The Saudi Initiative for Asthma

Guidelines for the Diagnosis and Management of Asthma in Adults and Children

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Saudi Initiative for Asthma Panel

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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 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.

How to cite SINA guidelines:

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Editorial

Welcome New Guidelines: Now The Hard Work Starts!

Prof. Andrew Bush
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Worldwide, asthma remains one of the major non-communicable disorders contributing to morbidity and mortality. It is a hugely depressing fact that, despite the availability of effective treatments and evidence-based guidelines, outcomes have stalled, prompting the recent Lancet asthma commission [1]. The fact is that if the basics are done well by health care professionals and patients and their families, asthma is a simple disease to manage. The recent update of the Saudi Initiative for Asthma: Guidelines for the diagnosis and Management of asthma and children (SINA) guidelines [2] is a welcome step to try to achieve improvements, and aligns closely with the recommendations of the commission. The first step is putting the diagnosis of asthma on a firm basis, and this is stressed by SINA. There can be few if any diseases in which simple diagnostic tests can be performed but in which patients are committed to long term treatment without testing being performed. Cognisant that many children [3] and adults [4] are misdiagnosed with asthma, the guidelines stress the importance of documenting fixed and variable airflow obstruction, and, where possible, airflow obstruction. Elsewhere the need to abandon the notion that history and physical examination are sufficient to diagnose asthma has been stressed [1, 5]; there can be few if any diseases in which simple diagnostic tests are available, but in which patients are committed to long term treatment without these tests being performed.
Pharmacotherapy is an important part of asthma management, and we know that low dose inhaled corticosteroids (ICS) are effective in reducing morbidity and mortality from asthma in a wide variety of settings [6, 7]. However, as stressed by the guidelines, there is a lot more to optimal asthma management than pharmacotherapy. Rightly it is stressed that failure to obtain control should mandate a complete re-evaluation, rather than merely prescribing more treatment uncritically. Two important North American studies absolutely support this approach. In the BADGER study, children symptomatic on fluticasone 100 mcg twice daily were given in random order additional salmeterol and montelukast and had the ICS dose increased to 500 mcg/day [8]. One important lesson was that very few children gained any benefit from the increased ICS dose. The second study tried to determine if, in children symptomatic on moderate dose ICS and long-acting β-2 agonist, it was better to add a leukotriene receptor antagonist or azithromycin [9]. The trial ended in futility because most of those recruited either did not have asthma or were not taking treatment. Furthermore, in a study to determine whether using exhaled nitric oxide to determine asthma treatment in inner city children [10], during the three weeks of protocolised therapy in the run-in period the children became so well that there was no scope for any further improvement.

It is also important that asthma attacks are taken seriously. These are not mere ‘exacerbations’, a feeble word implying a mild, reversible inconvenience [11, 12]. They should be a ‘never event’ like cutting off the wrong leg in the operating theatre. There is a welcome focus on trigger factors and their avoidance in the current guidelines, and measures to reduce risk, such as influenza immunization [13]. The steps in treatment are clearly set out, and rightly, careful monitoring during an attack is stressed. Importantly, the single biggest risk factor for another asthma attack is a previous attack [14].
So an asthma attack (or perhaps better, an asthma lung attack) needs to lead to a careful and focused re-appraisal of all aspects of the child’s management. In this regard, we have a lot to learn from the cardiologists, who in the patient who has had a heart attack (whoever heard a Cardiologist talk about a ‘heart exacerbation’!) implement detailed follow up and risk assessment protocols. As stressed by SINA, we need to stratify patients for future risk of an attack, and get professionals to understand that good control, desirable as it is, does not put the patient in a low risk group for attacks.

Much asthma is treated by non-specialists. The next challenge to SINA is implementation of the guidelines, getting them at the centre of asthma care. The UK National Review of Asthma Deaths [15] makes depressing reading in this regard. Around 60% of those who died were not under specialist care and were not thought to have ‘severe’ asthma! What was very clear was that there was easily avoidable mismanagement in most deaths. Basic measurements were not made during the attack. There was failure to appreciate that the patient was not accessing ICS, and accessing a huge number of canisters of short acting β-2 agonists. In this regard, a recent manuscript [16] highlighted the depressing complacency of so many so-called asthma experts about the risks of excessive short acting β-2 agonist prescribing. If conventional guidelines about level of control are accepted, no patient should need more than one canister per year (200 doses, equivalent to utilization two days/week). Yet the prescription of a canister a month (equivalent to more than 6 puffs/day) was regarded as acceptable, despite clear cut evidence to the contrary.

The National Review of Asthma Deaths (NRAD) is depressing because it is clear that, despite guidelines becoming more evidence-based, as in the case of SINA, outcomes have not improved.
So as a community we must do better implementing the guidelines that we have. The Finnish Asthma program [6] showed what can be done. Key to their success in driving down mortality and morbidity was education (stressed by SINA) and ensuring there were ‘asthma champions’ in every area who took responsibility for ensuring asthma management was optimal, ultimately reducing costs as well as improving outcomes.

So the SINA Guidelines group are to be congratulated on this update, which is thorough, scholarly, and wide-ranging. But the really hard work now starts. Unread guidelines never helped anyone. The Group now need to work on strategies to ensure that everyone treating asthma have this wisdom at their fingertips and are committed to implementation. It must be acknowledged that asthma is a killing disease and merits a focussed approach to management. Too often the diagnosis has not been taken seriously by patients and professionals across the world, with catastrophic results. This must change.

References

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

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

Asthma is a common heterogeneous inflammatory chronic disorder of the airways. It is “defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity often with variable expiratory airflow limitation can be demonstrated.(1, 2) Asthma is one of the most common chronic diseases in Saudi Arabia with increasing prevalence.(3) It has significant impact on patients, their families, and the community as a whole in terms of lost work and school days, poor quality of life, frequent emergency department visits, hospitalizations, and deaths.(4-10) As part of the commitment of the Saudi Thoracic Society (STS) toward a long-term enhancement plan for promoting best practice in the field of respiratory diseases, the Saudi Initiative for Asthma (SINA) was launched in 2008 with special attention to non-asthma specialists, including primary care and general practice physicians.(11-14) Sections related to asthma in children represent the views of a panel from the Saudi Pediatric Pulmonology Association, another subsidiary of the STS. The Saudi Allergy Asthma and Immunology Society has also contributed to this update. SINA guidelines received a comprehensive update from the previous 2016 version with an emphasis on personalized approaches reflecting better understanding of disease heterogeneity with integration of recommendations related to biologic agents, evidence-based updates on treatment, and the role of immunotherapy in management. The medication appendix was also updated with the addition of recent evidence, namely new indications for existing medication, and new medications.

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

Methods

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

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

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

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

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

Most of the studies investigating the prevalence of asthma in various countries have focused on children below the age of 15 years or adults above the age of 18 years. A study conducted by the STS investigated the prevalence of asthma and its 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. Out of 3,073 students, 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, physician-diagnosed asthma, and exercise-induced wheeze.(31) By utilizing the ISAAC questionnaire method, another study conducted among 5,188 primary school children in Madinah showed that the prevalence of asthma was 23.6%, while 41.7% had symptoms suggestive of at least one allergic disorder.(32)

A national Saudi household survey was conducted in 2013 estimated that the self-reported clinical diagnosis of asthma to be 4.05%. (33) Another survey using the European Community Respiratory Health Survey questionnaire conducted in Riyadh among a total of 2,405 Saudi nationals aged 20-44 years showed that the prevalence of wheezing in the last 12 months was 18.2%, physician diagnosed asthma reported was 11.3%, There were no significant differences between asthmatic and non-asthmatic patients with respect to living area, level of education and ≥ and vaping history.(34)
Inadequate knowledge, lack of familiarity with new drugs, and lack of awareness of the importance of disease control are common among primary care physicians who care for asthma patients in Saudi Arabia. (16, 20) In addition to these key factors, there are other attributes to the magnitude of disease burden such as socioeconomic status, number of siblings, knowledge of caregivers, and income. (21-26) Consequently, many asthma patients are uncontrolled and continue to be under-diagnosed, undertreated, and at risk of acute attacks resulting in missed work or school, increased use of expensive acute healthcare services, and reduced quality of life. (16, 27) This was also observed among pregnant ladies with asthma as one study from Saudi Arabia showed that almost half of pregnant ladies had the intention to stop asthma medications during pregnancy. (28)
2. Pathophysiology of Asthma

Asthma is a chronic inflammatory airway disease that results in narrow airway lumen. The airway narrowing is caused by increased mucus secretion as well as bronchial wall thickening thinking due to edema, smooth muscle hypertrophy and subepithelial fibrosis. The pathophysiological mechanisms that underlie these changes are diverse and heterogeneous (Box 2.1). They are driven by variety of cell types including immune cells; mainly T-helper cells (Th2, Th17, Th1), mast cells, eosinophils, and neutrophils; as well as structural bronchial cells such as epithelial cells, myofibroblasts, and smooth muscle cells. These mechanisms are broadly classified into four categories:

- **Type 2 eosinophilic inflammation:** This is the most common type and includes at least 60% of all asthma patients. It is defined by sputum eosinophilia of ≥2% of leukocytes in a sample. Patients frequently have blood eosinophilia of ≥300/µl. Eosinophils secrete mediators such as major basic protein and eosinophil cationic protein that can cause bronchial epithelial damage and fibrosis. Those patients usually respond well to inhaled corticosteroids (ICS) especially if they have mild or moderate disease. It is further subdivided into 2 types:
  - **Early-onset allergic eosinophilic airway inflammation (extrinsic asthma).** This type usually starts in childhood and can be triggered by allergen exposure. Allergens are taken up by dendritic cells and presented to naïve T-cells that develop into Th2 cells characterized by the secretion of type 2 cytokines: IL-4, 5, and 13. IL-4 and 13 are necessary for specific B-cell activation and switching into IgE producing cells. IgE binds to its high affinity receptor on mast cells. Subsequent cross linking of IgE molecules by the allergen will lead to mast cell degranulation and release of
mediators such as histamine and tryptase as well as type 2 cytokines. In addition, IL-13 causes smooth muscle and goblet cell hyperplasia. On the other hand, IL-5 is essential for eosinophil development and maturation and contributes with certain other chemokines to their recruitment to the bronchial airways. (36, 37)

- **Late-onset non-allergic eosinophilic airway inflammation (intrinsic asthma).** This type usually starts during adulthood. Patients typically have no allergies, but usually more severe airway limitation and hyperresponsiveness. It is triggered by microbes (bacteria and viruses), pollutants, and irritants. Bronchial epithelial cells will subsequently release IL-25, IL-33, and Thymic stromal lymphopoietin (TSLP) that will stimulate innate lymphoid cells type 2 (ILC2) to release IL-5 and IL-13. (38)

- **Neutrophilic inflammation:** Variously defined as neutrophils of ³40-60% of leukocytes in an induced sputum sample. It is less clearly characterized and involves release of Th1 and Th17 related cytokines and IL8, GM-CSF that attracts neutrophils to the airways. It is triggered by infections, irritants and tobacco smoke and may be a manifestation of the use of steroids in patients with eosinophilic inflammation. Those patients are mostly adults and do not respond to ICS as well. (39)

- **Mixed inflammation:** This type has features of both eosinophilic and neutrophilic inflammation including their cytokines profile. It is less common than the two previous types and tends to be more severe and more difficult to treat. (40)

- **Paucigranulocytic phenotype:** In this form there is not as much inflammation. The airway limitation is supposedly driven by other mechanisms. It is the least common and patients usually have milder disease. (41)
Box 2.1 Immunopathology of asthma*

**Eosinophilic Asthma**

- Allergic eosinophilic inflammation

**Health**

- Airway smooth muscle

**Non-Eosinophilic Asthma**

- Pauci-granulocytic asthma

**Non-allergic eosinophilic inflammation**

**T1/T17 neutrophilic inflammation**
Airway Hyperresponsiveness (AHR):
This is a major feature of all asthma phenotypes. Its mechanisms and mediators are poorly understood. It worsens during and immediately after asthma attacks. It is usually worse in patients with severe asthma. However, it does not correlate well with markers of inflammation. Smooth muscle hypertrophy and neurohumoral factors may play a role in determining AHR.(42)

Airway remodeling:
This is a major feature of asthma that starts early in the disease and causes incomplete reversibility by bronchodilator. It is characterized by bronchial epithelial damage, thickening of the basement membrane, and muscle hypertrophy.(43, 44). It is influenced by ongoing airway inflammation and recurrent bronchoconstriction.(45)

Acute Asthma
The pathophysiology of acute asthma is less clear due to the limited information. This is because of the difficulty in studying disease pathology and obtaining samples during the attack. The pathological manifestations generally depend on the trigger. At least 80% of cases of moderate to severe acute asthma are triggered by viruses, most commonly rhinovirus, but also respiratory syncytial and influenza viruses.(46) Viral infections can cause significant epithelial damage and symptoms tend to be more severe and last longer. On the other hand, allergen or irritant triggered attacks tend to be milder and resolves more quickly. Recurrent attacks may lead to progressive decline in lung function and increasing baseline asthma severity.(47-49)
3. Diagnosis of Asthma in Adults and Adolescent

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

History

The symptoms of wheezing, cough, shortness of breath, and chest tightness are not specific for asthma and can be seen with other pulmonary diseases. However, the combination of these symptoms increases the probability of asthma. The pattern of symptoms is usually variable over time and the patient may be entirely asymptomatic between attacks. Symptoms are usually worse at night, particularly in children, and can be provoked by exercise or other triggering factors such as viral infections and or smoke. Asthma diagnosis can be supported by taking detailed history including patient’s occupation, family history of asthma, other allergic disorders, and smoking and vaping. Box 3.1 lists the relevant questions that are commonly considered when taking a history where the diagnosis of asthma is under consideration. Asthma control may be worsened by coexisting symptomatic 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). Asthma and rhinosinusitis commonly coexist.
Box 3.1: Relevant questions in the diagnosis of asthma

- Does the patient or his/her family have a history of asthma or other atopic conditions, such as eczema or allergic rhinitis?
- Does the patient have recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient wheeze or cough after exercise?
- Does the patient experience wheezing, chest tightness, or cough after exposure to pollens, dust, feathered or furry animals, exercise, viral infection, or environmental smoke (cigarettes, burning incense “Bukhoor,” or wood?
- Does the patient experience worsening of symptoms after taking aspirin/nonsteroidal anti-inflammatory medication or use of B-blockers?
- Does the patient’s colds “go to the chest” or take more than 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 may be normal in stable and controlled asthma but the presence of bilateral expiratory widespread, high-pitched, variable musical wheezing, is a characteristic feature of asthma. This may be accompanied by shortness of breath or diminished oxygen saturation. Examination of the upper airways is important to look for evidence of allergic rhinitis, such as mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis,
also support the diagnosis of allergic asthma.\(^{(50, 56)}\) The presence of a localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.\(^{(57, 58)}\) Therefore, a careful consideration of any alternative diagnoses prior to commencing asthma treatment by a physician should be made.

**Investigations**

Spirometry is necessary to confirm airflow obstruction and demonstrates significant reversibility by performing a spirometry. The degree of significant reversibility is defined as an improvement in FEV\(_1\) \(\geq 12\%\) and \(\geq 200\) ml from the pre-bronchodilator value.\(^{(59)}\) It may also help to identify other alternative diagnoses such as upper airway obstruction. However, normal spirometry or failure to show reversibility does not rule out the diagnosis of asthma, as it can be normal with the patient still being symptomatic.\(^{(60)}\) Serial peak expiratory flow rate (PEFR) measurements may be helpful in the diagnosis of asthma by showing the characteristic increased variability and for follow-up after starting treatment. Bronchoprovocation testing is another tool to rule out asthma with atypical presentation and normal spirometry but it is not routinely required. A diagnostic therapeutic trial with an ICS and a bronchodilator combination may be useful in confirming a diagnosis when it shows a favorable response.\(^{(61)}\)

Chest X-ray is not routinely recommended unless the diagnosis is in doubt, when symptoms are not typical, or suggest alternative diagnoses. Peripheral eosinophilia and elevated IgE level are supportive of the diagnosis but are not routinely recommended unless dealing with moderate to severe asthma. Exhaled nitric oxide is an alternative method for detecting airway inflammation in eosinophilic asthma, but it is not widely available and can be suppressed with the use of ICS and in smokers.\(^{(62)}\) Skin prick testing and radioallergosorbtent test (RAST) may be helpful in identifying allergens to which the patient has been sensitized and in developing a strategy for avoiding allergen exposure.\(^{(63)}\)
4. Clinical Assessment in Adults and Adolescents

Principles of asthma assessment

The principles of optimal asthma management should initially consist of an assessment of asthma control.\(^{(64, 65)}\) Prior to commencing a patient on treatment, the SINA expert panel recommends ensuring the following:

- Assessment of asthma control [Box 4.1].
- Performance of pulmonary function testing with spirometry and/or PEFR to assess for airflow limitations and postbronchodilator reversibility.
- Documentation of current treatment and any related issues such as side effects, adherence, and inhaler technique.
- Utilization of a written asthma action plan.
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, anxiety, and exercise-induced laryngeal obstruction.\(^{(66)}\)
- Close monitoring for patients with severe asthma and history of asthma attacks.
- The use of expectorated sputum eosinophilia and exhaled nitric oxide analysis in the assessment of asthma control are not recommended in routine practice.
### Box 4.1: Assessing asthma control in adults

<table>
<thead>
<tr>
<th>Component of control</th>
<th>Controlled</th>
<th>Partly controlled (the presence of 1-2 features in any week)</th>
<th>Uncontrolled (the presence of 3-4 features in any week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms and/or use of rapid-onset β-2agonist for symptoms relief</td>
<td>None or less than twice a week</td>
<td>More than twice a week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Night time awakenings</td>
<td>None or once a month</td>
<td>Two or more attacks a month</td>
<td>Two or more attacks a week</td>
</tr>
<tr>
<td>Effect on daily activities</td>
<td>None</td>
<td>Some limitations</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% of predicted/personal best</td>
<td>60–80% of predicted/personal best</td>
<td>&lt;60% of predicted/personal best</td>
</tr>
<tr>
<td>Asthma Control Test score</td>
<td>≥ 20</td>
<td>16–19</td>
<td>&lt; 16</td>
</tr>
<tr>
<td>Attacks that require oral steroids or hospitalization</td>
<td>0</td>
<td>One attack per year</td>
<td>Two or more attack per year</td>
</tr>
</tbody>
</table>

**Asthma control test** (Arabic version page 121)

Asthma severity was historically used as the entry point to determine the management strategy. This trend was replaced by the concept of asthma control. Asthma control is a reflection of the adequacy of management by describing the clinical status of a patient as controlled, partially controlled, or uncontrolled. The control status may vary markedly over time and is recommended to entail short-term assessment of current asthma status, asthma burden, and medical management. Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reporting and subsequently treatment decisions by clinicians.
The SINA expert panel recommends the utilization of asthma control test (ACT) to initiate asthma treatment in adults and adjust it at follow-up. (69-71). The ACT is a commonly used tool to assess asthma control. It is a short, validated, self-administered questionnaire to assess asthma control [Box 4.2]. It consists of five items including limitation of activity, shortness of breath, frequency of night symptoms, use of rescue medication, and rating of overall control of the disease over the past 4 weeks. (72) The score of ACT is the sum of the five questions where each is scored from 1 (worst) to 5 (best), leading to a maximum best score of 25. The clinically important significant change in ACT score is considered to be ≥3 units. (73) The level of asthma control is categorized into: (71, 72, 74):

- Controlled: An ACT score of ≥20
- Partially controlled: An ACT score of 16-19
- Uncontrolled: An ACT score of <16
## Box 4.2: Asthma control test

<table>
<thead>
<tr>
<th>Asthma Control Test items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school, or at home?</strong></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><strong>2. During the past 4 weeks, how often have you had shortness of breath?</strong></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><strong>3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?</strong></td>
<td></td>
</tr>
<tr>
<td>4 or more nights a week</td>
<td>□ 1</td>
</tr>
<tr>
<td>2 to 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><strong>4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as salbutamol?</strong></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><strong>5. How would you rate your asthma control during the past 4 weeks?</strong></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>
</tbody>
</table>

**TOTAL SCORE**
Assessment when control is not achieved

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

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

Assessment of risk factors for future asthma attacks

The future risk of adverse outcomes should be assessed. This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effect of medications. The SINA expert panel recommends assessment of risk factors for poor asthma outcomes, especially in patients experiencing attacks.(2)

The presence of one or more of the following risk factors increases the risk of attack despite controlled asthma status:
• High usage of relievers medication.(2)
• ICS use.(2)
• Low forced expiratory volume in the first second (FEV$_1$).(2)
• Previous intensive care unit (ICU) admission.(2)
• Severe asthma attack in the previous 12 months.(2)
• Major psychological disorders or reduced socioeconomic status.(2)
• Continuous exposure to allergens.(2)
• Presence of comorbidities.
• Active smoking and vaping
• Frequent use of oral steroids
• Persistently elevated sputum or blood eosinophilia.(2)
• Pregnancy.(2)

Asthma severity assessment in clinical practice

There is a trend in clinical practice to retrospectively assess asthma severity based on the step of treatment required to control symptoms and attacks.(75-78) Prior to classifying asthma severity, it is essential to ensure that control is achieved and maintained while using the minimal level of medications over a few months. Since asthma severity level could change over years or months, therefore, asthma level of severity can be as classified as follows:

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

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

Box 5.1: Long-term goals of asthma management

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

Developing a partnership with the patient

The development of a partnership between patients and healthcare professionals leads to enhancement of knowledge, skills, and attitude that leads toward better understanding of asthma
and its management. Based upon agreed goals of management, a written self-management action plan should be offered to patients. A wide variety of plans are available which vary from patient-based to physician-based plans. This is expected to be reflected positively on patient adherence, which is a major issue in the management. Factors leading to non-adherence may be related to poor inhaler technique, a regimen with multiple drugs or devices, concern regarding side effects from the drugs, or the cost of medications.(79-81) 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.(82, 83)

Asthma education

The goal of asthma education is to provide patients with asthma (or the parents of a child with asthma) adequate training to enhance their knowledge and skills to be able to adjust treatment according to guided self-management.(65, 84-88) In order to enhance the level of knowledge and skills among asthma patients, education is recommended to include knowledge about asthma and skills related to prescribed inhaler devices, as there maybe misperceptions about the use of inhalers and the safety of ICS [Box 5.2]. (89-92) Asthma education is recommended to be conducted by a well-trained healthcare worker, who has good communication skills and is able to create an interactive dialogue 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.(93) It is essential to get the feedback from the patient in order 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.(94-97) Asthma should be structured based on the available resources.
Box 5.2: Outcomes of asthma education program

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

Identify and reduce exposure to risk factors

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

- **Indoor allergens and air pollutants**: There is a wide spectrum of indoor allergens that includes dust mites, animals (mainly cats), cockroaches, and fungi (e.g. alternaria and aspergillous). Single
allergen interventions are likely to fail. However, multifaceted, tailored and intensive interventions most likely will help in improving asthma control. There are still several gaps in the literature in this area. It will take a few months for the allergen level to become significantly lower from the implementation of the control measures.\(^{(98)}\) The most important indoor air pollutant is related to tobacco exposure. Measures to avoid tobacco exposure will lead to better asthma control and avoidance of long-term lung function impairment.

- **Outdoor allergens and dust:** Outdoor allergens such as pollens and molds are impossible to avoid completely; exposure may be reduced by closing windows and doors and using air conditioning if possible. It is recommended to avoid outdoor strenuous physical activities in cold weather, low humidity, or high air pollution. Sand storms do not usually lead to asthma attacks, but mild symptoms may worsen. It is advisable to avoid going out in the storm if possible especially for those with uncontrolled asthma.\(^{(99)}\)

- **Occupational exposures:** Whenever an occupational sensitizing agent is identified, it is advisable to keep the affected person away from that environment. The earlier the removal of this sensitizer takes place, the higher the chance of complete recovery from occupational asthma.

- **Food and drugs:** Food and food additives are uncommon triggers of asthma. Avoidance cannot be recommended until it is documented by a specialist. However, certain drugs that could worsen asthma symptoms should be avoided (e.g. beta blockers) if possible.

- **Vaccination:** Annual influenza vaccination is advised for individuals with asthma especially those with severe asthma.\(^{(100-102)}\) It usually becomes available early on the fall season. It is advisable to get it as soon as it is available. Pneumococcal vaccination is also recommended as per local guidelines.\(^{(10)}\)
6. Pharmacological Management in Adults and Adolescent

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

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

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

- A daily controller medication is the preferred recommendation for all steps except for step 1. ICS is considered the most effective controller and the corner stone of asthma treatment (Evidence A).(103, 104) Uncontrolled patients may require the addition of other controller medications.
- Relievers or rescue medications must be available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of worsening of asthma control (Evidence A).(105). The available relievers are:
  - A short acting bronchodilators (SABA), such as Salbutamol, that is recommended to be taken on “as needed basis” to relieve symptoms.
  - Formoterol/ICS combination could be used as a reliever therapy on “as needed basis” as per physician prescription. Formoterol is a LABA with fast acting bronchodilator effect (FABA) (Evidence B).(106-108)
Box 6.1: Outpatient asthma treatment for adults and adolescent

Outpatient Management of Asthma for Adults and Adolescents

**Initiation**
- History & physical examination
- Obtain ACT score and PEFR
- Patient education and environmental control of triggers/inducers
- Assess for aggravating factors e.g., GERD, allergic rhinitis
- Based on ACT result, initiate therapy as follows:
  - ACT ≥20
  - ACT = 16-19
  - ACT <16
  - Patients with risk factors or fixed obstruction
  - Severe uncontrolled asthma at presentation

**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 < 19: Uncontrolled → Step up

Introduce Self-management Plan

**STEP 1 Recommended**
- Salbutamol Inhaler as needed

**STEP 2 Recommended**
- Low dose ICS
- Alternative: Formoterol/ICS combination as needed
- LTRA

**STEP 2 Alternatives**
- Low-medium dose ICS+LABA
- Medium-high dose ICS
- Low-medium dose ICS + Theophylline

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

**STEP 4 Recommended**
- Medium-high dose ICS+LABA AND
- Tiotropium
- LTRA
- Theophylline

**STEP 5 Recommended**
- Step 4 options +
- Biologic therapy as appropriate
- AND/OR
- Long-term oral steroids
- Consider other modalities for severe asthma

Refer to a Specialist

A reliever inhaler on as needed basis (Salbutamol or Formoterol/ICS combination)

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
A daily controller medication is the preferred recommendation for all steps except for step 1. ICS is considered the most effective controller and the corner stone of asthma treatment (Evidence A).(103, 104) Uncontrolled patients may require the addition of other controller medications.

Relievers or rescue medications must be available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of worsening of asthma control (Evidence A).(105) The available relievers are:

- A short acting bronchodilators (SABA), such as Salbutamol, that is recommended to be taken on “as needed basis” to relieve symptoms.
- Formoterol/ICS combination could be used as a reliever therapy on “as needed basis” as per physician prescription. Formoterol is a LABA with fast acting bronchodilator effect (FABA) (Evidence B).(106-108)

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

Regular assessment for independent risk factors for attacks, especially severe attacks in the past 12 months or prior history of admission to an intensive care setting; especially if intubated. (109, 110) Other modifiable risk factors are recommended to be assessed; such as low initial FEV$_1$, pregnancy, inadequate ICS, smoking and vaping, comorbidities, and major psychological conditions.

Regular assessment of risk factors for fixed airway obstruction that include inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV$_1$, or sputum/blood eosinophilia. (76, 111)

Management of comorbidities with a special attention to concomitant rhinosinusitis. As this condition affects asthma control, its treatment is expected to improve asthma (Evidence A).(112-117) Treatment includes nasal saline washes and/or steroids, leukotriene receptor antagonists (LTRA), and antihistamines. Coexisting rhinosinusitis is recommended to be treated appropriately as well.
Initiation of treatment

Patients with asthma often underestimate the presence of symptoms and tend to assume their asthma is controlled even when this is not the case. Therefore, the consensus among the SINA expert panel is to simplify the approach and supplement the initiation of asthma therapy by utilizing an objective measurement with the ACT questionnaire [Box 4.2]. The following initial steps are recommended for naïve patients based on ACT score:

- **ACT Score ≥20:**
  - Step 1: SABA (such as salbutamol) on “as needed basis” for patients with mild and infrequent symptoms that occurs once or twice a week.(1, 2)
  - Step 2: Low dose ICS for patient with symptoms more than twice a week, the aforementioned risk factors for attack or fixed airway obstruction, low dose ICS is recommended (Evidence B).(71) (103, 118, 119) Early introduction of ICS leads to greater improvement of FEV$_1$ and lower the future doses of ICS. (119)
  - Step 2: Patients with seasonal asthma who are symptomatic during the season are recommended to start low dose ICS during the season and to be treated at step 1 for the rest of the year if their ACT score is ≥20 (Evidence D).

- **ACT score 16-19:**
  - Step 2: Low dose ICS for patients with an ACT score of 16-19. (Evidence B).(120) Alternative options may be considered as described in the adjustment section includes starting formoterol/ICS combination on “as needed basis” or leukotrienes modifiers.
• ACT score <16:
  o Step 3: A combination of regular low dose ICS and LABA as maintenance treatment for patients with an ACT score of <16. (Evidence B).(120)
  o Step 4: For patients who have poorly uncontrolled asthma at presentation, initiation of asthma treatment with a combination of medium dose ICS and LABA as regular maintenance treatment (Evidence D). However, for patients with early signs of attack at presentation, an initial short course of oral steroids may be required together with the prescription of the maintenance therapy.

Adjustment of treatment

After initiation of asthma treatment, it is recommended to assess the patient at 1-3 month intervals (Evidence D). The SINA expert panel recommends the utilization of stepwise approach of therapy to achieve asthma control. The stepwise approach consists of 5 steps as shown in Box 6.1. Upon follow-up, it is recommended to either maintain treatment until patients have achieved control, to step up for those who did not achieve control, or to step down for those who have maintained control for an extended period. Relievers or rescue medications must be made available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of asthma worsening (Evidence A).(105). The available relievers are detailed above.
The SINA panel recommends that the stepwise approach is not meant to be compartmental; it is rather a continuum of care based on patient engagement and close monitoring of the disease (Evidence D). (121) The following paragraphs will describe in detail each step.
Treatment at Step 1

- Recommended option: A reliever therapy on “as-needed basis” (described earlier in the section). Symptoms are usually mild and infrequent with an ACT score of ≥20. (105)
- Some patients may be recommended for low dose ICS if they are controlled at the time of assessment (an ACT score of ≥20) but have risk factors for attacks or fixed airway obstruction. (121, 122).

Treatment at Step 2

- Recommended option: A daily low dose ICS (<500mcg of beclomethasone or equivalent/day) with a reliever therapy on “as needed basis” (Evidence A). (103, 123)
- Alternative options:
  - Recent studies showed that the combination of budesonide/formoterol on “as needed basis” is an alternative option (Evidence B). (107, 108) When compared to regular maintenance with low dose ICS alone, it was found to be inferior with respect to controlling symptoms and non-inferior with respect to the rate of severe asthma attacks and time to first attack. Of note, the combination of budesonide/formoterol on “as needed basis” achieved the outcome with substantially lower ICS dose equivalent to 17-25% of the maintenance dose of ICS.
  - LTRA (Montelukast) is another alternative option especially for those patients who are reluctant to use ICS or continue to have side effects (such as voice hoarseness) despite preventive measures (Evidence A). (124) It should be noted that LTRA is less effective than ICS in achieving asthma control and in reducing the risk of attacks.
- Patients with mild and infrequent symptoms and an ACT score of ≥20 with risk factors for attack or fixed obstruction are recommended for low dose ICS between asthma attacks (Evidence B).(103, 118)
- Patients with seasonal asthma who are symptomatic during the season are recommended to be treated with low dose ICS prior to the beginning of the season, otherwise, it is recommended to be maintained at step 1 for the rest of the year (Evidence D).

**Treatment at Step 3**

- Recommended option: Adding a LABA to a low-medium dose ICS in a combination device improves asthma control for patient whose asthma is not controlled at step 2 (Evidence A).(118, 125, 126) The patient is recommended to continue on reliever treatment on “as needed basis” (Evidence A).
- ICS in the form of beclomethasone propionate, budesonide, mometasone furoate, or fluticasone propionate are currently combined with either salmeterol or formoterol. These are normally prescribed twice daily. Once a day combination of ICS and LABA is also available (refer to appendix 1).
- If a formoterol/ICS combination is selected, patient may be advised to use this combination for both maintenance and rescue by using extra puffs from the same inhaler (Evidence A).(106) The recommended dose is 1–2 puffs twice daily plus extra puffs that should not exceed 12 puffs per day. Those patients who require such high doses for 2-3 days should seek medical advice to step up maintenance therapy and they may require the use of a short course of oral prednisolone (Evidence A).
- If salmeterol/ICS combination is selected, an escalation of the regular daily doses to maximum dosing achieves well-controlled asthma status in a majority of patients on Steps 2 and 3 (Evidence A).(127) Salmeterol has a slow onset of action; therefore, it should only be used as a maintenance treatment.
The once a day combination of ICS/LABA can be prescribed based on availability. The approved product in the Saudi market is fluticasone furoate/vilanterol (Relvar) that can be prescribed for adults and children above 12 years at a dose of 100/25 microgram (Evidence A). (128, 129) Vilanterol has the advantage of an onset of action within 15 minutes and a long half-life; therefore, patient can use it only as a maintenance treatment.

Inhaled LABA should not be used alone in asthma management. (130) Asthma patients taking inhaled LABA without inhaled ICS are at an increased risk of asthma attacks, hospitalizations, and death. (131) Based on this evidence, the Saudi Food and Drug Administration (SFDA) withdrew all LABA monotherapy medications from the Saudi market by the end of 2010. (132) Therefore, the SINA panel has limited the use of relievers to SABA or to formoterol when combined with ICS.

Alternative and generally less effective strategies include: the continuation of ICS as a monotherapy by increasing the dose to the medium-high dose range (Evidence A), (131, 133) or the addition of LTRA to a low-medium dose ICS (Evidence A), (134, 135) especially in patients with concomitant rhinitis. (136) The addition of sustained release theophylline to a low-medium dose ICS is a possible but less favorable choice (Evidence B). (137)

Tiotropium is a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease (COPD). (138-140) Evidence has shown that when tiotropium is added to an ICS; it improves symptoms, reduces risk of attack, and improves the lung function in patients with inadequately controlled asthma. Its effect appears to be at least equivalent to LABA (Evidence A). (141-144) This evidence supports that tiotropium can be used as an alternative to LABA when added to ICS.

Consultation with an asthma specialist is recommended for patients whenever there is a difficulty in achieving control at step 3 (Evidence D).
**Treatment at Step 4**

- Recommended option: Escalation of treatment by combining medium-high dose ICS with LABA (Evidence A).(93, 133, 134, 145)
- In addition to the currently available combinations of ICS/LABA mentioned in step 3 section, the once a day combination of fluticasone furoate/vilanterol (Relvar) can be prescribed for adults and children above 12 years at a dose of 200/25 microgram dose. (128, 129)
- If symptom control is not achieved, adding tiotropium to the combination of ICS and LABA is a recommended option as it significantly improves lung function in uncontrolled cases (Evidence A).(138, 146, 147)
- Adding LTRA to the combination of high-dose ICS and LABA is also recommended but the evidence is less robust (Evidence B).(144, 148, 149)
- Adding theophylline to the combination of high-dose ICS and LABA is another less favorable alternative (Evidence B).(149, 150)
- If a patient is uncontrolled at step 4 despite adequate treatment and control of comorbid conditions, biologic therapy is recommended as described in step 5. Early consideration may save the patient from frequent or chronic use of oral corticosteroids.
- Consultation with an asthma specialist is recommended for patients who require this step of therapy (Evidence D).(151)
Treatment at Step 5

- Consultation with an asthma specialist is strongly recommended for patients requiring treatment at step 5 (Evidence D).
- To avoid frequent use of oral steroids, biologic therapy should be considered based on appropriate indications and availability.
- Anti IgE therapy (Omalizumab) may be considered for those patients uncontrolled on maximum treatment at step 4 despite modification of any triggers; and who have allergic asthma as determined by an IgE level in the appropriate therapeutic range, and positive skin test or RAST study (Evidence A), or a history of documented atopy (Evidence D). (133, 134, 145) If this treatment does not control asthma after 16 weeks of therapy, it should be stopped. (152-154)
- Anti-IL-5 therapy can be considered for uncontrolled eosinophilic asthma at step 4 with frequent attacks (for more information refer to appendix 1, medications section). There are no data to determine the duration before deciding on treatment ineffectiveness. However, till this evidence is available, the treatment may be continued for up to 6-12 months prior to the decision of stopping treatment (Evidence D). (155) The available options are (refer to medication section for more details):
  - **Mepolizumab**, an anti-IL-5 therapy that is indicated when eosinophil level is ≥150 cells/μL at treatment initiation or ≥300 cells/μL at any time in the prior 12 months. The recommended dose is 100 mg subcutaneously every 4 weeks.
  - **Benralizumab**, an anti-IL-5 receptor that is indicated when blood eosinophils level is ≥300 cells/μl at initiation of treatment. The recommended dose is 30 mg subcutaneously every 4 weeks for the first three months then every 8 weeks thereafter.
• There is no available evidence yet that compares anti IgE therapy to any of the anti-IL-5 therapies or directly comparing different anti-IL-5 agents.

• For patients with evidence of both atopy and high blood eosinophils, to date, there is no available evidence to favor either anti-IgE therapy versus anti-IL-5 agents. Omalizumab led to more reduction of asthma attacks in a category of asthma patients who showed >50% reduction in blood eosinophils during therapy. (156, 157) A recent study showed that anti-IL-5 receptor therapy reduced attacks by 46% and improved lung function in patients with severe, uncontrolled eosinophilic asthma regardless of the serum IgE concentrations and atopy status. (158) When choosing a biologic, several factors should be considered including the frequency of administration, cost, side effect profile, age at onset of asthma, presence of comorbid conditions such as nasal polyps, previous response, and physician experience with the treatment.

• If the patient does not have atopy, high blood eosinophils, or biologic therapy is not available or not adequately controlling the disease; the alternative approach is to use the lowest possible dose of long-term oral corticosteroids (Evidence D). (159) Other alternative are mentioned in the severe asthma section such as thermoplasty and long-term macrolides.

• For patients who require long-term systemic corticosteroids, the following are recommended to be considered:
  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, attempts to reduce the dose of systemic corticosteroids, preferably to every other day frequency. Maintaining high-dose ICS therapy may help to reduce the dose of systemic corticosteroid.
o Upward adjustment of the corticosteroid dose at the time of stress (e.g. infection, asthma attacks, surgery, etc.) 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).(93, 160) Follow-up should include monitoring and reviewing the patient’s written asthma action plan, medication adherence and inhaler technique, patient’s behaviors, comorbidities, and possible side effects of the medications. Once asthma is well controlled and the control is maintained for at least 3 months, a step down in pharmacologic therapy is recommended at the minimum level that can maintain the good control and minimize the side effects (Evidence D). The following are the general recommendations:

- Reduction in therapy is recommended to be gradual and closely monitored based on clinical judgment of the individual patient’s response to therapy and ACT score (Evidence D).
- If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25% every 3–6 months to the lowest dose possible that is required to maintain control (Evidence B),(86, 161, 162) and then changed to a single daily dose (Evidence A).(163) It is recommended to be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued.(164)
- If the patient is on combination of ICS/LABA at step 3 or 4, abrupt discontinuation of LABA is not recommended as it may lead to deterioration of the control.(165)
• If the patient is on a combination of ICS and LABA, LTRA, or other controllers; then start by tapering ICS to the lowest possible dose (Evidence B). (166, 167) If control is achieved, LTRA may be discontinued (Evidence D). (166)
• For significant side effects, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advise vigorous mouth washing after inhalation, use of spacer (concomitant with MDI devices), and/or use of appropriate local antifungal therapy for severe oral thrush. (168)
• 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:
• Uncertainty regarding the diagnosis.
• Difficulty achieving or maintaining asthma control.
• Immunotherapy or biologic therapy are being considered.
• Difficulty to achieve asthma control at step 3 or higher.
• Acute asthma attack requiring hospitalization.
• Request of a patient for second opinion or further advise.
**Allergen Immunotherapy (AIT)**

The AIT is a treatment modality to desensitize patients to specific allergens. It is considered for those with stable asthma and evidence of clinically relevant allergic sensitization at which the immunotherapy can be directed, especially if they have coexisting allergic rhinitis. Patients with poorly controlled asthma should not be started on immunotherapy. (169, 170) Though there are insufficient data on the impact of AIT on asthma attacks and quality of life scores, it has specifically been shown to:

- Improve asthma symptoms and stepping down asthma treatment (Evidence A) (171)
- Improve airway hyperresponsiveness (Evidence B). (172)
- Decrease the progression of allergic rhinitis to asthma (Evidence B). (173)
- Decrease the chance of development of new sensitizations (Evidence B) (169)

AIT is likely to be cost effective when appropriately used. (170) There are currently two types of AIT in clinical practice, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Most studies that compared SCIT to SLIT showed a better clinical efficacy of SCIT. However, SLIT has a better safety profile than SCIT as SCIT may rarely cause anaphylaxis. (171). Patients at risk are mainly those with asthma especially if uncontrolled. High level of caution should be taken in patients using beta-blockers due to the risk of more serious anaphylaxis that is resistant to treatment with epinephrine. (169) Data are limited in pediatrics, but AIT has been used safely in children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV$_1$. (174) Although beneficial effects may be observed a few months from starting AIT, treatment with AIT needs patient’s commitment for at least 3 years in order to have sustained desensitization after stopping the treatment. Furthermore, AIT can be continued, but not initiated, during pregnancy. Most studied allergens’ specific immunotherapy are dust mites, alternaria, grass pollens, ragweed, and cat. Omalizumab could improve tolerability to AIT in
patients with moderate to severe asthma. (175) If the patient is considered a candidate for AIT, referral to an allergist is recommended to explore this option further.

**Severe Asthma**

Severe asthma carries several names; each point to an aspect of the disease. Chronic severe asthma, steroid-dependent asthma, difficult-to-treat asthma, and refractory asthma are some of these terminologies. (176) Severe asthma is defined by the “requirement of asthma treatment with high dose inhaled ICS and a second controller or oral prednisolone, which remains uncontrolled despite this therapy, or to prevent it from becoming “uncontrolled”. (78) Severe asthma probably accounts for 5–10% of adult asthma, but the health cost is disproportionally high. (177) Morbidity and mortality are also higher compared to regular asthma patients because of increased side effects of treatment and much more frequent attacks and/or hospitalizations. (178, 179) Before a diagnosis of severe asthma is considered, patients must undergo a systematic assessment where the diagnosis of asthma is confirmed, and comorbidities are identified and treated. (53) Patients in whom poor asthma control is related to other factors, such as poor adherence or due to the presence of other diseases, are to be termed ‘difficult-to-treat asthma’. There are common comorbidities that need to be assessed in severe asthma such as allergic rhinoconjunctivitis (in 70% of cases), rhinosinusitis/nasal polyps (in 50%), COPD (in 20%), vocal cord dysfunction (in 32-50%), anxiety/depression (in 4-17%), obstructive sleep apnea (in 31%), gastroesophageal reflux (in 17-74%), bronchiectasis (in 25-40%), and allergic bronchopulmonary aspergillosis (in 1-2%). (180) The following steps are recommended for assessment of patients with severe asthma: (181-186)
• Ensure that the patient is adherent to all medications with a good inhalation technique.
• Be aware of possible misdiagnosis where the problem is not bronchial asthma to start with but another respiratory pathology that is mimicking asthma symptoms and not appropriately addressed, e.g. bronchiectasis, endobronchial tumors, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, or Churg-Strauss syndrome. (184, 187)
• Assess for the existence of comorbidities that can worsen bronchial asthma and makes it difficult to manage (e.g. chronic rhinosinusitis, GERD, sleep apnea syndrome, ABPA, obesity, and CHF). (188)
• Medications over use or side effects.
• Managing any psychosocial contributing factors.
• Identify confounding factors (e.g. presence of allergens at home or work, active or passive smoking and vaping, or psychosocial problems). (184)

Asthma Phenotyping: Phenotyping plays a major role in predicting the response to treatment of severe asthma. Inflammatory phenotyping is based on the type of and the extent of inflammatory reaction, while clinical phenotyping is based on combining clinical characteristics, physiological abnormalities, and inflammatory markers. Inflammatory phenotypes are based on the result of inflammatory cells identified in an induced sputum sample. There are four groups: neutrophilic asthma, eosinophilic asthma, mixed granulocytic asthma and pauci-granulocytic asthma. (189) Clinical phenotyping is based on age at onset, IgE-mediated allergy, eosinophilia or increased fractional exhaled nitric oxide, fixed airflow obstruction, and obesity. Clinical phenotypes can be recognized as an early-onset allergic phenotype, a later onset obese phenotype, or a later onset eosinophilic phenotype.
Selection of which biological agent is most appropriate for a particular patient can be achieved by
clinical phenotyping. History of allergy, airflow obstruction and attacks may predict a better effect of anti-IgE therapy. Eosinophilia combined with attacks may predict better effects of anti-IL5 therapy. While patients with irreversible airflow limitation and frequent attacks may benefit from tiotropium. (190) Details of biological agents and their indications are discussed in detail in earlier sections. As it may be difficult to achieve full control in many patients with severe asthma, the aim of treatment in this situation is to reach the best possible control. (190) After dealing with all comorbidities and other confounding factors that could have made asthma difficult to control, maximum therapy is recommended at step 5, which may include combination therapy of high-dose ICS/LABA, LTRA, LAMA and addition of one of the available biological therapies as appropriate. (155, 191, 192)

A significant percentage of patients with severe asthma do not respond adequately to high dose ICS and other controller therapy, thus, they need frequent or continuous oral steroid therapy to achieve a reasonable response. (193) Such control may be lost when oral steroid is discontinued. Patients may differ in the degree of their responsiveness to oral steroids. (194) Print Some patients may fail to improve their FEV\textsubscript{1} by more than 15% following treatment with oral prednisolone for two weeks, a condition called “corticosteroids-resistant asthma. (195, 196) If oral steroids are necessary, then it is recommended to use the lowest possible dose and to shorten the duration as much as possible. (197) In this situation, osteoporosis prophylaxis is recommended.

For patients with severe asthma that do not qualify or respond to biologic therapy, other modalities of treatment of severe asthma are recommended for consideration that includes:

- **Macrolides**: Due to their role in reducing neutrophilic airway inflammation, they were shown
to have a role in the management of severe asthma. A recent study has assessed the benefit of Azithromycin at a dose of 250-500 mg 3 days/week as add-on therapy for 48 weeks for patient with persistent symptomatic asthma. (198) Azithromycin significantly reduced the experience of at ‘least one asthma attack’ from 61% to 44%. It has significantly improved asthma-related quality of life measures, and responses in eosinophilic asthma were greater than in those without eosinophils.

- **Bronchial thermoplasty (BT):** Utilizing radiofrequency energy to alter the smooth muscles of the airways and possibly bronchial wall innervation, BT has been shown to reduce the risk of asthma attacks in clinical trials setting. (199) In well selected patients with moderate to severe asthma, it may improve various aspects of asthma, including FEV₁, quality of life, asthma control, attacks, and use of rescue medications. (200-202) Until solid evidence is available, it is recommended to perform it in the setting of clinical trials and approval of an independent Institutional Review Board. (78) Contraindications to BT include moderate and severe bronchiectasis, very high sputum production, and fixed airflow obstruction with FEV₁ levels below 50% of predicted.
7. Management of Acute Asthma in Adults and Adolescents

Acute asthma attack is a challenging clinical scenario that requires a systemic approach to rapidly diagnose the condition, evaluate its severity, and initiate therapy. The first step of managing acute asthma is the early recognition to prevent the occurrence of attacks. Asthma in general has a low mortality rate compared with other lung diseases. Nevertheless, asthma may lead to mortality, especially among patients with poorly controlled asthma whose condition deteriorates over a period of days before the final fatal event. It has been shown that over 80% of such attacks developed over more than 48 hours, allowing enough time for effective action to reduce the number of attacks requiring hospitalization. The most specific marker associated with increased asthma mortality is a history of repeated hospital admissions, particularly if patients required intensive care treatment or ventilatory assistance. The characteristics of patients admitted with near-fatal asthma in Saudi Arabia were found to be younger and predominantly males and used less ICS/LABA combination. Furthermore, it has been shown that a subgroup of patients who present with near-fatal asthma have blunted perception of dyspnea, and have a history of frequent emergency department 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 can be found in appendix 1.

Clinical assessment of acute asthma

The initial clinical assessment should rapidly determine whether the patient’s presenting symptoms are related to an acute asthma attack or not. Of note, it is necessary to recognize that acute asthma is
different from mild to moderate asthma attack secondary to poor asthma control that simply require a step-up in the chronic asthma therapy. Although most acute asthma attacks develop over a period of days, patients with brittle asthma may present with a much more dramatic deterioration [Box 7.1]. It is important to realize that most patients who die from an acute asthma attack had chronically uncontrolled asthma, had received inadequate treatment with ICS, and had inadequate monitoring of their asthma. (215-219) 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 emergency department.
- Brittle asthma.

Upon presentation, a patient should be carefully assessed to determine the severity of the attacks [Box 7.2] and the type of treatment required. (220, 221) PEFR and pulse oximetry measurements are complementary to history taking and physical examination. Major causes linked with asthma-related deaths are cardiac arrhythmia and asphyxia. The risk of cardiac arrhythmia is theoretically increased by hypokalemia and QTc interval prolongation related to the use of high dose SABA or IV aminophylline. (53, 222-224) However, in a series of patients with near-fatal attacks, only a few arrhythmias other than sinus tachycardia and bradycardia were reported. (109, 225) Hence; a more likely cause for death is probably related to asphyxia due to severe airflow obstruction and hypoxemia.
## Box 7.1: Levels of severity of acute asthma in adults

<table>
<thead>
<tr>
<th>Level</th>
<th>Characteristics</th>
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| Moderate asthma attacks| • Increasing symptoms  
                          • PEFR >50–75% best or predicted  
                          • No features of acute severe asthma                                                                                                     |
| Acute severe asthma    | • Any one of:  
                          o PEF 30–50% best or predicted  
                          o Respiratory rate ≥25/min  
                          o Heart rate ≥120/min  
                          • Inability to complete sentences in one breath                                                                                          |
| Life-threatening asthma | • Any one of the followings in a patient with severe asthma:  
                          o $\text{SpO}_2 < 92\%$ ($\text{PaO}_2 < 60 \text{ mmHg}$) on high-flow $\text{FIO}_2$  
                          o PEF <30% best or predicted  
                          o Bradycardia  
                          o Dysrhythmia  
                          o Cyanosis  
                          o Hypotension  
                          o Normal or high $\text{PaCO}_2$  
                          o Exhaustion  
                          o Confusion  
                          o Silent chest  
                          o Coma  
                          • Weak respiratory effort                                                                                                                  |
| Near-fatal asthma      | • Raised $\text{PaCO}_2$ and/or requiring mechanical ventilation                                                                                     |
| Brittle asthma         | • Type 1: Wide PEF variability (>40% diurnal variation for >50% of the time over a period >3–6 months) despite intense therapy  
                          • Type 2: Sudden severe attacks on a background of apparently well-controlled asthma                                                             |

*PEF = Peak expiratory flow*
This is supported by the pathologic evidence of extensive airway obstruction, mucous plugging, and dynamic hyperinflation found at autopsy in patients who died of acute severe asthma. (226) Treatment of acute asthma attacks requires a systematic approach similar to chronic asthma management. Acute asthma management is recommended to follow these steps:

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

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

**Assessment of acute asthma severity**

- **Mild acute asthma:** Patients presenting with mild asthma attack are usually treated in an outpatient setting by stepping up in asthma management; including increasing the dose of ICS. (227) However, some cases may require short course of oral steroids.

- **Moderate acute asthma:** Patients with moderate asthma attack are clinically stable. They are usually alert and oriented but may be agitated. They can communicate and talk in full sentences. They are tachypneic and may be using their respiratory accessory muscles. Heart rate is usually <120/min and blood pressure is normal. A prolonged expiratory wheeze is usually heard clearly over the lung fields but examination of the chest maybe relatively normal. Oxygen saturation is usually normal secondary to hyperventilation. The PEFR is usually in the range of 50–75% of predicted or previously documented best. Measurement of arterial blood gases (ABG) are not routinely required in this category; however, if done, it shows widened alveolar–arterial oxygen gradient and low PaCO$_2$, secondary to increased ventilation perfusion mismatch and hyperventilation, respectively. Chest X-ray is not usually required for moderate asthma attacks, unless pneumonia is suspected.
Box 7.2: Initial management of acute asthma for adults and adolescents

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

**Moderate**
- Talking Phrases or full sentences
- Agitated but alert
- Respiratory Rate 20-30/min
- May or may not use accessory muscles
- Heart Rate <120/min
- SaO₂ on R/A ≥92%
- PEFR of 50-75% of predicted

**Severe**
- Talking only words or unable to complete sentence
- Agitated
- Respiratory Rate >30/min
- Use of accessory muscles
- Heart Rate >120/min
- SaO₂ on R/A <92%
- PEFR of 30-50% of predicted

**Life Threatening**
- Unable to talk
- Confused, drowsy, or coma
- Respiratory Rate >30/min or in respiratory failure
- Use of accessory muscles
- Heart Rate >120/min or bradycardia, and silent chest
- SaO₂ on R/A <90% or Cyanosis
- Normal or high PaCO₂, Acidosis
- PEFR of <30% of predicted

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

**TREATMENT**

- Oxygen to keep SaO₂ ≥92%
- Salbutamol 2.5-5 mg every 20 min for 1 hour, then every 30-60 min according to response
- Nebulized salbutamol 2.5-5 mg every 20 min for 1 hour, then every 2 hours according to response
- Oral prednisone STAT: 1 mg/kg up to 50 mg

- Oxygen to keep SaO₂ ≥92%
- Salbutamol 2.5-5 mg every 20 min for 1 hour, then every 30-60 min according to response
- Nebulized salbutamol 2.5-5 mg every 20 min for 1 hour, then every 4-6 hours as needed
- Oral prednisone 1 mg/kg up to 50 mg STAT; alternatively, IV hydrocortisone 200 mg/day or IV methylprednisolone 80 mg/day
- Consider magnesium sulphate 1-2 g IV over 20 min
- Consider ABG, CXR

- High flow oxygen to keep SaO₂ ≥92%
- Continuous nebulized salbutamol 10-15 mg by with ipratropium bromide 1.5 mg, then Q4-6 hour according to response
- IV hydrocortisone 200 mg/day or IV methylprednisolone 80 mg/day
- Magnesium sulphate 1-2 g IV over 20 min
- ABG, CXR, CBC, electrolytes, urea, creatinine, glucose, ECG
- **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 (SaO₂<92% on room air) are usually evident. Chest examination reveals prolonged distant wheeze secondary to severe airflow limitation and hyperinflation; more ominously the chest may be silent on auscultation. The PEFR is usually in the range of 30–50% of predicted. ABG reveals significant hypoxemia and elevated alveolar–arterial oxygen gradient. PaCO₂ may be normal in patients with severe asthma attacks. Such finding is an alarming sign, as it indicates fatigue, inadequate ventilation, and pending respiratory failure. Chest radiograph is required if complications are clinically suspected such as pneumothorax, or pneumonia.

- **Life threatening acute asthma**: Patients with life-threatening asthma are severely breathless and unable to talk. They can present in extreme agitation, confusion, drowsiness, or coma. The patient usually breathes at a respiratory rate >30/min and use their accessory muscles secondary to increased work of breathing. Heart rate is usually >120/min, but at a later stage, patients can be bradycardiac. Patient may have arrhythmia secondary to hypoxia and ECG monitoring is recommended. Oxygen saturation is usually low (<90%) and not easily corrected with oxygen. ABG is mandatory in this category and usually reveal significant hypoxia and normal or high PaCO₂. 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 attack, it is recommended to base treatment on severity level [Box 7.2]. More details of medications are available in appendix 1.

- **Moderate asthma attack**
  - Low-flow oxygen is recommended to maintain saturation ≥92%.(228, 229) There is evidence that high-flow oxygen may be harmful for some patients.(230) Therefore, it is important to give a controlled dose of oxygen; patients who received 28% oxygen did better than those who received 100% oxygen.(230)
  - Salbutamol is recommended to be delivered by either:(231, 232)
    - MDI with spacer: 4–10 puffs every 20 min for 1 h, then every 1–2 h according to response (Evidence A).(233-235), or
    - Nebulizer: salbutamol 2.5–5 mg every 20 min for 1 h, then every 2 h according to response (driven by oxygen if patient is hypoxic) (Evidence A).(236)
  - Steroid therapy: Oral prednisolone 1mg/kg/day to maximum of 50 mg is recommended to be started as soon as possible.(237, 238).

- **Severe asthma attacks**
  - Adjusted oxygen flow is recommended to keep saturation ≥92% (avoids excess oxygen).(229, 239, 240)
  - Nebulized salbutamol (2.5–5 mg) is recommended to be repeated every 15–20 min for 1 h, then every 30-60 min according to response.(229) Oxygen-driven nebulizers are preferred for nebulizing salbutamol because of the risk of oxygen desaturation while using air-driven compressors (Evidence A).(237, 238, 241, 242)
Ipratropium bromide is recommended to be added to salbutamol at a dose of 0.5 mg every 20 minutes for three doses by the nebulized route then every 4–6 h as needed (Evidence B). Alternatively, ipratropium bromide can be administered by MDI at a dose of 4-8 puffs every 20 minutes, then every 4–6 h as needed.(243-246)

Systemic steroid is recommended to be started as soon as possible (Evidence A). If patient can tolerate oral medications, oral prednisolone 1 mg/kg/day to maximum of 50 mg daily is recommended. Alternatively, the following may be prescribed: daily hydrocortisone dose of 200 mg IV or daily methylprednisolone dose of 80 mg; in divided doses.(237, 247)

If there is no adequate response to previous measures, it is recommended to administer a single dose of IV magnesium sulphate at a dose of 1-2 g over 20 minutes. (Evidence B).(248)

Request 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.(249) The following steps are recommended for further management:

  - Consult ICU service. Intubation setting should be readily available.
  - Adequate oxygen flow to keep saturation ≥92%.(229)
  - Deliver continuous nebulized salbutamol at a dose of 10-15 mg with ipratropium bromide at a dose of 1.5 mg over one hour (Evidence A).(250, 251) Continuous treatment was found to be safe and well tolerated and led to better improvement in pulmonary functions and reduction in hospitalization when compared to intermittent delivery (Evidence A).(252) Oxygen-driven nebulizers are preferred due to the risk of oxygen desaturation while using air-driven compressors (Evidence A) (241, 242).
Once the patient showed response to continuous nebulization, shift to intermittent delivery is recommended (Evidence D).

Systemic steroid (Evidence A) to be started as soon as possible in one of the following forms: IV methylprednisolone 80 mg daily in divided doses or IV hydrocortisone 200 mg daily in divided doses. (237, 243, 246, 247, 253, 254).

Single dose of IV magnesium sulfate at a dose of 1–2 g over 20 min (Evidence B). (247, 254)

Frequent clinical evaluation and CXR, electrolytes, glucose, 12-lead ECG and ABG are recommended.
Box 7.3: Adjustment of acute asthma treatment for adults and adolescent

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

**Adequate Response**
- Improving symptoms and stable vital signs
- PEFR >60% of predicted
- SaO₂ ≥92%
- Adequate response to be maintained for at least 4 hours
- Continue bronchodilators for 1-4 hour PRN
- Continue oral prednisone for 5-7 days

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

**Poor Response**
- No improvement of respiratory symptoms
- Signs of fatigue or exhaustion
- PEFR <30% of predicted
- SaO₂ <92% with high flow oxygen
- ABG shows respiratory acidosis and/or rising PaCO₂

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 oral prednisone 1mg/kg (maximum dose 50mg) daily; alternatively, IV hydrocortisone 200 mg/day or IV methylprednisolone 80 mg/day
- Observe closely for any signs of fatigue or exhaustion
- Monitor O₂ saturation and PEFR
- If the patients is responding, follow “adequate response” track
- If there is no adequate response after 4 hours, consider admission

What is next?

- Continue bronchodilators and systematic steroids
- ICU consultation for possible admission
Follow-up after initial treatment

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

- **Adequate response**
  Adequate response is defined as:
  - Improvement of respiratory symptoms.
  - Stable vital signs with respiratory rate <25/min and heart rate <120/min.
  - Oxygen saturation ≥92% on room air.
  - PEFR or FEV\_1 ≥50% of predicted.

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

- **Partial response**
  Partial response is defined as:
  - Minimal improvement of respiratory symptoms.
- Stable vital signs with respiratory rate <25/min and heart rate <120/min.
- Oxygen saturation ≥92% on oxygen therapy.
- PEFR between 30-50% of predicted.

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

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

• **Poor response**
  
  Poor response is defined as:
  
  - No improvement of respiratory symptoms.
  - Altered level of consciousness, drowsiness, or severe agitation.
  - Signs of fatigue or exhaustion.
  - Oxygen saturation <92% with high-flow oxygen.
  - ABG analysis showing respiratory acidosis and/or rising PaCO₂.
  - PEFR <30% of predicted.

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

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

- **Criteria for ICU referral**

ICU referral is recommended for patients:

- requiring ventilatory support
- developing acute severe or life-threatening asthma
- failing to respond to therapy, evidenced by:
  - deteriorating PEFR
  - persisting or worsening hypoxia
  - hypercapnia
  - ABG analysis showing respiratory acidosis
  - exhaustion, shallow respiration
  - drowsiness, confusion, altered conscious state
8. Asthma in Special Situations

Cough-variant asthma

Patients with cough-variant asthma have chronic cough as their main symptom.(255, 256) Other diagnoses to be considered are drug-induced cough caused by angiotensin-converting enzyme inhibitors, GERD, chronic upper airway cough syndrome manifesting as postnasal drip, eosinophilic bronchitis, and chronic sinusitis. Once the diagnosis is established, treatment is recommended with ICS.(257, 258) This condition may be confused with eosinophilic bronchitis which is characterized by cough and sputum eosinophilia with normal spirometry and airway hyper responsiveness.(259)

Rhinitis/sinusitis and nasal polyp

Most asthma patients have coexisting rhinitis and/or sinusitis and around 40% of patients with rhinitis have asthma.(260) Rhinitis can be classified to allergic or non-allergic. 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 emergency department visits but not asthma control.(261, 262)

Exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction (EIB) is common in inadequately controlled asthma patients. However, asthma-like symptoms can sometimes be triggered only by physical activities. Normally, bronchodilation occurs during exercise and lasts for a few minutes. In patients with EIB, the initial bronchodilation is followed by bronchoconstriction that generally peaks within 10–15 minutes after
completing the exercise and resolves within 60 minutes. EIB can be prevented by using SABA a few
minutes before exercise.(263, 264) 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.(135, 264) Regular use of LTRA may help in this condition especially in children.(135, 264, 265)

Aspirin-exacerbated respiratory disease (AERD)

AERD is a special phenotype characterized by a triad of asthma, chronic rhinosinusitis with nasal
polyposis, and respiratory reactions to aspirin.(266) About 7% of adults with asthma and 14% with
severe asthma suffer from attacks in response to ASA or NSAIDs that inhibit cyclooxygenase-1 (COX-
1). This condition is more common in patients with severe asthma and poor lung function. Majority
of patients experience first symptoms during their third to fourth decade of life. Once ASA or NSAID
hypersensitivity develops, it persists for life. Characteristically, within minutes to two hours following
ingestion of ASA, an acute severe asthma attack develops. It is usually accompanied by rhinorrhea,
nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck.(267) A typical history
of upper and lower respiratory reaction to aspirin or NSAIDs is very suggestive for the diagnosis, which
is confirmed by aspirin challenge.(268) A normal sinus CT almost excludes AERD. Patients known to
have aspirin-induced asthma should avoid all aspirin-containing products and NSAIDs. Where an NSAID
is indicated, COX-2 inhibitors or alternative analgesics such as paracetamol are recommended.(269)
Prophylactic low-dose aspirin should also be avoided. However, referral to an allergy specialist for ASA
desensitization is recommended for patients for whom aspirin is required as anti-platelet therapy,
patients with difficult to manage polyposis, or patients with severe asthma who require recurrent
courses of systemic steroids.(270, 271) Aspirin and NSAID can be used in asthma patients who do not
have aspirin-induced asthma. (272) Montelukast may help in the treatment of this type of asthma in some patients. (273) IgE mediated reaction to individual NSAIDs is not related to AERD.

**Gastro-esophageal reflux disease (GERD)**

Gastro-esophageal reflux disease is more prevalent in patients with asthma compared to the general population. The mechanisms by which GERD worsens asthma include vagal mediated reflex and also reflux secondary to micro-aspiration of gastric contents into the upper and lower airways. (274) 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. (275-277) Benefit of proton pump inhibitors is limited to patients with symptomatic GERD and nighttime respiratory symptoms. Of note, patients with asymptomatic GERD do not benefit from empiric GERD therapy (Evidence A). (278)

**Pregnancy**

A study conducted in a tertiary care hospital in Saudi Arabia showed that almost half of pregnant ladies had the desire to stop asthma medications during pregnancy as they believed that asthma medications would harm them and their babies more than asthma itself. (28) The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics may have a worsening of their asthma control. (279) Maintaining adequate control of asthma during pregnancy is essential for the health and wellbeing of both the mother and her baby. Occurrence of asthma attacks during the first trimester of pregnancy significantly increase the risk of a congenital malformation. (280) 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 non-pregnant patient. Salbutamol is the preferred SABA due to its excellent safety profile. ICSs are the preferred treatment for long-term control.(281) ICS, theophylline, antihistamines, β-2 agonists, and LTRA are generally safe, and they have not been shown to increase the risk of fetal abnormalities.(282, 283) 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 non-pregnant patients (Evidence B), including systemic steroids if indicated (Evidence C). (279, 284-287) Fetal monitoring is recommended in severe asthma attack. If anesthesia is required during labor, regional anesthesia is recommended whenever possible (Evidence C).(288) The use of prostaglandin F2α may be associated with severe bronchospasm and should be avoided, if possible (Evidence D). If asthma is well controlled during pregnancy, acute asthma is rare during labor. In the absence of acute severe asthma, reserve Cesarean section for the usual obstetric indications. Pregnant asthma patients should be encouraged to breastfeed after delivery and to continue their usual asthma medications during lactation.(289-291)

**Occupational asthma**

All patients with asthma should be asked about their work history and exposures for possible related causal factors. A simple screening test is to ask the patient if their symptoms improve when they are away from work.(292) 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 are recommended for referral to an asthma expert for assessment and advice because of the legal implications of the diagnosis.(293, 294)
Asthma-COPD Overlap (ACO)

COPD is common above the age of 40 years.(295) Distinguishing asthma from COPD becomes more difficult as many patients may show features of both diseases. This has been called the Asthma-COPD Overlap. ACO is a unique complex entity sharing features of both COPD and asthma. At this stage, there is no formal definition of ACO as there is inadequate data to describe its features, characteristics, and its optimal therapeutic intervention.(2) However, when a patient has features of both asthma and COPD, the diagnosis of ACO could be considered.

ACO has been estimated to account for approximately 15-25% of the obstructive airway diseases in adults and patients may experience worse outcomes compared with asthma or COPD alone.(2) Patients with ACO have the combined risk factors of smoking and atopy. They are generally younger than patients with COPD and have frequent attacks, poor quality of life, a more rapid decline in lung function, higher mortality, greater health care utilization and low quality of life; compared to patients with COPD alone.(296-298)

Spirometry is required to confirm the diagnosis of chronic airflow limitation. Post-bronchodilator FEV$_1$/FVC of <0.7 is usually present and post-bronchodilator increase in FEV$_1$ by >12% and 200 mL from baseline is compatible with diagnosis of ACO. However, spirometry alone has limited value in distinguishing between asthma, COPD and ACO.

If the initial assessment suggests asthma or ACO, or there is uncertainty about the diagnosis of COPD, it is prudent to start treatment for asthma (ICS with or without LABA) until further investigation has been performed to confirm or exclude this diagnosis. Of note, it is important that patients should not be treated with a LABA alone if there are features suggestive of asthma.(299-301) Treatment of ACO is recommended to include advice about other therapeutic strategies including smoking cessation, pulmonary rehabilitation, vaccinations and treatment of comorbidities.
9. Management of Asthma in Children

Asthma represents the commonest chronic illness of childhood. It is also a leading cause for childhood morbidity as measured by school absences, emergency department visits and hospitalizations. From the prospective of both patient and society, the cost of not treating asthma is higher than the cost of asthma treatment.

Asthma Diagnosis in Children

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

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

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

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

Clinical suspicion of asthma mimics is an acceptable indication for 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.(307)
In preschool children, asthma diagnosis and management differ from that of older children and adolescent in many ways. Early childhood wheezing can evolve to different asthma phenotypes that can have variable response to standard therapy.(308) 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.(306, 309, 310)

Asthma phenotypes in children
Based on several longitudinal studies, wheezing has been categorized epidemiologically into transient and persistent wheeze phenotypes. It is also categorized based on symptoms into episodic/viral induced and multi-trigger wheeze phenotypes.(311, 312) Different responses to treatment and variable outcomes have been attributed to phenotype heterogeneity, overlap, and instability over time. Major factors that may predict persistent symptoms are allergic disease, reduced lung function, viral respiratory infection, and bacterial colonization in infancy. Asthma wheeze phenotype in children has been classified as: (311, 313):

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

The allocation of children into these categories still remains a subject of debate, as their clinical usefulness is still under investigation.(314)
Prediction of asthma in pre-school children

For early identification of the risk for persistent asthma among preschool children, the SINA expert panel recommends the utilization of the modified asthma predictive index (modified-API). This tool is a clinical scoring instrument that can be used to predict whether a child with intermittent wheezing before the age of 3 years will develop persistent asthma pattern during school-age years [Box 9.2]. Children with a history of four or more wheezing attacks (at least one is diagnosed by physician) and either one major or two minor criteria at 3 years of age will have 4-10 old increase in the risk of having asthma later in their childhood. On other side, children with negative modified-API will have 95% chance of outgrowing their asthma later on life.(317)

<table>
<thead>
<tr>
<th>Box 9.2: Modified Asthma Predictive Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of ≥4 wheezing episodes with at least one physician diagnosed and either</strong></td>
</tr>
<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>
<tr>
<td>Or</td>
</tr>
</tbody>
</table>
Strategies of Asthma Management in Children

The long-term goals of asthma management in children are not different from those of adults [Box 5.1].(67) Asthma management requires effective partnership between patients/caregivers and their healthcare providers.(318) 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.(319) Adherence to the prescribed medications and the proper use of their devices are recommended to be addressed before any modification of the treatment plan. It is extremely important to select the best device for optimal treatment delivery [Box 9.3].

<table>
<thead>
<tr>
<th>Box 9.3: Choosing an inhaler device for children*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>&lt;4 years</td>
</tr>
<tr>
<td>4-6 years</td>
</tr>
<tr>
<td>&gt;6 years</td>
</tr>
</tbody>
</table>

Asthma control reflects the adequacy of management by describing the clinical status of a child as controlled, partially controlled, or uncontrolled. Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reported by children and their caregivers and
subsequently treatment decisions by clinicians.(68) In children, assessment of asthma control is recommended to cover two domains:(299)

A. **Assessing future risk of adverse outcomes:** This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effect of medications [Box 9.4].

| Box 9.4: Assessment of future risk of adverse outcomes of asthma in children* |
|--------------------------|-----------------------------------------------|
| **Risk factors** | **Assessment** |
| Asthma attacks within the next few months | • Uncontrolled asthma symptoms  
• One or more severe asthma attacks in the previous year  
• The start of the child’s usual ‘flare-up’ season (especially if autumn/fall)  
• Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens, especially in combination with viral infection  
• Major psychological or socio-economic problems for child or family  
• Poor adherence manifested as underuse of ICS and/or over-use of SABAs |
| Fixed airflow limitation | • Severe asthma with several hospitalizations  
• History of bronchiolitis |
| Medication side-effects | • Systemic: Frequent courses of oral corticosteroids or high-dose ICS  
• Local: moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask |
B. **Assessing symptom control**: Asthma symptom control has been estimated by physician assessment during clinic visit and/or perception of patients and their caregivers toward asthma control. During each clinic visit, the physician is recommended to utilize asthma control criteria to assess disease control [Box 9.5]. Different numerical tools have been developed and validated to objectively assess asthma control utilizing patients and their caregiver perception. However, as these tools have some limitations, they are recommended to be used as a complimentary tool rather than replacing physician assessment. (320)

<table>
<thead>
<tr>
<th>Box 9.5: Levels of asthma control in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Daytime symptoms</td>
</tr>
<tr>
<td>Limitation of activities</td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
</tr>
<tr>
<td>Need for bronchodilator</td>
</tr>
</tbody>
</table>

The SINA expert panel recommends utilizing one of the following questionnaires based on age. The questionnaire is completed by patients and/or their caregiver prior to physician evaluation based on the age of the child:
• **Age group 5 to 12 years - The Childhood-Asthma Control Test (C-ACT):** (Arabic version page 122) The C-ACT is a validated test for children 5 to 12 years [Box 9.6]. C-ACT is a two-part questionnaire with a total of seven questions. The first part is to be answered by the patient and the second part by the caregiver. The final C-ACT score is made up of the sum of the scores of the two parts, ranging from 0 (poorest asthma control) to 27 (optimal asthma control). A score of ≤19 points suggests that a child’s asthma is not adequately controlled.(321)

**Box 9.6: The Childhood Asthma Control Test (C-ACT)**

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

C-ACT Score < 19 Indicates Uncontrolled Asthma | TOTAL SCORE
Age group <5 years - The Respiratory and Asthma Control in Kids (TRACK): (Arabic version page 123)

The TRACK is a validated test for children <5 years [Box 9.7]. It is a 5-item standardized questionnaire, with four questions that address the impairment domain and one question that address 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.(322)

Box 9.7: The Test for Respiratory and Asthma Control in Kids (TRACK)
Role of patient education

Patient education is recommended to be an integral part of asthma management strategy in children. It is recommended to involve the basic knowledge of the disease pathophysiology, identifying and avoiding triggering factors, environmental controls (especially cigarette smoke exposures), proper use of treatment devices, and recognition of worsening asthma symptoms and the optimal time to seek advice.\(^{(323, 324)}\) Proper asthma education can lead to a significant reduction in ED visits and hospitalizations, improve self-management of asthma attacks, and an overall reduction in the cost of asthma care.\(^{(325)}\)

Setting asthma action-plans

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

<table>
<thead>
<tr>
<th>Box 9.8: Components of asthma management action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
</tr>
<tr>
<td>Patient identification</td>
</tr>
<tr>
<td>List of patient’s medications</td>
</tr>
<tr>
<td>Recognition of asthma control status</td>
</tr>
<tr>
<td>Suggested action based on asthma control status</td>
</tr>
<tr>
<td>How to use inhalational devices</td>
</tr>
<tr>
<td>When and how to seek medical advice</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>
Prevention

Asthma attacks can be triggered by a variety of factors including: allergens, viral infection, pollutants, and drugs. Eliminating these exposures improves the control of asthma and reduces medication needs. Parents/caregivers of children with asthma should be strictly advised not to smoke at home at all. (67, 326) Breast-feeding and vitamin D supplementation may decrease the chance of developing early wheezing episodes, while probiotics benefit is still doubtful in preventing allergic disease. (327-329) A recent study on early-life use of probiotic supplementation did not show significant impact to prevent asthma or eczema at the age of 2 years for children at high risk.(330)

Outpatient Management of Asthma in Children

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

Controller therapy:
- ICS are considered the most effective first-line maintenance monotherapy for childhood asthma (Evidence A).(331, 332). Chronic use of ICS for more than 3 months in pre-pubertal-aged children can suppress growth velocity which is dose dependent. However, asthmatic
children when treated with low-dose ICS attain normal adult height but at a later age (Evidence A).(333, 334) 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 1.

- There are insufficient data to recommend short courses of high-dose ICS in children with mild intermittent asthma attacks (Evidence B).(335). Safety of this approach has not been established.
- Children with frequent or severe asthma attacks are recommended to receive regular treatment with ICS (Evidence A).(336) Doubling the dose or even quintupling it at the early stages of loss of control did not result in reduction of asthma attacks or improvement in other outcomes.(337)
- 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).(338, 339)

**Reliever therapy:**

- Oral bronchodilator therapy is not recommended to be prescribed due to slower onset of action and higher side effects.(340, 341).
- LABA should not be used alone as maintenance monotherapy in children (Evidence A).(342) LABA should be used only in combination with ICS. There are different combinations available in the Saudi market (Appendix 1).
Devices:

- As inhalers are the main method of delivering medications, it is recommended to choose the appropriate device [Box 9.3]. Use of valved-holding spacer, with mouthpiece when possible, is recommended when an MDI is prescribed (Evidence B).(343) Breath-actuated devices (e.g. DPIs) represent an effective and simpler option for maintenance therapy in children 5 to 12 years of age (Evidence C).(344, 345) For more information about medications, refer to Appendix 1.

- Nebulizers are not superior to MDI delivered by spacer in both acute and chronic asthma management (Evidence A).(346)

The SINA expert panel recommend ensuring consistency in the approach of asthma in adults, adolescents and children. Therefore, outpatient treatment will be described in three phases: initiation, adjustment, and maintenance. The recommendations in the following sections are further stratified based on age groups: < 5 years and ≥ 5 years.

**Initiation of Asthma Treatment in Children**

Prior to initiating asthma treatment in children, it is recommended to document important findings obtained during the initial clinical assessment, such as the status of asthma control, assessing for risk factors, obtaining C-CAT score for children aged ≥ 5 years, and TRACK score for children <5 years. It is also recommended to provide teaching of inhalers technique, action plan and ensure that patient has a follow-up visit. The SINA expert panel recommends placing the child on one of the steps based on the common clinical scenarios described below:
• **Step 1:**
  o SABA (such as salbutamol) on “as needed basis” for a child with minimal symptoms (less than twice a week) that qualify for a controlled status based on physician assessment and is complemented with a C-ACT score of ≥20 for a child aged 5 to 12 years or TRACK score of >80 for a child aged <5 years.
  o SABA (such as salbutamol) on “as needed basis for a child with intermittent viral-induced wheeze. (347-349)

• **Step 2:**
Personalizing the treatment options for children in step 2 may be predicted by stratification based on asthma-phenotype, assessment of aeroallergen sensitization, and determining the eosinophil count. Positive sensitization and high eosinophil count may favor ICS as a primary controller intervention. (350) The following are recommended:
  o Low dose ICS for a child with more symptoms (more than twice a week) that qualify to partially controlled status based on physician assessment and is complemented with a C-ACT score of ≤19 for a child aged 5 to 12 years or TRACK score of ≤80 for a child aged <5 years (Evidence A). (351-353) Different options of ICS are available in appendix 1.
  o LTRA for a child who cannot or will not use ICSs, though it is a less effective option (Evidence B). (354-356)
  o Low dose ICS for a child <5 years with a history of asthma attack in the past year or has ever been admitted to ICU. (Evidence D)
  o In addition to a low-to-moderate dose of ICS, a short course of oral prednisolone is recommended to be considered for a child aged 5-12 years with early signs of asthma attack at presentation.
• **Step 3**
  - For a child <5 years with more persistent symptoms, commence treatment on double dose of ICS. (357, 358)

**Adjustment of Asthma Treatment in Children**

Assessment of adherence, proper device use, control of environment, and confirmation of the diagnosis especially if there is a failure to respond to therapy is recommended each time before treatment adjustments. (359) For a child seen in the clinic for the first time while on controller treatment, the managing physician should ensure that the child is receiving the appropriate treatment based on recommendations given in the section on treatment initiation.

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

- **A child with uncontrolled asthma:** escalation of treatment to at least the next step. Uncontrolled status is determined based on physician assessment complemented by a C-ACT score of ≤19 for a child aged 5 to 12 years or TRACK score of ≤80 for a child aged <5 years.

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

The SINA expert panel recommends the following concepts of treatment adjustment based on age in the following section.
Box 9.9: Outpatient management of Asthma for children aged 5 to 12 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 C-ACT Score to further assess asthma control**

- Challenge diagnosis (is it asthma?)
- Environmental control
- Asthma education
- Evaluate compliance
- Risk assessment

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

**STEP 1**
Low dose ICS
Alternative: Leukotriene modifier
Salbutamol (As needed)

**STEP 2**
Low dose ICS + LABA
Alternative: Medium - high dose ICS, Or Low dose ICS + Leukotriene modifier

**STEP 3**
Medium - high dose ICS + LABA +/- Leukotriene modifier

**STEP 4**
Medium - high dose ICS + LABA +/- Leukotriene modifier

**STEP 5**
Step 4 regimen + Systemic Steroid
Consider: Biologic Therapy

**ABBREVIATION:**
- **ABG:** Arterial Blood Gas
- **CXR:** Chest X-Ray
- **IV:** Intravenous
- **O2:** Oxygen
- **PICU:** Pediatric Intensive Care Unit
- **PRAM:** Pediatric Respiratory Assessment Measure
- **SaO2:** Oxygen Saturation
- **RA:** Room Air

Refer to Specialist
Salbutamol (As needed)
• **Children aged 5 to 12 years [Box 9.9]**
  - A child is not controlled at step 1: The preferred option is escalating to step 2 with low dose ICS (step 2) (Evidence A).(331, 332)
  - 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).(118) Alternatively, LTRA can be added to low dose ICS or the dose of ICS escalated to moderate dose (Evidence A).(360-365)
  - A child is not controlled at step 3: It is recommended to escalate to step 4 by changing the combination inhaler to medium dose of ICS/ LABA (step 4). LTRA may be added to this combination if control is not achieved.
  - Whenever there is a difficulty to control asthma at step 4, it is strongly recommended to refer patient to a physician specialized in asthma for further evaluation.
  - There is growing evidence to support the use of anti-IgE in children 6-12 years of age who fulfill the following criteria (Evidence A): severe persistent allergic asthma with frequent daytime symptoms or night-time awakenings, and who have multiple documented severe asthma attacks despite daily high-dose ICS plus LABA.(366, 367) However, this line of management is recommended to only be restricted to physicians specialized in asthma (Evidence C).(368, 369)
  - Data related to specific immunotherapy in pediatrics are limited, but it can be used for children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV\textsubscript{1} as detailed in immunotherapy subsection.(174) It should be initiated by an asthma and allergy specialist.
  - There is no evidence to support the use of LAMA in children <12 years.
Box 9.10: Outpatient management of Asthma for children aged <5 year

**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

- Challenge diagnosis (is it asthma?)
- Environmental control
- Asthma education
- Evaluate compliance
- Risk assessment

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

**STEP 1**
Low dose ICS
Alternative: Leukotriene modifier

**STEP 2**
Preferred: double dose ICS
Alternative: Low dose ICS + Leukotriene modifier

**STEP 3**
Double dose ICS + Leukotriene modifier

**STEP 4**
Step 4 Regimen + Systemic steroid

**STEP 5**
Refer to Specialist

**ABBRéviation:**
• **Children aged <5 years [Box 9.10]**
  
  o A child is not controlled at step 1: The preferred option is to escalate to step 2 with low dose ICS (Evidence A).(331, 332)
  
  o 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).(363, 370, 371) Alternatively, adding LTRA to low dose ICS is another option, although this is considered as less effective.(357, 358)
  
  o 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).(372-374)
  
  o Whenever there is a difficulty to control asthma at step 4, it is strongly recommended to refer patient to a physician specialized in asthma for further evaluation and options in step 5.
  
  o There is no evidence to support the use of LABA in children <5 years.

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

**Maintenance of Asthma Treatment in Children**

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 to 12 years or TRACK score for children aged <5
years. Based on clinical assessment and asthma control status [Box 9.6 and 9.7], the SINA expert panel recommends the following:

- Step up treatment for children who are uncontrolled based on physician assessment and complemented by a C-ACT score of ≤19 for a child aged 5 to 12 years or TRACK score of ≤80 for a child aged <5 years. It is recommended to rule out any modifiable factors preventing reaching optimal asthma control.
- Patient should be clinically assessed regarding medications and doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors.
- Maintain treatment for children who reached controlled status based on physician assessment complemented by a C-ACT score of ≥20 for a child aged 5 to 12 years or TRACK score of >80 for a child aged <5 years.
- Consider stepping down treatment for children who are controlled for at least 3 months.

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

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

- **Children aged 5 to 12 years [Box 9.9]**
  If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25-50% every 3-6 months to the lowest possible dose that is required to maintain control (Evidence B),(161, 162),(163) It should be clearly explained to the patient and/or caregiver that asthma control may deteriorate if treatment is abruptly...
discontinued.(164) 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.(165)
- If the patient is on a combination of ICS with LABA or LTRA, taper ICS to the lowest possible dose (Evidence B).(166, 167) If control is maintained, LABA or LTRA may then be discontinued (Evidence D).(166)
- 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.(168)
- For patients on continuous oral steroids, the dose is recommended to be tapered to the lowest dose and preferably to every other day (Evidence D). It is recommended to refer the child to a specialized physician in asthma management.

• **Children aged <5 years [Box 9.10]**
  - The need for continuation of ICS should be regularly assessed as wheeze remits in a significant portion of children.(375)
  - 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).(161, 162) It is recommended to be clearly explained to the caregiver that asthma control may deteriorate if treatment is abruptly discontinued.(164) if asthma symptom is recurred, an action plan that contains instruction on resuming controller therapy is recommended to be
provided to patients and their caregiver.

- For significant side effects, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advice for a mouth washing after inhalation if possible, enforce use of MDI with spacer, and/or use of appropriate local antifungal therapy for severe oral thrush.\(^{(168)}\)
- Uncontrolled asthma in preschool children can lead to developmental disadvantages due to the negative impact of uncontrolled asthma on their social interaction and sleep. Caregivers of preschool children are recommended to be educated that asthma control is an achievable target and affected children should not be prevented from engagement in age-appropriate activities.

**Referral to an asthma specialist**

Referral to an asthma specialist for consultation or co-management is recommended in the following situations:

- There is uncertainty regarding the diagnosis.
- There is difficulty achieving or maintaining control of asthma.
- Immunotherapy or omalizumab is being considered.
- The patient requires step 4 care or higher.
- The patient has had an asthma attack requiring a hospitalization or 2 or more oral corticosteroids in the past 12 months.
10. Management of Acute Asthma in Children

Early recognition of acute asthma

Recognition of early signs of acute asthma is essential especially for those <5 years. Early symptoms of acute asthma include (Evidence D):

- An attack of shortness of breath with wheeze or increase of shortness of breath with wheeze.
- Cough, especially at night although this is non-specific.
- Impairment of daily activity.
- An increased need for or poor response to SABA.
- For a child <2 years, the presence of lethargy and poor feeding should raise the suspicion of acute asthma attack. However, viral bronchiolitis is a common differential diagnosis in this age group during winter season.

In a child aged 2-5 years, the combination of the above features can predict approximately 70% of acute asthma attacks with low false positive rate. (376) Moreover, upper respiratory tract infection (URTI) may frequently precede acute asthma attack in children. Clinical assessment is essential in children as the utilization of objective measure such as PFT is problematic, especially in the younger age groups.

Initial management of acute asthma at home

The SINA expert panel recommends management of a child with asthma to include an action plan that enable the caregiver to recognize worsening of asthma and the advices for initial treatment. (Evidence D). The action plan is recommended to include features that mandate the need for urgent medical care that includes acute distress of the child, difficulty to complete few words in one breath, and poor response to SABA treatment at home.
In the case of acute attack, initial management at home by the caregiver should be started with salbutamol inhaler 2-4 puffs by a spacer that may be repeated every 20 minutes for a total of three doses. If the child improves, asthma therapy is recommended to be stepped up as per instructions in the action plan and medical advice should be sought as soon as possible. If the child does not adequately improve within or after the initial period, urgent medical care is recommended.

**Assessment of asthma severity in the emergency department**

Assessment of acute asthma severity in children has an important role in various components of acute asthma management such as: pharmacological interventions, need for hospitalization, and need for intensive care unit admission. The assessment of acute asthma severity in young children is also important for clinical decision-making and evaluation of treatment effectiveness.(68, 99, 377-386) This is supported by the fact that PFT measurement is not feasible as more than half of asthma attacks in children presented to emergency departments for children <5 years.(378)

<table>
<thead>
<tr>
<th>Box 10.1: The pediatric respiratory assessment measure (PRAM) score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sign</strong></td>
</tr>
<tr>
<td>Suprasternal retraction</td>
</tr>
<tr>
<td>Scalene muscle contraction</td>
</tr>
<tr>
<td>Air entry</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>O2 saturation</td>
</tr>
</tbody>
</table>
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. (378, 387) The PRAM represents a useful means to record clinical signs in a standardized fashion [Box 10.1]. (68) The PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing. (385) 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. (388, 389) The SINA expert panel recommends measuring PRAM score for asthmatic patients in emergency as it can categorize the risk of hospitalization:

- **Total score of 1–3**: low risk with a chance of <10% for hospital admission
- **Total score of 4–7**: moderate risk with a chance of 10-50% for hospital admission
- **Total score of 8–12**: high risk with a chance of >50% for hospital admission

**Management of acute asthma in the emergency department**

After performing the necessary clinical assessment, the SINA expert panel recommends the utilization of PRAM as a tool to assess patients in the emergency department and guide further management as well. The PRAM score should be obtained at the initial assessment and after initiation of treatment as well. After initial clinical assessment and starting initial appropriate therapy, managing physician is recommended to focus on obtained history to identify risk factors for ICU admission, including (390):

- Previous life-threatening asthma attack
- Previous ICU admission
- Previous intubation
- Deterioration while already on systemic steroid
In addition, managing physician is recommended to be aware of the following clinical features of severe or life-threatening asthma that require immediate medical attention:

- Child is unable to speak or drink
- Central cyanosis
- Confusion or drowsiness
- Significant subcostal or subglottic retraction
- Oxygen saturation <92%
- Silent chest on auscultation
- Tachycardia

Implementation of clinical pathway that utilizes PRAM score for acute asthma management in children with moderate to severe asthma attacks markedly decrease the rate of hospitalization without increasing the rate of return to emergency care (Evidence B) [Box 10.2]. (389, 391-393) This has been supported by a study showing that PRAM score after 3 hours of initial management was associated with a significant improvement in the prediction of admission rate compared to pure clinical judgment at triage. (387) Ancillary investigation that includes chest- X-ray and ABG are not routinely recommended. (390) ABG is indicated in severe bronchial asthma that failed to respond to maximum therapy and required ICU admission. While Chest-X-ray is recommended in the following conditions:

- Suspected bacterial pneumonia that presents with fever >39°C and presence of focal finding of decreased breath sound and crackles.
- To rule out bronchial asthma complications such as pneumothorax.
- Severe disease that does not respond to maximum treatment.
- Uncertainty about the diagnosis.
- Hypoxemia apparently disproportionate to the attack severity.
Viral infection is the usual cause of asthma attacks in children and thus routine use of antibiotics is strongly discouraged. (394) Antibiotics are recommended when bacterial pneumonia is clinically suspected. (391, 392) Acute asthma management based on PRAM: 

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

**Mild - PRAM score of 1–3**

- **Management:**
  - Obtain vital signs initially and at discharge.
  - Prescribe appropriate oxygen dose to keep Saturation ≥92%.
  - Salbutamol dose based on weight: (346, 395)
    - Less than 20 Kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer
    - 20 Kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer - titrate MDI dose based on response)
    - In mild cases, SABA with spacer is not inferior to nebulized SABA.
  - Ipratropium bromide may be considered at a dose of 4 puffs by MDI/spacer or 250 mcg by nebulizer every 20 minutes for the first hour only.(396)
  - Consider oral steroid if there is no response to the first dose of salbutamol. Prednisolone dose is 1-2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2-5 years, and 60 mg for children 5-12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose of 16mg. (254)
  - Re-assess PRAM after 1 hour.
Management after initial treatment based on PRAM score:

- **PRAM score is 1-3:**
  - The child may be discharged on salbutamol inhaler and ICS inhaler with a spacer.
  - If oral steroids course is given initially, dexamethasone is recommended for extra one day and prednisolone for total of 3-5 days.
  - It is recommended to offer the child an action plan, education on inhalers technique, and a follow-up visit within one week to the appropriate clinic.

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

**Moderate - PRAM score of 4–7**

- **Management:**
  - Obtain vital signs.
  - Prescribe appropriate oxygen dose to keep Saturation ≥92%.
  - Salbutamol dose based on weight: (346, 395)
    - Less than 20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer.
    - 20 kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer - titrate MDI dose based on response).
    - Ipratropium bromide at a dose of 4 puffs or 250 mcg by nebulizer every 20 minutes for the first hour only) (395-397).
  - The combination of salbutamol and ipratropium bromide has been shown to be effective in this situation (Evidence B).(395)
  - Systemic steroids after the first dose of SABA. Prednisolone dose is 1-2 mg/kg up to a
maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2-5 years, and 60 mg for children 5-12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16mg. (237, 254)
  - Re-assess PRAM after 1 hour.
  - If PRAM score after 1 hour is 1-3, observe for another hour.
- Management after initial treatment based on PRAM score:
  - PRAM score is 1-3:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment.
    - Complete the course of oral steroids. Dexamethasone is recommended for extra one day and prednisolone for total of 3-5 days; both as once daily dose.
    - It is recommended to offer the child an action plan, education on inhalers technique, and a follow-up visit within one week to the appropriate clinic.
  - PRAM score is 4-7: It is recommended to continue treatment with salbutamol every 30 minutes for three doses and to assess PRAM score every 30 minutes. Further evaluation is based on PRAM re-assessment:
    - If PRAM score improves to 1-3, the child can be managed as above.
    - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40-50 mg/kg to a maximum of 2 gm by slow IV infusion over 20-30 minutes. The child needs close monitoring for blood pressure and appropriate intravenous fluids. Admission is recommended to be considered. (398-400)
  - PRAM score is 8-12: treat as severe asthma attacks (see below)
Severe - PRAM score of 8-12

- Management:
  - Obtain vital signs every 20 minutes till improvement.
  - Prescribe appropriate oxygen dose to keep Saturation ≥94%.
  - Salbutamol nebulizer at a dose of 2.5 mg for those weighted <20 Kg or 5 mg for those weighted ≥20 Kg and ipratropium bromide at a dose of 250 mcg by nebulizer every 20 minutes for the first hour. (395-397, 401) This combination has been shown to be effective in this situation (Evidence B). (395)
  - Systemic steroids after the first dose of SABA. Prednisolone dose is 1-2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2-5 years, and 60 mg for children 5-12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16mg. (237, 254)
  - Re-assess PRAM after 1 hour.
  - Consider IV access and appropriate IV fluids.
  - If PRAM score after 1 hour is 1-3, Observe for another hour.

- Management after initial treatment based on PRAM score:
  - PRAM score is 1-3:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment.
    - Complete the course of oral steroids. Dexamethasone is recommended for extra one day and prednisolone for total of 3-5 days; both as once daily dose. (237, 254)
    - It is recommended to offer the child/care giver an action plan, education on inhalers technique, and a follow-up visit within one week to the appropriate clinic.
- PRAM score is 4-7: It is recommended to continue treatment with salbutamol every 30 minutes for three doses and to assess PRAM score every 30 minutes. Further evaluation is based on PRAM re-assessment:
  - If PRAM score improves to 1-3, the child can be managed as above.
  - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40-50 mg/kg to a maximum of 2 gm by slow IV infusion over 20-30 minutes. The child needs close monitoring for blood pressure and appropriate intravenous fluids. Admission is recommended to be considered. (398-400)
- PRAM score is 8-12: Deterioration of clinical status despite adequate treatment in the initial period warrants special care and attention. It is recommended to
  - establish IV access and to start on appropriate IV fluids.
  - Continue nebulized salbutamol back-to-back every 20 minutes or use continuous salbutamol nebulization at a dose of 7.5mg/hour for those weighted <10 kg, 11.25mg/hour for those weighted 10-20 kg, or 15mg/hour for those weighted >20kg. (252, 402)
  - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40-50 mg/kg to a maximum of 2 gm by slow IV infusion over 20-30 minutes.
  - If no improvement in PRAM score, start IV salbutamol at a dose of 1 mcg/kg/min then titrate based on response for a maximum dose of 10 mcg/kg/min). (399, 400)
  - ABG, CXR and electrolyte are recommended to be obtained and the pediatrics critical care or equivalent service must be consulted.
Box 10.2: Assessment and treatment of acute asthma in 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>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalene Contraction</td>
<td>Absent</td>
<td>Ok</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. Initial Salbutamol, re-assess, if no response:
   - Continue Salbutamol Q 20 min for two doses
   - Consider Ipratropium bromide and oral steroids
4. Re-assess PRAM after one hour.

- **PRAM 1-3**
  - Salbutamol PRN
  - Complete the course of prescribed oral steroids
  - Inhaled steroid, if indicated.
  - Provide action plan/ asthma education
  - Clinic visit within one week

- **PRAM 4-7**
  - Follow instruction under “Moderate” pathway

**MODERATE PRAM: 4-7**

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

- **PRAM 1-3**
  - Observe for 1 hour after last bronchodilator
  - If PRAM ≤3 discharge home
  - Salbutamol Q 4-6 hours X 24 hours then PRN
  - Inhaled steroids till next clinic visit
  - Complete oral steroids course
  - Provide action plan/ asthma education
  - Clinic visit within one week

- **PRAM 4-7**
  - Continue salbutamol Q 30 min for 3 doses, Reassess PRAM
  - IV magnesium sulphate
  - Admission is recommended

- **PRAM 8-12**
  - IV access and fluids
  - Continuous Salbutamol Nebulizer
  - Consider IV Salbutamol
  - ABG and consider CXR
  - Monitor electrolytes
  - Contact PICU for Admission

(Discharge Plan)
SEVERE
PRAM: 8-12

1. Vital signs Q 20 min until improvement
2. O₂ Supplementation to keep SaO₂ ≥94%
3. Salbutamol + Ipratropium bromide 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 to complete the course
• Provide action plan/ asthma education
• Clinic visit within one week

PRAM 4-7

• Continue Salbutamol Q 30 min for 3 doses, Re-Assess PRAM

PRAM 8-12

If PRAM 4-7
• IV magnesium sulphate
• Admission is recommended

If PRAM <8
• IV access and fluids
• Continuous Salbutamol Nebulizer
• Consider IV Salbutamol
• ABG and consider CXR
• Monitor electrolytes
• Re-assess PRAM after 1 hour

Consult PICU for Admission

ABBREVIATION:

ABG: Arterial Blood Gas, CXR: Chest X-Ray, IV: Intravenous, O₂: Oxygen, PICU: Pediatric Intensive Care Unit,
PRAM: Pediatric Respiratory Assessment Measure, SaO₂: Oxygen Saturation, R/A: Room Air
Appendix 1: Medications Used for the Treatment of Asthma

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

Controller medications

Inhaled corticosteroids
ICS are currently the most effective anti-inflammatory medications for the treatment of asthma. They reduce symptoms, improve quality of life, improve lung function, decrease airway hyper reactivity (AH), control airway inflammation, reduce frequency and severity of asthma attacks, and reduce asthma mortality. Early initiation of low dose ICS in asthma leads to improvement in lung functions. When they are discontinued prematurely or abruptly, deterioration of clinical control follows within weeks to months in most patients. ICS differ in their potency and bioavailability. Most of the benefits from ICS are achieved in adults and children at relatively low doses [Box11-1 and Box 11-2]. Exposure to tobacco smoking or vaping, including secondary and tertiary, reduces the responsiveness to ICS. To reach control, add-on therapy with another class of controller is preferred to increase the dose of ICS.
**Box 11.1: List of inhaled corticosteroid inhalers**

<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 &amp; 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>

CFC: chlorofluorocarbon propellant; DPI: Dry powder inhaler; HFA: chlorofluoroalkane propellant

**Based on availability in the Saudi market for children

Local adverse effects can occur and include oropharyngeal candidiasis and dysphonia; with metered dose inhalers (MDI), these effects are reduced by using a spacer device. Mouth and throat washing after inhalation may reduce oral candidiasis. The small risk of adverse events from the use of ICS is well balanced by their efficacy. Therefore, low-medium dose of ICS is generally safe and well tolerated in children. Formulations with small size particles are believed to be more effective and safer as it lead to better deposition in the peripheral small airways. Some studies have shown that ciclesonide had relatively lower local and systemic side effects especially in children. Systemic side effects are occasionally reported with high doses and long-term treatment.
Box 11.2: List of inhaled corticosteroids inhalers*

<table>
<thead>
<tr>
<th>Drug (Doses in mcg)**</th>
<th>Less than 5 years</th>
<th>Children above 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>

CFC: chlorofluorocarbon propellant; DPI: Dry powder inhaler; HFA: chlorofluoroalkane propellant

**Based on availability in the Saudi market for children

Special considerations for use of ICS in children

Growth retardation may be seen with all ICS when a high dose ICS is chronically used. Systematic reviews showed a reduction may affect height velocity in pre-pubertal children over 12 months use of low-to-medium dose of ICS, especially during the first year of life.(410) 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.(411) Moreover, more studies demonstrated the negative impact of medium-to-high doses ICS on bone mineralization.
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. In summary, the potential adverse effects of ICS need to be weighed against the well-established benefit to control persistent asthma. Therefore, it is important to target the lowest possible ICS dose that maintains adequate asthma control.

**Long-acting inhaled β2-agonists**

The commonly used long-acting inhaled β2-agonists, formoterol and salmeterol, are used on a twice daily basis. Novel LABA agents with a 24 h duration of action are available e.g., indacaterol, vilanterol, and olodaterol. Due to lack of anti-inflammatory effect, LABA should not be used alone as monotherapy in asthma as this can lead to increased mortality, and indeed they should only be prescribed in combination in the same device with ICS. When used in combination with ICS, there is an improvement in symptoms, decreased nocturnal asthma, improved lung function, decreased use of inhaled β-2 agonists, reduced number of asthma attacks and better control at a lower dose of ICS. LABA provides longer protection to prevent exercise-induced bronchospasm than short-acting inhaled β-2 agonists (SABA). Their side effects are limited to tachycardia, tremor, headaches, muscle cramps, and sometimes hypokalemia. Regular use of LABA combined with ICS may lead to a reduction in their side effects. Furthermore, patients rarely develop tolerance to LABA. The effect of LABA has not been adequately studied in children of <5 years.
Fixed Combination of ICS and LABA

Fixed Combination of ICS and LABA are considered more convenient for patients. Combination therapy is generally safe and did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma attacks. 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. Fixed combination inhalers of ICS and LABA have been available in the form of fluticasone propionate and salmeterol (Seretide) or budesonide and formoterol (Symbicort). However, new formulations are available in different devices in the Saudi Market [Box 11-3] such as beclomethasone and formoterol (Foster), fluticasone propionate and salmeterol (Rolenium), and fluticasone propionate and formoterol (Flutiform).

Once a day dry powder combination of ICS/LABA with fluticasone furoate and vilanterol (Relvar) is available in two strengths of 100/25 and 200/25 microgram with dispensed equivalent dose of 92/22 and 184/22 microgram, respectively. The dose of fluticasone furoate of 100 mcg is equivalent to fluticasone propionate 250 mcg. Such a combination has a potential adherence advantage while maintaining the same safety as the combination of fluticasone propionate and salmeterol.
### Box 11.3: List of fixed combinations of inhaled steroid and long acting β2 agonists

<table>
<thead>
<tr>
<th>Inhaled Steroid (Doses in mcg)</th>
<th>Long Acting β2 agonist (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, 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, 250)</td>
<td>Salmeterol (25)</td>
<td>Seretide®</td>
<td>MDI</td>
<td>Evohaler™</td>
</tr>
<tr>
<td>Fluticasone propionate (100, 250, 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 (50,125,250)</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>

MDI: Metered dose inhaler, DPI: Dry powder inhaler

*Based on availability in the Saudi market for children

**Once a day combination
Leukotriene modifiers

Leukotriene modifying agents reduce airway inflammation and improve asthma symptoms and lung function, but with a less consistent effect on asthma attacks, especially when compared to ICS. They may be used as an alternative treatment to ICS for patients with mild asthma, especially in those who have clinical rhinitis. Some patients with aspirin-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. (431, 432) LTRA are generally well tolerated. In children, studies have shown that LTRA may be useful for reducing the number of asthma attacks induced by viruses and for reducing bronchial inflammation in atopic children. (433-436) There are no clinical data to support their use under the age of 6 months.

Long Acting Anti-Muscarinic Agents

Long acting anti-muscarinic (cholinergic) agents (LAMA) inhibit the effect of acetylcholine on M3 receptors. Tiotropium was the first agent used in managing patient with COPD. Tiotropium use has been extended to asthma. The more recent LAMAs (such as aclidinium bromide, glycopyrronium) have not been studied in asthma yet. Given tiotropium’s bronchodilatation duration of action of more than 24 hours, it is used on a daily base. (437, 438) The earlier studies on tiotropium were conducted using the HandiHaler device. Later studies were conducted using the new Respimat device. Till date, tiotropium is available in the Saudi Market in the HandiHaler device in an 18 mcg capsule format. The Respimat device is not yet widely available in the Saudi market. Tiotropium was first shown to be
effective in treatment stepping-down when added to a combination of ICS/LABA. Tiotropium was found to be not inferior to salmeterol in the management of asthma not adequately controlled on ICS or combination of ICS/LABA. 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 attacks (Evidence A). Anticholinergic drugs are considered to be safe. The main side effect is dryness of mouth. Although mild prostatic symptoms have been reported, there is no evidence of a direct causal relationship.

**Theophylline**

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

**Oral β2-agonists**

The side effect profile is much higher than that of inhaled β-2agonists. Therefore, their use is highly discouraged in asthma management. Oral route is not recommended in children.
Cromones

Cromones (sodium cromoglycate and nedocromil sodium) are not recommended for preschool children. They have limited role in the long-term treatment of older children. Evidence showed that low-dose ICS is superior to cromones in the management of asthma.(443). They are no longer available as an option to treat asthma.

Systemic corticosteroids

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

Reliever medications

Relievers are medications used on an “as-needed basis”, and act quickly to reverse bronchoconstriction and relieve symptoms.
Rapid onset inhaled β2-agonists

Short acting bronchodilators, such as salbutamol, are the medications of choice for relief of symptoms of acute attacks of asthma and for the pretreatment of exercise-induced bronchoconstriction. Use of MDI with a chamber is as effective as the nebulized route in treatment of acute episodes of wheeze in children.(234) Regular long-term use of SABA is not recommended. Formoterol is a LABA that has a fast-acting component but is not available alone in the Saudi market in a single inhaler; however, it can be used as a rescue medication in formoterol containing combination with ICS.(106-108) Vilanterol is another LABA used once a day that has a fast onset of action within 15 minutes and long half-life; hence, the patient should be advised to only use it once a day on a regular basis and not a rescue medication.(128, 129)

In acute asthma, inhaled salbutamol is the preferred choice.(231, 236) Repeated doses are recommended to be given at 15–20 min intervals. Alternatively, continuous nebulization (salbutamol at 5–10 mg/h) could be used for 1 h if there is an inadequate response to initial treatment. However, a meta-analysis of randomized controlled trials of adults with acute asthma found no significant differences between the continuous or intermittent methods in terms of pulmonary function or hospital admission; nevertheless, patients treated by continuous nebulization had fewer side effects.(444) In patients who are able to use the inhaler devices, 6–12 puffs of MDI with a spacer are equivalent to 5 mg of salbutamol by nebulizer. As the inhaled route has a faster onset of action and fewer adverse effects, the use of IV β-2-agonists in the initial treatment of patients with acute severe asthma is not generally recommended. (445) IV therapy should not be considered routinely and only used cautiously if the response to the inhaled drug is poor or if the patient cannot tolerate the inhaled route.
Anticholinergics

Anticholinergics are less effective than SABA in asthma. However, when used in combination with SABA in acute asthma, they provide an additional benefit.\(^{(395)}\) It can also be an alternative bronchodilator for patients who experience adverse effects such as tachycardia, arrhythmia, and tremor from rapid-acting β\(^{-2}\)-agonists. Their side effects include dryness of the mouth and a bitter taste.

In moderate to severe acute asthma, combining ipratropium bromide with salbutamol was shown to have additional bronchodilation effect and faster improvement in lung function, compared to salbutamol alone.\(^{(243, 246)}\) A systematic review showed the combination therapy has an added benefit in reducing hospitalizations.\(^{(245)}\) Combining both agents led to reduction in hospital admission rates by 38-57\%, improvement in lung function, and substantial cost saving.\(^{(246, 446, 447)}\) No evidence of benefit for length of hospital stay and other markers of response when inhaled anticholinergics are added to short-acting β\(^{-2}\)-agonists in hospitalized asthmatic children with acute attacks.\(^{(448)}\) The adult dosing of nebulized ipratropium bromide is 500 μg every 20 minutes for three doses, then as needed. Alternatively, ipratropium bromide can be administered by MDI at a dose of 4-8 puffs (80-160 μg) every 20 minutes, then as needed for up to three hours.

Intravenous magnesium sulphate

In a systematic review, magnesium sulfate was shown to reduce hospitalizations in patients with severe or life-threatening asthma attacks that failed to respond to initial treatment.\(^{(450)}\) A single dose of IV magnesium sulfate at a dose of 1–2 g over 20 minutes is safe and effective in acute severe asthma.\(^{(248)}\)
Aerosol devices used in asthma

Medication aerosol can be delivered using three devices:

Small-Volume Nebulizer (SVN)

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

Pressurized Metered-Dose Inhaler (MDI)

It is a pre-pressurized inhaler with medication and a propellant, which when actuated will give one dose of the drug for a single inspiration. An MDI typically requires slow inspiratory flow (≤30 L/min). One of its main advantages is that it is premixed and the ability to provide multiple doses in a short period of time. It is also small and portable with limited contamination. Disadvantages include the need of patient training to coordinate inhalation with actuation, and if this is not done properly, there is a potential of high deposition of drug in the oropharynx and poor drug delivery. 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 (DPI)

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

Breath-actuated inhalers

These inhalers automatically release a spray of medication when the person begins to inhale. They are easy to use and improve asthma control and compliance to medications.(451-454)

Biologics in Asthma Treatment

The recent progress in biologic therapy in asthma has made a step forward toward the practice of precision medicine for asthma patients. This section describes the biologic agents that received appropriate approvals.(455) We also included agents that are potential therapies in the near future, other agents are still in the pipeline and yet being evaluated by ongoing trials.
Anti-Immunoglobulin E (Anti-IgE):
Omalizumab is a recombinant humanized monoclonal antibody against soluble IgE. It prevents binding of IgE to its high affinity receptor and subsequently lowers its expression and the activation of mast cells, basophils, and dendritic cells. Omalizumab is indicated for patients ≥6 years of age with severe allergic asthma (at least one positive aeroallergen on skin prick testing or an elevated specific aeroallergen IgE level) uncontrolled on high-dose ICS combined with LABA and other controllers and who have an IgE level of within therapeutic range. It was shown to reduce attacks, hospitalizations and allow stepping down of ICS dose. Baseline IgE level does not predict response, but is necessary, in addition to the weight, to calculate the dose. The side effects include pain and bruising at injection site and very rarely anaphylaxis (0.1%). This drug requires careful monitoring and should only be initially prescribed by an expert physician in asthma treatment. There is an extensive experience with omalizumab of more than 15 years. It is classified as category B for use in pregnant women based on current cumulative experience. Therefore, it is not recommended to start omalizumab during pregnancy, but can be continued for those who already use it if the benefit outweigh the risk.

Anti-interleukin 5 (Anti-IL5):
IL5 is critical for the development and maturation of eosinophils. Anti-IL5 monoclonal antibody treatment is directed to patients with severe eosinophilic asthma who are not controlled on step 4 of treatment with two or more attacks in the past year and who have peripheral blood eosinophils according to specific anti-IL5 agent. Anti-IL5 therapy reduces attacks by 40-60% with improvement in lung function and allow about 50% reduction of oral glucocorticoids. Mepolizumab is approved for patients ≥12 years. It recieved recent approval for use in patients aged 6-11 years.
by the European Medicine Agency’s Committee, this is currently limited to European countries. Benralizumab is approved for patients ≥12 years. Reslizumab is approved for patients ≥18 years. Patients with more severe disease and higher eosinophil counts are expected to benefit more. (461)

There is no available evidence that compares anti-IgE therapy to any of the anti-IL-5 therapies or directly comparing different anti-IL-5 agents. As there is currently no data to guide when to stop anti-IL-5 therapy, the treatment may be continued for up to 6-12 months prior to the stopping decision (Evidence D). (155)

These medications should be avoided in patients with active helminthic infection. No enough data regarding use during pregnancy. There are currently 3 different Anti-IL5 medications in clinical use:

- **Mepolizumab** binds circulating IL5. Blood eosinophils should be >150/ul at the time of treatment initiation or >300/ul within the last 12 months. It is given as 100 mg monthly subcutaneously by injections.

- **Reslizumab** binds circulating IL5. Blood eosinophils should be >400/ul. It is given as monthly IV infusion of 3 mg/kg over 20-50 min. (462) Oropharyngeal pain and elevated CPK were reported in less than 10% of patients. Since the dose is weight adjusted, reslizumab could be more efficacious when fixed dose mepolizumab is not adequate. (463)

- **Benralizumab** binds to the α chain of IL5 receptor leading to eosinophil apoptosis. (464) Blood eosinophils should be >300/ul. It is given as 30 mg by subcutaneous injection once every 4 weeks for the first 3 doses and once every 8 weeks thereafter.

**Anti-interleukin 4 receptor α (Anti-IL4Rα):**

- **Dupilumab** is a monoclonal antibody against the α chain of the IL4 receptor. This chain is shared with the IL13 receptor. Therefore, this biologic impedes the signaling of both IL4 and IL13, two important cytokines in the development of TH₂ cells and IgE producing B-cells. It was recently
approved for the treatment of moderate to severe eosinophilic asthma with blood eosinophils >300/ul and oral steroids dependent severe asthma regardless of blood eosinophils in patients ≥12 years of age. It improves asthma symptoms, lung function, and reduced the rate of attacks.\(^{(465, 466)}\) The initial dose for the eosinophilic phenotype is 400 mg subcutaneously then 200 mg every two weeks; while initial dose for oral steroid dependent asthma is 600 mg subcutaneously then 300 mg every two weeks. Adverse effects include upper respiratory tract infections and injection site reaction. Patients on dupilumab should avoid live vaccines.

**Potential future therapies.**

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

- **Fevipiprant** is an oral treatment for asthma that is intended for the treatment of uncontrolled severe asthma.\(^{(467)}\) It competitively and reversibly antagonizes the prostaglandin D\(_2\) receptor that

- **Tezepelumab** is a human monoclonal antibody specific for the epithelial-cell–derived cytokine thymic stromal lymphopoietin (TSLP) that is intended to patients whose asthma remained uncontrolled despite treatment.\(^{(468)}\)

**Reference**

Please refer to the Annals of Thoracic Medicine
Arabic version for assessment of Asthma control questionnaires

استمارات قياس التحكم بالربو
التحكم بالربو، للأشخاص من عمر 12 سنة وما فوق

إذا كان ولدك المراهق بعمر 13 سنة أو أكثر، دعه يكمل الاختبار الآن. ثم ناقش النتائج مع طبيبك.

الخطوة (1) أكتب رقم كل إجابة في المربع المخصص للنتيجة.

الخطوة (2) أمض النقاط في كل مربع إلى المجموع الكلي.

الخطوة (3) اخذ الاختبار إلى الطبيب ليحدثك عن سجل النقاط الإجمالي.

إذا كان المجموع الكلي 19 أو أقل فإن الربو قد لا يكون متحكمًا فيه جيدًا.

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<tr>
<th>الدرجة المطلقة</th>
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المجموع الكلي

التاريخ: / / 20
اختبار التحكم في الربو الشعبي عند الأطفال
لل عمر من 5 - 12 سنة

اختبار التحكم في الربو الشعبي عند الأطفال هو وسيلة لمساعدة الطبيب في تحديد ما إذا كانت أعراض الربو عند طفلك هي تحت السيطرة. نرجو الإجابة على الأسئلة أدناه ومن ثم مشاركة النتائج مع الطبيب المعالج لطفالك. وبناءً على النتيجة، فقد يُستحسن الطبيب بتقديم بعض النصائح الطبية أو التغيير في الخطة العلاجية وتقدم بعض الخيارات التي تتساوى إلى الوصول إلى التحكم في أعراض الربو عند ابنك.

تم تصميم اختبار التحكم في الربو الشعبي عند الأطفال للفئة العمرية من 4 إلى 11 سنة. إذا كان عمر طفلك هو 12 سنة أو أكثر، أو إذا كنت راضيًا وتوقع من الربو الشعبي، فنصح بإستعمال اختبار التحكم في الربو الشعبي عند الكبار.

كيفية عمل اختبار التحكم في الربو الشعبي عند الأطفال:

اطلب من طفلك إجابة على الأسئلة الأولى (من 1 إلى 4) إذا كان طفلك يحتاج مساعدة لقراءة السؤال أو فهمه. ينصح بتقديم المساعدة له، ولكن يرجى إخبار الطبيب بذلك.

أكمل انت الأسئلة الثلاث الختامية (من 5 إلى 7) بنفسك ولا تجعل إجابات طفلك تؤثر على إجاباتك.

<table>
<thead>
<tr>
<th>الأسئلة</th>
<th>الدرج</th>
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<tbody>
<tr>
<td>1. كيف هو حالك اليوم مع الربو؟</td>
<td>سيء</td>
</tr>
<tr>
<td>2. هل الربو يسبب لك مشكلة أثناء الحلم والركض وممارسة الرياضة؟</td>
<td>مشكلة كبيرة</td>
</tr>
<tr>
<td>3. هل تسبب الربو لك كحة وسعال؟</td>
<td>نعم، كل الوقت</td>
</tr>
<tr>
<td>4. هل تستيقظ من النوم ليلاً بسبب الربو؟</td>
<td>نعم، كل الوقت</td>
</tr>
</tbody>
</table>

الدرجات:

- هذه الجزء يعبّر بواسطة الأدب أو الأنا. أرجو إكمال الأسئلة الثلاث الختامية (من 5 إلى 7) بنفسك ولا تجعل إجابات طفلك تؤثر على إجاباتك.

- 5. خلال الأسابيع الماضية، كم يومًا يعاني ابنك من أعراض الربو أثناء النهار؟
  - كل يوم:
    - من 6 إلى 7
  - لا يومًا:
    - من 0 إلى 2 يوم

- 6. خلال الأسابيع الماضية، كم يومًا يعاني ابنك من أعراض الربو أثناء النهار؟
  - كل يوم:
    - من 6 إلى 7
  - لا يومًا:
    - من 0 إلى 2 يوم

- 7. خلال الأسابيع الماضية، كم ليلة يعاني ابنك من أعراض الربو أثناء النهار؟
  - كل ليلة:
    - من 6 إلى 7
  - لا ليلة:
    - من 0 إلى 2 ليلة
اختبار التحكم في الربو الشعبي والأعراض التنفسية عند الأطفال
لل العمر أقل من 5 سنوات

اختبار التحكم في الربو الشعبي عند الأطفال هو وسيلة لمساعدة الطبيب في تحديد ما إذا كانت أعراض الربو عند طفلك هي تحت السيطرة.

1. الأطفال الذين عن طريق الطبيب.

2. تأثير مرضي للإصابة بـ 2 أو أكثر من نوبات السعال أو الأزيز الصدر أو مضيق في التنفس بحيث تدوم كل نوبة لأكثر من 12 ساعة.

3. يتم وضع الطفل على علاج موضع للشعب الهوائية (مثل مانج الفنولات أو بإخراج المذاب ونحوه) أو تخفيف الطفل بأنه مصاب بالربو الشعبي.

اختبار كيفية عمل اختبار التحكم في الربو الشعبي والأعراض التنفسية عند الأطفال:

• الخطوة 1: ضع علاج أسباب الجهاز التنفسي عند الطفل، أو فحص الجهاز التنفسي على الأكياس للسما.

• الخطوة 2: ضع نتائج الجهاز التنفسي للسما في أدبيات الجهاز التنفسي من السما.

• الخطوة 3: مقدمي لجميع الأعراض لكل سما وضمنها إلقاء الأعراض التنفسية للسما. أصل الصفحة.

• الخطوة 4: يتم تعديل هذا الاختبار الطفلك من علاج أبتك عند مراجعته في العلاج.

<table>
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<th>الدرجة</th>
<th>اختبار التحكم في الربو الشعبي والأعراض التنفسية عند الأطفال</th>
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<tbody>
<tr>
<td>1. خلال (٥) الأعراض الأسباب الماشية، كم مرة كان يعني ابتك من مشكلة تنفسية مثل القحة أو ضيق التنفس.</td>
<td></td>
</tr>
<tr>
<td>2. خلال (٤) الأعراض الأسباب الماشية، كم مرة كان يعني ابتك من مشكلة تنفسية مثل القحة أو ضيق التنفس.</td>
<td></td>
</tr>
<tr>
<td>3. خلال (٣) الأعراض الأسباب الماشية، كم مرة كان يعني ابتك من مشكلة تنفسية مثل القحة أو ضيق التنفس.</td>
<td></td>
</tr>
<tr>
<td>4. خلال (٢) الأعراض الأسباب الماشية، كم مرة كان يعني ابتك من مشكلة تنفسية مثل القحة أو ضيق التنفس.</td>
<td></td>
</tr>
<tr>
<td>5. خلال (١) الأعراض الأسباب الماشية، كم مرة كان يعني ابتك من مشكلة تنفسية مثل القحة أو ضيق التنفس.</td>
<td></td>
</tr>
</tbody>
</table>

النهاية(final results):

• إذا كانت النتيجة النهائية أقل من 10، فإن الأعراض التنفسية والربو عند ابتك غير محتمل بها ويجب إتباع الأشادات العلاجية عن طريق الطبيب.

• إذا كانت النتيجة النهائية 10 أو أكثر، فإن الأعراض التنفسية والربو عند ابتك محتمل بها ويجب إتباع الأشادات العلاجية عن طريق الطبيب والالتزام بالخطوات العلاجية.