The Saudi Initiative for Asthma 2016

Guidelines for the diagnosis and management of asthma in adults and children

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The Saudi Initiative for Asthma - 2016 update
Guidelines for the diagnosis and management of asthma in adults and children
Disclaimer:
These guidelines for the diagnosis and management of asthma in adults and children developed by the Saudi Initiative for Asthma panel are not meant to replace clinical judgments of physicians but to be used only 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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Editorial

Achieving asthma control: Providing a framework for clinicians

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Globally, asthma remains a major public health challenge. Although effective therapies are available, a significant minority of patients have uncontrolled disease. In response to this challenge, both nationally and internationally, management strategies have been developed to improve asthma care. A big challenge for an international document, such as the Global Initiative in Asthma (GINA) report, is making it relevant to a particular country or region.[1]

The newly published updated guidelines for the diagnosis and management of asthma in adults and children for asthma by the Saudi Thoracic Society is an excellent example of how such a document should be created.[2] As well as providing the fundamentals of asthma care, the report highlights the regional epidemiology of asthma and also the regional phenomenon of sand storms, which an international document, could not hope to capture. In addition, the document captures local regulatory issues such as the fact long-acting beta-agonists are not available in single medication formulations but must always be marketed in a combination inhaler.

The importance of establishing an accurate diagnosis for asthma is complemented by an outline of the sequential approach of taking a detailed clinical history. The need for objective confirmation of the diagnosis of asthma is emphasized, with the use of spirometry including an assessment
of reversibility and if necessary, use of inhalational challenge testing to document airway hyper-responsiveness. The diagnosis of asthma is crucial to ensuring asthma mimics, which are outlined in detail in the new report, are not being inappropriately treated.

Like all management strategies, the current document is primarily focused on the stepped care approach to asthma. The fundamental role of inhaled corticosteroids as the foundation therapy for treating asthma severity of all levels is emphasized. The document also recognizes the benefits of the early use of combination therapy with a long-acting beta-agonist and inhaled corticosteroid as opposed to increasing the dose of inhaled corticosteroids. Use of leukotriene receptor antagonists and theophylline therapy as adjunct therapies is also discussed. The recent regulatory approval of tiotropium as add-on therapy to both inhaled corticosteroids as well as combination therapy is outlined. The incremental benefit of improved asthma control and reduction in asthma exacerbations when tiotropium is added to combination therapy is discussed.

Although the majority of asthma can be classified as mild, these patients remain at risk of an asthma exacerbation. In contrast, severe uncontrolled asthma occurs in about 5–10% of patients but drives about 50% of the cost of asthma. This is a challenging group of patients to manage. A precursor to treating this patient group is to distinguish between actual severe asthma versus uncontrolled asthma based on a number of key scenarios. By far, the most important is the lack of adherence to asthma treatment especially inhaled corticosteroids. Many times, the clinician will make correct therapeutic decision, but the prescription will not be filled or medication only used infrequently. The other common scenario is the patient fills the prescription but uses the medication with improper inhaler technique. These two factors are common to many patients referred to a severe asthma clinic. Additional factors seen include the failure to address comorbidities, especially sinusitis and gastroesophageal reflux. An important masquerade of uncontrolled asthma is vocal
cord dysfunction.[3] This can occur alone or more commonly see in conjunction with asthma where its presence suggests a much more severe form of disease. Although not always easy to diagnose, it is suggested by asthma symptoms that are disproportionate to well-preserved lung function and a symptom complex often driven by exposure to irritants such as odors, perfumes, or diesel fumes. The patient typically has difficulty taking a deep breath in as opposed to exhaling which is the more common scenario in pure asthma. The document gives practical framework to identify this and other confounding diagnoses.

Once this assessment is complete and ideally in the setting of a difficult to control asthma clinic, the clinician can consider the use of more expensive options. Historically, this has been limited to omalizumab, a targeted therapy that affects immunoglobulin E levels. More recently, thermoplasty has received regulatory approval and offers a novel treatment option for carefully selected patients who should be treated in centers with appropriate expertise. As we move forward, many novel targeted therapies will become available with mepolumizab, which targets interleukin-5 being the next therapy, which likely will receive approval.[4] There will follow many other novel therapies, which will become available over the next 5–10 years. The challenge we have with these treatments will be establishing their cost-effectiveness in an environment where health care costs are rising in parallel with an aging population of patients with multiple chronic comorbidities. Robust economic modeling and cost-effectiveness studies will be required to ensure these treatments are used in an appropriate manner.

Although these therapies will bring exciting new options to the management of asthma, we strongly feel that the strong emphasis placed on addressing adherence and proper use of inhaler devices both in the Saudi document and GINA report are the key to improving asthma outcomes. Although we feel genomics are important, we feel equally strongly that humanomics with its focus on improved
patient and physician communication is as important.[5] This is especially true with the recognition of low-health-literacy levels generally but, especially health literacy and how this impacts patient outcomes. An overarching need for all asthma patients is education with a written action plan, especially with regard to the management of asthma worsening.

In conclusion, the newly updated Saudi document provides an excellent framework for the management of asthma locally in the context of a global evidence base.

References


This editorial can be cited as follow:

The Saudi Initiative for Asthma - 2016 Update
Guidelines for the Diagnosis and Management of Asthma in Adults and Children

Introduction

Asthma is a common heterogeneous chronic disorder of the airways, characterized by variable usually reversible and recurring symptoms related to one or more of airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation. It is one of the most common chronic diseases in Saudi Arabia, affecting more than 2 million Saudis.\[1\] Its impact is manifested in 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.\[2-4\] As part of the commitment of the Saudi Thoracic Society (STS) toward a long-term enhancement plan for promoting the best practice in the field of respiratory diseases,\[5-23\] the Saudi Initiative for Asthma (SINA) was developed in 2009 with special attention to nonasthma specialists, including primary care and general practice physicians.\[24,25\] Sections related to asthma in children represent the views of a panel from the Saudi Pediatric Pulmonology Association, another subsidiary of the STS. SINA guidelines previously updated in 2012 with an emphasis on new evidence including a new section on difficult to treat asthma (DTA), easy to use charts, and more information related to asthma in children.\[25\]

SINA panel is a group of Saudi experts with well-respected academic backgrounds and experience in the field of asthma. Since SINA aims to have updated guidelines, which are simple to understand and easy to use, 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, SINA expert panel has stratified the guidelines based on the following age groups: adults age above 18 years, adolescents age 12–18 years, and children who were stratified into two groups such as 5–11 years and below 5 years.

**Methods**

SINA guidelines were initially based on two existing international guidelines, the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program.[26-31] These were customized based on reviewing the available local literature and the current setting in Saudi Arabia. The same approach was continued in 2012 and 2016 update.[32] Consensus among the SINA panel was followed whenever there was lack of evidence in the form of nonrandomized controlled trials or nonrandomized studies.[33] 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 has been continued where each section was internally reviewed by at least two other members. SINA panel conducted round-table discussions frequently and jointly reviewed it. A panel of international experts reviewed the guidelines, and their recommendations were thoughtfully considered. The expected outcome will lead to a safe and high-quality patient care.
Epidemiology

Asthma is one of the most common chronic illnesses in Saudi Arabia, and local reports suggest that the prevalence of asthma is increasing. Poor knowledge, fear of the use of new drugs, and the lack of awareness of the importance of disease control are common among primary care physicians who care for asthma patients in Saudi Arabia. In addition to these important factors, there are other attributes to the magnitude of disease burdens such as socioeconomic status, number of siblings, knowledge of caregivers, and income. Consequently, many asthma patients continue to be underdiagnosed, undertreated, and at risk of acute exacerbations resulting in missed work or school, increased use of expensive acute healthcare services, and reduced quality of life. A study by Al-Kabbaa et al. found that only 39% of primary care physicians met the standards of the national guidelines in management of asthma. In addition, the overall level of awareness among physicians was low (52%). Their proficiency in general knowledge, diagnosis, classification of severity, and management was also low. An asthma control survey of patients showed that only 5% of the patients were controlled, 31% were partially controlled, and 64% were uncontrolled.

The prevalence of asthma in two population of school children aged between 8 and 16 years was studied using an internationally designed protocol in 1986 and 1995. Comparison of the data from Riyadh versus Hail (inland desert areas with dry environment) and Jeddah versus Jazan (coastal humid environment) revealed that the prevalence of asthma in similar population increased significantly from 8% in 1986 to 23% in 1995. The study also revealed that there was increased exposure to environmental factors such as tobacco smoke and indoor animals in Saudi houses, which may have contributed. Bener et al compared the prevalence of physician-diagnosed asthma among Saudi school boys in the industrial city of Yanbu to two nonindustrial villages in a cross-sectional study. The prevalences in industrial and nonindustrial areas were 13.9% and 8%, respectively.
Hijazi et al. conducted a study of 1020 urban and 424 rural children aged 12 years. They attempted to compare the prevalence of allergic symptoms among those living in urban and rural areas of the Saudi Arabia and investigate factors associated with any differences found. The prevalence of allergic symptoms was found to be significantly greater among urban children than the rural ones and was more among Saudi than non-Saudi children. Males were more susceptible to have certain respiratory symptoms and females had more eye and skin symptoms. The educational level and occupation of the father did not influence the likelihood of having symptoms.

Most of the studies investigating the prevalence of asthma in various countries have focused on children below the age of 15 years or adults above the age of 18 years. There is limited knowledge concerning the prevalence of asthma in 16–18 years old adolescents. A study conducted by STS investigated the prevalence of asthma and associated symptoms in 16–18 years old 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 (1504 boys and 1569 girls), the prevalence of lifetime wheeze, wheeze during the past 12 months, and physician-diagnosed asthma were 25.3%, 18.5%, and 19.6%, respectively. The prevalence of exercise-induced wheezing and night coughing in the previous 12 months were 20.2% and 25.7%, respectively. The prevalence of rhinitis symptoms in students with lifetime wheeze, physician-diagnosed asthma, and exercise-induced wheeze were 61.1%, 59.9%, and 57.4%, respectively. Rhinitis symptoms were significantly associated with lifetime wheeze (odds ratio [OR] = 2.5, P < 0.001), physician-diagnosed asthma (OR = 2.2, P < 0.001), and exercise-induced wheeze (OR = 1.9, P < 0.001). By utilizing the ISAAC questionnaire method, a recent study by Nahhas et al conducted among 5188 primary school children in Madinah showed that the prevalence of asthma was 23.6%, where 41.7% had symptoms suggestive of at least one allergic disorder.
Although the prevalence of asthma in Saudi Arabian adults is unknown, 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 highest prevalence of physician-diagnosed asthma in Saudi Arabia was reported to be 25% in 2004.\textsuperscript{[55]} 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.\textsuperscript{[56]}
Diagnosis of asthma in adults and adolescent

The diagnosis of asthma is based on clinical assessment as there is no gold standard diagnostic test for asthma. This includes a detailed history and physical examination supplemented by spirometry with reversibility testing to support the diagnosis.

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 variable over time, and the patient may be entirely asymptomatic between exacerbations.[57,58] 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.

Box 1 lists the relevant questions that are commonly considered when taking a history. Asthma control may be worsened by coexisting symptomatic gastro-esophageal 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).[59] Asthma and rhinosinusitis commonly coexist.[60,61]
### Box 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 flare-ups 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 B-blockers?
- Does the patient’s cold “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?

### Physical examination

It is important to note that the examination of the chest maybe normal but the presence of bilateral expiratory wheezing is suggestive of a diagnosis of asthma. Examination of the upper airways is important to look for evidence of allergic rhinitises such as mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis and/or eczema, also support the diagnosis of allergic asthma.\[^{57,62}\] The presence of a localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.\[^{63,64}\] Therefore, there should be a careful consideration of any possible alternative diagnosis before commencing asthma treatment by a physician.
Essential Investigations

Spirometry is necessary to confirm airflow obstruction, assess severity and demonstrates significant reversibility [Box 2]. It may help identify other diagnoses, for example, upper airway obstruction. However, normal spirometry, including a failure to show reversibility, does not rule out the diagnosis of asthma as it can be normal with the patient still being symptomatic.\textsuperscript{[65]} Serial peak expiratory flow rate (PEFR) measurements may be helpful in the diagnosis of asthma by showing the characteristic variability and for follow-up after starting treatment. Bronchoprovocation testing is another tool to rule out asthma when the result is negative. A diagnostic, therapeutic trial with an inhaled steroids and a bronchodilator may be useful in confirming a diagnosis when it shows a favorable response.\textsuperscript{[66]}

Chest X-ray is not routinely recommended unless the diagnosis is in doubt, when symptoms are not typical, or suggest other diagnoses. Peripheral eosinophilia and elevated immunoglobulin E (IgE) level are supportive of the diagnosis but are not routinely recommended. Skin 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.\textsuperscript{[67]}

<table>
<thead>
<tr>
<th>Box 2: Acceptable spirometry and significant bronchodilator response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper instructions on how to perform the forced expiratory maneuver must be given to patients, and the highest value of three readings taken</td>
</tr>
<tr>
<td>The degree of significant reversibility is defined as an improvement in $\text{FEV}_1 \geq 12%$ and $\geq 200$ mL from the prebronchodilator value</td>
</tr>
<tr>
<td>*Reference.\textsuperscript{[459]} $\text{FEV}_1 =$ Forced expiratory volume in 1 s</td>
</tr>
</tbody>
</table>
Clinical assessment in adults and adolescents

Principles of asthma assessment

The principles of optimal asthma management should consist initially of an assessment of asthma control. Before commencing a patient on treatment, SINA expert panel recommends to ensure the following:

- Assessment of asthma control [Box 3]
- Physiological measurement with tools such as spirometry or peak flow meter
- Documentation of current treatment and any related issues such as side effects, adherence, and inhaler technique
- Provision of a written asthma action plan
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, and anxiety
- Close monitoring for patients with severe asthma and history of asthma exacerbations.\textsuperscript{[69]}

Asthma control test

Asthma severity was historically used as the entry point to determine the management strategy. This trend has been replaced by the concept of asthma control.\textsuperscript{[70]} 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 short period and is recommended to entail short-term assessment of current asthma status, asthma burden, and medical management.\textsuperscript{[71]} Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reporting and subsequently treatment decisions by clinicians.\textsuperscript{[71]} In addition to assessing the control status, future risk of adverse outcomes should be assessed. This is achieved by assessing future risk of exacerbations, fixed airflow obstruction, and adverse effect of medications.
### Box 3: Assessing asthma control in adults

<table>
<thead>
<tr>
<th>Component of control</th>
<th>Classification of asthma control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled</strong></td>
<td><strong>Partial control</strong></td>
</tr>
<tr>
<td>Symptoms and/or use of rapid-onset B2-agonist for symptoms relief</td>
<td>None or less than twice a week</td>
</tr>
<tr>
<td>Night time awakenings</td>
<td>None or once a month</td>
</tr>
<tr>
<td>Effect on daily activities</td>
<td>None</td>
</tr>
<tr>
<td>FEV$_1$ or peak flow</td>
<td>&gt;80% of predicted/personal best</td>
</tr>
<tr>
<td>Asthma control test score</td>
<td>≥20</td>
</tr>
<tr>
<td>Flare-ups that requires oral steroids or hospitalization</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted with modification from the GINA.[26] FEV$_1$=Forced expiratory volume in 1 s, GINA=Global Initiative for asthma
SINA expert panel recommends the utilization of asthma control test (ACT) to initiate asthma treatment in adults and adjust it at follow-up.\textsuperscript{[72-74]} ACT is a commonly used tool to assess asthma control. It is a short, validated, self-administered questionnaire to assess asthma control [Box 4]. 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.\textsuperscript{[75]} 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 change in ACT score is considered \( \geq 3 \) units.\textsuperscript{[76]} The level of asthma control is categorized into:\textsuperscript{[74,75,77]}

- Controlled: An ACT score of \( \geq 20 \)
- Partially controlled: An ACT score of 16–19
- Uncontrolled: An ACT score of <16.
### Box 4: Asthma control test*

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

*Adapted from reference number.[75] SOB=Shortness of breath
Assessment when control is not achieved

If asthma control is not achieved at any step during therapy, 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
- Problems and difficulties faced by the patient taking the medications (e.g., cost, time, and lack of perceived need)
- Patient’s concerns about asthma medications.

Assessment of risk factors for asthma exacerbations

SINA expert panel recommends assessment of risk factors for poor asthma outcomes, especially those patients experiencing exacerbations.[31] The presence of one or more of the following risk factors increases the risk of exacerbation despite controlled asthma status:

- High usage of relievers medication[78]
- Inadequate inhaled corticosteroid (ICS) use[79]
- Low forced expiratory volume in 1 s (FEV$_1$)[80]
- Previous Intensive Care Unit (ICU) admission[81]
- A severe asthma exacerbation in the previous 12 months[82]
- Major psychological disorders or reduced socioeconomic status[83]
- Continuous exposure to allergens[84]
• Presence of comorbidities
• Sputum or blood eosinophils\textsuperscript{[85]}
• Pregnancy.\textsuperscript{[86]}

**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 exacerbations.\textsuperscript{[31,87-89]} Before classifying asthma severity, “it is essential to ensure that control is achieved on the minimal level of medications over a few months.” Such asthma severity level could change over years or months. Therefore, asthma level of severity can be as follows:

- **Mild asthma:** Controlled asthma at step 1 or 2 (as needed reliever treatment, monotherapy of low-dose ICS, or leukotriene receptor antagonist [LTRA])
- **Moderate asthma:** Controlled asthma at step 3 (on combination of ICS/long-acting beta 2 agonist [LABA] or other alternative options at steps 3)
- **Severe asthma:** Asthma that requires treatment step 4 or 5 (on combination of high-dose ICS/LABA with or without add-on treatment).
Nonpharmacological management

The long-term goal of asthma therapy is to achieve and maintain asthma control by utilizing pharmacological and nonpharmacological measures [Box 5]. Appropriate implementation of nonpharmacological measures is expected to lead to utilization of the least possible dose of medications to minimize the risk of their side effects if any.

**Box 5: Long-term goals of asthma management**

<table>
<thead>
<tr>
<th>Control asthma symptoms (cough, wheezing, or SOB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent and minimal use (≤2 days a week) of reliever therapy</td>
</tr>
<tr>
<td>Maintain (near) normal pulmonary function</td>
</tr>
<tr>
<td>Maintain normal exercise and physical activity levels</td>
</tr>
<tr>
<td>Prevent recurrent of asthma flare-ups, and minimize the need for ED visits or hospitalizations</td>
</tr>
<tr>
<td>Optimize asthma control with the minimal dose of medications</td>
</tr>
<tr>
<td>Reduce mortality</td>
</tr>
<tr>
<td>Optimize quality of life</td>
</tr>
<tr>
<td>ED=Emergency department, SOB=Shortness of breath</td>
</tr>
</tbody>
</table>

Developing partnership with the patient

The development of partnership between patients and healthcare professionals leads to enhancement of knowledge, skills, and attitude toward understanding asthma and its management. Based upon agreed goals of management, a written self-management action plan should be offered
to the patient. 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, concern regarding side effects from the drugs, or the cost of medications.\textsuperscript{[90-92]} 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.\textsuperscript{[93,94]}

**Asthma education**

The goal of asthma education is to provide a patient 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.\textsuperscript{[69,95-99]} To enhance the level of knowledge and skills among asthma patients, education is recommended to include knowledge about asthma and skills related to inhaler devices prescribed, as there maybe misperceptions about the use of inhalers and the safety of ICS.\textsuperscript{[100-103]} Asthma education should be conducted by a well-trained healthcare worker, who has good communication skills and can 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.\textsuperscript{[104]} 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.\textsuperscript{[105-108]} Asthma should be structured based on the available resources [Box 6].
### Box 6: Outcomes of asthma education program

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

### Written action plan for asthma

It is considered an integral part of asthma management for patients and doctors. It helps recognize the loss of control of asthma and gives clear instructions for early intervention to prevent asthma exacerbations. The asthma action plan may be based on symptoms or PEFR measurements [Box 7].[^109^] Regular review of the asthma action plan is important as a person’s level of asthma control may change over time. If a patient has an asthma exacerbation, the patient should be assessed to see if he/she has effectively used their action plan.
### Box 7: Action plan for asthma for adults and adolescent

**Action plan for asthma in adults and children above the age of 12**

<table>
<thead>
<tr>
<th>Controlled</th>
<th>Partially Controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT ≥20</td>
<td>ACT = 16-19</td>
<td>ACT &lt; 16</td>
</tr>
</tbody>
</table>

#### Recommendations

**Continue same treatment**
- Regular follow up every 3 - 4 months

**Modify treatment**
- Increase inhaled bronchodilator to ___ puffs every four hours if needed
- Increase ICS (____________) to ___ puffs ___ times per day
- Increase inhaled combined ICS/LABA ___ puff(s) ___ times per day
- Add: ___________________

**Maximize treatment**
- Increase inhaled bronchodilator to ___ puff(s) every four hours if needed
- Increase inhaled combined ICS/LABA ___ puff(s) ___ times per day
- Add: ___________________

- Consider step down if well controlled for at least 3 months.
- Schedule follow up within 1 month
- If symptoms persist and rapidly increase, seek medical help or proceed to Emergency Room.
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 exacerbations, 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 includes domestic mites, furred animals, cockroaches, and fungi.\textsuperscript{[110,111]} The most important indoor air pollutant is related to tobacco exposure.\textsuperscript{[112]} Measures to avoid tobacco exposure will lead to better asthma control and avoidance of long-term lung function impairment.

Outdoor allergens

Outdoor allergens such as pollens and molds are impossible to avoid completely; exposure may be reduced by closing windows and doors, remaining indoors during dust storms, and initial rainy seasons, and using air conditioning if possible. It is recommended to avoid outdoor strenuous physical activities in cold weather, low humidity, or high air pollution.\textsuperscript{[113]}

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 whenever identified should be avoided (e.g., beta blockers).

Influenza vaccination

Annual influenza vaccination is advised for individuals with asthma, especially those with severe asthma.[114,115]
Pharmacological management in adults and adolescent

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

- Initiation of treatment
- Adjustment of treatment

At each phase, the patient is recommended to have clinical assessment that includes symptoms assessment by ACT, physiological measurement with PEFR or spirometry, review of current medications and patients’ adherence and inhaler technique, risk for exacerbations, and response to treatment. Based on clinical and physiological assessment, the patient is placed on the appropriate step of treatment [Box 8]. Appendix 2 contains more information about medications used in asthma treatment. In general, SINA expert panel recommends the following strategies for treating patient with asthma:

- A daily controller medication is needed. ICS is considered the most effective controller especially for mild to moderate disease (Evidence A)[116,117]

- Relievers or rescue medications must be available to patients at all steps. Short-acting bronchodilators (SABAs) are recommended to be taken on “as needed bases” to relieve symptoms. Increasing the use of reliever treatment is usually an early sign of worsening of asthma control (Evidence A)[118]

- Regular assessment of adequate doses of treatment, proper technique, and adherence

- Management of comorbidities with special attention to concomitant rhinosinusitis. As this condition affects asthma control, its treatment is expected to improve asthma (Evidence A).[119-124] The treatment includes nasal steroids, LTRA, and antihistamines. Coexisting rhinosinusitis is recommended to be treated appropriately as well.
Box 8: Initiation, adjustment and maintenance of outpatient asthma treatment in adults & adolescent patient

**Initiation**
- History & Physical Examination
- Obtain ACT score and PEFR
- Patient education and environmental control of triggers/inducers
- Treat aggravating factors e.g., GERD, Allergic Rhinitis
- Based on ACT result, initiate therapy as follows:

**ACT ≥20**
- Patients with risk factors or fixed obstruction
  - No
  - Yes

**ACT = 16-19**
- Severe uncontrolled asthma at presentation
  - No
  - Yes

**ACT <16**

**Adjustment and Maintenance**
- Clinical Assessment
- Obtain ACT score and PEFR
- Based on ACT, adjust treatment as follows:
  - ACT = 20-25: Well controlled → Maintain treatment with lowest dose of ICS or step down
  - ACT = 16-19: Partial control → Step up
  - ACT < 16: Uncontrolled → Step up

Introduce Self-management Plan

**STEP 1** Recommended
- Low Dose ICS
  - Alternative: LTRA

**STEP 2** Recommended
- Low-Medium Dose ICS + LABA
  - Alternatives:
    - Low-Medium Dose ICS + LTRA
    - Medium-high Dose ICS
    - Low-Medium Dose ICS + Theophylline

**STEP 3** Recommended
- Use high-dose ICS + LABA AND
  - Tiotropium
  - LTRA
  - Theophylline

**STEP 4** Recommended
- Omalizumab in Allergic Asthma, if applicable

**STEP 5** Recommended
- Step 4 options +
- Long-term Oral Steroids

Refer to a Specialist

Salbutamol Inhaler (PRN) for all patients

**Patient education, environmental control, and management of comorbidities**

ACT = Asthma Control Test, ICS = Inhaled Corticosteroids, LABA = Long Acting β2-Agonist, LTRA = Leukotriene Receptor Antagonist, PEFR = Peak Expiratory Flow Rate
Initiation of treatment

Patients with asthma often underestimate the presence of asthma symptoms and also tend to assume their asthma is controlled when this is not the case.\cite{125} Therefore, the consensus among SINA expert panel is to simplify the approach and supplement the initiation of asthma therapy by utilizing an objective measurement with the ACT [Box 4]. The following initial steps are recommended based on ACT score:

- **ACT score ≥20:**
  - Step 1: For patients with mild and infrequent symptoms (Evidence B)\cite{74}
  - Step 2: For patients with risk factors for exacerbation or fixed obstruction (Evidence B).\cite{116,126} It is also recommended for patients with seasonal asthma who are symptomatic during the season, otherwise, it is recommended to be treated at step 1 for the rest of the year if their score is ≥20 (Evidence D).

- **ACT score 16-19:**
  - Step 2: For patients with an ACT score of 16–19 who also qualified for partially controlled asthma status (Evidence B).\cite{74} This includes those with a history of asthma exacerbation in the past year.

- **ACT score <16:**
  - Step 3: For most patients with an ACT score of <16 (Evidence B).\cite{74} However, for patients with early signs of exacerbation at presentation, a short course of oral steroids may be required
  - Step 4: For patients who have severely uncontrolled asthma at presentation, initiation of asthma treatment at a higher step with a combination of high-dose ICS and/LABA may be required (Evidence D).
Adjustment of treatment

After initiation of asthma treatment, it is recommended to assess the patient in 1–3 months (Evidence D). SINA expert panel recommends the utilization of stepwise approach to therapy to achieve asthma control. The stepwise approach consists of 5 steps as shown in Box 8. Upon follow-up, it is recommended to either maintain treatment until patients have achieved control, to step up for those did not achieve control (assuming adherence and appropriate inhaler technique have been confirmed), or step down for those who have maintained control for an extended period. It is important to determine the minimal amount of medications required to maintain control to reduce the risk of side effects. The following paragraphs will describe each step in detail.

Treatment at step 1

- Recommended option: SABA on “as-needed bases.” Symptoms are usually mild and infrequent with an ACT score of ≥20 (Evidence A).[118,127]
- Some patients may be recommended for a higher step if they are controlled during the time of assessment (an ACT score of ≥20), but have risk factors for exacerbations or fixed airway obstruction (see below).

Treatment at step 2

- Recommended option: A daily low-dose ICS (<500 mcg of beclomethasone or equivalent/day) with SABA on “as needed bases” (Evidence A)[116,128]
- An alternative treatment is LTRA (montelukast), especially in those patients reluctant to use ICS, resisting its use or continue to have voice hoarseness despite preventive measures (Evidence A).[129] It should be noted LTRA is less-effective than ICS in achieving asthma control and also less-effective in reducing the risk of exacerbations.
• Patients with mild and infrequent symptoms and an ACT score of ≥20 with risk factors for exacerbation or fixed obstruction are recommended for at least step 2 between asthma exacerbations (Evidence B).[116,126]

• Patients with seasonal asthma who are symptomatic during the season are recommended to be treated at step 2 during the season, otherwise, it is recommended to be maintained at step 1 for the rest of the year; i.e., using SABA on “as needed bases” (Evidence D).

**Treatment at step 3**

• Recommended option: Adding a LABA to a low-medium dose ICS in a combination device improves asthma control for patients whose asthma is not controlled at step 2 (Evidence A).[126,130,131] The patient is recommended to continue on reliever treatment on “as needed bases” (Evidence A)

• ICSs in the form of beclomethasone propionate, budesonide, momethasone furoate, or fluticasone propionate are currently combined with either salmeterol or formoterol. These are normally prescribed twice daily [refer to Appendix 2]

• If a combination inhaler containing formoterol is selected, patient may be advised to use it for both maintenance and rescue using extra puffs from the same inhaler (Evidence A).[132] When combination of budesonide and formoterol is used (Symbicort Turbohaler - 160/4.5), the recommended dose is 1–2 puffs twice daily plus extra puffs that should not exceed 12 puffs/day. Those patients who require such high-doses for 2–3 days should seek medical advice to step up therapy as they may require the use of a short course of oral prednisolone (Evidence A)
If a twice a day combination of fluticasone propionate/salmeterol (Seretide) is selected, an escalation of the regular daily doses was found to achieve well-controlled asthma status in 85% of patients and totally controlled asthma status in 30% (Evidence A).\(^{[133]}\)

The new once a day combination of ICS/ultra LABA can be prescribed based on availability. The approved product in Saudi market is fluticasone furoate/vilanterol (Relvar) that can be prescribed for adults and children above 12 years at a dose of 100/25 mcg dose (Evidence A).\(^{[134,135]}\) The ultra LABA (Vilanterol) has the advantage of onset of action within 15 min and a long half-life; therefore, the patient should be advised to only use it once a day on a regular basis.

There has been a warning about the use of inhaled LABAs alone in asthma management.\(^{[136]}\) Asthma patients taking inhaled LABAs without inhaled ICS are at an increased risk of asthma exacerbations, hospitalizations, and death.\(^{[137]}\) Based on this evidence, the Saudi Food and Drug Administration withdrew all LABA monotherapy medications from the Saudi market by the end of 2010.\(^{[138]}\) Therefore, the SINA panel has limited the use of relievers to SABA or formoterol containing combination when SMART approach is used.

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),\(^{[137,139]}\) and the addition of LTRA to a low-medium dose ICS (Evidence A),\(^{[140,141]}\) especially in patients with concomitant rhinitis.\(^{[142]}\) The addition of sustained release theophylline to a low-medium dose ICS is a possible but not favorable choice (Evidence B).\(^{[143]}\)

Tiotropium is a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease (COPD).\(^{[144-146]}\) Recent evidence has shown that when
tiotropium when added to an ICS, improves symptoms, reduce risk of exacerbation, and improve lung function in patients with inadequately controlled asthma. Its effect appears to be at least equivalent to LABA (Evidence A).[147-149] This evidence supports that tiotropium can be used as an alternative to LABA when added to ICS.

- Consultation with a 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 high-dose ICS with LABA (Evidence A)[104,139,140,150]

- In addition to the currently available combinations of ICS/LABA mentioned in step three section, the new 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 mcg dose[134,135]

- 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 reduce exacerbations (Evidence A)[144,151,152]

- Adding LTRA to the combination of high-dose ICS and LABA is also recommended but the evidence for this is less robust (Evidence B)[153,154]

- Adding theophylline to the combination of high-dose ICS and LABA is another less favorable alternative (Evidence B)[154,155]

- Omalizumab may be considered for those patients uncontrolled on maximum treatment
Treatment at step 5

- Consultation with an asthma specialist is strongly recommended for patients having difficulty in achieving asthma control at step 4 and requires step-up to step 5 (Evidence D).

- In patients who continue to be symptomatic despite step 4 level of care, omalizumab is recommended for patients who have allergic asthma and persistent symptoms despite the maximum therapy mentioned above (Evidence A). \[^{139,140,150}\]

- If the patient does not have allergic asthma or omalizumab 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). However, there are many new monoclonal antibodies in the horizon for management of asthma that are not yet available in the local market. \[^{89}\]

- For patients who require long-term systemic corticosteroids, the following are recommended to be considered:
o Use the lowest possible dose to maintain control

o Closely monitor the development of corticosteroid-related side effects

o When asthma control is achieved, continue attempts to reduce the dose of systemic corticosteroids, preferably to every other day frequency. Maintaining high-dose of ICS therapy may help to reduce the dose of systemic steroid

o Adjustment of steroid dose at the time of stress (e.g., infection, asthma exacerbations, and surgery) is essential

o 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).[104,158] Follow-up should include monitoring and reviewing the patient’s written asthma action plan, medication adherence and inhaler technique, patient’s behaviors, and possible side effects of medications. Once asthma is well controlled and the control is maintained for at least 3 months, a step down in pharmacologic therapy is recommended to at the minimum therapy level that can maintain good control and minimize side effects (Evidence D). The following are recommended:
• 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), and then changed to a single daily dose (Evidence A). It is recommended to be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued.

• If the patient is on a combination of ICS, LABA, LTRA, or other controllers, taper ICS to the lowest possible dose (Evidence B). If control is achieved, LTRA may be discontinued (Evidence D).

• 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 such as mycostatin mouth wash, for severe oral thrush.

• 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 co-management include:

- There is uncertainty regarding the diagnosis
- There is difficulty achieving or maintaining control of asthma
- Immunotherapy or omalizumab is considered
- Difficulty to achieve asthma control at step 3 or higher
- The patient has had acute asthma exacerbation requiring hospitalization.

Immunotherapy

Allergen-specific immunotherapy (AIT) is the practice of administering gradually increasing quantities of an allergen product to an individual with IgE-mediated allergic disease to ameliorate the symptoms associated with subsequent exposure to a causative allergen. It is administered either subcutaneously or sublingually. AIT is the only currently available medical intervention that has the potential to affect the natural course of the disease. There are available data shown that AIT can achieve substantial benefit for patients, improving the allergic individuals’ quality of life, reducing the long-term costs and burden of allergies, and changing the course of the disease. AIT does not only effectively alleviate allergy symptoms, but it has a long-term effect and can prevent the progression of allergic diseases. AIT is more effective in seasonal asthma than in perennial asthma, particularly when used against a single allergen. It may be considered if strict environmental avoidance and comprehensive pharmacologic intervention by an asthma specialist have failed to control the disease.
AIT has been a controversial treatment for asthma; however, beneficial clinical effects have been demonstrated in randomized controlled trials including Cochrane Systematic Reviews. Overall, there was a reduction in asthma symptoms, medications, and improvement in bronchial hyper-reactivity following immunotherapy. Allergen immunotherapy reduces allergen-specific bronchial hyper-reactivity, with some reduction in nonspecific bronchial hyper-reactivity as well. In addition to concerns regarding safety and cost, there is no consistent effect on lung function.

Management of acute asthma in adults and adolescents

Acute asthma exacerbation 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 exacerbations. Asthma, in general, has a low mortality rate compared with other lung diseases. Nevertheless, patients do die, especially patients with poorly controlled asthma whose condition deteriorates over a period of days before the final fatal event. The most specific marker associated with increased asthma mortality would be a history of repeated hospital admissions, particularly if patients required intensive care treatment or ventilatory assistance. A recent study from Saudi Arabia by Al-Dorzi et al compared 30 patients admitted with near fatal asthma to a control group. They were found to be younger and predominantly males and used less ICS/LABA combination. Near fatal asthma, outcomes included neuromyopathy (23%), mechanical ventilation duration of 6.4 ± 4.7 days, tracheostomy (13%) with no deaths. In addition, 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. 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 is shown in Appendix 2.
Clinical assessment of acute asthma

The initial clinical assessment should rapidly determine whether the patient’s presenting symptoms are related to an acute asthma exacerbation or not. Of note, it is necessary to recognize that acute asthma is different from mild to moderate asthma exacerbation secondary to poor asthma control that simply require a step-up in the chronic asthma therapy. Although most acute asthma exacerbations develop over a period of days, patients with brittle asthma may present with a much more dramatic deterioration [Box 9]. It is important to realize that most patients who die from an acute asthma exacerbation had chronically uncontrolled asthma, had received inadequate treatment with ICS, and had inadequate monitoring of their asthma.\textsuperscript{[186-190]} Furthermore, it has been shown that over 80\% of such exacerbations developed over more than 48 h, allowing enough time for effective action to reduce the number of exacerbations requiring hospitalization.\textsuperscript{[191-194]}

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.
<table>
<thead>
<tr>
<th>Level</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Moderate asthma flare-ups   | 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 following in a patient with severe asthma  
SpO₂ <92% (PaO₂ <60 mmHg) on high-flow FIO₂  
PEF <33% best or predicted  
Bradycardia  
Dysrhythmia  
Cyanosis  
Hypotension  
Normal or high PaCO₂  
Exhaustion  
Confusion  
Silent chest  
Coma  
Weak respiratory effort   |
| Near-fatal asthma           | Raised PaCO₂ 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 flare-ups on a background of apparently well-controlled asthma                                                                 |

PEF=Peak expiratory flow, PEFR=Peak expiratory flow rate
Upon presentation, a patient should be carefully assessed to determine the severity of the exacerbations [Box 9] and the type of treatment required. PEFR and pulse oximetry measurements are complementary to history taking and physical examination. Treatment of acute asthma exacerbations requires a systematic approach similar to chronic asthma management. Acute asthma management is recommended to follow these steps:

1. Assess severity of the exacerbation
2. Initiate treatment to rapidly control the exacerbation

The following levels of acute asthma severity should be quickly identified, as approach to management and prognosis varies significantly [Box 10].
Box 10: Initial management of acute asthma in adults and adolescents

Assess Asthma Severity by History, Physical Examination, Oxygen Saturation, and PEFR

<table>
<thead>
<tr>
<th>Moderate</th>
<th>Severe</th>
<th>Life Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talking Phrases or full sentences</td>
<td>Talking only words or unable to complete sentence</td>
<td>Unable to talk</td>
</tr>
<tr>
<td>Agitated but alert</td>
<td>Agitated</td>
<td>Confused, drowsy, or coma</td>
</tr>
<tr>
<td>Respiratory Rate 20-30/min</td>
<td>Respiratory Rate &gt;30/min</td>
<td>Respiratory Rate &gt;30/min or in respiratory failure</td>
</tr>
<tr>
<td>May or may not use accessory muscles</td>
<td>Use of accessory muscles</td>
<td>Use of accessory muscles</td>
</tr>
<tr>
<td>Heart Rate &lt;120/min</td>
<td>Heart Rate &gt;120/min</td>
<td>Heart Rate &gt;120/min or bradycardia and silent chest</td>
</tr>
<tr>
<td>SaO₂ on R/A ≥92%</td>
<td>SaO₂ on R/A &lt;92%</td>
<td>SaO₂ on R/A &lt;90% or Cyanosis</td>
</tr>
<tr>
<td>PEFR of 50-75% of predicted</td>
<td>PEFR of 30-50% of predicted</td>
<td>Normal or high PaCO₂, Acidosis</td>
</tr>
</tbody>
</table>

If patient has features of more than one level of severity, patient should be classified to the higher level and managed accordingly.

Assess response to treatment by assessing mental status, respiratory rate, heart rate, SaO₂ and PEFR every 30-60 min.

TREATMENT

- Oxygen to keep SaO₂ ≥92%
- Salbutamol can be delivered by either:
  - MDI with spacer: 6-12 puffs every 20 min for 1 hour, then every 2-4 hours according to the response
  - Nebulizer: 2.5 - 5 mg salbutamol every 20 min for 1 hour, then every 2-4 hours according to response
- Oral Prednisone 50 mg PO STAT

TREATMENT

- Oxygen to keep SaO₂ ≥92%
- Salbutamol 2.5-5 mg plus Ipratropium bromide 0.5 mg nebulized with oxygen every 20 min for 1 hour, then every 2-4 hours according to patient response
- Hydrocortisone 200 mg IV STAT then 100-200 mg every 6 hr, or Methyprednisolone 40-60 mg IV STAT then 40 mg every 8 hr
- Magnesium Sulphate 1-2 g IV over 20 min if no response to initial bronchodilators
- Consider: ABGs, CXR, CBC, Electrolytes, Urea, Creatinine, Glucose, ECG

TREATMENT

- High flow Oxygen to keep SaO₂ ≥92%
- Salbutamol 10 mg by continuous nebulization plus Ipratropium Bromide 0.5 mg nebulized with oxygen every 10-20 min for 1 hour, then q4-6 hour according to patient response
- Hydrocortisone 200 mg IV STAT then 100-200 mg every 6 hr, or Methyprednisolone 80-125 mg IV STAT then 40 mg every 8 hr
- Magnesium Sulphate 1-2 g IV over 20 min
- ABGs, CXR, CBC, Electrolytes, Urea, Creatinine, Glucose, ECG

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Assessment of acute asthma severity

Mild acute asthma

Patients presenting with mild asthma exacerbation are usually treated in an outpatient by stepping up in asthma management, including increasing the dose of ICS. However, some cases may require short course of oral steroids.

Moderate acute asthma

Patients with moderate asthma exacerbation are clinically stable. They are usually alert and oriented, but may be agitated. They can communicate and talk in full sentences. They are tachypnoeic and may be using their respiratory accessory muscles. Heart rate is <120/min and blood pressure is normal. A prolonged expiratory wheeze is usually heard clearly over the lung fields but examination of the chest maybe relatively normal. Oxygen saturation is usually normal secondary to hyperventilation. PEFR is usually in the range of 50–75% of predicted or previously documented best. Measurement of arterial blood gases (ABGs) is not routinely required in this category; however, if done, it shows widened alveolar–arterial oxygen gradient and low PaCO₂, secondary to increased ventilation perfusion mismatch and hyperventilation, respectively. Chest X-ray is not usually required for moderate asthma exacerbations 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 ($\text{SaO}_2 < 92\%$ on room air) are usually evident. Chest examination reveals prolonged distant wheeze secondary to severe airflow limitation and hyperinflation; more ominously the chest maybe silent on auscultation. PEFR is usually in the range of 33–50\% of predicted. ABGs reveal significant hypoxemia and elevated alveolar–arterial oxygen gradient. PaCO$_2$ may be normal in patients with severe asthma exacerbations. 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, but at a later stage, patients can be bradycardic. Patient may have arrhythmia secondary to hypoxia and electrocardiogram (ECG) monitoring is recommended. Oxygen saturation is usually low ($< 90\%$) and not easily corrected with oxygen. ABGs are mandatory in this category and usually reveal significant hypoxia and normal or high PaCO$_2$. Respiratory acidosis may be present. PEFR is usually very low ($< 30\%$ of the predicted). Chest X-ray 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 exacerbation, it is recommended to base treatment on severity level [Box 10]. More details of medications are available in Appendix 2.

Moderate asthma exacerbation

- Low-flow oxygen is recommended to maintain saturation ≥92%.\(^{[198,199]}\) There is evidence that high-flow oxygen may be harmful to some patients.\(^{[200]}\) Therefore, it is important to give a controlled dose of oxygen; patients who received 28% oxygen did better than those who received 100% oxygen\(^{[200]}\)

- SABA are recommended to be delivered by either:\(^{[201,202]}\)
  - MDI with spacer: 6–12 puffs every 20 min for 1 h, then every 2–4 h according to response (Evidence A),\(^{[203-205]}\) or
  - Nebulizer: 2.5–5 mg salbutamol every 20 min for 1 h, then every 2 h according to response (driven by oxygen if patient is hypoxic) (Evidence A)\(^{[206]}\)

- Steroid therapy: Oral prednisolone 1 mg/kg to maximum of 50 mg is recommended to be started as soon as possible.\(^{[207,208]}\)

Severe asthma exacerbations

- Adjusted oxygen flow is recommended to keep saturation ≥92% (avoids excess oxygen)\(^{[199,209,210]}\)
• Nebulized SABA (2.5–5 mg) are recommended to be repeated every 15–20 min for 1 h, then hourly according to response.[199] Oxygen-driven nebulizers are preferred for nebulizing SABA because of the risk of oxygen desaturation while using air-driven compressors (Evidence A)[207,208,211,212]

• 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 then every 4–6 h as needed (Evidence B). Alternatively, ipratropium can be administered by MDI at a dose of 4–8 puffs (80–160 mcg) every 20 min, then every 4–6 h as needed[213-216]

• Systemic steroid is recommended to be started as soon as possible (Evidence A). If patient can tolerate orally, oral prednisolone 1 mg/kg to maximum of 50 mg daily is recommended. Alternatively, the following may be prescribed: Intravenous (IV) methylprednisolone 60–80 mg daily in divided doses or IV hydrocortisone 200 mg daily in divided doses[207,217]

• If there is no adequate response to previous measures, it is recommended to administer a single dose of IV magnesium sulfate (1–2 g) intravenously over 20 min (Evidence B)[218]

• Chest X-ray, 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.[219] The following steps are recommended for further management:

• Consult ICU service. Intubation setting should be readily available
• Adequate oxygen flow to keep saturation ≥92%\textsuperscript{[199]}

• Deliver nebulized SABA (10 mg) continuously over 1 h (Evidence A).\textsuperscript{[220,221]} Oxygen-driven nebulizers are preferred due to the risk of oxygen desaturation while using air-driven compressors (Evidence A)\textsuperscript{[211,212]}

• 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 then every 4–6 h as needed (Evidence B). Alternatively, ipratropium can be administered by MDI at a dose of 4–8 puffs (80–160 mcg) every 20 min, then 4–6 h as needed.\textsuperscript{[213-216]}

• Systemic steroid (Evidence A) to be started as soon as possible in one of the following forms: IV methylprednisolone 60–80 mg daily in divided doses or IV hydrocortisone 200 mg daily in divided doses.\textsuperscript{[207,213,216,217,222,223]}

• Single dose of IV magnesium sulfate (1–2 g) intravenously over 20 min (Evidence B)\textsuperscript{[217,223]}

• Frequent clinical evaluation and CXR, electrolytes, glucose, 12-lead ECG, and ABGs are recommended.

**Follow-up after initial treatment**

Close evaluation of treatment response is recommended that 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 such as adequate, partial, or poor response [Box 11].
Box 11: Adjustment of acute asthma treatment in adults and adolescent patients

**Adequate Response**
- Improving Symptoms and stable vital signs
- PEFR >50% of predicted
- SaO₂ ≥92%
- Adequate response to be maintained for at least 4 hours
- Continue bronchodilators for 1-4 hour PRN
- May be safely discharged
- Continue oral Prednisone for 5-7 days

**Partial Response**
- Minimal improvement of respiratory symptoms after 4 hours of therapy
- Stable vital sings
- SaO₂ ≥92% on oxygen therapy
- PEFR 30-50% of predicted
- Continue bronchodilators therapy (β₂Agonist + ipratropium bromide) every 1-4 hour

**Poor Response**
- No improvement of respiratory symptoms after 4 hours of therapy
- Fatigue and acidosis
- PEFR <30% of predicted
- SaO₂ <92% with high flow oxygen

**What is next?**
- Continue oral steroid in the form of oral prednisone 1mg/kg (maximum dose 50mg) daily if the patient can tolerate orally
- Observe closely for any signs of fatigue of exhaustion
- Monitor O₂ saturation, serum electrolytes, ECG and PEFR
- If the patients is responding, follow "adequate response" track
- If there is no adequate response after 4 hours, consider admission

**Upon Discharge**
- Ensure stable on a 4 hourly inhaled bronchodilator
- Prescribe combination of inhaled steroids/LABA
- Review inhaler technique and encourage compliance
- Ensure adequate rescue treatment
- Provide written asthma self-management action plan
- Arrange follow up in pulmonary clinic or primary care clinic within a few days

**What is next?**
- Continue bronchodilators and systemic steroids
- ICU consultation for possible admission
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 exacerbation
- 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 SABA on “as needed bases”
- A clearly written asthma self-management action plan
- A follow-up appointment within 1 week.

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
- 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 (SABA every 1 h and/or ipratropium bromide), unless limited by side effects (significant arrhythmia or severe hypokalemia)
- Continue systemic steroid: IV hydrocortisone 200 mg every 6–8 h, IV methylprednisolone 40 mg every 8 h, or oral prednisolone 1 mg/kg to maximum of 50 mg g daily
- 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
- ABGs analysis showing respiratory acidosis and/or rising PaCO₂
- PEFR of <30%.

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

- Consider ICU admission
- Deliver continuous nebulization of SABA, unless limited by side effects
- Continue systemic steroid: IV hydrocortisone 200 mg every 6–8 h or IV methylprednisolone 40 mg every 8 h.
Criteria for Intensive Care Unit 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
  - Respiratory arrest.
Asthma in special situations

**Cough-variant asthma**

Patients with cough-variant asthma have chronic cough as their main symptom.[224,225] It is particularly common in children and is often more problematic at night. Other diagnoses considered are drug-induced cough caused by angiotensin-converting enzyme inhibitors, GERD, postnasal drip, eosinophilic bronchitis, and chronic sinusitis. This condition must be also differentiated from eosinophilic bronchitis which is characterized by cough with sputum eosinophilia while spirometry and airway hyper-responsiveness (AH) are normal.[226] Once the diagnosis is established, treatment is recommended with ICS.[227,228]

**Rhinitis/sinusitis and nasal polyp**

Most asthma patients have coexisting rhinitis or sinusitis and around 40% of patients with rhinitis have asthma.[229] 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.[230,231]

**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 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 by the use of SABA a few minutes before exercise.\textsuperscript{[232]} 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.\textsuperscript{[141]} Regular use of LTRA may help in this condition especially in children.\textsuperscript{[141,233]}

**Aspirin-exacerbated respiratory disease**

About 10–20\% of adults with asthma suffer from exacerbations in response to ASA or NSAIDs that inhibit cyclooxygenase-1. This condition is more common in patients with severe asthma and poor lung function. The majority of the patients experience first symptoms during their third to fourth decade of life. Once ASA or NSAID hypersensitivity develops, it is present for life. Characteristically, within minutes to 2 h following ingestion of ASA, an acute severe asthma exacerbations develops. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck.\textsuperscript{[234]} A typical history of reaction is considered adequate for diagnosis of ASA-induced asthma. Patients known to have ASA-induced asthma are recommended to avoid all ASA-containing products and NSAIDs. Where an NSAID is strongly indicated, alternative analgesics such as paracetamol are recommended. Prophylactic low-dose ASA is recommended also to be avoided; however, patients for whom ASA is considered essential can be referred to an allergy specialist for ASA desensitization.\textsuperscript{[235]} ASA and NSAID can be used in asthma patients who do not have ASA-induced asthma.\textsuperscript{[236]} Montelukast may be protective against this type of asthma and, therefore, is recommended to be part of the treatment regimen.\textsuperscript{[237]}

**Gastroesophageal reflux disease**

GERD 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 micro-
aspiration of gastric contents into the upper and lower airways. 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. 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 GERD therapy (Evidence A).

Pregnancy

The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics may have a worsening of their asthma control. Maintaining adequate control of asthma during pregnancy is essential for the health and wellbeing of both the mother and her baby. Occurrence of Asthma exacerbations during the first trimester of pregnancy significantly increase the risk of a congenital malformation. 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. ICS, theophylline, antihistamines, B2-agonists, and LTRA are generally safe, and they have not been shown to increase the risk of fetal abnormalities. 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). Fetal monitoring is recommended in severe asthma exacerbation. If anesthesia is required during labor, regional anesthesia is recommended whenever possible (Evidence C). 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. As asthma treatment is safe in pregnancy, patients are recommended to continue their usual asthma medications during pregnancy and in 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.[253-255]

**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 if they are away from work.[256] Once identified, early identification and elimination of occupational sensitizers and removal of patients from further exposure are an essential aspect of management. Patient with suspected or confirmed occupational asthma is recommended for referral to an asthma expert for assessment and advice because of the legal implications of the diagnosis.[257,258]

**Difficult to treat asthma**

DTA carries several names; each one points to an aspect of the disease.[259] Chronic severe asthma, steroid-dependent asthma, difficult to control asthma, and refractory asthma are some of these terminologies. It is simply defined as persistence of asthma symptoms in patients who require step 4 or step 5 level of therapy. DTA probably accounts for 5–10% of adult asthma, but the health cost is disproportionally high.[260] Morbidity and mortality are also higher compared to regular asthma patients because of increased side effects of treatment and much more frequent exacerbations.[261,262] Before labeling a patient as a case of DTA, the following are recommended:[83,263-267]
• Ensure that the patient is adherent to medications with a good inhalation technique

• Misdiagnosis where the problem is not bronchial asthma to start with but another respiratory pathology that is not appropriately addressed, for example, bronchiectasis, endobronchial tumors, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, or Churg–Strauss syndrome[265,268]

• Comorbidity that worsens bronchial asthma and makes it difficult to manage (e.g., chronic sinusitis, GERD, sleep apnea syndrome, obesity, and congestive heart failure [CHF])[269]

• Confounding factors (e.g., presence of allergens at home or work, active or passive smoking, or psychosocial problems).[265]

A significant percentage of patients with DTA do not respond adequately to high-doses of ICS and other controller therapy, thus, they need frequent or continuous oral steroid therapy to achieve a reasonable response.[270] Such control may be lost when oral steroid is discontinued. Patients may differ in the degree of their responsiveness to oral steroids.[271] Some patients may fail to improve their FEV₁ by more than 15% following treatment with oral prednisolone (30–40 mg) daily for 2 weeks, a condition called “corticosteroids-resistant asthma.”[272,273]

It is strongly recommended to refer DTA patients to an asthma specialist. As it may be difficult to achieve full control in some patients, the aim of the treatment in this situation is to reach the best possible control.[274] After dealing with all comorbidities that could have made asthma difficult to control, maximum therapy is recommended (i.e., step 5), which may include combination therapy of high-dose ICS/LABA, LTRA, and long-acting anti-muscarinic (cholinergic) agent (LAMA).[275] Anti-IgE treatment (omalizumab) is recommended if the patients fulfill the criteria for this treatment.
If oral steroids are necessary, it is recommended to use the lowest possible dose and to shorten the duration as possible. In this situation, osteoporosis prophylaxis is recommended. New modalities of drug treatment are promising and may help to further control DTA. These modalities need to be considered by a specialized physician in asthma management. Some of these modalities are:

- Mepolizumab is a humanized immunoglobulin G (IgG) monoclonal antibody specific to interleukin-5 (IL-5) and preventing it from binding to its receptor on the surface of the eosinophils. It has been shown to reduce asthma exacerbations and improves asthma control in patients with refractory eosinophilic asthma. It is now approved for use in patients above 18 presenting with eosinophilic asthma at a dose of 100 mg via subcutaneous injections or 75 mg intravenously every 4 weeks.

- Bronchial thermoplasty is a novel treatment modality that utilizes radiofrequency energy to alter the smooth muscles of the airways. However, in selected patients with moderate to severe persistent asthma, it has shown to improve various measures of asthma, including FEV$_1$, quality of life, asthma control, exacerbations, and use of rescue medications.

Asthma-chronic obstructive pulmonary disease overlap syndrome

In adult patients older than 40 years with a chronic airways disease, COPD becomes more common than asthma. Distinguishing asthma from COPD becomes more difficult as many patients may show features of both diseases. This has been called the asthma-COPD overlap syndrome (ACOS). ACOS is a unique complex syndrome sharing features of both COPD and asthma. At this stage, there is no formal definition of ACOS as there is inadequate data to describe its features, characteristics, and
its optimal therapeutic intervention.\textsuperscript{[31]} However, when a patient has features of both asthma and COPD, the diagnosis of ACOS should be considered.

ACOS 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.\textsuperscript{[31]} Patients with ACOS have the combined risk factors of smoking and atopy. They are generally younger than patients with COPD and have frequent exacerbations, poor quality of life, a more rapid decline in lung function, higher mortality, greater health care utilization and low quality of life; compared to patients with COPD alone.\textsuperscript{[284-286]}

Spirometry is required to confirm the diagnosis of chronic airflow limitation. Postbronchodilator FEV\textsubscript{1}/forced vital capacity of <0.7 is usually present and postbronchodilator increase in FEV\textsubscript{1} by >12\% and 200 mL from baseline is compatible with diagnosis of ACOS. However, spirometry alone has limited value in distinguishing between asthma, COPD, and ACOS.

If the initial assessment suggests asthma or ACOS or there is uncertainty about the diagnosis of COPD, it is prudent to start treatment for asthma (ICS ± LABA) until further investigation has been performed to confirm or exclude this diagnosis. However, it is important that patients should not be treated with a LABA alone if there are features suggestive of asthma.\textsuperscript{[287-289]} Treatment of ACOS 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 commonest chronic illness of childhood.\cite{1,290} It is also considered a leading cause for childhood morbidity as measured by school absences, ED visits, and hospitalizations.\cite{291} From the prospective of both patient and society, the cost of not treating asthma is higher than the cost of asthma treatment.\cite{70,292}

Asthma diagnosis in children

Accurate diagnosis of asthma in children is crucial to prevent inappropriate management and reducing morbidity and mortality due to under-or over-diagnosis.\cite{293,294} 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 be supported by the presence of atopy, early sensitization, and a family history of atopy. Whenever possible, spirometry is recommended to be performed to show reversibility of airway obstruction after bronchodilator therapy.\cite{295} In general, spirometry can be performed in children aged ≥5 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 12 presents a summary of symptoms and signs 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, and
symptoms that are not associated with typical triggers. Clinical suspicion of asthma mimics is an acceptable indication for chest X-ray in a child suspected of having asthma; however, a routine chest X-ray is not recommended to be part of the initial routine work up of asthma in children.\textsuperscript{[296]}

<table>
<thead>
<tr>
<th>Box 12: Diagnosis of asthma in children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom and sign</strong></td>
</tr>
<tr>
<td>History of multiple flare-ups of SOB</td>
</tr>
<tr>
<td>or wheezing in a season</td>
</tr>
<tr>
<td>Coughing</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>Atopy</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Breath sounds</td>
</tr>
<tr>
<td>Therapeutic trial</td>
</tr>
<tr>
<td>Spirometry</td>
</tr>
<tr>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Tests for hypersensitivity</td>
</tr>
</tbody>
</table>

SOB=Shortness of breath, URTI=Upper respiratory tract infection, IgE=Immunoglobulin E

In preschool children, asthma diagnosis and management differs 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.\textsuperscript{[297]} 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.[295,298,299]

**Asthma phenotypes in children**

Based on several longitudinal studies, wheezing has been categorized epidemiologically into transient and persistent wheeze phenotype. It is also categorized based on symptoms into episodic/viral induced and multi-trigger wheeze phenotypes.[300,301] Different responses to treatment and variable outcomes have been attributed to phenotype heterogeneity, overlap, and instability over time. On contrary, 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:[300,302]

- 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 continue after the age of 6 years
- Late-onset wheezing between 3 and 6 years of age.

The allocation of children into these categories remains a subject of debate, as their clinical usefulness is still under investigation.[303]

**Prediction of asthma in preschool children**

For early identification of the risk for persistent asthma among preschool children, 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 13].
Children with a history of four or more wheezing exacerbations (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 during later childhood. On other side, children with negative modified-API will have 95% chance of outgrowing their asthma later on life.\[306\]

**Box 13: Modified asthma predicative index**

<table>
<thead>
<tr>
<th>History of ≥4 wheezing episodes with at least one physician-diagnosed and either</th>
</tr>
</thead>
<tbody>
<tr>
<td>One (or more) of the major criteria</td>
</tr>
<tr>
<td>Parental history of asthma</td>
</tr>
<tr>
<td>Skin test positive to aero-allergens</td>
</tr>
<tr>
<td>Eczema (physician-diagnosed atopic dermatitis)</td>
</tr>
</tbody>
</table>

Adapted from reference\[305\]

**Principles of asthma assessment in children**

**Strategy of asthma management in children**

The long-term goals of asthma management in children are not different from those of adults [Box 5].\[70]\ Asthma management requires effective partnership between patients/caregivers and their healthcare providers.\[307]\ 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. 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 14].

<table>
<thead>
<tr>
<th>Age</th>
<th>Preferred device</th>
<th>Alternative device</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 years</td>
<td>MDI + spacer with face mask</td>
<td>Nebulizer with face mask</td>
</tr>
<tr>
<td>4–6 years</td>
<td>MDI + spacer with mouthpiece</td>
<td>Nebulizer with mouthpiece</td>
</tr>
<tr>
<td>&gt;6 years</td>
<td>Dry powder inhaler, breath actuated pressurized MDI,</td>
<td>Nebulizer with mouthpiece</td>
</tr>
<tr>
<td></td>
<td>MDI + spacer with mouthpiece</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the GINA. MDI=Metered dose inhaler, GINA=Global Initiative for Asthma

- 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. Proper asthma education can lead to a significant reduction in ED visits and hospitalizations, improve self-management of asthma exacerbations, and an overall reduction in the cost of asthma care

- Action plan: An action plan that includes medications, doses, and 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 advice of treatment modification in these situations [Box 15]
**Box 15: Components of asthma management action plan**

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

- Prevention: Asthma exacerbations 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.\(^ {70,312} \) Breastfeeding and Vitamin D supplementation may decrease the chance of developing early wheezing episodes\(^ {313} \) while probiotics benefit is still doubtful in preventing allergic disease.\(^ {314,315} \)

**Asthma control level**

Asthma control is a reflection of 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 reporting by children and their caregivers and subsequently treatment decisions by clinicians.\(^ {71} \) In children, assessment of asthma control is recommended to cover two domains:\(^ {287} \)
A. Assessing future risk of adverse outcomes: This achieved by assessing future risk of exacerbations, fixed airflow obstruction, and adverse effect of medications [Box 16]

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Assessment</th>
</tr>
</thead>
</table>
| Asthma flare-ups within the next few months | Uncontrolled asthma symptoms  
One or more severe asthma flare-ups 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 |
| 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 |

*B Adapted from reference. *ICS=Inhaled corticosteroid

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 GINA criteria for asthma
control [Box 17] to assess disease control. 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.\textsuperscript{[316]}

<table>
<thead>
<tr>
<th>Box 17: Levels of asthma control in children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Daytime symptoms</td>
</tr>
<tr>
<td>Limitations of activities</td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
</tr>
<tr>
<td>Need for bronchodilator</td>
</tr>
</tbody>
</table>

Adapted from the GINA.\textsuperscript{[70]} GINA=Global Initiative for Asthma

SINA expert panel recommends the following questionnaires to be completed by patients and/or their caregiver before physician evaluation based on the age of the child:

- Age group 5–11 years: The childhood-ACT (C-ACT).

The C-ACT is a validated test for 4–12 years old children [Box 18]. 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.\textsuperscript{[317]}
### Box 18: The Childhood Asthma Control Test*

**THE CHILDHOOD ASThma CONTROL TEST (C-ACT) FOR KIDS 4-12 YEARS OF AGE**

<table>
<thead>
<tr>
<th>CHILD</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. How is your asthma today?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Very bad (0)</td>
<td>○ Bad (1)</td>
</tr>
<tr>
<td><strong>2. How much of a problem is your asthma when you run, exercise, or play sports?</strong></td>
<td></td>
</tr>
<tr>
<td>○ It's a big problem; I can't do what I want to do! (0)</td>
<td>○ It's a problem &amp; I don't like it (1)</td>
</tr>
<tr>
<td><strong>3. Do you cough because of your asthma?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Yes, all of the time (0)</td>
<td>○ Yes, most of the time (1)</td>
</tr>
<tr>
<td><strong>4. Do you wake up during the night because of your asthma?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Yes, all of the time (0)</td>
<td>○ Yes, most of the time (1)</td>
</tr>
<tr>
<td><strong>5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Not at all (5)</td>
<td>○ 1-3 days (4)</td>
</tr>
<tr>
<td><strong>6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Not at all (5)</td>
<td>○ 1-3 days (4)</td>
</tr>
<tr>
<td><strong>7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Not at all (5)</td>
<td>○ 1-3 days (4)</td>
</tr>
</tbody>
</table>

**C-ACT Score < 19 Indicates Uncontrolled Asthma**

- **Age group <5 years:** The Test for Respiratory and Asthma Control in Kids (TRACK).

The TRACK is a validated test for children <5 years [Box 19]. It is a 5-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.\[^{318}\]
Outpatient treatment of asthma in children

Treatment 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. Though the stepwise approach is stratified into age categories (<5 years and 5–11 years), there are common concepts in the two age groups that include:

- 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.
• Assessment of adherence, proper device use, control of environment, and confirmation of the diagnosis, especially if there is a failure to respond to therapy is recommended each time before treatment adjustments

• ICS is considered the most effective first-line maintenance monotherapy for childhood asthma (Evidence A)[319,320]

• Chronic use of ICS for more than 3 months in prepubertal-aged children can suppress growth velocity; however, this effect is dose dependent. Asthmatic children when treated with low-dose ICS attain normal adult height but at a later age (Evidence A).[321,322] 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 is available in Appendix 2

• There are insufficient data to recommend short courses of high-dose ICS in children with mild intermittent asthma exacerbations (Evidence B).[323] Safety of this approach has not been established

• Children with frequent or severe asthma exacerbations are recommended to receive regular treatment with ICS (Evidence A)[324]

• 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)[325,326]

• LTRAs can reduce viral-induced asthma exacerbations in children aged 2–5 years with history of intermittent asthma (Evidence B)[327]

• Oral bronchodilators therapy is not recommended due to slower onset of action and higher side effects[328]
• LABA should not be used alone as maintenance monotherapy in children (Evidence A)\textsuperscript{[329]}

• LABA should be used only in combination with ICS. There are different combinations available in the Saudi market [Appendix 2]

• There is no evidence to support the use of LABA in children <5 years

• There is no evidence to support the use of LAMA in children <12 years

• There is a 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 exacerbations despite daily high-dose ICS plus LABA.\textsuperscript{[330,331]} However, this line of management is recommended to only be restricted to physicians specialized in asthma (Evidence C)\textsuperscript{[332,333]}

• As inhalers are the main method of delivering medications, it is recommended to choose the appropriate device [Box 14]. Use of valved-spacer, with mouthpiece when possible, is recommended when an MDI is prescribed (Evidence B).\textsuperscript{[334]} Breath-actuated devices (e.g., dry powder inhalers) represent an effective and simpler option for maintenance therapy in children ≥5 years of age (Evidence C).\textsuperscript{[335,336]} For more information about medications, refer to Appendix 2

• Nebulizers are not superior to MDI delivered by spacer in both acute and chronic asthma management (Evidence A).\textsuperscript{[337]}

In these guidelines, the SINA expert panel ensures consistency in the approach of asthma in adults, adolescents, and children. Therefore, outpatient treatment will be described in three phases such as initiation, adjustment, and maintenance. The recommendations in the following sections are further stratified based on age groups <5 years and 5–11 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 and risk factors, obtaining C-CAT score for children aged 5–11 years, and TRACK score for children <5 years. It is also recommended to provide teaching of inhalers technique, action plan and ensure that patient has a follow-up visit. SINA expert panel recommends the following for initiation of treatment based on the common clinical scenarios described below:

- A child with minimal symptoms and use of SABA (less than twice a week for both) that qualify for a controlled status based on physician assessment and is complemented with a C-ACT score of ≥20 for a child aged 5–11 years or TRACK score of >80 for a child aged <5 years, the following actions are recommended:
  - Initiation of treatment with SABA on “as needed bases”[^338]
  - For a child <5 years with intermittent viral-induced wheeze, it is recommended to initiate treatment with SABA on “as needed bases”[^339-341]
  - Initiation of treatment with low-dose ICS for a child with a history of asthma exacerbation in the past year or has ever been admitted to ICU (Evidence D).

- A child with more symptoms and use of SABA (more than twice a week for both) that qualify to partially controlled status based on physician assessment and is complemented with a C-ACT score of ≤19 for a child aged 5–11 years or TRACK score of ≤80 for a child aged <5 years, the following actions are recommended:
  - Initiation of treatment with low-dose of ICS (Evidence A).[^342-344] Different options of ICS are available in Appendix 2
Initiation of treatment with LTRA for children who cannot or will not use ICSs though it is considered a less-effective option (Evidence B)\textsuperscript{[345-347]}

For a child with early signs of asthma exacerbation at presentation, a short course of oral steroids may be considered in addition to a low-moderate of ICS

For a child <5 years of age with:

- more persistent symptoms: Commence treatment on double dose of ICS. Alternatively, commence patient on a combination of low-dose ICS and LTRA\textsuperscript{[348,349]}
- intermittent asthma and frequent viral-induced asthma exacerbations may benefit from LTRA (Evidence B).\textsuperscript{[327]}

**Adjustment of asthma treatment for children**

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 5–11 years or TRACK score for children aged <5 years. Patient should be clinically assessed regarding medications and doses, compliance to treatment, and accuracy of inhalers technique [Boxes 20 and 21]. Based on clinical assessment and the level of asthma control, the followings are recommended:

- 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 $\leq 19$ for a child aged 5–11 years or TRACK score of $\leq 80$ 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 exacerbations.
Controlled status is determined based on physician assessment complemented by a C-ACT score of $\geq 20$ for a child aged 5–11 years or TRACK score of $>80$ for a child aged <5 years.

SINA expert panel recommends the following concepts of treatment adjustment based on age in the following section.

**Children aged 5–11 years [Box 20]**

- A child is not controlled at step 1: The preferred option is to start low-dose ICS (step 2) (Evidence A)$^{[319,320]}$

- 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)$^{[126]}$. Alternatively, LTRA can be added to low-dose ICS or the dose of ICS escalated to moderate dose (Evidence A)$^{[350-355]}$

- A child is not controlled at step 3: It is recommended to change the combination inhaler to medium dose of ICS/LABA (step 4). LTRA may be added to this combination.

Whenever there is a difficulty to control asthma at step 4, it is strongly recommended to refer patient to a physician specialized in asthma.
Box 20: Outpatient management of asthma in children aged 5–11 years

**PHYSICIAN ASSESSMENT OF ASTHMA CONTROL**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled (all of the following)</th>
<th>Partially controlled (any of the following)</th>
<th>Uncontrolled (≥3 of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (twice or less/week)</td>
<td>&gt;2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Bronchodilator use</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
</tbody>
</table>

**Additionally, you may use TRACK Score to further Assess Asthma Control (Follow TRACK Table)**

**Use Step-Up approach if uncontrolled or Step-Down approach if controlled for 6-12 weeks**

**STEP 1**
Salbutamol (PRN)

**STEP 2**
Low dose ICS*
*Alternative: Leukotriene modifier

**STEP 3**
Preferred: Double dose ICS* + Leukotriene modifier
*Alternative: Low dose ICS + Leukotriene modifier

**STEP 4**
Double dose ICS + Systemic Steroid

**STEP 5**
Step 4 Regimen + Systemic Steroid

Refer to Specialist

Salbutamol (PRN)

- Challenge diagnosis (is it asthma?)
- Environmental Control
- Asthma Education
- Evaluate Compliance
Children aged <5 years [Box 21]

- A child is not controlled at step 1: The preferred option is to start low-dose ICS (step 2) (Evidence A)[319,320]
- 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).[353,356,357] Alternatively, adding LTRA to low-dose ICS is another option although this is considered less-effective[348,349]
- 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).[358-360]
Box 21: Outpatient management of asthma in children aged <5 years

**PHYSICIAN ASSESSMENT OF ASTHMA CONTROL**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled (all of the following)</th>
<th>Partially controlled (any of the following)</th>
<th>Uncontrolled (&gt;3 of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (twice or less/week)</td>
<td>&gt;2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Bronchodilator use</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
</tbody>
</table>

Additionally, you may use TRACK Score to further Assess Asthma Control (Follow TRACK Table)

Use Step-Up approach if uncontrolled or Step-Down approach if controlled for 6-12 weeks

**STEP 1**
Salbutamol (PRN)

**STEP 2**
Low dose ICS*
*Alternative: Leukotriene modifier

**STEP 3**
Preferred: Double dose ICS
*Alternative: Low dose ICS + Leukotriene modifier

**STEP 4**
Double dose ICS + Systemic Steroid

****STEP 5****
Step 4 Regimen + Systemic Steroid

Refer to Specialist

**Salbutamol (PRN)**

- Challenge diagnosis (is it asthma?)
- Asthma Education
- Environmental Control
- Evaluate Compliance
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 for children**

Upon follow-up, it is recommended to perform a full clinical assessment including asthma control status and obtaining C-ACT score for children aged 5–11 years or TRACK score for children aged <5 years. Based on clinical assessment and asthma control status [Boxes 20 and 21], 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 5–11 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
- Maintain treatment for children who reached controlled status based on physician assessment complemented by a C-ACT score of ≥20 for a child aged 5–11 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. In addition, close monitoring upon treatment stepping down is recommended for patient who has risk of asthma exacerbation especially during seasonal variation or for those with prior acute asthma exacerbation in the past year or history of ICU admission.

SINA expert panel recommends the following concepts for treatment stepping down based on age.

**Children aged 5–11 years [Box 20]**

- 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).

**Children aged <5 years [Box 21]**

• The need for continuation of ICS should be regularly assessed as wheeze remits in a significant portion of children\[^{361}\].

• 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 recurs, 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 exacerbation requiring a hospitalization.

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
- 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 exacerbation.
In a child aged 2–5 years, the combination of the above features can predict approximately 70% of acute asthma exacerbations with low false positive rate.\textsuperscript{[362]} Moreover, upper respiratory tract infection may frequently precede acute asthma exacerbation in children. Clinical assessment is essential in children as the utilization of objective measure such as PFT is problematic, especially in the younger age groups.

**Initial management of acute asthma at home**

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 advice for initial treatment (Evidence D). The action plan [Box 15] is recommended to include the 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 exacerbation, 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 3 doses. If the child improves, asthma therapy is recommended to be stepped up as per instructions in the action plan (see above under adjustment of asthma treatment for children) 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.\[71,363-373\] This is supported by the fact that PFT measurement is not feasible as more than half of asthma exacerbations in children presented to EDs are of preschool-aged children.\[364\]

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.\[364,374\] PRAM represents a useful means to record clinical signs in a standardized fashion [Box 22].\[71\] PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing.\[371\] 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.\[375,376\] 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 (<10%) of hospital admission
- Total score of 4–7: Moderate risk (10–50%) of hospital admission
- Total score of 8–12: High risk (>50%) of hospital admission.
Box 22: The Pediatric Respiratory Assessment Measure score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprasternal retraction</td>
<td>Absent</td>
<td></td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Scalene muscle contraction</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air entry</td>
<td>Normal</td>
<td>Decreased at bases</td>
<td>Widespread decreased</td>
<td>Absent/minimal</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Absent</td>
<td>Expiratory only</td>
<td>Inspiratory and expiratory</td>
<td>Audible without stethoscope/silent chest with minimal air entry</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>≥95</td>
<td>92–94</td>
<td>&lt;92</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from reference[371]

Management of acute asthma in the emergency department

After performing the necessary clinical assessment, SINA expert panel recommends the utilization of PRAM as a tool to assess patients in ED and guide further management. PRAM score should be obtained at the initial assessment and after initiation of treatment as well. 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
- 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 exacerbations markedly decrease the rate of hospitalization without increasing the rate of return to emergency care (Evidence B) [Box 23]. 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 PRAM at triage.

Viral infection is the usual cause of asthma exacerbations in children, and thus routine use of antibiotics is strongly discouraged. Antibiotics should only be used when pneumonia or bacterial bronchitis are clinically suspected.

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
  - Keep Saturation ≥92% with the appropriate dose of oxygen, if necessary
  - Salbutamol (<20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer, ≥20 kg: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response). Physician can consider the addition of ipratropium bromide (4 puffs by MDI/spacer or 250 mcg by nebulizer) every 20 min for the 1st h only. In mild cases, SABA with spacer are not inferior to nebulized SABA
Box 23: Initial assessment of acute asthma in the emergency room for Children

**OBTAIN PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM)**

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprasternal indrawing</td>
<td>Absent</td>
<td></td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Scalenene Contraction</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air-entry</td>
<td>Normal</td>
<td>Decreased at bases</td>
<td>Widespread decrease</td>
<td>Absent/Minimal</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Absent</td>
<td>Expiratory only</td>
<td>Inspiratory &amp; expiratory</td>
<td>Audible wheezing/silent chest</td>
</tr>
<tr>
<td>SaO₂ on R/A</td>
<td>≥95%</td>
<td>92 – 94%</td>
<td>&lt;92%</td>
<td></td>
</tr>
</tbody>
</table>

**ER PRAM PATHWAY INCLUSION CRITERIA:**
- Children 1-14 yrs of age presenting to ER with shortness of breath and wheezing, and either of the following:
  1. Prior diagnosis of asthma by an MD,
  2. Past history of wheezing attack responsive to bronchodilator.
- Exclude infants presenting with first wheezing episode or children presenting with features of upper airway obstruction (e.g. stridor) as the cause for their shortness of breath.

**MILD PRAM: 1-3**
1. Vital signs initially & at discharge
2. Keep SaO₂ >92% (use O₂ if needed)
3. Salbutamol, consider Ipratropium
4. Consider Oral Steroids
5. Re-assess PRAM after 1 hour

**(Discharge Plan)**
- Salbutamol PRN
- Inhaled steroid till next clinic visit
- Provide action plan
- Provide asthma education
- Clinic visit within one week

**MEDIUM PRAM: 1-3**
1. Vital signs initially & at discharge
2. Keep SaO₂ >92% (use O₂ if needed)
3. Salbutamol and Ipratropium Q 20 min for 3 times
4. Systemic steroid after first Bronchodilator
5. Re-assess PRAM after 1 hour

**(Discharge Plan)**
- Continue Salbutamol
- Ipratropium Q 30-60 min
- Re-assess PRAM hourly for 4 hours:
  - if PRAM 1-3 after 4 hours, admission is recommended

**MODERATE PRAM: 4-7**

**(Discharge Plan)**
- IV access and fluids
- Continuous IV Salbutamol
- IV MgSO₄
- ABG and consider CXR
- Monitor electrolytes
- Contact PICU for Admission
Box 23: Initial assessment of acute asthma in the emergency room for Children (continued)

SEVERE
PRAM: 8-12

1. Vital signs Q 20 min until improvement
2. O2 Supplementation to keep SaO2 ≥ 94%
3. Salbutamol + Ipratropium Q 20 min for 3 times
4. Systemic steroid after first Bronchodilator
5. Consider IV access and fluids
6. Re-assess PRAM after 1 hour

PRAM 1-3

(DischARGE Plan)
• Observe for 1 hour after last
  Bronchodilator
• If PRAM ≤ 3 discharge home
• Salbutamol Q 4-6 hours
  for 24 hours then PRN
• Inhaled steroids till next clinic visit
• Oral steroid for 3-5 days
• Provide action plan
• Provide asthma education
• Clinic visit within one week

PRAM 4-7

• Continue Salbutamol
  + Ipratropium Q 30-60
  min
• Re-assess PRAM hourly for 4 hours:
  - If PRAM 4-7 after 4
  hours admission is
  recommended

PRAM 1-3

PRAM 8-12

PRAM 8-12

• IV access and fluids
• Continuous IV Salbutamol
• IV MgSO4
• ABG and consider CXR
• Monitor electrolytes
• Re-assess PRAM after
  1 hour

• Consult PICU for Admission

ABBREVIATION:

ABC: Arterial Blood Gas, CXR: Chest X-Ray, IV: Intravenous,
MgSO4: Magnesium Sulphate, O2: Oxygen, PICU: Pediatric Intensive Care Unit, PRAM: Pediatric Respiratory Assessment
Measure, PRN: As Needed, SaO2: Oxygen Saturation, R/A: Room Air
Consider oral steroids (prednisolone 1–2 mg/kg up to a maximum dose as the following: 20 mg for children <2 years, 30 mg for children 2–5 years, and 50 mg for children 5–12 years)[223]

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 with a spacer and ICS if the patient is not already on controller treatment. 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 is score 4–7: Treat as a moderate asthma exacerbations (see below)

- PRAM is score 8–12: Treat as a severe asthma exacerbations (see below).

**Moderate - Pediatric Respiratory Assessment Measure score of 4–7**

- Management:

  - Obtain vital signs

  - Keep Saturation ≥92% with the appropriate dose of oxygen, if necessary

  - Salbutamol (<20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer, ≥20 kg: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response) and ipratropium bromide (2 puffs 80 mcg or 250 mcg by nebulizer every 20 min for the 1st h only).[381-383] This combination has been shown to be effective in this situation (Evidence B)[382]
• Systemic steroids after the first dose of SABA (oral prednisolone or IV methylprednisolone 1–2 mg/kg up to a maximum dose as the following: 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years)

• Reassess 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:
  
  o 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. Oral steroids may be considered (oral prednisolone up to a maximum dose as the following: 20 mg for children <2 years, 30 mg for children 2–5 years, and 50 mg for children 5–12 years). 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.

  o PRAM score is 4–7: It is recommended to continue on treatment with salbutamol and ipratropium bromide every 30–60 min. It is also recommended to assess PRAM score hourly. If PRAM score improves to 1–3, the child can be managed as above. If PRAM score does not improve, admission is recommended.

  o PRAM score is 8–12: Special care and frequent monitoring are needed. IV access is recommended to be established, and appropriate IV fluids started. IV salbutamol (1 mcg/kg/min then titrate based on response for a maximum dose of 10 mcg/kg/min) and IV magnesium sulfate (single dose of 40 mg/kg to the maximum of 2 g by slow IV infusion) might also be considered. ABG, CXR, and electrolyte are recommended to be obtained, and the pediatrics critical care or equivalent service must be consulted.
Severe - Pediatric Respiratory Assessment Measure score of 8–12

• Management:
  
  o Obtain vital signs every 20 min till improvement
  
  o Keep Saturation ≥94% with the appropriate dose of oxygen if necessary
  
  o Salbutamol (<20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer, >20 kg: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response) and ipratropium bromide (2 puffs 80 mcg or 250 mcg by nebulizer every 20 min for the 1st h only).[381-383] This combination has been shown to be effective in this situation (Evidence B)[382]
  
  o Systemic steroids after first dose of SABA (oral prednisolone or IV methylprednisolone 1-2 mg/kg up to a maximum dose as the following: 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years)[207,223]
  
  o Re-assess PRAM after 1 h
  
  o Consider IV access and appropriate IV fluids
  
  o If PRAM score after 1 h is 1–3, Observe for another hour.

• Management after initial treatment based on PRAM score:
  
  o 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. Oral steroids may be considered (oral prednisolone up to a maximum of 20 mg for children <2 years, 30 mg
for children 2–5 years, and 50 mg for children 5–12 years).\(^{[207,223]}\) It is recommended to offer the child/care giver 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 on treatment with salbutamol and ipratropium bromide every 30–60 min. It is also recommended to assess PRAM score hourly. If PRAM score improves to 1-3, manage as above. If PRAM score does not improve, admission is recommended.

- PRAM score 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. IV salbutamol (1 mcg/kg/min then titrate based on response to a maximum dose of 10 mcg/kg/min), and IV magnesium sulfate (single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion) might be considered.\(^{[384,385]}\) ABG, CXR, electrolyte, and consultation for the pediatrics critical care service must be sought.

“united airway disease.” In clinical practice, failure to recognize and treat rhinosinusitis may affect asthma control.\(^{[394]}\)
Appendix 1: Pathophysiology of asthma

Airways inflammation

Asthma is a complex syndrome characterized by AH and is caused by a multicellular inflammatory reaction that leads to airway limitation [Box 24]. Recruitment and activation of mast cells, macrophages, antigen-presenting dendritic cells, neutrophils, eosinophils, and T lymphocytes result in an inflammatory and cellular infiltration of the airways. Type 2 T-helper cells have a major role in the activation of the immune cascade that leads to the release of many mediators such as ILs IL-3, IL-4, IL-5, IL-13, and granulocyte macrophage colony stimulating factor (GM-CSF).

Some mediators such as IL-4 and IL-13 activate B lymphocytes to produce IgE while others (e.g., IL-3, IL-5, and GM-CSF) are related to eosinophilic inflammation pathway. Severe asthma may present in various inflammatory phenotypes, such as persistent eosinophilic bronchitis, neutrophilic infiltration of the airway, and a pauci-granulocytopenic type of inflammation. Such persistent inflammation results in airway remodeling which includes increased deposition of extracellular proteins, smooth muscle hypertrophy and hyperplasia, and increased goblet cells. The airway epithelium becomes fragile and thin, and the epithelial basement membrane thickens. There is also increased mucus production and endothelial leakage, which leads to mucosal edema. Mediator-induced abnormalities in the parasympathetic and nonadrenergic noncholinergic nervous systems may also lead to increased bronchial hyper-responsiveness. Recent data have shown that all asthmatic patients have inflammation in the upper airways, irrespective of the presence of symptoms of rhinosinusitis. Studies have also shown that stimulation by an irritant instilled in the nose leads to eosinophilic inflammation in the lungs within a few hours. Such co-existence of inflammation in both the upper and lower airways has led to the suggestion of the terminology
Airway remodeling

Structural airway changes may develop even before the disease becomes symptomatic. They can also occur in patients with allergic rhinitis, who are associated with an increased risk of developing asthma. The most prominent changes include epithelial damage, subepithelial fibrosis, increased airway vasculature, increases in extracellular matrix proteins including collagens and proteoglycans, and increased smooth muscle mass. The mucus hypersecretion observed in asthma is related to an increase in the number of secretory glands and cells such as goblet cells. These changes are generally attributed to the underlying inflammatory process, although other mechanisms may play a role.\[^{386}\] It has been proposed that remodeling may be involved in the development and persistence of asthma, in the accelerated decline of pulmonary function, and in the development of a more “fixed” component of airway obstruction in some asthmatic, particularly in severe cases. Although a relationship has been found between the severity of asthma and some of the components of airway remodeling, researchers have not yet been able to adequately distinguish severe asthma from milder forms on the basis of histological features alone.\[^{402}\] Prevention of airway remodeling has not been well studied, but it is certain that sustained treatment with anti-inflammatory medications as well as the prevention of asthma exacerbations have a role in preventing or delaying airway remodeling.
Airways hyper-responsiveness

AH to direct (histamine or methacholine) and indirect (exercise, cold air, mannitol, adenosine monophosphate, or isocapnic hyperventilation) challenges is a characteristic of asthma. When asthma symptoms are present, there is a relatively good correlation between the severity of disease and the degree of AH. AH is not a static feature of asthma; it may increase after sensitizing exposures and may decrease after anti-inflammatory treatments or if there is a reduction in relevant environmental exposures. Asthma has a variable component, which is related to airway inflammation, and a more refractory component that is largely attributed to the underlying airway structural changes, which is also known as remodeling.

Early and late responses

Following presentation of the antigen by dendritic cells in a sensitized patient, certain inflammatory cascades become activated leading to the attachment of the IgE antibodies to inflammatory cells such as mast cells. Cross-linking of IgE receptors leads to degranulation of inflammatory cells and liberation of various mediators, which are responsible for the allergic response. The allergen-induced airway response may be immediate (early response) with a fall in expiratory flow within an hour of exposure, or may be delayed (late response) with the fall in expiratory flow being observed within 2–8 h. An increase in AH and the variability of airway obstruction may occur within the following 2–3 days depending on the intensity of the response.
Box 24: Pathophysiology of asthma

Box 1: Pathophysiology of asthma
APC = Antigen presenting cell
ILs = Interleukins
TH2 = T-lymphocyte Helper cell 2
Appendix 2: 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. Relievers are medications used on an “as-needed bases” 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. They reduce symptoms, improve quality of life, improve lung function, decrease AH, control airway inflammation, reduce frequency and severity of asthma exacerbations, and reduce asthma mortality. Early initiation of low-dose ICS in asthma leads to improvement in lung function. When they are discontinued, deterioration of clinical control follows within weeks to months in most patients. ICS differs in its potency and bioavailability. Most of the benefits from ICS are achieved in adults and children at relatively low-doses [Boxes 25 and 26]. Exposure to tobacco smoking, including secondary and tertiary, reduces the responsiveness to ICS. To reach control, add-on therapy with another class of controller is preferred to increasing the dose of ICS.

Local adverse effects can occur and include oropharyngeal candidiasis and dysphonia; with MDIs, these effects may be reduced using a spacer device. Mouth washing after inhalation may reduce oral candidiasis. Systemic side effects are occasionally reported with high-doses and long-term treatment. The small risk of adverse events from the use of ICS is well balanced by their efficacy.
Though low-medium dose ICS may affect growth in children, this effect is clinically insignificant and may be reversible. Therefore, low-medium dose of ICS is generally safe and well tolerated in children. Formulations with small size particles, such as beclomethasone or ciclesonide, are believed to be more effective and safer as it led to better deposition in the peripheral small airways.\textsuperscript{[409,410]} Some studies have shown that ciclesonide has relatively lower local and systemic side effects, especially in children.\textsuperscript{[411]}

### Box 25: List ICS inhalers available in the Saudi market for adults and adolescents*

<table>
<thead>
<tr>
<th>Drug (doses in mcg)</th>
<th>Low - dose</th>
<th>Medium dose</th>
<th>High-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (CFC)</td>
<td>200 - 500</td>
<td>&gt;500 - 1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (HFA)</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200 - 400</td>
<td>&gt;400 - 800</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Ciclesonide (HFA)</td>
<td>80 - 160</td>
<td>&gt;160 - 320</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI and HFA)</td>
<td>100 - 250</td>
<td>&gt;250 - 500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110 - 220</td>
<td>&gt;220 - 440</td>
<td>&gt;440</td>
</tr>
</tbody>
</table>

*Adapted from reference.\textsuperscript{[31]} CFC=Chlorofluorocarbon propellant, DPI=Dry powder inhaler, HFA=Hydrofluoroalkane, ICS=Inhaled corticosteroid
### Box 26: List of ICS inhalers available in the Saudi market for children*

<table>
<thead>
<tr>
<th>Drug (doses in mcg)</th>
<th>&lt;5 years</th>
<th>Children &gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-dose</td>
<td>Low-dose</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (CFC)</td>
<td>100</td>
<td>100–200</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (HFA)</td>
<td>100</td>
<td>50–100</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200</td>
<td>100–200</td>
</tr>
<tr>
<td>Budesonide (Nebules)</td>
<td>500</td>
<td>250–500</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>160</td>
<td>80</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
<td>Not applicable</td>
<td>100–200</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100</td>
<td>100–200</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Not studied</td>
<td>110–220</td>
</tr>
</tbody>
</table>

*Adapted from reference.[31] CFC=Chlorofluorocarbon propellant, DPI=Dry powder inhaler, HFA=Hydrofluoroalkane

### Special considerations for use of inhaled corticosteroid in children

Growth retardation may be seen with all ICSs when a high-dose ICS is chronically used. Based on recent systematic reviews, a mean reduction of 0.48 cm/year in linear height velocity was observed in prepubertal children over 12 months use of low to medium dose of ICS, especially during the 1st year of life.[412] Though 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.[413] Moreover, more studies demonstrated the negative impact of medium to high doses ICS on bone mineralization.[414-416] 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.[417] 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 B2-agonists**

The commonly used long-acting inhaled B2-agonists, include formoterol and salmeterol, are used twice daily. Novel ultra LABA agents with a 24 h duration of action are available, e.g., indacaterol, vilanterol, and olodaterol.[418-424] The ultra LABA has a compliance-enhancing advantage. Due to lack of anti-inflammatory effect, this category should not be used alone as monotherapy in asthma as it leads to increased mortality. When used in combination with ICS, there is an improvement in symptoms, decreased nocturnal asthma, improved lung function, decreased use of inhaled B2-agonists, reduced number of asthma exacerbations, and achieving more clinical control of asthma in more patients, more rapidly at a lower dose of ICS. LABA provides longer protection to prevent exercise-induced bronchospasm than short-acting inhaled B2-agonists (SABA).[425] 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 these side effects. Furthermore, patients rarely develop a tolerance to LABAs. The effect of LABA products has not been adequately studied in children of 5 years and below.
Fixed combination of inhaled corticosteroid and long-acting beta 2 agonists

Fixed combination of ICS and LABAs is considered more convenient for patients. 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.\[132\] Fixed combination inhalers of ICS and LABAs have been available in the form of fluticasone propionate and salmeterol (Seretide) or budesonide and formoterol (Symbicort). New formulations are available in different devices in the Saudi market [Box 27] such as beclomethasone and formoterol (Foster), mometasone and formoterol (Dulera), fluticasone propionate and salmeterol (Rolenium), budesonide and formoterol (Pulmoton), and fluticasone propionate and formoterol (Flutiform).\[426-429\]

New once a day, dry powder combinations of ICS/ultra LABA are expected to be available soon in the Saudi market. One of these, the dry powder combination of fluticasone furoate and vilanterol (Relvar) that comes in two strengths of 100/25 and 200/25 mcg with dispensed equivalent dose of 92/22 and 184/22 mcg, respectively.\[134,135\] The dose of fluticasone furoate of 100 mcg was found to be equivalent to fluticasone propionate 250 mcg.\[430\] Such a combination has a potential adherence advantage while maintaining the same safety as the combination of fluticasone propionate and salmeterol.\[431\]
<table>
<thead>
<tr>
<th>Inhaled steroid (doses in mcg)</th>
<th>LABA (doses in mcg)</th>
<th>Brand name</th>
<th>Device type</th>
<th>Device name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone (100)</td>
<td>Formoterol (6)</td>
<td>Foster*</td>
<td>MDI</td>
<td></td>
</tr>
<tr>
<td>Budesonide (80, 160, and 320)</td>
<td>Formoterol (4.5, 9)</td>
<td>Symbicort*</td>
<td>DPI</td>
<td>Turbuhaler™</td>
</tr>
<tr>
<td>Budesonide (200, 400)</td>
<td>Formoterol (6, 12)</td>
<td>Pulmoton*</td>
<td>DPI</td>
<td>Elpenhaler™</td>
</tr>
<tr>
<td>Fluticasone propionate (50, 125, and 250)</td>
<td>Salmeterol (25)</td>
<td>Seretide*</td>
<td>MDI</td>
<td>Evohaler™</td>
</tr>
<tr>
<td>Fluticasone propionate (100, 250, and 500)</td>
<td>Salmeterol (50)</td>
<td>Seretide*</td>
<td>DPI</td>
<td>Diskus™</td>
</tr>
<tr>
<td>Fluticasone furoate (100, 200)</td>
<td>Vilanterol (25)</td>
<td>Relvar*</td>
<td>DPI*</td>
<td>Ellipta™</td>
</tr>
<tr>
<td>Fluticasone propionate (50, 125, and 250)</td>
<td>Formoterol (5, 10)</td>
<td>Flutiform*</td>
<td>MDI</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate (250, 500)</td>
<td>Salmeterol (50)</td>
<td>Rolenium*</td>
<td>DPI</td>
<td>Elpenhaler™</td>
</tr>
<tr>
<td>Mometasone furoate (100)</td>
<td>Formoterol (5)</td>
<td>Dulera*</td>
<td>MDI</td>
<td></td>
</tr>
</tbody>
</table>

*Once a day combination. MDI=Metered dose inhaler, DPI=Dry powder inhaler, LABA=Long-acting beta 2 agonist
Leukotriene modifiers

Leukotriene modifier agents reduce airway inflammation and improve asthma symptoms and lung function, but with a less consistent effect on asthma exacerbations, 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.[432,433] LTRA is generally well tolerated. In children, studies have shown that LTRA may be useful for reducing the number of asthma exacerbations induced by viruses and for reducing bronchial inflammation in atopic children.[433-437] There are no clinical data to support their use under the age of 6 months.

Long-acting anti-muscarinic (cholinergic) agents

LAMAs inhibit the effect of acetylcholine on M3 receptors. Tiotropium was the first agent used in managing patient with COPD. Recently, tiotropium use has been extended to asthma. The more recent LAMA (such as aclidinium bromide, glycopyrronium) has not been studied in asthma yet. The bronchodilatation duration of action of more than 24 h; therefore, it is used once daily.[438,439] The earlier studies for the use of tiotropium were conducted in the HandiHaler. Later studies were conducted in the new Respimat device. Tiotropium is available in the Saudi market with the HandiHaler device where the dose is available in a capsule format that contains 18 mcg. The Respimat device is not yet available in the Saudi market. Tiotropium was first shown to be effective in step-down of treatment when added to a combination of ICS/LABA.[440] More recently, tiotropium was found to be not inferior to salmeterol in the management of
asthma not adequately controlled on ICS or combination of ICS/LABA.\cite{145,146,152,441} Anticholinergic drugs are considered 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 and LTRA. Theophylline is not recommended for use as monotherapy in asthma treatment. Recent data have shown that low-dose theophylline (300 mg/day) may have an important role in improving steroid resistance in patients with severe asthma requiring high-dose ICS.\cite{386,442} Their side effects include gastrointestinal symptoms, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the early symptoms of toxicity. Liver disease, CHF, quinolones, and some macrolides may increase the risk of toxicity. Use of lower doses may decrease these side effects.

**Anti-immunoglobulin E**

Anti-IgE is a recombinant humanized IgG1 monoclonal antibody that binds IgE with high affinity and has been developed for the treatment of allergic diseases.\cite{443} Anti-IgE (omalizumab) is indicated for patients of 6 years and above with severe allergic asthma uncontrolled on high-dose ICS and other controllers and who have an IgE level in the appropriate therapeutic range.\cite{444,446} As this drug is expensive and requires careful monitoring, it should only be prescribed by a specialist. The side effects include pain and bruising at injection site and very rarely anaphylaxis (0.1%).
Oral B2-agonists

The side effect profile is much higher than that of inhaled B2-agonists. Therefore, their use is highly discouraged. 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.[447]

Systemic corticosteroids

Long-term oral steroid therapy (excluding short courses for acute exacerbations of asthma for 1–2 weeks) may be required to control difficult 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 OCS. 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 are recommended.
**Reliever medications**

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

**Rapid onset inhaled B2-agonists**

SABA, such as salbutamol, is the medications of choice for relief of symptoms of acute exacerbations of asthma and the pretreatment of EIB. MDI with chamber is as effective as the nebulized route in treatment of acute episodes of wheeze in children. Formoterol is a LABA that has a fast acting component and is not currently available in the Saudi market as a single inhaler; however, it can be used as a rescue medication in formoterol containing combination of ICS/LABA. Regular long-term use of SABA is not recommended.

In acute asthma, inhaled salbutamol is the preferred choice. Repeated doses are recommended to be given at 15–20 min intervals. Alternatively, continuous nebulization (salbutamol at 5–10 mg/h) should 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 lower side effects. In patients who can 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 beta 2 agonists in the initial treatment of patients with acute severe asthma is not generally recommended. IV therapy should not be considered routinely and only 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 effect.\textsuperscript{[382]} It can also be an alternative bronchodilator for patients who experience adverse effects such as tachycardia, arrhythmia, and tremor from rapid-acting B2-agonists. Their side effects include dryness of the mouth and a bitter taste.

In moderate to severe acute asthma, combining ipratropium bromide with salbutamol has shown to have additional bronchodilation effect and faster improvement in lung function, compared to salbutamol alone.\textsuperscript{[213,216]} A recent systematic review showed the combination therapy has an added benefit in reducing hospitalizations.\textsuperscript{[215]} It has been shown that combining both agents led to reduction in hospital admission rates by 38–57\% improvement in lung function, and substantial cost saving.\textsuperscript{[216,450,451]} 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 exacerbations.\textsuperscript{[452]} The adult dosing of nebulized ipratropium bromide is 500 μg every 20 min for three doses, then as needed. Alternatively, ipratropium 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 benefit, and the drug has high levels of toxicity and side effects.\textsuperscript{[453]}
Intravenous magnesium sulfate

In a systematic review, magnesium sulfate has shown to reduce hospitalizations in patients with severe or life-threatening asthma exacerbations that fails to respond to initial treatment.[454] A single dose of IV magnesium sulfate (1–2 g) has been shown to be a safe and effective in acute severe asthma.[218]

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 nebulizers 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 prepressurized inhaler with medication and a propellant, which when actuated will give one dose of the drug for a single inspiration. MDIs typically require 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 not done properly, there is a potential of high deposition of drug in the oropharynx and poor drug delivery. Also, because it does not have dose counter, it is difficult to determine the dose remaining in the canister. Compared to the older chlorofluorocarbon (CFC) propellant formulations, hydrofluoroalkane (HFA) 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 that it is breath-actuated, and there is 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 the device. Therefore, it may not be suitable for very young or very old patients. The commonly available devices in Saudi Arabia are the Turbohaler, Diskus, Handihaler, Easi-Breathe, Ellipta, and Breezhaler devices. HFA formulations provide smaller size particle aerosols with less oral deposition, hence less oral side effects and greater proportion of lung deposition than the older CFC propellant formulations.

**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.