rate is usually >30/min and use of accessory muscles is common. Significant tachycardia (pulse rate >120/min) and hypoxia (SaO_2 <92% on room air) are usually evident. Chest examination reveals prolonged distant wheeze secondary to severe airflow limitation and hyperinflation; more ominously, the chest may be silent on auscultation. The PEFR is usually in the range of 30%–50% of predicted. ABG reveals significant hypoxemia and elevated alveolar–arterial oxygen gradient. $PaCO_2$ may be normal in patients with severe asthma attacks. Such finding is an alarming sign as it indicates fatigue, inadequate ventilation, and pending respiratory failure. Chest radiograph is required if complications are clinically suspected such as pneumothorax or pneumonia
- Life-threatening acute asthma: Patients with life-threatening asthma are severely breathless and unable to talk. They can present in extreme agitation, confusion, drowsiness, or coma. The patient usually breathes at a respiratory rate >30/min and uses their accessory muscles secondary to increased work of breathing. Heart rate is usually >120/min; however, at a later stage, patients can be bradycardiac. Patient may have arrhythmia secondary to hypoxia and electrocardiography (ECG) monitoring is recommended. Oxygen saturation is usually low (<90%) and not easily corrected with oxygen. ABG is mandatory in this category and usually reveals significant hypoxia and normal or high $PaCO_2$. Respiratory acidosis may be present. PEFR is usually very low (<30% of the predicted). CXR is mandatory in life-threatening asthma to rule out complications such as pneumothorax or pneumomediastinum. It is important to realize that some patients might have features from more than one level of acute asthma severity. For the patients' safety, they should be classified at the higher level and managed accordingly.

Initial treatment of acute asthma

After initial assessment of asthma attack, it is recommended to base treatment on severity level [Box 7.2]. More details of medications are available in Appendix 1.

- Moderate asthma attack
  - Low-flow oxygen is recommended to maintain saturation ≥92%.[224,225] There is evidence that high-flow oxygen may be harmful for some patients.[226] Therefore, it is important to give a controlled dose of oxygen; patients who received 28% oxygen did better than those who received 100% oxygen[226]
  - Salbutamol is recommended to be delivered by either:[227,228]
    - MDI with spacer: 4–10 puffs every 20 min for 1 h, then every 1–2 h according to response (Evidence A)[229-231]
    - Nebulizer: Salbutamol 2.5–5 mg every 20 min for 1 h, then every 2 h according to response (driven by oxygen if patient is hypoxic) (Evidence A).[232]
  - Steroid therapy: Oral prednisolone 1 mg/kg/day to maximum of 50 mg is recommended to be started as soon as possible.[233,234]
- Severe asthma attacks
  - Adjusted oxygen flow is recommended to keep saturation ≥92% (avoids excess oxygen)[225,235,236]
  - Nebulized salbutamol (2.5–5 mg) is recommended to be repeated every 15–20 min for 1 h and then every 30–60 min according to response.[225] Oxygen-driven nebulizers are preferred for nebulizing salbutamol because of the

risk of oxygen desaturation while using air-driven compressors (Evidence A)[233,234,237,238]
- Ipratropium bromide is recommended to be added to salbutamol at a dose of 0.5 mg every 20 min for three doses by the nebulized route and then every 4–6 h as needed (Evidence B). Alternatively, ipratropium bromide can be administered by MDI at a dose of 4–8 puffs every 20 min and then every 4–6 h as needed[239-242]
- Systemic steroid is recommended to be started as soon as possible (Evidence A). If patient can tolerate oral medications, oral prednisolone 1 mg/kg/day to maximum of 50 mg daily is recommended. Alternatively, the following may be prescribed: daily hydrocortisone dose of 200 mg IV or daily methylprednisolone dose of 80 mg, in divided doses[233,243]
- If there is no adequate response to previous measures, it is recommended to administer a single dose of IV magnesium sulfate at a dose of 1–2 g over 20 min (Evidence B)[244]
- Request CXR, electrolytes, glucose, 12-lead ECG, and ABG,

- Life-threatening asthma
  Patients in this category can progress rapidly to near-fatal asthma, respiratory failure, and death. Hence, an aggressive management approach and continuous monitoring are mandatory.[245] The following steps are recommended for further management:
  - Consult ICU service. Intubation setting should be readily available
  - Adequate oxygen flow to keep saturation ≥92%[225]
  - Deliver continuous nebulized salbutamol at a dose of 10–15 mg with ipratropium bromide at a dose of 1.5 mg over 1 h (Evidence A).[246,247] Continuous treatment was found to be safe and well tolerated and led to better improvement in pulmonary functions and reduction in hospitalization when compared to intermittent delivery (Evidence A).[248] Oxygen-driven nebulizers are preferred due to the risk of oxygen desaturation while using air-driven compressors (Evidence A)[237,238]
  - Once the patient showed response to continuous nebulization, shift to intermittent delivery is recommended (Evidence D)
  - Systemic steroid (Evidence A) to be started as soon as possible in one of the following forms: IV methylprednisolone 80 mg daily in divided doses or IV hydrocortisone 200 mg daily in divided doses[233,239,242,243,249,250]
  - Single dose of IV magnesium sulfate at a dose of 1–2 g over 20 min (Evidence B)[243,250]
  - Frequent clinical evaluation and CXR, electrolytes, glucose, 12-lead ECG, and ABG are recommended.

Follow-up after initial treatment

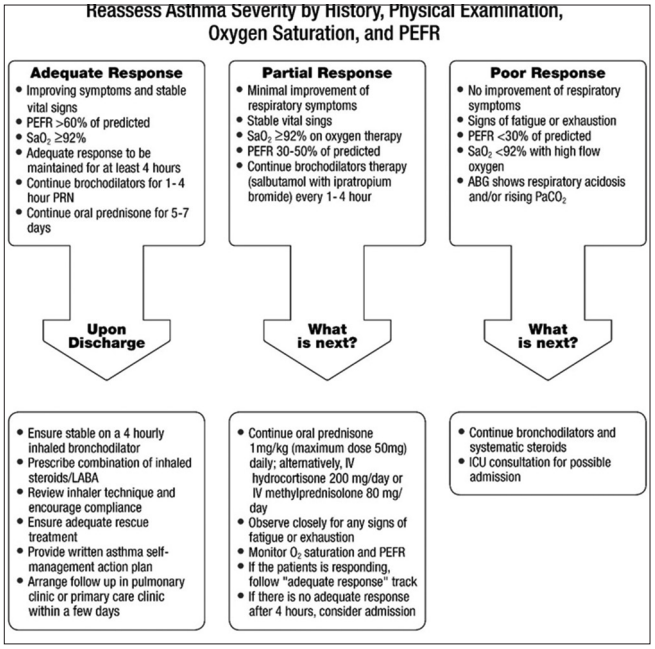
Close evaluation of treatment response is recommended that and includes patient's mental and physical status, respiratory rate, heart rate, blood pressure, oxygen saturation, and PEFR. Response to treatment is divided into three categories that are adequate, partial, or poor response [Box 7.3].

- Adequate response
  Adequate response is defined as:
  - Improvement of respiratory symptoms
  - Stable vital signs with respiratory rate <25/min and heart rate <120/min
  - Oxygen saturation ≥92% on room air
  - PEFR or FEV_1 >50% of predicted.

Management

If the above criteria are met and maintained for at least 4 h, the patient can be safely discharged with the following recommendations:
- Review and reverse of any treatable cause of the attack
- Review of inhaler technique and encourage adherence
- Step up of asthma treatment to at least step 3
- Prescription of oral steroid for 5–7 days
- Adequate reliever therapy on "as-needed basis"
- A clearly written asthma self-management action plan
- A close follow-up appointment.

- Partial response
  Partial response is defined as:
  - Minimal improvement of respiratory symptoms
  - Stable vital signs with respiratory rate <25/min and heart rate <120/min



Box 7.3: Adjustment of acute asthma treatment for adults and adolescent

- Oxygen saturation ≥92% on oxygen therapy
- PEFR between 30% and 50% of predicted.

Management

Patients who only achieved partial response after 4 h of the above-described therapy are recommended for the following:

- Continue bronchodilator therapy (salbutamol every 1–2 h with ipratropium bromide every 2–4 h), unless limited by side effects (significant arrhythmia or severe hypokalemia)
- Continue systemic steroid: Oral prednisolone 1 mg/kg to maximum of 50 mg g daily. Alternatively, IV hydrocortisone 200 mg daily or IV methylprednisolone 80 mg in divided doses
- Observe closely for any signs of fatigue or exhaustion
- Monitor oxygen saturation, serum electrolytes, ECG, and PEFR
- Admit to hospital if the patient fails to show adequate response.

- Poor response

  Poor response is defined as:
  - No improvement of respiratory symptoms
  - Altered level of consciousness, drowsiness, or severe agitation
  - Signs of fatigue or exhaustion
  - Oxygen saturation <92% with high-flow oxygen
  - ABG analysis showing respiratory acidosis and/or rising $PaCO_2$
  - PEFR <30% of predicted.

Management

Patients showing poor response after 4 h of therapy should have the following recommendations:

- Consider ICU admission
- Deliver continuous nebulization of salbutamol and ipratropium bromide, unless limited by side effects
- Continue systemic steroid: IV hydrocortisone 200 mg daily or IV methylprednisolone 80 mg in divided doses.

- Criteria for ICU referral

  ICU referral is recommended for patients:
  - Requiring ventilatory support
  - Developing acute severe or life-threatening asthma
  - Failing to respond to therapy, evidenced by:
    - Deteriorating PEFR
    - Persisting or worsening hypoxia
    - Hypercapnia
    - ABG analysis showing respiratory acidosis
    - Exhaustion, shallow respiration
    - Drowsiness, confusion, altered conscious state.

Asthma in Special Situations

Cough-variant asthma

Patients with cough-variant asthma have chronic cough as their main symptom.[251,252] Other diagnoses to be considered are drug-induced cough caused by angiotensin-converting enzyme inhibitors, GERD, chronic upper airway cough syndrome manifesting as postnasal drip, eosinophilic bronchitis, and chronic sinusitis. Once the diagnosis is established, treatment is recommended with ICS.[253,254] This condition may be confused with eosinophilic bronchitis which is characterized by cough and sputum eosinophilia with normal spirometry and AHR.[255]

Rhinitis/sinusitis and nasal polyp

Most asthma patients have coexisting rhinitis and/or sinusitis, and around 40% of patients with rhinitis have asthma.[256] Rhinitis can be classified to allergic or nonallergic. Asking patients about rhinitis symptoms and examination of upper airways is recommended to be part of the routine management of asthma. Treatment with intranasal corticosteroids has been associated with a decrease in asthma hospitalization and ED visits but not asthma control.[257,258]

Exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction (EIB) is common in inadequately controlled asthma patients. However, asthma-like symptoms can sometimes be triggered only by physical activities. Normally, bronchodilation occurs during exercise and lasts for a few minutes. In patients with EIB, the initial bronchodilation is followed by bronchoconstriction that generally peaks within 10–15 min after completing the exercise and resolves within 60 min. EIB can be prevented using SABA a few minutes before exercise.[60,259] A warm-up period before exercise may also reduce EIB symptoms. If this approach does not control the symptoms, the patient is recommended to have maintenance therapy with ICS.[133,260] Regular use of LTRA may help in this condition, especially in children.[133,260,261]

Aspirin-exacerbated respiratory disease

ASA-exacerbated respiratory disease (AERD) is a special phenotype characterized by a triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to ASA.[262] About 7% of adults with asthma and 14% with severe asthma suffer from attacks in response to ASA or NSAIDs that inhibit cyclooxygenase-1 (COX-1). This condition is more common in patients with severe asthma and poor lung function. Majority of patients experience first symptoms during their third to fourth decade of life. Once ASA or NSAID hypersensitivity develops, it persists for life. Characteristically, within minutes to 2 h following ingestion of ASA, an acute severe asthma attack develops. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck.[263] A typical history of upper and lower respiratory reaction to ASA

or NSAIDs is very suggestive for the diagnosis, which is confirmed by ASA challenge.[264] A normal sinus CT almost excludes AERD. Patients known to have ASA-induced asthma should avoid all ASA-containing products and NSAIDs. Where an NSAID is indicated, COX-2 inhibitors or alternative analgesics such as paracetamol are recommended.[265] Prophylactic low-dose ASA should also be avoided. However, referral to an allergy specialist for ASA desensitization is recommended for patients, for whom ASA is required as antiplatelet therapy, patients with difficult to manage polyposis, or patients with severe asthma who require recurrent courses of systemic steroids.[266,267] ASA and NSAID can be used in asthma patients who do not have ASA-induced asthma.[268] Montelukast may help in the treatment of this type of asthma in some patients.[269] IgE-mediated reaction to individual NSAIDs is not related to AERD.

Gastroesophageal reflux disease

GERD disease is more prevalent in patients with asthma compared to the general population. The mechanisms by which GERD worsens asthma include vagal-mediated reflex and also reflux secondary to microaspiration of gastric contents into the upper and lower airways.[270] All patients with asthma should be questioned about symptoms of GERD. If symptoms are present, a trial of anti-GERD measures (including a proton pump inhibitor) is recommended for 6–8 weeks.[271-273] Benefit of proton pump inhibitors is limited to patients with symptomatic GERD and nighttime respiratory symptoms. Of note, patients with asymptomatic GERD do not benefit from empiric GERD therapy (Evidence A).[274]

Pregnancy

A study conducted in a tertiary care hospital in Saudi Arabia showed that almost half of pregnant women had the desire to stop asthma medications during pregnancy as they believed that asthma medications would harm them and their babies more than asthma itself.[28] The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics may have a worsening of their asthma control.[275] Maintaining adequate control of asthma during pregnancy is essential for the health and well-being of both the mother and her baby. Occurrence of asthma attacks during the first trimester of pregnancy significantly increases the risk of a congenital malformation.[276] Identifying and avoiding triggers are recommended as the first step of therapy for asthma during pregnancy. Treatment is recommended to take the same stepwise approach as in the nonpregnant patient. Salbutamol is the preferred SABA due to its excellent safety profile. ICSs are the preferred treatment for long-term control.[277] ICS, theophylline, antihistamines, β2-agonists, and LTRA are generally safe, and they have not been shown to increase the risk of fetal abnormalities.[278,279] Prolonged use of systemic steroids may be associated with pregnancy-related complications, especially in the first trimester.

Pregnant women are recommended to receive the same drug treatment for acute asthma as nonpregnant patients (Evidence B), including systemic steroids if indicated (Evidence C).[275,280-283] Fetal monitoring is recommended in severe asthma attack. If anesthesia is required during labor, regional anesthesia is recommended whenever possible (Evidence C).[284] The use of prostaglandin F2α may be associated with severe bronchospasm and should be avoided, if possible (Evidence D). If asthma is well controlled during pregnancy, acute asthma is rare during labor. In the absence of acute severe asthma, reserve cesarean section for the usual obstetric indications. Pregnant asthma patients should be encouraged to breastfeed after delivery and to continue their usual asthma medications during lactation.[285-287]

Occupational asthma

All patients with asthma should be asked about their work history and exposures for possible related causal factors. A simple screening test is to ask the patient if their symptoms improve when they are away from work.[288] Once identified, early identification and elimination of occupational sensitizers and removal of patients from further exposure are an essential aspect of management. Patients with suspected or confirmed occupational asthma are recommended for referral to an asthma expert for assessment and advice because of the legal implications of the diagnosis.[289,290]

Asthma-chronic obstructive pulmonary disease overlap

COPD is common above the age of 40 years.[291] Distinguishing asthma from COPD becomes more difficult as many patients may show features of both diseases. This has been called the asthma-COPD overlap (ACO). ACO is a unique complex entity sharing features of both COPD and asthma. At this stage, there is no formal definition of ACO as there is inadequate data to describe its features, characteristics, and its optimal therapeutic intervention.[2] However, when a patient has features of both asthma and COPD, the diagnosis of ACO could be considered.

ACO has been estimated to account for approximately 15%–25% of the obstructive airway diseases in adults, and patients may experience worse outcomes compared with asthma or COPD alone.[2] Patients with ACO have the combined risk factors of smoking and atopy. They are generally younger than patients with COPD and have frequent attacks, poor quality of life, more rapid decline in lung function, higher mortality, greater health care

utilization, and low quality of life, compared to patients with COPD alone.[292-296]

Spirometry is required to confirm the diagnosis of chronic airflow limitation. Postbronchodilator FEV_1/FVC of <0.7 is usually present, and postbronchodilator increase in FEV_1 by >12% and 200 mL from baseline is compatible with diagnosis of ACO. However, spirometry alone has limited value in distinguishing between asthma, COPD, and ACO.

If the initial assessment suggests asthma or ACO, or there is uncertainty about the diagnosis of COPD, it is prudent to start treatment for asthma (ICS with or without LABA) until further investigation has been performed to confirm or exclude this diagnosis. Of note, it is important that patients should not be treated with an LABA alone if there are features suggestive of asthma.[295-297] Treatment of ACO is recommended to include advice about other therapeutic strategies, including smoking cessation, pulmonary rehabilitation, vaccinations, and treatment of comorbidities.

Management of Asthma in Children

Asthma represents the most common chronic illness of childhood.[2] It is also a leading cause for childhood morbidity as measured by school absences, ED visits, and hospitalizations.[298] From the prospective of both patient and society, the cost of not treating asthma is higher than the cost of asthma treatment.[66,299]

Asthma diagnosis in children

Clinical considerations

Accurate diagnosis of asthma in children is crucial to prevent inappropriate management and reducing morbidity and mortality due to under- or over-diagnosis.[300,301] Therefore, asthma diagnosis in children should be based on a careful clinical assessment that includes recurrent or chronic symptoms related to airway obstruction, such as wheezing, coughing, night symptoms, activity limitation, and shortness of breath. These symptoms typically result from AH or various stimuli that would be reversible either spontaneously or after receiving a bronchodilator. The diagnosis can be further supported by the presence of atopy, early sensitization, and family history of atopy. Whenever possible, spirometry is recommended to be performed to show reversibility of airway obstruction after bronchodilator therapy.[302] Generally, spirometry can be performed in children aged 5–12 years. It is preferably planned when the initial diagnosis is made and after 3–6 months of controller therapy initiation with subsequent follow-up assessment. Box 9.1 presents a summary of signs and symptoms suggestive of the diagnosis of asthma in children.

Asthma mimics should be suspected when any of the following is present:

- Failure to thrive
- Onset of symptoms during infancy
- Vomiting associated with respiratory symptoms
- Continuous wheezing
- Failure to respond to asthma controller medication
- Clubbing or focal auscultation signs
- Symptoms that are not associated with typical triggers.

Clinical suspicion of asthma mimics is an acceptable indication for CXR in a child suspected of having asthma; however, a routine CXR is not recommended to be part of the initial routine workup of asthma in children.[303]

In preschool children, asthma diagnosis and management differ from that of older children and adolescent in many ways. Early childhood wheezing can evolve to different asthma phenotypes that can have variable response to standard therapy.[304] In addition to the diagnosis of asthma, wheezing in preschool children can be due to unique differential diagnoses (e.g., congenital defects, infections, especially viral bronchiolitis, bronchopulmonary dysplasia, and cystic fibrosis). In this age group, asthma diagnosis represents a challenging clinical judgment due to the lack of objective assessment (e.g., pulmonary function test or biomarkers). "Reactive airway disease" as a terminology is discouraged as it can restrain full clinical assessment and proper management of asthmatic children in this age group.[302,305,306]

Box 9.1: Diagnosis of asthma in children

Symptom and sign	Remarks
History of multiple attacks of SOB or wheezing in a season	>3 attacks/season
Coughing	>2 weeks, during sleep, not related to URTI
Wheezing	Equal at both sides of the chest, during expiratory phase, especially on forced expiration
Atopy	Eczema, environmental/food sensitization
Family history	Atopy
Breath sounds	Prolonged expiratory phase
Therapeutic trial	Trial of short-acting bronchodilator or corticosteroid therapy
Spirometry	Typically, in children >6 years with bronchodilator response assessment
Chest X-ray	May be considered in infants to rule out congenital causes
Tests for hypersensitivity	Both skin testing or/and allergen-specific IgE blood testing

SOB=Shortness of breath, URTI=Upper respiratory tract infection

Asthma phenotypes in children

Based on several longitudinal studies, wheezing has been categorized epidemiologically into transient and persistent wheeze phenotypes. It is also categorized based on symptoms into episodic/viral-induced and multi-trigger wheeze phenotypes.[307,308] Different responses to treatment and variable outcomes have been attributed to phenotype heterogeneity, overlap, and instability over time. Major factors that may predict persistent symptoms are allergic disease, reduced lung function, viral respiratory infection, and bacterial colonization in infancy. Asthma wheeze phenotype in children has been classified as:[307,309]

- Early transient wheezing before the age of 3 years with resolution by the age of 6 years
- Persistent wheezing that starts before the age of 3 years and continues after the age of 6 years
- Late-onset wheezing between 3 and 6 years of age.

The allocation of children into these categories still remains a subject of debate as their clinical usefulness is still under investigation.[310]

Prediction of asthma in preschool children

For early identification of the risk for persistent asthma among preschool children, the SINA expert panel recommends the utilization of the modified asthma predictive index (modified-API). This tool is a clinical scoring instrument that can be used to predict whether a child with intermittent wheezing before the age of 3 years will develop persistent asthma pattern during school-age years [Box 9.2].[311,312] Children with a history of four or more wheezing attacks (at least one is diagnosed by physician) and either one major or two minor criteria at 3 years of age will have 4–10-fold increase in the risk of having asthma later in their childhood. On the other side, children with negative modified-API will have 95% chance of outgrowing their asthma later on life.[313]

Strategies of asthma management in children

The long-term goals of asthma management in children are not different from those of adults [Box 5.1].[66] Asthma management requires effective partnership between patients/caregivers and their healthcare providers.[314] Once established and strengthened, this relationship will positively impact asthma control. The asthma management strategy should include:

Assessment of asthma control combined with proper treatment

This implies a periodical assessment of asthma control combined with adjustments (if needed) of treatment based on the level of control. It is strongly recommended to use asthma treatment in a stepwise approach with the ultimate goal of achieving "optimal" control with "minimal" amount of medications and dosage.[315] Adherence to the prescribed medications and the proper use of their devices are recommended to be addressed before any modification of the treatment plan. It is extremely important to select the best device for optimal treatment delivery [Box 9.3].

Asthma control reflects the adequacy of management by describing the clinical status of a child as controlled, partially controlled, or uncontrolled. Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reported by children and their caregivers and subsequently treatment decisions by clinicians.[67] In children, assessment of asthma control is recommended to cover two domains:[295]

A. Assessing future risk of adverse outcomes: This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effect of medications [Box 9.4]
B. Assessing symptom control: Asthma symptom control has been estimated by physician assessment during clinic visit and/or perception of patients and their caregivers toward asthma control. During each clinic visit, the physician is recommended to utilize asthma control criteria to assess disease control [Box 9.5]. Different numerical tools have been developed and validated to objectively assess asthma control utilizing patients and their caregiver perception. However, as these tools have some limitations, they are recommended to be used as a complimentary tool rather than replacing physician assessment.[316]
   The SINA expert panel recommends utilizing one of the following questionnaires based on age. The questionnaire is completed by patients and/or their

Box 9.2: Modified asthma predictive index

History of ≥4 wheezing episodes with at least one physician diagnosed and either

One (or more) of the major criteria	Or	Two (or more) of the minor criteria
Parental history of asthma		Eosinophilia (≥4%)
Skin test positive to aero-allergens		Wheezing unrelated to colds
Eczema (physician-diagnosed atopic dermatitis)		Allergic sensitization to milk, egg, or peanuts

Adapted from Castro-Rodriguez[312]

Box 9.3: Choosing an inhaler device for children

Age (years)	Preferred device	Alternative device
<4	MDI + spacer with face mask	Nebulizer with face mask
4-6	MDI + spacer with mouthpiece	Nebulizer with mouthpiece
>6	Dry powder inhaler, breath actuated pressurized MDI, MDI + spacer with mouthpiece	Nebulizer with mouthpiece

Adapted from the Global Initiative for Asthma and Pedersen *et al*.[66]
MDI=Metered-dose inhaler

Box 9.4: Assessment of future risk of adverse outcomes of asthma in children*

Risk factors	Assessment
Asthma attacks within the next few months	Uncontrolled asthma symptoms
	One or more severe asthma attacks in the previous year
	The start of the child's usual "flare-up" season (especially if autumn/fall)
	Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens, especially in combination with viral infection
	Major psychological or socioeconomic problems for child or family
	Poor adherence manifested as underuse of ICS and/or over-use of SABAs
Fixed airflow limitation	Severe asthma with several hospitalizations
	History of bronchiolitis
Medication side effects	Systemic: Frequent courses of oral corticosteroids or high-dose ICS
	Local: moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask

*Adapted from the Global Initiative for Asthma.[2] ICS=Inhaled corticosteroid, SABAs=Short-acting bronchodilators

Box 9.5: Levels of asthma control in children

Characteristics	Controlled (all the following)	Partly controlled (any measure present in any week)	Uncontrolled (≥3 of any features of the partly controlled asthma in any week)
Daytime symptoms	None (<2/week)	>2 days/week	>2 days/week
Limitation of activities	None	Any	Any
Nocturnal symptoms/awakening	None	Any	Any
Need for bronchodilator	≤2 days/week	>2 days/week	>2 days/week

Adapted from the Global Initiative for Asthma[2]

THE CHILDHOOD ASTHMA CONTROL TEST (C-ACT) FOR KIDS 4-12 YEARS OF AGE				SCORE
CHILD	1. How is your asthma today?			
	○ Very bad (0)	○ Bad (1)	○ Good (2)	○ Very good (3)
	2. How much of a problem is your asthma when you run, exercise, or play sports?			
	○ It's a big problem; I can't do what I want to do! (0)	○ It's a problem & I don't like it (1)	○ It's a little problem and but it's okay (2)	○ It's not a problem (3)
	3. Do you cough because of your asthma?			
	○ Yes, all of the time (0)	○ Yes, most of the time (1)	○ Yes, some of the time (2)	○ No, none of the time (3)
	4. Do you wake up during the night because of your asthma?			
	○ Yes, all of the time (0)	○ Yes, most of the time (1)	○ Yes, some of the time (2)	○ No, none of the time (3)
CAREGIVER	5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?			
	○ Not at all (5)	○ 1-3 days (4)	○ 4-10 days (3)	○ 11-18 days (2)
	6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?			
	○ Not at all (5)	○ 1-3 days (4)	○ 4-10 days (3)	○ 11-18 days (2)
	7. During the last 4 weeks, how many days did your child wake up during the nigh because of asthma?			
	○ Not at all (5)	○ 1-3 days (4)	○ 4-10 days (3)	○ 11-18 days (2)
			C-ACT Score < 19 Indicates Uncontrolled Asthma	TOTAL SCORE

Box 9.6: The Childhood Asthma Control Test (C-ACT)*.
*Adapted from the Global Initiative for Asthma[2]

THE TEST FOR RESPIRATORY AND ASTHMA CONTROL IN KIDS (TRACK) FOR CHILDREN < 5 YEARS OF AGE					SCORE
1. During the past 4 weeks, how often was your child bothered by breathing problems (wheezing, coughing, SOB)?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
2. During the past 4 weeks, how often did your child's breathing problems, such as wheezing, coughing, or SOB, wake him/her at night?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
3. During the past 4 weeks, to what extent did your child's breathing problems, such as wheezing, coughing, or SOB, interfere with his/her ability to play, go to school, or engage in usual activities that a child should be doing at his/her age?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
4. During the past 3 months, how often did you need to treat your child's breathing problems (wheezing, coughing, or SOB) with quick-relief medications?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
5. In the past 12 months, how often did your child need to take oral corticosteroids for breathing problems not controlled by other medications?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
			TRACK Score < 80 Indicates Uncontrolled Asthma		TOTAL SCORE

Box 9.7: The Test for Respiratory and Asthma Control in Kids (TRACK)*.
*Adapted from Zeiger *et al*.[318]

caregiver before physician evaluation based on the age of the child:

- Age group 5–12 years: The Childhood-Asthma-Control Test (C-ACT)
  The C-ACT is a validated test for children aged 5–12 years [Box 9.6]. C-ACT is a two-part questionnaire with a total of seven questions. The first part is to be answered by the patient and the second part by the caregiver. The final C-ACT score is made up of the sum of the scores of the two parts, ranging from 0 (poorest asthma control) to 27 (optimal asthma control). A score of ≤19 points suggests that a child's asthma is not adequately controlled.[317]
- Age group <5 years: The Respiratory and Asthma Control in Kids (TRACK)
  The TRACK is a validated test for children <5 years [Box 9.7]. It is a five-item standardized questionnaire, with four questions that address the impairment domain and one question that addresses the risk domain of asthma control. Each item is scored from 0 to 20 points on a 5-point Likert-type scale for a total score ranging from 0 to 100. Higher scores would indicate better respiratory and asthma control; a score of 80 points suggests that a child's asthma is not controlled.[318]

Role of patient education

Patient education is recommended to be an integral part of asthma management strategy in children. It is recommended to involve the basic knowledge of the disease pathophysiology, identifying and avoiding triggering factors, environmental controls (especially cigarette smoke exposures), proper use of treatment devices, and recognition of worsening asthma symptoms and the optimal time to seek advice.[319,320] Proper asthma education can lead to a significant reduction in ED visits and hospitalizations, improve self-management

of asthma attacks, and an overall reduction in the cost of asthma care.[321]

Setting asthma action plans

An action plan that documents medications, doses, and device technique should be provided to patients and their caregivers. The action plan is also recommended to include information for patient and caregiver on how to recognize worsening of asthma symptoms and advices of treatment modification in these situations [Box 9.8].

Prevention

Asthma attacks can be triggered by a variety of factors including allergens, viral infection, pollutants, and drugs. Eliminating these exposures improves the control of asthma and reduces medication needs. Parents/caregivers of children with asthma should be strictly advised not to smoke at home at all.[66,322] Breastfeeding and Vitamin D supplementation may decrease the chance of developing early wheezing episodes, while probiotics benefit is still doubtful in preventing allergic disease.[323-325] A recent study on early-life use of probiotic supplementation did not show significant impact to prevent asthma or eczema at the age of 2 years for children at high risk.[326]

Outpatient management of asthma in children

Management of asthma should be adjusted continuously based on asthma control. If current treatment has failed to achieve control, then treatment should be stepped up until control is achieved. Whenever control is maintained for at least 3 months, then treatment can be stepped down. This stepwise approach is essential to maintain optimum control with lowest step to maximize safety and minimize cost. Although the stepwise approach is stratified into age categories (<5 years and ≥5 years), there are common concepts in the two age groups that include:

Box 9.8: Components of asthma management action plan

Item	Description
Patient identification	Name, medical record number, age, and weight
List of patient's medications	Dosage, frequency, controller versus rescuer medications
Recognition of asthma control status	In simple terms and color coded
Suggested action based on asthma control status	
How to use inhalational devices	Use illustrations
When and how to seek medical advice	Access to emergency care or call center
Others	How to clean and advices on environmental control inhalers and spacer

Controller therapy

- ICSs are considered the most effective first-line maintenance monotherapy for childhood asthma (Evidence A).[327,328] Chronic use of ICS for >3 months in prepubertal-aged children can suppress growth velocity which is dose dependent. However, asthmatic children when treated with low-dose ICS attain normal adult height but at a later age (Evidence A).[329,330] Any potential adverse effects of ICS need to be weighed against the well-established benefit to control persistent asthma. More details of the use of ICS in children are available in Appendix 1
- There are insufficient data to recommend short courses of high-dose ICS in children with mild intermittent asthma attacks (Evidence B).[331] Safety of this approach has not been established
- Children with frequent or severe asthma attacks are recommended to receive regular treatment with ICS (Evidence A).[332] Doubling the dose or even quintupling it at the early stages of loss of control did not result in reduction of asthma attacks or improvement in other outcomes[333]
- The clinical benefits of intermittent inhaled or systemic steroid for children with intermittent and viral-induced wheezing remain controversial. This practice is recommended to be discouraged until clear evidence-based practices are available on this strategy of asthma management (Evidence C).[334,335]

Reliever therapy

- Oral bronchodilator therapy is not recommended to be prescribed due to slower onset of action and higher side effects[336,337]
- LABA should not be used alone as maintenance monotherapy in children (Evidence A).[338] LABA should be used only in combination with ICS. There are different combinations available in the Saudi market [Appendix 1].

Devices

- As inhalers are the main method of delivering medications, it is recommended to choose the appropriate device [Box 9.3]. Use of valved-holding spacer, with mouthpiece when possible, is recommended when an MDI is prescribed (Evidence B).[339] Breath-actuated devices (e.g., dry powder inhalers) represent an effective and simpler option for maintenance therapy in children 5–12 years of age (Evidence C).[340,341] For more information about medications, refer to Appendix 1
- Nebulizers are not superior to MDI delivered by spacer in both acute and chronic asthma management (Evidence A).[342]

The SINA expert panel recommends ensuring consistency in the approach of asthma in adults, adolescents,

and children. Therefore, outpatient treatment will be described in three phases: initiation, adjustment, and maintenance. The recommendations in the following sections are further stratified based on age groups: <5 years and ≥5 years.

Initiation of Asthma Treatment in Children

Before initiating asthma treatment in children, it is recommended to document important findings obtained during the initial clinical assessment, such as the status of asthma control, assessing for risk factors, obtaining C-CAT score for children aged ≥5 years, and TRACK score for children <5 years. It is also recommended to provide teaching of inhalers technique and action plan and ensure that patient has a follow-up visit. The SINA expert panel recommends placing the child on one of the steps based on the common clinical scenarios described below:

- **Step 1**
  - SABA (such as salbutamol) on "as-needed basis" for a child with minimal symptoms (less than twice a week) that qualify for a controlled status based on physician assessment and are complemented with a C-ACT score of ≥20 for a child aged 5–12 years or TRACK score of >80 for a child aged <5 years
  - SABA (such as salbutamol) on "as-needed basis for a child with intermittent viral-induced wheeze.[343-345]
- **Step 2**

  Personalizing the treatment options for children in step 2 may be predicted by stratification based on asthma phenotype, assessment of aeroallergen sensitization, and determining the eosinophil count. Positive sensitization and high eosinophil count may favor ICS as a primary controller intervention.[346] The following are recommended:
  - Low-dose ICS for a child with more symptoms (more than twice a week) that qualify to partially controlled status based on physician assessment and are complemented with a C-ACT score of ≤19 for a child aged 5–12 years or TRACK score of ≤80 for a child aged <5 years (Evidence A).[347-349] Different options of ICS are available in Appendix 1
  - LTRA for a child who cannot or will not use ICSs though it is a less-effective option (Evidence B)[350-352]
  - Low-dose ICS for a child <5 years with a history of asthma attack in the past year or has ever been admitted to ICU (Evidence D)
  - In addition to a low-to-moderate dose of ICS, a short course of oral prednisolone is recommended to be considered for a child aged 5–12 years with early signs of asthma attack at presentation.
- **Step 3**
  - For a child <5 years with more persistent symptoms, commence treatment on double dose of ICS.[353,354]

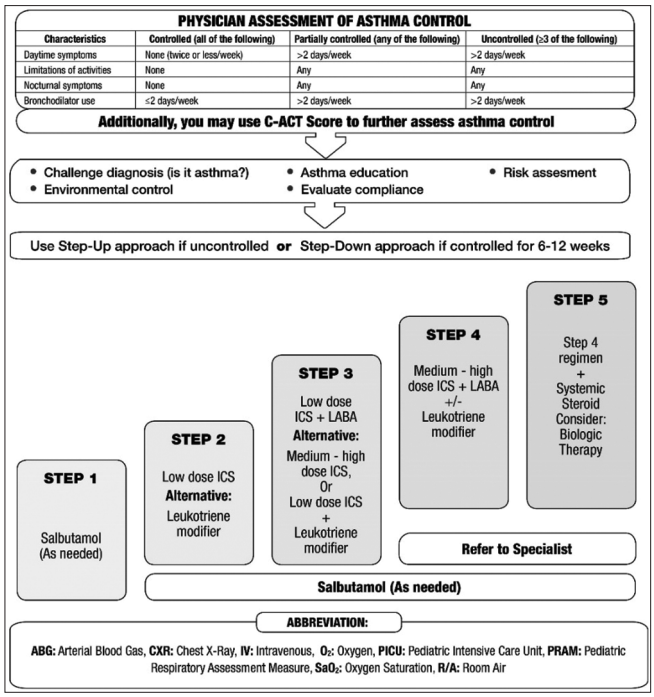
Adjustment of asthma treatment in children

Assessment of adherence, proper device use, control of environment, and confirmation of the diagnosis, especially if there is a failure to respond to therapy, are recommended each time before treatment adjustments.[355] For a child seen in the clinic for the first time while on controller treatment, the managing physician should ensure that the child is receiving the appropriate treatment based on recommendations given in the section on treatment initiation.

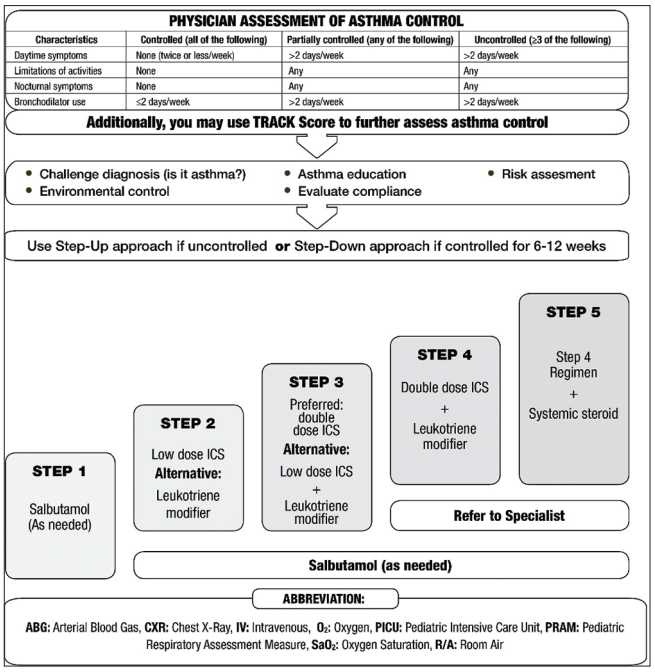
Adjustment of therapy is recommended after 1–3 months depending on the level of asthma control upon presentation and the C-ACT score for children aged 5–12 years or TRACK score for children aged <5 years. Patient should be clinically assessed regarding medications and doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors. Based on clinical assessment and the level of asthma control, the following are recommended [Boxes 9.9 and 9.10]:

- A child with uncontrolled asthma: Escalation of treatment to at least the next step. Uncontrolled status is determined based on physician assessment complemented by a C-ACT score of ≤19 for a child aged 5–12 years or TRACK score of ≤80 for a child aged <5 years
- A child with controlled asthma: Treatment is recommended to be maintained at the same step; however, stepping down may be considered during low seasons for asthma attacks. Controlled status is determined based on physician assessment complemented by a C-ACT score of ≥20 for a child aged 5–12 years or TRACK score of >80 for a child aged <5 years.

  The SINA expert panel recommends the following concepts of treatment adjustment based on age in the following section.
- Children aged 5–12 years [Box 9.9]
  - A child is not controlled at step 1: The preferred option is escalating to step 2 with low dose ICS (step 2) (Evidence A)[327,328]
  - A child with asthma control is not achieved at step 2: Escalation of treatment to step 3 by adding LABA to low-dose ICS (Evidence A).[117] Alternatively, LTRA can be added to low-dose ICS or the dose of ICS escalated to moderate dose (Evidence A)[356-361]
  - A child is not controlled at step 3: It is recommended to escalate to step 4 by changing the combination inhaler to medium dose of ICS/LABA (step 4). LTRA may be added to this combination if control is not achieved.
  - Whenever there is a difficulty to control asthma at



Box 9.9: Outpatient management of Asthma for children aged 5 to 12 years



Box 9.10: Outpatient management of Asthma for children aged <5 years

step 4, it is strongly recommended to refer patient to a physician specialized in asthma for further evaluation
- There is growing evidence to support the use of anti-IgE in children 6–12 years of age who fulfill the following criteria (Evidence A): Severe persistent allergic asthma with frequent daytime symptoms or night-time awakenings and who have multiple documented severe asthma attacks despite daily high-dose ICS plus LABA.[362,363] However, this line of management is recommended to only be restricted to physicians specialized in asthma (Evidence C)[364,365]
- Data related to specific immunotherapy in pediatrics are limited, but it can be used for children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV_1 as detailed in immunotherapy subsection.[172] It should be initiated by an asthma and allergy specialist
- There is no evidence to support the use of LAMA in children <12 years.

- Children aged <5 years [Box 9.10]
  - A child is not controlled at step 1: The preferred option is to escalate to step 2 with low-dose ICS (Evidence A)[327,328]
  - A child with asthma control is not achieved at step 2: It is recommended to escalate treatment to step 3. The recommended option is to double the dose of ICS (Evidence A).[359,366,367] Alternatively, adding LTRA to low-dose ICS is another option although this is considered as less effective.[353,354]
  - A child is not controlled at step 3: It is recommended to escalate treatment to step 4 by the addition of LTRA to moderate-dose ICS (Evidence B)[368-370]
  - Whenever there is a difficulty to control asthma at step 4, it is strongly recommended to refer patient to a physician specialized in asthma for further evaluation and options in step 5
  - There is no evidence to support the use of LABA in children <5 years

It is recommended to provide the caregiver an asthma action plan and a follow-up visit in 1–3 months depending on clinical status. Uncontrolled asthma in preschool children can lead to developmental disadvantages due to the negative impact of uncontrolled asthma on their social interaction and sleep. Caregivers of preschool children should be educated that asthma control is an achievable target and affected children should not be prevented from engagement in age-appropriate activities.

Maintenance of asthma treatment in children

On follow-up, it is recommended to perform a full clinical assessment including asthma control status and obtaining C-ACT score for children aged 5–12 years or TRACK score for children aged <5 years. Based on clinical assessment and asthma control status [Boxes 9.6 and 9.7], the SINA expert panel recommends the following:

- Step up treatment for children who are uncontrolled based on physician assessment and complemented by a C-ACT score of ≤19 for a child aged 5–12 years or TRACK score of ≤80 for a child aged <5 years. It

is recommended to rule out any modifiable factors preventing reaching optimal asthma control
- Patient should be clinically assessed regarding medications and doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors
- Maintain treatment for children who reached controlled status based on physician assessment complemented by a C-ACT score of ≥20 for a child aged 5–12 years or TRACK score of >80 for a child aged <5 years
- Consider stepping down treatment for children who are controlled for at least 3 months.

Reduction in therapy should be gradual and closely monitored based on clinical judgment complemented by either C-ACT score or TRACK score. Furthermore, close monitoring on treatment stepping down is recommended for patient who has risk of asthma attack, especially during seasonal variation or for those with prior acute asthma attack in the past year or history of ICU admission.

The SINA expert panel recommends the following concepts for stepping down treatment based on age.
- Children aged 5–12 years [Box 9.9].
  If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25%–50% every 3–6 months to the lowest possible dose that is required to maintain control (Evidence B).[159-161] It should be clearly explained to the patient and/or caregiver that asthma control may deteriorate if treatment is abruptly discontinued.[162] In such a situation, an action plan that contains instruction on resuming controller therapy if asthma symptoms recurred is recommended to be provided to patients and their caregiver.
  - If the patient is on combination of ICS/LABA at step 3 or 4, abrupt discontinuation of LABA may lead to deterioration of asthma control[163]
  - If the patient is on a combination of ICS with LABA or LTRA, taper ICS to the lowest possible dose (Evidence B).[164,165] If control is maintained, LABA or LTRA may then be discontinued (Evidence D)[164]
  - For significant local side effects of ICS, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advice for a vigorous mouth washing after inhalation, enforce use of MDI with spacer, and/or use of appropriate local antifungal therapy for severe oral thrush[166]
  - For patients on continuous oral steroids, the dose is recommended to be tapered to the lowest dose and preferably to every other day (Evidence D). It is recommended to refer the child to a specialized physician in asthma management.
- Children aged <5 years [Box 9.10]
  - The need for continuation of ICS should be regularly assessed as wheeze remits in a significant portion of children[371]
  - If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25%–50% every 3–6 months to the lowest possible dose that is required to maintain control (Evidence B).[159,160] It is recommended to be clearly explained to the caregiver that asthma control may deteriorate if treatment is abruptly discontinued.[162] If asthma symptom is recurred, an action plan that contains instruction on resuming controller therapy is recommended to be provided to patients and their caregiver
  - For significant side effects, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advice for a mouth washing after inhalation if possible, enforce use of MDI with spacer, and/or use of appropriate local antifungal therapy for severe oral thrush[166]
  - Uncontrolled asthma in preschool children can lead to developmental disadvantages due to the negative impact of uncontrolled asthma on their social interaction and sleep. Caregivers of preschool children are recommended to be educated that asthma control is an achievable target and affected children should not be prevented from engagement in age-appropriate activities.

Referral to an asthma specialist

Referral to an asthma specialist for consultation or co-management is recommended in the following situations:
- There is uncertainty regarding the diagnosis
- There is difficulty achieving or maintaining control of asthma
- Immunotherapy or omalizumab is being considered
- The patient requires step 4 care or higher
- The patient has had an asthma attack requiring a hospitalization or 2 or more oral corticosteroids in the past 12 months.

Management of Acute Asthma in Children

Early recognition of acute asthma

Recognition of early signs of acute asthma is essential especially for those <5 years. Early symptoms of acute asthma include (Evidence D):
- An attack of shortness of breath with wheeze or increase of shortness of breath with wheeze
- Cough, especially at night although this is nonspecific
- Impairment of daily activity
- An increased need for or poor response to SABA
- For a child <2 years, the presence of lethargy and poor feeding should raise the suspicion of acute asthma

attack. However, viral bronchiolitis is a common differential diagnosis in this age group during winter season.

In a child aged 2–5 years, the combination of the above features can predict approximately 70% of acute asthma attacks with low false-positive rate.[372] Moreover, upper respiratory tract infection (URTI) may frequently precede acute asthma attack in children. Clinical assessment is essential in children as the utilization of objective measure such as Pulmonary function tests (PFT) is problematic, especially in the younger age groups.

Initial management of acute asthma at home

The SINA expert panel recommends management of a child with asthma to include an action plan that enable the caregiver to recognize worsening of asthma and the advices for initial treatment (Evidence D). The action plan is recommended to include features that mandate the need for urgent medical care that includes acute distress of the child, difficulty to complete few words in one breath, and poor response to SABA treatment at home.

In the case of acute attack, initial management at home by the caregiver should be started with salbutamol inhaler 2–4 puffs by a spacer that may be repeated every 20 min for a total of three doses. If the child improves, asthma therapy is recommended to be stepped up as per instructions in the action plan and medical advice should be sought as soon as possible. If the child does not adequately improve within or after the initial period, urgent medical care is recommended.

Assessment of asthma severity in the emergency department

Assessment of acute asthma severity in children has an important role in various components of acute asthma management such as pharmacological interventions, need for hospitalization, and need for ICU admission. The assessment of acute asthma severity in young children is also important for clinical decision-making and evaluation of treatment effectiveness.[67,98,373-382] This is supported by the fact that PFT measurement is not feasible as more than half of asthma attacks in children presented to EDs for children <5 years.[374]

The Pediatric Respiratory Assessment Measure (PRAM) has been found to be feasible, valid, responsive, and reliable tool to determine acute asthma severity in children aged 2–17 years.[374,383] The PRAM represents a useful means to record clinical signs in a standardized fashion [Box 10.1].[67] The PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing.[381] Clinical pathways based on PRAM for inpatient asthma management has been shown to decrease the length of stay and bronchodilator use with no adverse outcomes or increased acute care encounters.[384,385] The SINA expert panel recommends measuring PRAM score for asthmatic patients in emergency as it can categorize the risk of hospitalization:

- Total score of 1–3: Low risk with a chance of <10% for hospital admission
- Total score of 4–7: Moderate risk with a chance of 10%–50% for hospital admission
- Total score of 8–12: High risk with a chance of >50% for hospital admission.

Management of acute asthma in the emergency department

After performing the necessary clinical assessment, the SINA expert panel recommends the utilization of PRAM as a tool to assess patients in the ED and guide further management as well. The PRAM score should be obtained at the initial assessment and after initiation of treatment as well. After initial clinical assessment and starting initial appropriate therapy, managing physician is recommended to focus on obtained history to identify risk factors for ICU admission, including:[386]

- Previous life-threatening asthma attack
- Previous ICU admission
- Previous intubation
- Deterioration while already on systemic steroid.

In addition, managing physician is recommended to be aware of the following clinical features of severe or life-threatening asthma that require immediate medical attention:

- Child is unable to speak or drink
- Central cyanosis
- Confusion or drowsiness

Box 10.1: The pediatric respiratory assessment measure score*

Sign	0	1	2	3
Suprasternal retraction	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry	Normal	Decreased at bases	Widespread decreased	Absent/minimal
Wheezing	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥95%	92-94%	<92%	

*Adapted from Chalut *et al*.[381]

- Significant subcostal or subglottic retraction
- Oxygen saturation <92%
- Silent chest on auscultation
- Tachycardia.

Implementation of clinical pathway that utilizes PRAM score for acute asthma management in children with moderate-to-severe asthma attacks markedly decrease the rate of hospitalization without increasing the rate of return to emergency care (Evidence B) [Box 10.2].[384,387-389] This has been supported by a study showing that PRAM score after 3 h of initial management was associated with a significant improvement in the prediction of admission rate compared to pure clinical judgment at triage.[383] Ancillary investigation that includes CXR and ABG are not routinely recommended.[386] ABG is indicated in severe bronchial asthma that failed to respond to maximum therapy and required ICU admission. However, CXR is recommended in the following conditions:

- Suspected bacterial pneumonia that presents with fever >39°C and presence of focal finding of decreased breath sound and crackles
- To rule out bronchial asthma complications such as pneumothorax
- Severe disease that does not respond to maximum treatment
- Uncertainty about the diagnosis
- Hypoxemia apparently disproportionate to the attack severity.

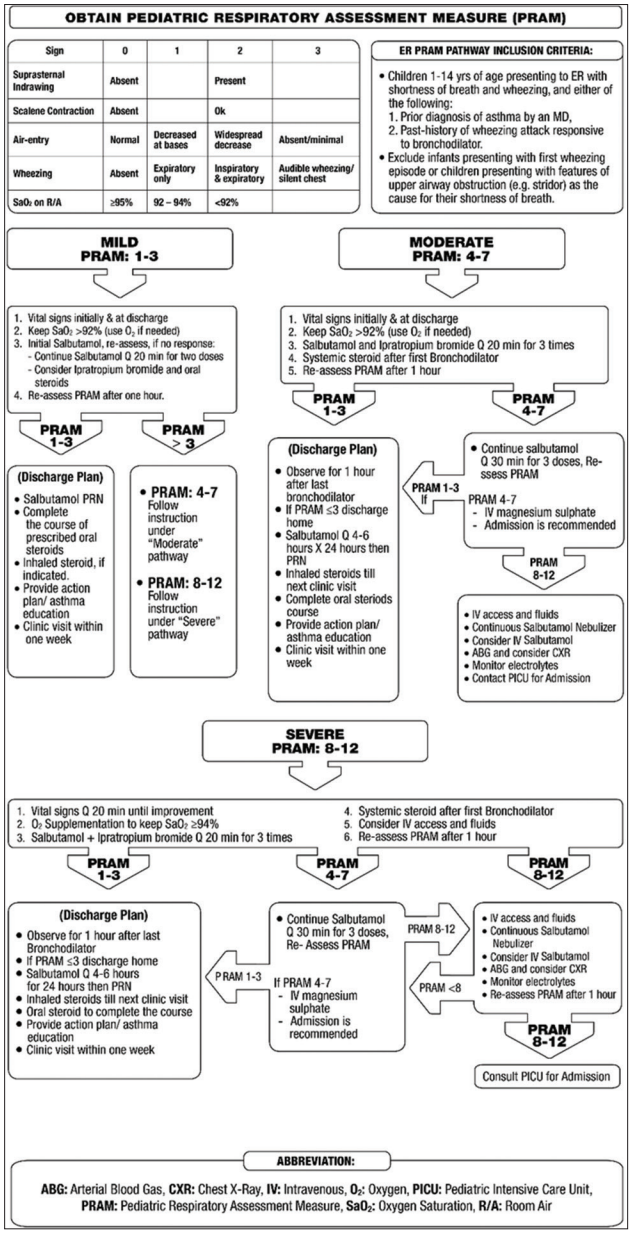
Viral infection is the usual cause of asthma attacks in children, and thus, routine use of antibiotics is strongly discouraged.[390] Antibiotics are recommended when bacterial pneumonia is clinically suspected.[387,388]

Acute asthma management based on Pediatric Respiratory Assessment Measure:

The SINA expert panel recommends managing asthma based on PRAM score obtained at initial assessment:

Mild-Pediatric Respiratory Assessment Measure score of 1–3

- Management
  - Obtain vital signs initially and at discharge
  - Prescribe appropriate oxygen dose to keep saturation ≥92%
  - Salbutamol dose based on weight:[342,391]
    - Less than 20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer
    - 20 kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response)
    - In mild cases, SABA with spacer is not inferior to nebulized SABA.
  - Ipratropium bromide may be considered at a dose of 4 puffs by MDI/spacer or 250 mcg by nebulizer every 20 min for the 1st h only[392]
  - Consider oral steroid if there is no response to the first dose of salbutamol. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose of 16 mg[250]
  - Re-assess PRAM after 1 h.
- Management after initial treatment based on PRAM score
  - PRAM score is 1–3
    - The child may be discharged on salbutamol inhaler and ICS inhaler with a spacer



Box 10.2: Assessment and treatment of acute asthma in children

- If oral steroids course is given initially, dexamethasone is recommended for extra one day and prednisolone for total of 3–5 days
- It is recommended to offer the child an action plan, education on inhalers technique, and a follow-up visit within 1 week to the appropriate clinic.

- PRAM score is 4–7: Treat as a moderate asthma attack (see below).
- PRAM score is 8–12: Treat as a severe asthma attack (see below).

Moderate-Pediatric Respiratory Assessment Measure score of 4–7

- Management
  - Obtain vital signs.
  - Prescribe appropriate oxygen dose to keep saturation ≥92%.
  - Salbutamol dose based on weight:[342,391]
    - Less than 20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer
    - 20 kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response
    - Ipratropium bromide at a dose of 4 puffs or 250 mcg by nebulizer every 20 min for the 1st h only.[391-393]
  - The combination of salbutamol and ipratropium bromide has been shown to be effective in this situation (Evidence B)[391]
  - Systemic steroids after the first dose of SABA. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16 mg[233,250]
  - Re-assess PRAM after 1 h.
  - If PRAM score after 1 h is 1–3, observe for another hour.
- Management after initial treatment based on PRAM score:
  - PRAM score is 1–:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment
    - Complete the course of oral steroids. Dexamethasone is recommended for extra 1 day and prednisolone for total of 3–5 days; both as once daily dose
    - It is recommended to offer the child an action plan, education on inhalers technique, and a follow-up visit within 1 week to the appropriate clinic.
  - PRAM score is 4–7: It is recommended to continue treatment with salbutamol every 30 min for three doses and to assess PRAM score every 30 min. Further evaluation is based on PRAM re-assessment:
    - If PRAM score improves to 1–3, the child can be managed as above
    - If PRAM score does not improve, IV magnesium sulfate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min. The child needs close monitoring for blood pressure and appropriate IV fluids. Admission is recommended to be considered.[394-396]
  - PRAM score is 8–12: Treat as severe asthma attacks (see below).

Severe-Pediatric Respiratory Assessment Measure score of 8–12

- Management
  - Obtain vital signs every 20 min till improvement
  - Prescribe appropriate oxygen dose to keep saturation ≥94%
  - Salbutamol nebulizer at a dose of 2.5 mg for those weighted <20 kg or 5 mg for those weighted ≥20 kg and ipratropium bromide at a dose of 250 mcg by nebulizer every 20 min for the 1st h.[391-393,397] This combination has been shown to be effective in this situation (Evidence B)[391]
  - Systemic steroids after the first dose of SABA. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16 mg[233,250]
  - Re-assess PRAM after 1 h
  - Consider IV access and appropriate IV fluids
  - If PRAM score after 1 h is 1–3, Observe for another hour.
- Management after initial treatment based on PRAM score:
  - PRAM score is 1–3:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment
    - Complete the course of oral steroids. Dexamethasone is recommended for extra 1 day and prednisolone for total of 3–5 days; both as once daily dose[233,250]
    - It is recommended to offer the child/care giver an action plan, education on inhalers technique, and a follow-up visit within one week to the appropriate clinic.
  - PRAM score is 4–7: It is recommended to continue treatment with salbutamol every 30 min for three doses and to assess PRAM score every 30 min. Further evaluation is based on PRAM re-assessment:
    - If PRAM score improves to 1–3, the child can be managed as above

- If PRAM score does not improve, IV Magnesium sulfate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min. The child needs close monitoring for blood pressure and appropriate IV fluids. Admission is recommended to be considered.[394-396]

- PRAM score is 8–12: Deterioration of clinical status despite adequate treatment in the initial period warrants special care and attention. It is recommended to:
  - Establish IV access and to start on appropriate IV fluids
  - Continue nebulized salbutamol back-to-back every 20 min or use continuous salbutamol nebulization at a dose of 7.5 mg/h for those weighted <10 kg, 11.25 mg/h for those weighted 10–20 kg, or 15 mg/h for those weighted >20 kg[248,398]
  - If PRAM score does not improve, IV magnesium sulfate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min
  - If no improvement in PRAM score, start IV salbutamol at a dose of 1 mcg/kg/min, then titrate based on response for a maximum dose of 10 mcg/kg/min[395,396]
  - ABG, CXR, and electrolyte are recommended to be obtained and the pediatrics critical care or equivalent service must be consulted.

Appendix 1: Medications Used for the Treatment of Asthma

The objective of asthma treatment is to achieve and maintain control of the disease. Medications used to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control through their anti-inflammatory effects.[399] Relievers are medications used on an "as-needed basis" that act quickly to reverse bronchoconstriction and relieve symptoms.

Controller medications

Inhaled corticosteroids

ICSs are currently the most effective anti-inflammatory medications for the treatment of asthma.[45,102,400] They reduce symptoms, improve quality of life, improve lung function, decrease airway hyperreactivity, control airway inflammation, reduce frequency and severity of asthma attacks, and reduce asthma mortality. Early initiation of low-dose ICS in asthma leads to improvement in lung functions.[118] When they are discontinued prematurely or abruptly, deterioration of clinical control follows within weeks to months in most patients. ICSs differ in their potency and bioavailability. Most of the benefits from ICS are achieved in adults and children at relatively low doses [Boxes 11.1 and 11.2]. Exposure to tobacco smoking or vaping, including secondary and tertiary, reduces the responsiveness to ICS. To reach control, add-on therapy with another class of controller is preferred to increase the dose of ICS.[129,401]

Box 11.1: List of inhaled corticosteroid inhalers*

Drug (Doses in mcg)**	Low dose	Medium dose	High dose
Beclomethasone dipropionate (CFC)	200-500	>500-1000	>1000
Beclomethasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone propionate (DPI and HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440

*Adapted from the Global Initiative for Asthma,[2] **Based on availability in the Saudi market for children. CFC=Chlorofluorocarbon propellant, DPI=Dry powder inhaler, HFA=Chlorofluoroalkane propellant

Box 11.2: List of inhaled corticosteroids inhalers*

Drug (doses in mcg)**	<5 years	Children above 5 years		
	Low dose	Low dose	Medium dose	High dose
Beclomethasone dipropionate (CFC)	100	100-200	>200-400	>400
Beclomethasone dipropionate (HFA)	100	50-100	>100-200	>200
Budesonide	200	100-200	>200-400	>400
Budesonide (Nebules)	500	250-500	>500-1000	>1000
Ciclesonide	160	80	>80-160	>160
Fluticasone propionate (DPI)	Not applicable	100-200	>200-400	>400
Fluticasone propionate (HFA)	100	100-200	>200-500	>500
Mometasone furoate	Not studied	110-220	>220-440	>440

*Adapted from the Global Initiative for Asthma,[2] **Based on availability in the Saudi market for children. CFC=Chlorofluorocarbon propellant, DPI=Dry powder inhaler, HFA=Chlorofluoroalkane propellant

Local adverse effects can occur and include oropharyngeal candidiasis and dysphonia; with MDIs, these effects are reduced using a spacer device. Mouth and throat washing after inhalation may reduce oral candidiasis. The small risk of adverse events from the use of ICS is well balanced by their efficacy.[402] Therefore, low-medium dose of ICS is generally safe and well tolerated in children. Formulations with small size particles are believed to be more effective and safer as it leads to better deposition in the peripheral small airways.[403,404] Some studies have shown that ciclesonide had relatively lower local and systemic side effects, especially in children.[405] Systemic side effects are occasionally reported with high doses and long-term treatment.

Special considerations for use of inhaled corticosteroids in children

Growth retardation may be seen with all ICS when a high-dose ICS is chronically used. Systematic reviews showed a reduction may affect height velocity in prepubertal children over 12 months use of low-to-medium dose of ICS, especially during the 1st year of life.[406] Although this effect was statistically significant, it is not clear if that will be of significant clinical impact. For instance, use of moderate-dose ICS resulted in 1.2 cm reduction in the final adult height after more than 4 years use.[407] Moreover, more studies demonstrated the negative impact of medium-to-high doses ICS on bone mineralization.[408-410] However, it is crucial to remember that long-term use of ICS is safer than frequent bursts of oral corticosteroids on bone mineralization. Adequate nutrition with sufficient intake of calcium and Vitamin D can blunt these effects.[411] In summary, the potential adverse effects of ICS need to be weighed against the well-established benefit to control persistent asthma. Therefore, it is important to target the lowest possible ICS dose that maintains adequate asthma control.

Long-acting inhaled β2-agonists

The commonly used long-acting inhaled β2-agonists, formoterol and salmeterol, are used on a twice daily basis. Novel LABA agents with a 24-h duration of action are available, e.g., indacaterol, vilanterol, and olodaterol.[412-418] Due to lack of anti-inflammatory effect, LABA should not be used alone as monotherapy in asthma as this can lead to increased mortality, and indeed, they should only be prescribed in combination in the same device with ICS. When used in combination with ICS, there is an improvement in symptoms, decreased nocturnal asthma, improved lung function, decreased use of inhaled β2-agonists, reduced number of asthma attacks, and better control at a lower dose of ICS. LABA provides longer protection to prevent exercise-induced bronchospasm than short-acting inhaled β2-agonists (SABA).[419] Their side effects are limited to tachycardia, tremor, headaches, muscle cramps, and sometimes hypokalemia. Regular use of LABA combined with ICS may lead to a reduction in their side effects. Furthermore, patients rarely develop tolerance to LABA. The effect of LABA has not been adequately studied in children of <5 years.

Fixed combination of inhaled corticosteroids and LABA

Fixed combination of ICS and LABA is considered more convenient for patients. Combination therapy is generally safe and did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma attacks.[420] They increase adherence and ensure that LABA is always accompanied by ICS. Although salmeterol and formoterol provide a similar duration of bronchodilation and protection against bronchoconstriction, formoterol has a more rapid onset of action than salmeterol. Therefore, combination inhalers containing formoterol may be used for both rescue and maintenance of control.[105,420] Fixed combination inhalers of ICS and LABA have been available in the form of fluticasone propionate and salmeterol (Seretide) or budesonide and formoterol (Symbicort). However, new formulations are available in different devices in the Saudi market [Box 11.3] such as beclomethasone and formoterol (Foster), fluticasone propionate and salmeterol (Rolenium), and fluticasone propionate and formoterol (Flutiform).[421-424]

Box 11.3: List of fixed combinations of inhaled steroid and long-acting β2 agonists

Inhaled steroid (doses in mcg)	Long acting β2 agonist (doses in mcg)	Brand name	Device type	Device name
Beclomethasone (100)	Formoterol (6)	Foster®	MDI	
Budesonide (80,160, 320)	Formoterol (4.5, 9)	Symbicort®	DPI	Turbuhaler™
Budesonide (200, 400)	Formoterol (6, 12)	Pulmoton®	DPI	Elpenhaler™
Fluticasone propionate (50, 125, 250)	Salmeterol (25)	Seretide®	MDI	Evohaler™
Fluticasone propionate (100, 250, 500)	Salmeterol (50)	Seretide®	DPI	Diskus™
Fluticasone furoate (100, 200)	Vilanterol (25)	Relvar®	DPI**	ElliptaM
Fluticasone propionate (50,125,250)	Formoterol (5, 10)	Flutiform®	MDI	
Fluticasone propionate (250, 500)	Salmeterol (50)	Rolenium®	DPI	Elpenhaler™
Mometasone furoate (100)	Formoterol (5)	Dulera®	MDI	

Based on availability in the Saudi market for children, **Once a day combination. MDI=Metered-dose inhaler, DPI=Dry powder inhaler

Once a day dry powder combination of ICS/LABA with fluticasone furoate and vilanterol (Relvar) is available in two strengths of 100/25 and 200/25 μg with dispensed equivalent dose of 92/22 and 184/22 μg, respectively.[126,127] The dose of fluticasone furoate of 100 mcg is equivalent to fluticasone propionate 250 mcg.[425] Such a combination has a potential adherence advantage while maintaining the same safety as the combination of fluticasone propionate and salmeterol.[426]

Leukotriene modifiers

Leukotriene-modifying agents reduce airway inflammation and improve asthma symptoms and lung function, but with a less consistent effect on asthma attacks, especially when compared to ICS. They may be used as an alternative treatment to ICS for patients with mild asthma, especially in those who have clinical rhinitis. Some patients with ASA-sensitive asthma respond well to the LTRA. However, when used alone as a controller, their effects are generally less than that of low-dose ICS. When added to ICS, LTRA may reduce the dose of ICS required by patients with uncontrolled asthma and may improve asthma control.[427,428] LTRA are generally well tolerated. In children, studies have shown that LTRA may be useful for reducing the number of asthma attacks induced by viruses and for reducing bronchial inflammation in atopic children.[429-432] There are no clinical data to support their use under the age of 6 months.

Long-acting antimuscarinic agents

LAMAs inhibit the effect of acetylcholine on M3 receptors. Tiotropium was the first agent used in managing patient with COPD. Tiotropium use has been extended to asthma. The more recent LAMAs (such as aclidinium bromide and glycopyrronium) have not been studied in asthma yet. Given tiotropium's bronchodilatation duration of action of >24 h, it is used on a daily base.[433,434] The earlier studies on tiotropium were conducted using the HandiHaler device. Later studies were conducted using the new Respimat device. Till date, tiotropium is available in the Saudi market in the HandiHaler device in an 18-mcg capsule format. The Respimat device is not yet widely available in the Saudi market. Tiotropium was first shown to be effective in treatment stepping-down when added to a combination of ICS/LABA.[435] Tiotropium was found to be not inferior to salmeterol in the management of asthma not adequately controlled on ICS or combination of ICS/LABA.[14,137,138,436] If symptom control is not achieved, adding tiotropium to the combination of ICS and LABA is a recommended option as it significantly improves lung function in uncontrolled cases and reduces attacks (Evidence A).[136,144,145] Anticholinergic drugs are considered to be safe. The main side effect is dryness of mouth. Although mild prostatic symptoms have been reported, there is no evidence of a direct causal relationship.

Theophylline

Theophylline is a weak bronchodilator with modest anti-inflammatory properties. It may provide benefits as an add-on therapy in patients who do not achieve control with ICS alone but is less effective than LABA or LTRA. Theophylline is not recommended for use as monotherapy in asthma treatment. Low-dose theophylline (300 mg/day) may have an important role in improving steroid resistance in patients with severe asthma requiring high-dose ICS.[437,438] Side effects include gastrointestinal symptoms, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the early symptoms of toxicity. Liver disease and CHF may increase the risk of toxicity. Use of lower doses may decrease these side effects. Theophylline has drug interaction with quinolones, and some macrolides may increase the risk of toxicity.

Oral β2-agonists

The side effect profile is much higher than that of inhaled β2-agonists. Therefore, their use is highly discouraged in asthma management. Oral route is not recommended in children.

Cromones

Cromones (sodium cromoglycate and nedocromil sodium) are not recommended for preschool children. They have limited role in the long-term treatment of older children. Evidence showed that low-dose ICS is superior to cromones in the management of asthma.[439] They are no longer available as an option to treat asthma.

Systemic corticosteroids

Long-term oral steroid therapy (excluding short courses for acute attacks of asthma for a period of 1–2 weeks) may be required to control difficult-to-treat asthma despite maximum standard therapy. The dose should be reduced to the lowest possible and other controllers are recommended to be maximized to minimize the side effects from the oral corticosteroids. Its use is limited by the risk of significant adverse effects. Use of intramuscular long-acting steroids is highly discouraged because of the increased risk of side effects. The side effects include osteoporosis, hypertension, diabetes, adrenal insufficiency, obesity, cataracts, glaucoma, skin thinning, and muscle weakness. Withdrawal can elicit adrenal failure. In patients prescribed long-term systemic corticosteroids, prophylactic treatment for osteoporosis is recommended.

Reliever medications

Relievers are medications used on an "as-needed basis" and act quickly to reverse bronchoconstriction and relieve symptoms.

Rapid-onset inhaled β2-agonists

Short-acting bronchodilators, such as salbutamol, are the medications of choice for relief of symptoms of acute attacks of asthma and for the pretreatment of exercise-induced bronchoconstriction. Use of MDI with a chamber is as effective as the nebulized route in treatment of acute episodes of wheeze in children.[230] Regular long-term use of SABA is not recommended. Formoterol is an LABA that has a fast-acting component but is not available alone in the Saudi market in a single inhaler; however, it can be used as a rescue medication in formoterol containing combination with ICS.[105-107] Vilanterol is another LABA used once a day that has a fast onset of action within 15 min and long half-life; hence, the patient should be advised to only use it once a day on a regular basis and not a rescue medication.[126,127]

In acute asthma, inhaled salbutamol is the preferred choice.[227,232] Repeated doses are recommended to be given at 15–20 min intervals. Alternatively, continuous nebulization (salbutamol at 5–10 mg/h) could be used for 1 h if there is an inadequate response to initial treatment. However, a meta-analysis of randomized controlled trials of adults with acute asthma found no significant differences between the continuous or intermittent methods in terms of pulmonary function or hospital admission; nevertheless, patients treated by continuous nebulization had fewer side effects.[440] In patients who are able to use the inhaler devices, 6–12 puffs of MDI with a spacer are equivalent to 5 mg of salbutamol by nebulizer. As the inhaled route has a faster onset of action and fewer adverse effects, the use of IV β2-agonists in the initial treatment of patients with acute severe asthma is not generally recommended.[441] IV therapy should not be considered routinely and only used cautiously if the response to the inhaled drug is poor or if the patient cannot tolerate the inhaled route.

Anticholinergics

Anticholinergics are less effective than SABA in asthma. However, when used in combination with SABA in acute asthma, they provide an additional benefit.[391] It can also be an alternative bronchodilator for patients who experience adverse effects, such as tachycardia, arrhythmia, and tremor from rapid-acting β2-agonists. Their side effects include dryness of the mouth and a bitter taste.

In moderate-to-severe acute asthma, combining ipratropium bromide with salbutamol was shown to have additional bronchodilation effect and faster improvement in lung function, compared to salbutamol alone.[239,242] A systematic review showed the combination therapy has an added benefit in reducing hospitalizations.[241] Combining both agents led to reduction in hospital admission rates by 38%–57%, improvement in lung function, and substantial cost saving.[242,442,443] No evidence of benefit for length of hospital stay and other markers of response when inhaled anticholinergics are added to short-acting β2-agonists in hospitalized asthmatic children with acute attacks.[444] The adult dosing of nebulized ipratropium bromide is 500 μg every 20 min for three doses, then as needed. Alternatively, ipratropium bromide can be administered by MDI at a dose of 4–8 puffs (80–160 μg) every 20 min, then as needed for up to 3 h.

Theophylline

There is no evidence supporting the routine use of theophylline in treating acute asthma and its routine use is discouraged. Similarly, routine use of IV aminophylline in acute asthma is strongly discouraged as there is no evidence to show added benefit and the drug has high levels of toxicity and side effects.[445]

Intravenous magnesium sulfate

In a systematic review, magnesium sulfate was shown to reduce hospitalizations in patients with severe or life-threatening asthma attacks that failed to respond to initial treatment.[446] A single dose of IV magnesium sulfate at a dose of 1–2 g over 20 min is safe and effective in acute severe asthma.[244]

Aerosol devices used in asthma

Medication aerosol can be delivered using three devices:

Small-volume nebulizer

It is the most popular for patients and clinicians in acute asthma. Small-volume nebulizer (SVNs) are predominately powered by a compressed gas (air or oxygen) to convert one or more drug solutions or suspensions at any concentrations and dose into aerosols. One of its main advantages is that it requires minimal patient cooperation and is therefore suitable for all ages, with normal breathing and no inspiratory pause required. One of its main disadvantages is importability, time to deliver the medication (10–25 min), and potential of contamination. There are high-output aerosol nebulizers that have an output rate of 30–50 ml/h and a flow rate of 10–15 L/min. It provides up to 8 h of continuous nebulization and has a 240-ml reservoir.

Pressurized metered-dose inhaler

It is a pre-pressurized inhaler with medication and a propellant, which when actuated will give one dose of the drug for a single inspiration. An MDI typically requires slow inspiratory flow (≤30 L/min). One of its main advantages is that it is premixed and the ability to provide multiple doses in a short period. It is also small and portable with limited contamination. Disadvantages include the need of patient training to coordinate

inhalation with actuation, and if this is not done properly, there is a potential of high deposition of drug in the oropharynx and poor drug delivery. Furthermore, because it does not have dose counter, it is difficult to determine the dose remaining in the canister. Compared to the older chlorofluorocarbon propellant formulations, hydrofluroalkane formulations provide smaller particle size aerosols with less oral deposition, hence less oral side effects and greater proportion of lung deposition.

Dry powder inhaler

It is not pressurized (no propellant) and therefore requires high inspiratory flows (60-90 L/min) to disperse a full dose. In addition to its portability, advantages include easier inhaler technique and a built-in dose counter. Disadvantages include the need for adequate inspiratory flow to disperse a full dose. If not used properly, high oropharyngeal impaction may occur and exhaled humidity into mouthpiece might affect the function of some devices. Therefore, it may not be suitable for very young or very old patients. The commonly available devices in Saudi Arabia include Turbohaler, Diskus, Handihaler, Easi-Breathe, Ellipta, and Breezhaler devices.

Breath-actuated inhalers

These inhalers automatically release a spray of medication when the person begins to inhale. They are easy to use and improve asthma control and compliance to medications.[447-450]

Biologics in asthma treatment

The recent progress in biologic therapy in asthma has made a step forward toward the practice of precision medicine for asthma patients. This section describes the biologic agents that received appropriate approvals.[451] We also included agents that are potential therapies in the near future, while other agents are still in the pipeline and yet being evaluated by ongoing trials.

Anti-immunoglobulin E

Omalizumab is a recombinant humanized monoclonal antibody against soluble IgE. It prevents binding of IgE to its high affinity receptor and subsequently lowers its expression and the activation of mast cells, basophils, and dendritic cells. Omalizumab is indicated for patients ≥6 years of age with severe allergic asthma (at least one positive aeroallergen on skin prick testing or an elevated specific aeroallergen IgE level) uncontrolled on high-dose ICS combined with LABA and other controllers and who have an IgE level of within therapeutic range. It was shown to reduce attacks, reduce hospitalizations, and allow stepping down of ICS dose.[452,453] Baseline IgE level does not predict response but is necessary, in addition to the weight, to calculate the dose. The side effects include pain and bruising at injection site and very rarely anaphylaxis (0.1%). This drug requires careful monitoring and should only be initially prescribed by an expert physician in asthma treatment. There is an extensive experience with omalizumab of >15 years. It is classified as category B for use in pregnant women based on the current cumulative experience. Therefore, it is not recommended to start omalizumab during pregnancy but can be continued for those who already use it if the benefit outweighs the risk.

Anti-interleukin 5

IL-5 is critical for the development and maturation of eosinophils. Anti-IL-5 monoclonal antibody treatment is directed to patients with severe eosinophilic asthma who are not controlled on step 4 of treatment with two or more attacks in the past year and who have peripheral blood eosinophils according to specific anti-IL-5 agent. Anti-IL-5 therapy reduces attacks by 40%–60% with improvement in lung function and allows about 50% reduction of oral glucocorticoids.[454-456] They are approved for patients ≥12 years (reslizumab is approved for patients ≥18 years). Patients with more severe disease and higher eosinophil counts are expected to benefit more.[457] There is no available evidence that compares anti-IgE therapy to any of the anti-IL-5 therapies or directly comparing different anti-IL-5 agents. As there are currently no data to guide when to stop anti-IL5 therapy, the treatment may be continued for up to 6–12 months before the stopping decision (Evidence D).[153]

These medications should be avoided in patients with active helminthic infection. No enough data regarding use during pregnancy. There are currently three different anti-IL5 medications in clinical use:

- Mepolizumab binds circulating IL5. Blood eosinophils should be >150/μl at the time of treatment initiation or >300/μl within the last 12 months. It is given as 100 mg monthly subcutaneously by injections
- Reslizumab binds circulating IL5. Blood eosinophils should be >400/μl. It is given as monthly IV infusion of 3 mg/kg over 20–50 min.[458] Oropharyngeal pain and elevated creatine phosphokinase (CPK) were reported in <10% of patients. Since the dose is weight adjusted, reslizumab could be more efficacious when fixed-dose mepolizumab is not adequate[459]
- Benralizumab binds to the α chain of IL5 receptor, leading to eosinophil apoptosis.[460] Blood eosinophils should be >300/μl. It is given as 30 mg by subcutaneous injection once every 4 weeks for the first three doses and once every 8 weeks thereafter.

Anti-interleukin 4 receptor α

- Dupilumab is a monoclonal antibody against α chain of the IL-4 receptor. This chain is shared with the IL-13 receptor. Therefore, this biologic impedes the signaling of both IL-4

and IL-13, two important cytokines in the development of TH2 cells and IgE-producing B-cells. It was recently approved for the treatment of moderate-to-severe eosinophilic asthma with blood eosinophils >300/μl and oral steroid-dependent severe asthma, regardless of blood eosinophils in patients ≥12 years of age. It improves asthma symptoms, improves lung function, and reduces the rate of attacks.[461,462] The initial dose for the eosinophilic phenotype is 400 mg subcutaneously and then 200 mg every 2 weeks, while initial dose for oral steroid dependent asthma is 600 mg subcutaneously and then 300 mg every 2 weeks Adverse effects include URTIs and injection site reaction. Patients on dupilumab should avoid live vaccines.

Potential future biologic therapies

There are different biologic agents under development that target the inflammatory pathway. It did not receive any regulatory agent approval yet.

- Fevipiprant is an oral treatment for asthma that is intended for the treatment of uncontrolled severe asthma.[463] It competitively and reversibly antagonizes the prostaglandin D_2 receptor
- Tezepelumab is a human monoclonal antibody specific for the epithelial-cell–derived cytokine TSLP that is intended to patients whose asthma remained uncontrolled despite treatment.[464]

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Disclaimer

These guidelines for the diagnosis and management of asthma in adults and children, developed by the SINA panel, are not meant to replace clinical judgments of physicians but to be used as tools to help the practicing physicians to manage asthma patients. Although a lot of effort was exerted to ensure the accurate names and doses of medications, the authors encourage the readers to refer to the relevant information of specific drugs for further clarification.

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