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The Saudi Initiative for 2021 Asthma

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



Fifth edition - January 2021

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**The Saudi Initiative for Asthma - 2021 update
Guidelines for the Diagnosis and Management of
Asthma in Adults and Children**



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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.

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Abstract

The Saudi Initiative for Asthma 2021 (SINA-2021) is the fifth version of asthma guidelines for the diagnosis and management of asthma for adults and children that is developed by the 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 aligned for age groups: adults, adolescents, children aged 5 -12 years, and children aged less than 5 years. SINA 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.

Section 1: Introduction

Asthma is a chronic heterogeneous disease usually characterized by chronic airflow limitation. 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, together with variable expiratory airflow limitation.(1) Asthma is one of the most common chronic diseases in Saudi Arabia with increasing prevalence in the past decades.(2) 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.(3-5) As part of its long-term commitment of to promote best practice in the field of respiratory diseases, the Saudi Thoracic Society (STS) launched the Saudi Initiative for Asthma (SINA) group in 2008. The SINA panel is a group of Saudi experts with well-respected academic backgrounds and experience in the field of asthma. Sections related to asthma in children represent the views of a panel from the Saudi Paediatric Pulmonology Association, another subsidiary of the STS. The SINA panel aims to have updated guidelines, which are simple to understand and easy to use. It also aims toward enhancing the multidisciplinary care of asthma patients with special attention to non-asthma specialists, including primary care and general practice physicians and other healthcare workers. (6-9) The updated 2021 version of SINA guidelines received a comprehensive update with an emphasis on personalized approaches reflecting a better understanding of disease heterogeneity with integration of recommendations related to new medications, approved biologic agents, evidence-based updates on treatment especially on mild asthma, and the role of immunotherapy in management. A special attention is made to managing asthma during the time of emerging acute respiratory infections such as the recent coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SINA panel stratified the guidelines based on the following age groups: adults: age

above 18 years; adolescents: age of 13 to 18 years; and children that were stratified into two groups: age of 5 to 12 years and age below 5 years.(10)

Methods

The SINA guidelines document was initially based on the Global Initiative for Asthma (GINA) strategies with reference to related major international guidelines.(10) 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.(11) 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 similar approach to previous updates has been employed, whereby each section has been internally reviewed at least twice by SINA panel members. The SINA panel conducted frequent round-table discussions and virtual 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.(3, 12, 13) 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.(14, 15) 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.(16-19) 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. (12, 20) 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.(21)

A meta-analysis on the prevalence of asthma in different regions in Saudi Arabia showed a rise in the prevalence from 1990 to 2000 with stabilization in the prevalence of asthma since 2000.(3) The pooled weighted prevalence rates of asthma was 14.3%, lifetime wheeze was 16.5%, and rhinitis was 21.4%. The prevalence of asthma varied in different regions without any disparity in prevalence in the rural and urban areas of Saudi Arabia.(3) The overall prevalence of asthma in children from Saudi Arabia have 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, sandstorms, 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.(22, 23) 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.(24) 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. 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.(25) A national Saudi household survey was conducted in 2013 estimated that the self-reported clinical diagnosis of asthma to be 4.05%.(26) 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%, and 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 vaping history.(27).

Among a group of university students in Najran, a report revealed that the overall prevalence of physician-diagnosed allergic diseases was 27% for asthma, 13.1% for atopic dermatitis, and 5% for allergic rhinitis. (28) The prevalence of physician-diagnosed asthma among school students in Jazan , Najran, Taif and Madinah were 10%, 27%, 13% and 23%, respectively.(29) A cross-sectional study was conducted in adult patients with asthma who attended primary care clinics at three major hospitals in Riyadh, 58.9% of men and 77.0% of women had uncontrolled asthma. Factors associated with uncontrolled asthma were stress, smoking, obesity and low socioeconomic status.(30) In the Epidemiological Study on the Management of Asthma in Asthmatic Middle East Adult population (ESMAA), 1,009 patients from Saudi Arabia were analysed and found that 30.1% have controlled asthma. Controlled asthma was more prevalent among male patients and those with high educational level, while age, body mass index, and adherence to treatment were found to have no effect on asthma control.(31)

Data regarding the relationship between asthma and SARS-CoV-2 is limited and most of the current knowledge derived from studies addressing the outcomes of multiple medical conditions including asthma on patients with COVID-19. The most frequent trigger factor of asthma exacerbation is airway infections particularly viral infection. But interestingly, SARS-CoV-2 infection does not increase the risk of asthma exacerbations or mortality. Several studies including several thousand patients from different countries found that the co-morbidity rates of COVID-19 with asthma were significantly low. In a review of 1,265 consecutive patients, the prevalence of asthma was found to be 12.6%. When compared with non-asthmatics, COVID-19 did not lead to significant impact on length of stay, hospital readmission, intubation, tracheostomy tube placement or mortality.(32) Older adults with underlying chronic medical conditions like hypertension, diabetes, cardiovascular diseases, obesity, COPD but not asthma are at a higher risk of severe COVID-19 and death (33-36) In spite of this, the SINA panel emphasizes

that physicians should not underestimate COVID-19 in asthma patients. Asthma medications should continue the same and physicians should follow the usual step approach management of asthma. It is worth to notice that the knowledge regarding COVID19 is rapidly growing and by the time of publishing these guidelines, maybe new data will be published in regards to the interaction between asthma and SARS-CoV-2, we highly encourage the reader to keep updated to the most recent data

Section 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 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), B-cells, mast cells, eosinophils, dendritic cells, and neutrophils; as well as structural bronchial cells such as epithelial cells, myofibroblasts, and smooth muscle cells.(37) These mechanisms can be broadly classified into four categories (endotypes). Other classifications exist, but this classification is more pertinent to severe asthma and, therefore, has special implications on biological therapy:

Type 2-high (eosinophilic) asthma: This is the most common type and includes 40-70% of asthma patients. It is defined by sputum eosinophilia of $\geq 2\%$ of leukocytes in a sample. Patients frequently have blood eosinophilia of $\geq 150/\mu\text{l}$ and FeNO ≥ 20 ppb. This eosinophils cut-off is way below the lower normal peripheral eosinophil count. This is because patients with severe asthma are already on high dose ICS or maintenance systemic OCS. Eosinophils secrete mediators such as major basic protein and eosinophil cationic protein that can cause bronchial epithelial damage and subepithelial 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

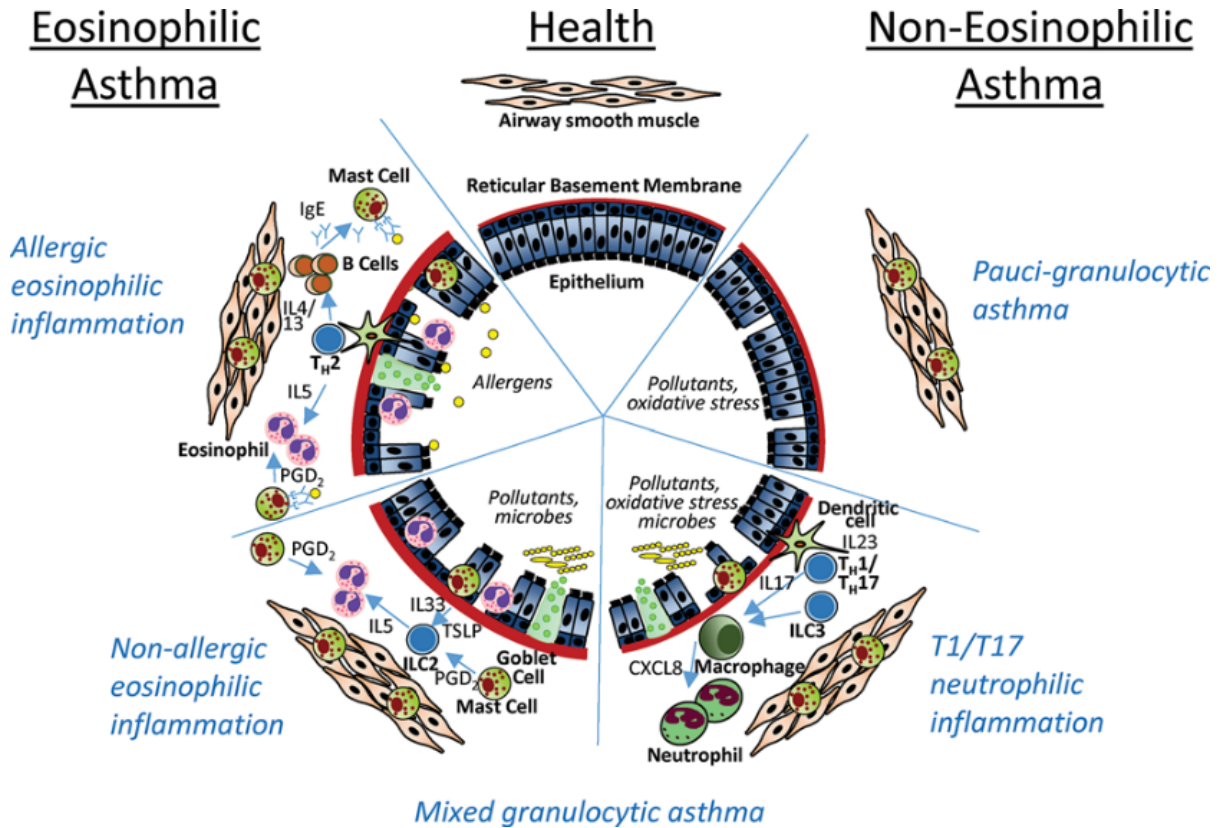
cytokines: IL-4, 5, and 13. IL-4 and 13 are necessary for specific B-cell activation and switching into IgE producing cells. IgE binds to its high affinity receptor on mast cells. Subsequent cross-linking of IgE molecules by the allergen will lead to mast cell degranulation and release of mediators such 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 maturation, and survival and contributes with certain other chemokines to their recruitment to the bronchial airways.(38, 39) Symptoms could also be triggered by similar triggers of the non-allergic type (see below).

- 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 lymphopoiectin (TSLP) that will stimulate innate lymphoid cells type 2 (ILC2) to release IL-5 and IL-13.(40)

Type 2-low (non-eosinophilic) asthma: This can further be subdivided into 2 types:

- Neutrophilic inflammation: Variably 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 attract 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.(41)
- Pauci-granulocytic: 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.(42)

Box 2.1 Immunopathology of Asthma*



Mixed type 2-high and type 2-low (granulocytic) asthma: This type has features of both eosinophilic and neutrophilic inflammation including their cytokines profile. It is less common than the two previous main types and tends to be more severe and more difficult to treat. (43)

Airway Hyperresponsiveness (AHR): This is a major feature of all asthma endotypes. 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.(44)

Airway remodelling: This is a major feature of asthma that starts early in the disease process and causes incomplete reversibility by bronchodilators. It is characterized by bronchial epithelial damage, thickening of the basement membrane, and muscle hypertrophy.(45, 46) It is influenced by the ongoing airway inflammation and recurrent bronchoconstriction.(47)

Pathophysiology of 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 exacerbations. 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.(48) 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.(49-51)

Section 3: Diagnosis of Asthma in Adults and Adolescents

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

History: The symptoms of asthma are wheezing, cough, shortness of breath, and chest tightness but they 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.(52, 53) 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).(54, 55) Asthma and rhinosinusitis commonly coexist.(56, 57)

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: The physical 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 nasal mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis, also support the diagnosis of allergic asthma.(52, 58) The presence of a localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.

(59, 60) 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 ≥ 200 ml from the pre-bronchodilator value.(61) 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.(62, 63) Serial peak expiratory flow rate (PEF) 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 favourable response.(63)

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 inhaled corticosteroids (ICS) in smokers. (64) Skin prick testing and radioallergosorbent test (RAST) may be helpful in identifying allergens to which the patient has been sensitized and in developing a strategy for avoiding allergen exposure.(65)

Section 4: Clinical Assessment in Adults and Adolescents

Principles of asthma assessment: The principles of optimal asthma management is recommended to initially consist of an assessment of asthma control.(66) Prior to commencing a patient on treatment, the SINA panel recommends ensuring the following:

- Assessment of asthma control.
- Assessment of risk factors for poor asthma control and fixed airway obstruction.
- Performance of pulmonary function testing with spirometry and/or PEF to assess for airflow limitations and postbronchodilator reversibility.
- Documentation of current treatment and any issues related to adherence, inhaler technique, or side effects.
- Utilization of a written asthma action plan.
- Assessment of comorbidities such as rhinosinusitis, gastroesophageal reflux disease (GERD), obesity, obstructive sleep apnoea, anxiety, and exercise-induced laryngeal obstruction.(67)
- Close monitoring for patients with severe asthma and history of asthma attacks.

Assessment of asthma symptoms control: In adults and adolescents, asthma control is based on assessing asthma symptoms, use of reliever medications, and impact on daily activities. Asthma control reflects the adequacy of management by describing the clinical status of a patient as controlled, partly controlled, or uncontrolled over the past four weeks. The control status may vary markedly over time and is recommended to entail frequent assessment of current asthma status, asthma burden, and medical management.(68) Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reporting and subsequently treatment decisions by clinicians.(69) Poor asthma

control is associated with increased burden of the disease, asthma attacks and mortality.(70) Therefore, symptoms control assessment should be carried out during any clinical evaluation. The SINA panel recommends the utilization of either the GINA assessment of asthma symptoms control or the asthma control test (ACT).

GINA assessment of asthma symptoms control: It is a short questionnaire utilized to assess asthma control over the past four weeks [Box 4.1].(1) It consists of four items: 1) daytime symptoms more than twice a week, 2) any night waking due to asthma, 3) reliever needed for symptoms more than twice a week, and 4) any activity limitation due to asthma.(1) Control status is classified as follows:

- Controlled: None of the items is present
- Partly controlled: 1-2 items are present
- Uncontrolled: 3-4 items present

Box 4.1: GINA Assessment of Asthma Control in Adults and Adolescents

Asthma symptom control		Level of asthma symptom control		
In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes <input type="checkbox"/> No <input type="checkbox"/>	} None of these	} 1-2 of these	} 3-4 of these
• Any night waking due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>			
• SABA reliever for symptoms more than twice/week?*	Yes <input type="checkbox"/> No <input type="checkbox"/>			
• Any activity limitation due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>			

Source Reference (71)

Asthma control test (ACT): The ACT is a commonly used tool to assess asthma control which is correlated with GINA asthma symptoms assessment.(72, 73). It is a short, validated, self-administered questionnaire to assess asthma control in the past four weeks [Box 4.2].(74) 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 four weeks.(75) The score of ACT is the sum of the five questions where each is scored from 1 (worst) to 5 (best), leading to a maximum best score of 25. The SINA panel recommends the utilization of asthma control test (ACT) to initiate asthma treatment in adults and adjust it at follow-up.(76-78). The clinically important significant change in ACT score is considered to be ≥ 3 units.(79) The level of asthma control is categorized into:

- Controlled: An ACT score of ≥ 20
- Partly controlled: An ACT score of 16-19
- Uncontrolled: An ACT score of < 16

Box 4.2: Asthma Control Test*

Asthma Control Test items					Score
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school, or at home?					
All of the time	Most of the time	Some of the time	A little of the time	None of the time	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
2. During the past 4 weeks, how often have you had shortness of breath?					
More than once a day	Once a day	3–6 times a week	Once or twice a week	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
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?					
4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as salbutamol?					
3 or more times per day	1 or 2 times per day	2 or 3 time per week	Once a week or less	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
5. How would you rate your asthma control during the past 4 weeks?					
Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
				TOTAL SCORE	
*Adapted from reference number (75)					

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.(1) The SINA panel recommends assessment of risk factors for poor asthma outcomes, especially in patients experiencing attacks by assessing risk factors for:

- Independent risk factors for acute severe asthma attacks in the past 12 months or prior history of admission to an intensive care unit; especially if intubated. (80, 81)
- Other modifiable risk factors are recommended to be addressed, such as high usage of relievers, frequent use of OCS, low forced expiratory volume in the first second (FEV1), pregnancy, inadequate ICS, smoking and vaping, comorbidities, major psychological disorders, reduced socioeconomic status, presence of comorbidities
- Risk factors for fixed airway obstruction includes inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV1, or sputum/blood eosinophilia. (82)

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.(10, 82-84) 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.(1) Since asthma severity level could change over years or months, therefore, asthma level of severity can be 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

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

- Appropriateness of prescribed medications and doses.
- Patient's adherence and correct technique in using devices.

Selection of the appropriate device and appropriate spacer with pressurized metered-dose inhaler (pMDI) device.

- Obstacles in taking prescribed medications (e.g. cost, time, patients' concerns on lack of perceived need, etc.).
- Environmental exposure to allergens at home.
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, and anxiety.
- Future risk of attacks and fixed airflow obstruction.

Section 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]. The appropriate implementation of non-pharmacological measures also aims to the use of the least possible doses of asthma medications to minimize their side effects.

Box 5.1: Long-term goals of asthma management

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

Developing a partnership with the patient: The development of a partnership between patients and healthcare professionals leads to the enhancement of knowledge, skills, and attitude towards a better understanding of asthma and its management. Based upon agreed goals of management, a written self-management action plan should be offered to all patients. A wide variety of plans are available. This is expected to reflect 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, and cost of medications.(85-88) 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. (31, 89)

Asthma education: The goal of asthma education is to provide patients with adequate training to enhance their knowledge and skills to be able to adjust treatment according to guided self-management plan.(90-93) In order to enhance the level of knowledge and skills among asthma patients, it is recommended to include knowledge about asthma and skills related to prescribed inhaler devices, as there may be misperceptions about the use of inhalers and the safety of ICS [Box 5.2].(94-97) Asthma education should 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 are expected to continue on the management plan and be reassured about the control of their asthma.(98) It is essential to get feedback from the patient in order to maintain a bidirectional rapport. Reproducible evidence has shown that a well-structured asthma education program improves the quality of life, reduces cost, and decreases the utilization of healthcare resources. (99-101) Asthma should be structured based on 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 aspergillus). Single allergen

interventions are likely to fail. However, multifaceted, tailored and intensive interventions may help in improving asthma control. There are still several gaps in the literature in this area. It may take a few months for the allergen level to become significantly lower from the implementation of the related control measures.(102) The most important indoor air pollutant is related to tobacco exposure. Measures to avoid tobacco exposure is expected to 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; however, exposure may be reduced by closing windows and doors and using air conditioning. It is recommended to avoid strenuous outdoor physical activities in cold weather, low humidity, or high air pollution. In a single-center study in Saudi Arabia, sandstorms were shown to worsen asthma symptoms but not hospital admission in children with asthma. It is advisable to avoid going out in the storm, especially for those with uncontrolled asthma.(103)
- **Occupational exposures:** Whenever an occupational sensitizer is identified, it is advisable to keep the affected person away from that environment. The earlier the removal of this sensitizer takes place, the higher the chance of complete recovery from occupational asthma (see Asthma in Special Situation).
- **Food and drugs:** Food and food additives are uncommon triggers of asthma. Avoidance is not generally recommended until it is documented by a specialist. However, certain drugs that could worsen asthma symptoms should be avoided (e.g. beta blockers), whenever possible.
- **Vaccination:** Annual influenza vaccination is strongly recommended for individuals with asthma, especially those with severe asthma.(104-106) It usually becomes available early on the fall season. Pneumococcal vaccination is also recommended as per the local guidelines.(107)

Section 6: Pharmacological Management in Adults and Adolescent

The SINA 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 PEF or spirometry, review of current medications and patients' adherence and inhaler technique, a risk for attacks, and the response to treatment. Based on the clinical and physiological assessment, the patient is placed on the appropriate treatment step. The medication appendix contains more information about medications used in asthma treatment. The SINA panel recommends the following strategies for asthma treatment:

- A controller medication is recommended for all steps. ICS is considered the most effective controller and the cornerstone of asthma treatment (Evidence A).(108, 109) Uncontrolled patients may require the addition of other controllers.
- Relievers medications must be available to patients at all steps. Increasing the use of reliever treatment should be considered as an early sign of worsening of asthma control (Evidence A).(110).

The available relievers are:

- A short-acting bronchodilators (SABA), such as salbutamol, is recommended to be taken as needed to relieve symptoms. Using SABA alone was found to increase the risk of asthma attacks and asthma-related death, therefore, asthma patients are not recommended to use it without being on a controller treatment; alternatively, ICS is recommended to be used whenever SABA is needed in step 1.(111, 112)

- 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 A).(113-115) For step 3-5, it is only recommended when the combination of Formoterol/ICS is prescribed as maintenance therapy. The maximum recommended dose of formoterol component is 72 mcg. Exceeding this level for 2-3 days may be a warning sign of deterioration of asthma control.(116-118)
- Regular assessment of adequate doses of treatment, proper technique, and adherence.
- Regular assessment for independent risk factors for acute asthma attacks in the past 12 months or prior history of admission to an intensive care unit; especially if intubated. (80, 119) Other modifiable risk factors are recommended to be addressed, such as low initial FEV1, pregnancy, inadequate ICS, smoking and vaping, comorbidities, and major psychological conditions.
- Regular assessment of risk factors for fixed airway obstruction that includes inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV1, or sputum/ blood eosinophilia. (120)
- Management of comorbidities with special attention to concomitant rhinosinusitis. As this condition affects asthma control, its treatment is expected to improve asthma outcome (Evidence A).(121-123) Treatment includes nasal saline washes, nasal steroids, leukotriene receptor antagonists (LTRA), and antihistamines. Concomitant 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 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].(78) The following initial steps are recommended for treatment-naïve patients based on ACT score [Box 6.1]:

ACT Score ≥ 20 (Controlled status):

- An anti-inflammatory reliever therapy in the form of ICS/formoterol combination on as needed basis (Evidence A).(116, 124)
- An alternative option is to use SABA together with low dose ICS both on as needed basis (Evidence B).(111, 112, 125)
- Maintenance daily low-dose ICS is recommended in special situations:
 - For patient with symptoms more than twice a week and risk factors for acute attack (severe attacks in the past 12 months or prior history of admission to an intensive care unit; especially if intubated) or evidence of fixed airway obstruction (Evidence B).(120, 123, 126) Early introduction of ICS leads to greater improvement of FEV1 and lower the future doses of ICS. (126)

ACT score 16-19 (Partially controlled status):

- Low-dose ICS for patients with an ACT score of 16-19. (Evidence A).(127) Alternative options may be considered as described in the adjustment section below, which includes starting formoterol/ICS combination on as needed basis or LTRA.

ACT score <16 (Uncontrolled status):

- A combination of regular low dose ICS and LABA as maintenance treatment for patients with an ACT score of <16. (Evidence B).(127)
- For patients who have poorly uncontrolled asthma at presentation, initiation of asthma treatment with a combination of medium dose ICS and LABA as a maintenance treatment such as those with aforementioned risk factors (Evidence D).
- For patients with early signs of attack at presentation, it is recommended to prescribe medium dose ICS and LABA and consider a short course of oral steroids.(128)

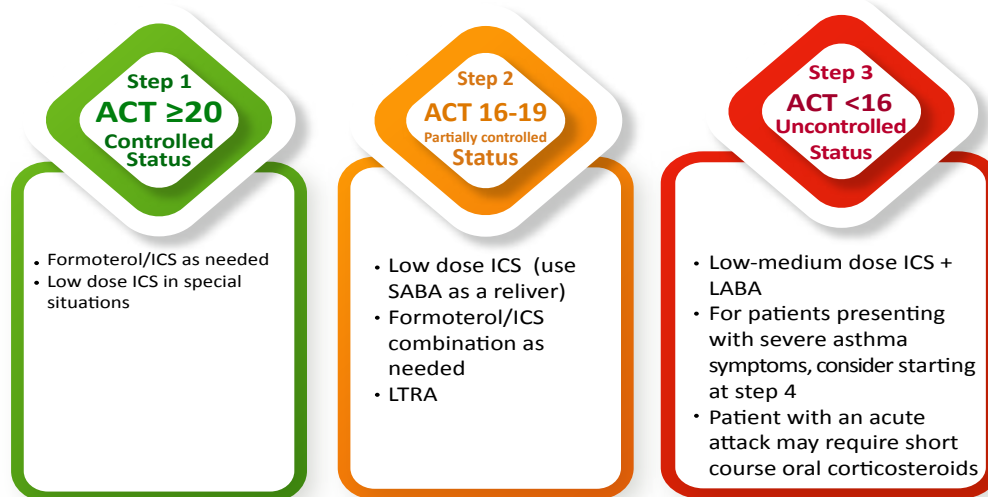
Box 6.1: Initiation of asthma treatment for adults and adolescents

The SINA* Approach for Asthma Treatment Initiation

*Saudi Initiative for Asthma

- Obtain history and perform physical examination
- Assess symptoms and obtain PEF measurement (spirometry if needed)
- Assess aggravating factors and treat commodities
- Ensure optimizing patient education and proper assessment of aggravating factors

Initiate asthma treatment at appropriate step based on asthma system



ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists; SABA: Short acting beta-agonists

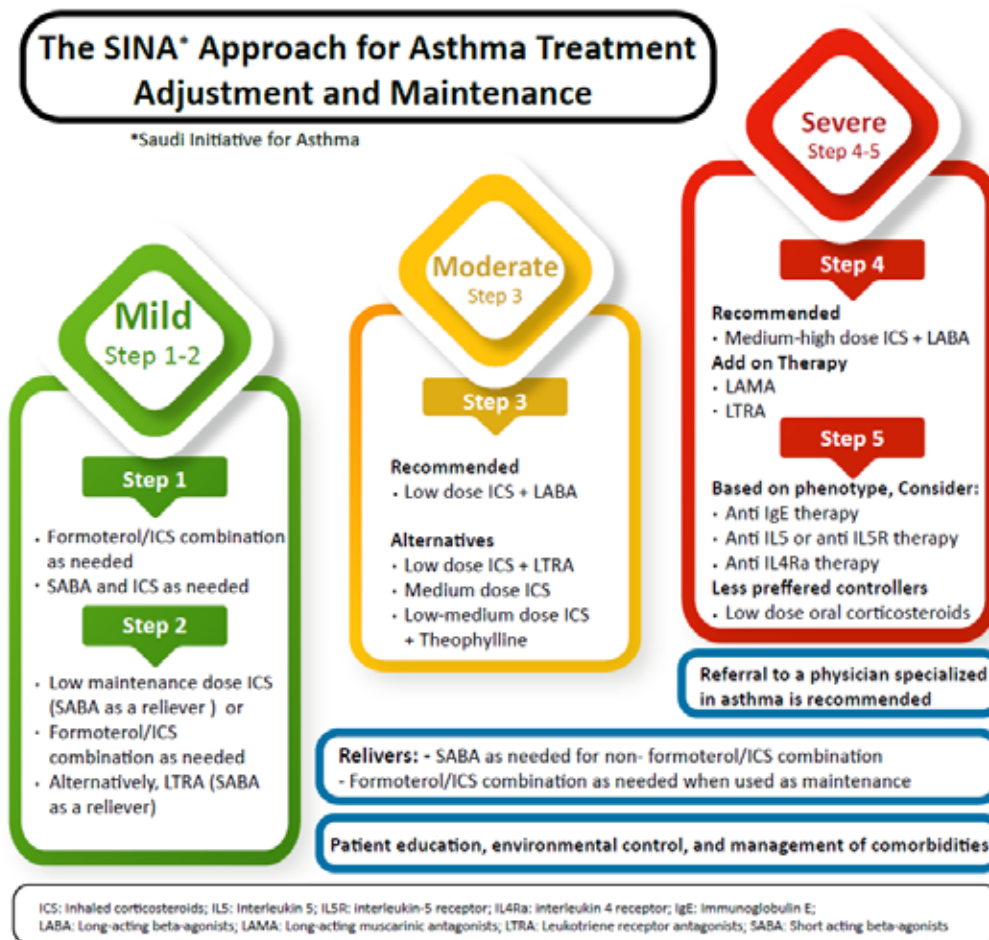
Adjustment of treatment

After initiation of asthma treatment, it is recommended to assess the patient at 1-3 month intervals (Evidence D).(129) The SINA panel recommends the utilization of stepwise approach of therapy to achieve asthma control. The stepwise approach consists of 5 steps as shown in Box 6.2. 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).(130) In clinical practice, asthma severity can be retrospectively assessed based on the step of treatment required to control symptoms:(10, 82-84)

- **Mild asthma:** controlled asthma at step 1 or 2
- **Moderate asthma:** controlled asthma at step 3
- **Severe asthma:** requires asthma management at step 4 or 5

Relievers 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).(110, 131) Approximately one in five patients with mild asthma may develop at least one attack of severe asthma in 12 months.(116, 132, 133) The available relievers are detailed above. The following paragraphs will describe asthma treatment at each step.

Box 6.2: Outpatient asthma treatment for adults and adolescents



Treatment at Step 1

- **Recommended option:** Anti-inflammatory reliever therapy in the form of ICS/formoterol on as needed basis (Evidence A).(116, 118, 124) Symptoms are usually mild and infrequent (usually < twice a month) with an ACT score of ≥ 20 and no risk factors for asthma attacks.
- **Alternative option:** Use SABA together with low dose ICS both on as needed basis (Evidence B).(111, 112, 125)
- 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 (Evidence D).

Treatment at Step 2

- **Recommended options:**
 - A daily low maintenance dose ICS with as needed SABA (Evidence A).(108, 134)
 - Combination of ICS/formoterol on “as needed basis” (Evidence A).(114, 115) 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. The combination of budesonide/formoterol on “as needed basis” achieved such outcome with substantially lower ICS dose equivalent to 17-25% of the maintenance dose of ICS.
- **Alternative options:**
 - LTRA (Montelukast) especially for those patients who are reluctant to use ICS or continue to have side effects despite preventive measures (Evidence A).(135) LTRA is less effective than low dose ICS in achieving asthma control and in reducing the risk of attacks.

- Maintenance of low dose ICS could be recommended for patients who are controlled at the time of assessment (an ACT score of ≥ 20) but have risk factors for asthma attacks or fixed airway obstruction (Evidence B).(108, 130, 136, 137).

Treatment at Step 3

Combined low dose ICS with LABA was found to improve asthma control for patient whose asthma is not controlled at step 2 and reduce asthma attacks (Evidence A).(138, 139) The patient is recommended to continue on reliever treatment on “as needed basis” (Evidence A). ICS with LABA are available (refer to the medication appendix) as follow:

- ICS combined with formoterol can be used as maintenance and reliever without adding SABA.
- ICS in the form of beclomethasone propionate, budesonide, or fluticasone propionate are available in combination with salmeterol. These are normally prescribed twice daily with SABA as a reliever.
- Once a day combination of ICS and LABA (fluticasone furoate with vilanterol) is also available. SABA should be utilized as a reliever.

Inhaled LABA alone is not available in the Saudi market since it should never be used alone in asthma management.(140) Asthma patients taking inhaled LABA without inhaled ICS are at an increased risk of asthma attacks, hospitalizations, and death.(141)

- **Recommended options:**
 - If a formoterol/ICS combination is prescribed, it is recommended to be used as maintenance with 1–2 inhalations twice daily. Extra doses up to 12 inhalations per day can be used as the reliever therapy from the same device (Evidence A).(111-113, 125). 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).(142)

- If salmeterol/ICS combination is selected, an escalation of the regular daily doses to maximum dosing achieves asthma control in a majority of patients on uncontrolled at steps 2 and 3 (Evidence A).(143) Salmeterol has a slow onset of action; therefore, it should only be used as a maintenance treatment with SABA as a reliever.
- The once a day combination of ICS/LABA in the form of fluticasone furoate/vilanterol (Relvar) can be prescribed at a daily inhalation dose of 100/25 microgram for adults and children above 12 years (Evidence A).(144, 145) As vilanterol has an onset of action within 15 minutes and a long half-life; it can only be used as a maintenance treatment while continue using SABA as a reliever.
- **Alternative options:**
 - The continuation of ICS as a monotherapy by increasing the dose to the medium level is generally less effective strategy (Evidence A).(146, 147)
 - The addition of LTRA to a low-medium dose ICS is another option especially in patients with concomitant rhinitis (Evidence A).(148-150)
 - Tiotropium is a long-acting anticholinergic (antimuscarinic) agent (LAMA) approved for the treatment of chronic obstructive pulmonary disease (COPD).(151-153) 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).(154-156) This evidence supports that tiotropium can be combined with ICS whenever LABA cannot be used.(157)

- Consultation with an asthma specialist is recommended whenever there is a difficulty in achieving control at step 3 (Evidence D).

Treatment at Step 4

Consultation with an asthma specialist is recommended for patients who require this step of therapy (Evidence D).(158)

- **Recommended option:**

- Escalation to a combination of medium-dose ICS with LABA is recommended (Evidence A).(98, 147, 149, 159)
- The combination of fluticasone furoate/vilanterol (Relvar) can be prescribed for adults and children above 12 years at a single inhalation daily dose of 200/25 microgram dose. (144, 145)

- **Additional options:**

If control is not achieved with the recommended options, the following can be considered:

- Once a day combination of fluticasone furoate (100 mcg), umeclidinium (62.5 mcg), and vilanterol (25 mcg) (Trelegy Ellipta®) is an option for adults. Adding umeclidinium to the combination of ICS/LABA was found to be effective treatment option with a favorable risk-benefit profile as it led to improved symptoms and FEV₁ but did not result in significant reduction in moderate and/or severe exacerbations.(160) Higher dose of fluticasone furoate (200 mcg) primarily reduced the rate of exacerbations, particularly in patients with raised biomarkers of type 2 airway inflammation.

- Adding tiotropium to the combination of medium-dose ICS and LABA is another option as it significantly improves lung function in uncontrolled cases and modestly reduces asthma attacks (Evidence A).(161-163)
- Adding LTRA to the combination of medium-dose ICS and LABA can be considered but the evidence is less robust (Evidence B).(164-166)
- Adding theophylline to the combination of medium-dose ICS and LABA is another less favorable alternative (Evidence B).(164, 167)
- **Other considerations:**
 - High dose ICS/LABA may be considered in some patients who are uncontrolled on medium dose ICS/LABA.(168, 169) However, it is recommended to step down whenever possible to avoid potential side effects.(146, 170) An additional controller is recommended to be introduced prior to considering the high dose ICS.
 - If a patient is still uncontrolled at step 4, biologic therapy is recommended to be considered as described in step 5.

Treatment at Step 5

Early consideration of biological therapy may save the patient from frequent or chronic use of oral corticosteroids and reduce asthma attacks. This therapy is recommended to be considered based on appropriate indications and availability. When choosing a biological agent, 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. Consultation with an asthma specialist is strongly recommended for patients requiring treatment at step 5 (Evidence D). The following biological agents are available for step 5:

- Anti IgE therapy (Omalizumab) is recommended for those patients uncontrolled on maximum treatment at step 4, who have allergic asthma as determined by a positive skin test or RAST study and IgE level within the appropriate therapeutic range (for more information refer to the medication appendix, medications section) (Evidence A). A history of documented atopy might be used as a marker of allergic asthma if RAST test and skin test are unavailable (Evidence D).(147, 149, 159) During the course of therapy, anti-IgE led to more reduction of asthma attacks in a category of asthma patients who showed >50% reduction in blood eosinophils.(171, 172) The dose is determined by the IgE level and weight. If this treatment does not control asthma after 16 weeks of therapy, it should be stopped. (173-175)
- Anti-interleukin 5 (Anti-IL-5) therapy can be considered for uncontrolled eosinophilic asthma or ≥ 2 attacks in the past 12 months requiring systemic corticosteroids at step 4 (for more information refer to the medication appendix).(176) There are no data to determine the duration before deciding on treatment ineffectiveness. However, until this evidence is available, the treatment may be continued for up to 6 months prior to the decision of stopping/switching treatment (Evidence D). (177) The available options are:
 - Mepolizumab, an anti-IL-5 therapy, that is indicated when blood eosinophils count is ≥ 150 cells/ μ L at treatment initiation or ≥ 300 cells/ μ L at any time in the prior 12 months. The recommended dose is 100 mg subcutaneously every 4 weeks.

- Benralizumab, an anti-IL-5 receptor therapy, that is indicated when blood eosinophils count at initiation of treatment is ≥ 300 cells/ μ l or ≥ 150 cells/ μ l for patients with prolonged OCS. (178) The recommended dose is 30 mg subcutaneously every 4 weeks for the first three months then every 8 weeks thereafter.
- Dupilumab is an anti-interleukin 4 receptor α (Anti-IL4R α) antibody indicated in severe eosinophilic asthma with blood eosinophils ≥ 150 / μ l or FeNo > 25 . (179) It is also indicated for oral steroids dependent severe asthma regardless of blood eosinophils count, although patients with eosinophil count > 300 / μ l had significantly more benefit. It is approved for patients ≥ 12 years of age. For eosinophilic asthma phenotype, the dose is 400 mg SC once, then 200 mg every two weeks. (180) For the oral steroid dependent asthma or those with comorbid conditions responsive to dupilumab such as moderate to severe atopic dermatitis or chronic rhinosinusitis with nasal polyposis, the dose is 600 mg once then 300 mg every two weeks (Please refer to more information in the medications index). It is recommended not to start Dupilumab in patients with blood eosinophil count > 1500 / μ l.
- To date, there is no available evidence to favor either anti-IgE therapy versus anti-IL-5 agents or anti-IL4R α for patients with evidence of both atopy and high blood eosinophils counts

If the patient does not have any of the biological therapy phenotypes, 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). (181) Other alternatives are mentioned in the severe asthma section, such as thermoplasty and long-term macrolides.

For patients who require long-term systemic corticosteroids, the following are recommended to be considered:

- Use the lowest possible dose to maintain control.
- Closely monitor the development of corticosteroid-related side effects.
- When asthma control is achieved, attempts to reduce the dose of systemic corticosteroids, preferably to every other day frequency, is recommended. Maintaining high-dose of ICS therapy may help to reduce the dose of systemic corticosteroid.
- Upward adjustment of the corticosteroid dose at the time of stress (e.g. infection, asthma attacks, surgery, etc.) is essential.
- 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 is strongly recommended (Evidence C).

Maintaining asthma control

Regular follow-up by a healthcare worker is essential. Depending on the level of asthma control, it is recommended have a follow-up at 1–3 month intervals after treatment initiation (Evidence D).(98, 182) Follow-up is recommended to 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 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 gradually every 3–6 months to the lowest dose possible that is required to maintain control (Evidence B),(91, 183, 184) and then changed to a single daily dose (Evidence A).(185) It is recommended to be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued.(186)
- 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. Therefore, initial gradual reduction of ICS to the lowest possible ICS dose before discontinuation of LABA is recommended.(187)
- 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).(188, 189) If control is achieved, LTRA may be discontinued first (Evidence D).(188)
- 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.(190)

- Patients should be informed that asthma control may deteriorate if treatment is completely discontinued. (186)

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.(191, 192) 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) (193)

- Improve airway hyperresponsiveness (Evidence B).(194)
- Decrease the progression of allergic rhinitis to asthma (Evidence B). (195)
- Decrease the chance of development of new sensitizations (Evidence B). (191)

AIT is likely to be cost effective when appropriately used.(192) 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.(193) 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.(191) Data are limited in paediatrics, but AIT has been used safely in children over 5 years of age and was shown to reduce long-term asthma medication use and improve FEV₁.(196) 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. Anti-IgE therapy could improve tolerability to AIT in patients with moderate to severe asthma.(197) If the patient is considered a candidate for AIT, referral to an allergist is recommended to explore this option further.

Severe Asthma

There are several terms used in practice for uncontrolled asthma where each point to an aspect of the disease such as chronic severe asthma, steroid-dependent asthma, and refractory asthma are some of these terminologies.(198, 199) However; it is important to distinguish between severe asthma and uncontrolled asthma. Severe asthma is defined as the “Uncontrolled asthma at SINA step 4 despite adequate adherence and after addressing all comorbidities”.(84) Severe asthma probably accounts for 5–10% of adult asthma, but the health cost is disproportionately high.(200) Morbidity and mortality are also higher compared to regular asthma patients because of increased side effects of treatment and more frequent attacks and/or hospitalizations.(201, 202) 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.(203) Patients whose poor asthma control is related to other factors, such as poor adherence, inhaler use technique, or due to the presence of other diseases, are to be termed ‘difficult-to-treat asthma’.(1) There are common comorbidities that need to be assessed in severe asthma such as allergic rhinoconjunctivitis, rhinosinusitis/nasal polyps (in 50%), COPD, vocal cord dysfunction (in 32-50%), anxiety/depression (in 4-17%), obstructive sleep apnoea (in 31%), GERD (in 17-74%), bronchiectasis (in 25-40%), and allergic bronchopulmonary aspergillosis (in 1-2%).(204) The following are recommended for assessment of patients with severe asthma: (205-210)

- Patient is adherent to all medications with a good inhalation technique.
- Other possible misdiagnosis where the problem is not bronchial asthma to start with but other diseases that mimic asthma symptoms, e.g. bronchiectasis, endobronchial tumors, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).(208, 211)

- Comorbidities that can worsen bronchial asthma and makes it difficult to manage (e.g. chronic rhinosinusitis, GERD, sleep apnea syndrome, ABPA, obesity, and CHF).(212)
- Medications overuse or side effects.
- Any psychosocial contributing factors.
- Other confounding factors e.g. presence of allergens at home or work, active or passive smoking and vaping, or psychosocial problems. (208)

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.(213) 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, or LAMA and addition of one of the available biological therapies as appropriate. (177, 214, 215)

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.(216) Such control may be lost when oral steroid is discontinued. Patients may differ in the degree of their responsiveness to oral steroids.(217)Some patients may fail to improve their FEV₁ by more than 15% following treatment with oral prednisolone for two weeks, a condition called “corticosteroids-resistant asthma. (218, 219) If oral steroids are necessary, then it is recommended to use the lowest possible dose and to shorten the duration as much as possible.(220) 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 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.(221) 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.(222) 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.(223-225) 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.(84) Contraindications to BT include moderate and severe bronchiectasis, very high sputum production, and fixed airflow obstruction with FEV₁ levels below 50% as predicted.

Section 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, evaluate, and initiate therapy. The most specific marker associated with increased asthma mortality is a history of repeated hospital admissions, particularly if the patient required intensive care treatment or ventilatory assistance.(226, 227) Patients admitted with severe asthma attack in Saudi Arabia were found to be younger and predominantly males and used less ICS/LABA combination.(2, 228)

This section includes assessment of the patients presented with acute asthma, initial management and follow-up after hospital discharge. Detailed information about medications used in acute asthma can be found in the medication appendix. Box 7.1 shows the summary of the key recommendations of acute asthma management.

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 [Box 7.2]. Although most acute asthma attacks develop over a period of days, patients with brittle asthma may present with a much more dramatic deterioration.(229, 230) It is important to realize that most patients who die from an acute asthma attack had chronically uncontrolled asthma, had received suboptimal treatment with ICS, and had inadequate monitoring of their asthma. (231) Management of acute asthma is the extreme spectrum of uncontrolled asthma and represents the failure to reach adequate asthma control. Poor prognostic features of acute asthma include previous history of near-fatal asthma or hospital admission in the last year, heavy usage of SABA, patients who are not on regular ICS, a history of psychiatric or psychosocial illness, and poor adherence to asthma medications and lack of asthma action plan.(232, 233)

Box 7.1 Key recommendations of acute asthma management

- Assess the severity of the attack based on the degree of dyspnea, pulse rate, respiratory rate, peak-expiratory flow rate, and oxygen saturation
- Start treatment immediately by repeated administration of salbutamol, controlled oxygen concentration and systemic steroid
- Review response to treatment after 1 hour of continuous therapy
- Consider other therapy (ipratropium bromide and magnesium sulfate) in severe attacks
- DO NOT request routine CXR or blood gases routinely unless indicated
- DO NOT prescribe routine antibiotics or sedatives
- Evaluate the need of hospital admission based on response to therapy, history of previous admission, and the ability to manage at home

On presentation, the patient should be carefully assessed to determine the severity of the attacks [Box 7.3] and the type of treatment required [Box 7.4].(234, 235) PEF and pulse oximetry measurements are complementary to history taking and physical examination. The likely cause for death in acute asthma is probably related to asphyxia due to severe airflow obstruction and hypoxemia. 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.(236)

SINA Panel recommends the following steps for the management of acute asthma:

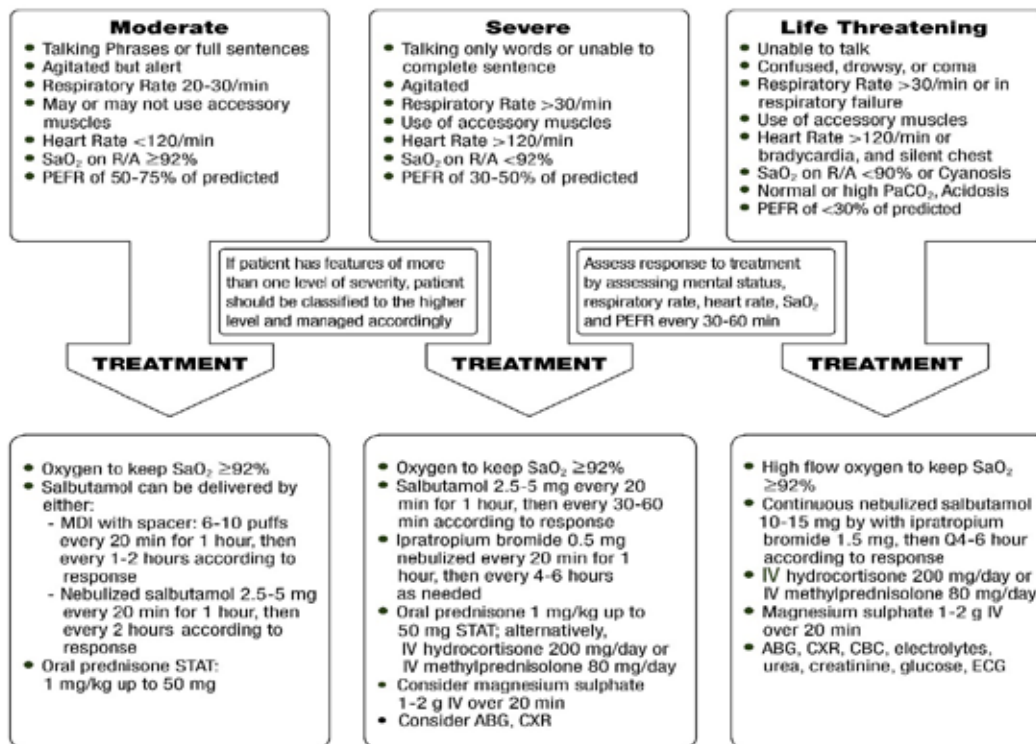
- Assess severity of the attack.
- Initiate treatment to rapidly control the attack.
- Evaluate continuously the response to treatment.

Box 7.2: Levels of severity of acute asthma in adults	
Level	Characteristics
Moderate asthma attacks	<ul style="list-style-type: none"> • Increasing symptoms • PEF >50 – 75% best or predicted reading • No features of acute severe asthma
Acute severe asthma	<ul style="list-style-type: none"> • Any one of the following: <ul style="list-style-type: none"> ○ PEF 30 – 50% best or predicted reading ○ Respiratory rate \geq25/min ○ Heart rate \geq120/min • Inability to complete sentences in one breath
Life-threatening asthma	<ul style="list-style-type: none"> • Any one of the following in a patient with severe asthma: <ul style="list-style-type: none"> ○ SpO₂<92% (PaO₂<60 mmHg) on high-flow FIO₂ ○ PEF <30% best or predicted ○ Bradycardia ○ Dysrhythmia ○ Cyanosis ○ Hypotension ○ Normal or high PaCO₂ ○ Exhaustion ○ Confusion ○ Silent chest ○ Coma • Weak respiratory effort
Near-fatal asthma	<ul style="list-style-type: none"> • Raised PaCO₂ and/or requiring mechanical ventilation
Brittle asthma	<ul style="list-style-type: none"> • Type 1: Wide PEF variability (>40% diurnal variation for >50% of the time over a period of >3–6 months) despite intense therapy • Type 2: Sudden severe attacks on a background of apparently well-controlled asthma

PEF=Peak expiratory flow

Box 7.3: Initial management of acute asthma for adults and adolescents

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



The levels of acute asthma severity and the initial management are summarized in Box 7.3 and 7.4 respectively. It is recommended to adjust treatment intensity based on the severity of the attack and the following are the general guidelines for the treatment of acute asthma.

1. **Oxygen:** Controlled concentration of oxygen is recommended to maintain saturation between 92-95%. There is evidence that high concentration of oxygen may be harmful.(237, 238)
2. **SABA:** Salbutamol is the bronchodilator of choice in acute asthma.(239, 240) It could be delivered by either:
 - pMDI with spacer: 4–10 puffs every 20 min for 1 h, then adjusting the dose based on the patient's response (Evidence A), or
 - Nebulizer: salbutamol 2.5–5 mg every 20 min for 1 h, then adjusting the dose based on the patient's response (driven by oxygen if patient is hypoxic) (Evidence A)

Because the nebulizers increase the risk of disseminating viruses to other patients and to health care professionals, in the time of viral pandemic (such as COVID-19), the pressurized metered dose inhaler via a spacer is the preferred treatment during severe attacks. The routine use of intravenous β_2 agonist is not supported by the current evidence but may be used in life threatening asthma when inhaled therapy could not be tolerated by the patient.

3. **Steroid therapy:** If the patient can tolerate orally, oral prednisolone 1 mg/kg/day (to the maximum of 50 mg daily) should be started as soon as possible. Alternatively, IV hydrocortisone 200-400 mg or methylprednisolone 80 mg in divided doses should be administered.(241) Adding high dose ICS to systemic corticosteroid in acute asthma is controversial; however, keeping it may ensure continuation of therapy after discharge.(242)

4. **Ipratropium bromide** is recommended to be added to salbutamol in moderate-severe acute asthma. The initial dose is 4-8 puffs every 20 minutes by pMDI with a spacer or 0.5 mg every 20 minutes or by a nebulizer for three doses (Evidence B).(243) This therapy has been shown to improve treatment effectiveness by reducing the rate of hospital admission and improving lung function when it is added to SABA in severe acute asthma.(243)
5. **Magnesium sulfate** is not recommended routinely in acute asthma. However, in severe cases with inadequate response to the initial therapy, a single dose of IV magnesium sulphate of 1-2 g over 20 minutes is recommended to be considered as it has been shown to reduce hospital admission, especially in those patients who present with a very low lung function ($FEV_1 < 30\%$ of the predicted). (Evidence A).(244)
6. **Intravenous aminophylline** use in acute asthma is associated with severe, and potentially fatal, side effects; hence, its use in acute asthma is prohibited.(242)
7. **Antibiotics and sedatives:** Unless there is a strong evidence of pneumonia, the routine use of antibiotics in acute asthma is not recommended. Similarly, the use of anxiolytic and hypnotic drugs should be strictly avoided in acute asthma, as their usage have been associated with respiratory failure and death.(242)

Management of life threatening/near fatal asthma:

Patients in this category can progress rapidly to respiratory failure and death. Hence, an aggressive management approach and continuous monitoring are mandatory. Aside from the routine initial therapy, the following steps are recommended in the management of life threatening or near fatal asthma:

- Consult ICU service and ensure that the intubation setting is readily available.
- Administer adequate oxygen concentration to keep saturation $\geq 92\%$.(233)
- Deliver continuous nebulized salbutamol (10-15 mg) with ipratropium bromide dose of 1.5 mg over one hour (Evidence A).(242, 245, 246) 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).(242, 245, 246) Oxygen-driven nebulizers is recommended to be used to avoid the risk of oxygen desaturation while using air-driven compressors (Evidence A).(242, 245, 246) Strict infection-control measure should be taken to prevent the dissemination of viral infection to the health care professionals or other patients during the nebulization sessions especially of time of viral infections pandemics (such as COVID-19). Once the patient showed adequate response to continuous nebulization, shift to intermittent delivery is recommended.(247)
- Systemic steroid is recommended to be initiated as soon as possible
- Consider a single dose of intravenous magnesium sulfate
- Other adjunct therapy (e.g. intramuscular epinephrine, intravenous β_2 agonist and helium oxygen therapy) may be considered in selected cases, but the evidence supporting their use is less robust.
- Non-invasive ventilation: The data of the use of non-invasive ventilation is less robust in acute asthma compared to COPD attack.(245, 246) If used, the patient should be monitored closely for signs of fatigue or respiratory failure. NIV should be avoided in agitated patients and in those who are in impending respiratory failure.
- Extracorporeal membrane oxygenation: Extracorporeal membrane oxygenation (ECMO) may be considered in cases of acute respiratory failure secondary to near fatal or life-threatening asthma. Few case

series suggested that early introduction of ECMO in those patients may lead to dramatic improvement in gas exchange and lung mechanics and avoid the serious complications of mechanical ventilation.(248)

- Frequent clinical evaluation and serial CXR, electrolytes, glucose, 12-lead ECG and ABGs are recommended in this patients' population.

Follow-up after initial treatment and discharge planning.:

Close evaluation of the treatment response is essential. This includes patient's mental and physical status, respiratory rate, heart rate, blood pressure, oxygen saturation, and PEF. Response to treatment is defined as adequate, partial, or poor. Assessment of the treatment response, subsequent action, and discharge planning are illustrated in Box 7.4.

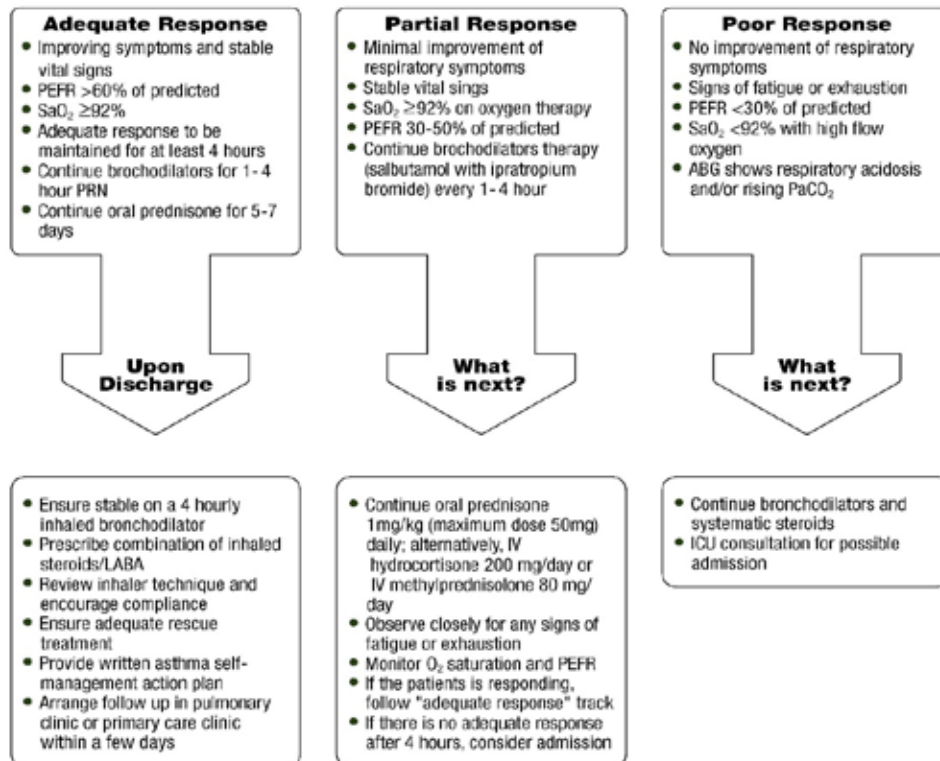
Criteria for ICU referral

ICU referral is recommended for patients who are:

- presenting, or progressing to, severe acute or life-threatening asthma
- failing to respond to initial therapy, as defined by:
 - requiring ventilatory support
 - deteriorating lung function (FEV1/PEF)
 - persisting or worsening hypoxia
 - hypercapnia (either initially or subsequently)
 - ABG analysis showing respiratory acidosis
 - exhaustion, shallow respiration or drowsiness

Box 7.4: Adjustment of acute asthma treatment for adults and adolescent

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



Section 8: Asthma in Special Situations

Gastro-oesophageal reflux disease (GERD): GERD is more prevalent in patients with asthma, compared to the general population.(249, 250) 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.(251) All patients with asthma should be questioned about symptoms of GERD. If present, a trial of anti-GERD measures, including a proton pump inhibitor and lifestyle modifications, is recommended for 6–8 weeks. However, if symptoms are not resolved, further investigation is warranted. Benefit of proton pump inhibitors is limited to patients with symptomatic GERD and night-time respiratory symptoms. On the contrary, patients with uncontrolled asthma and asymptomatic GERD are not likely to benefit from empiric GERD therap.(252)

Rhinitis/sinusitis and nasal polyp: Most asthma patients have coexisting rhinitis and/or sinusitis and around 40% of patients with rhinitis do have asthma.(253) Asking patients about rhinitis symptoms and examination of the 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.(199, 254, 255)

Obesity and asthma: Asthma is more common in obese than non-obese patients.(256) Obese asthma patients have more symptoms, more frequent and severe exacerbations, reduced response to asthma medications, and poor quality of life. This could be in part related to reduced lung volumes, lack of fitness, and associated sleep apnea and GERD. However, recent work has shown the obesity is associated with peripheral airways dysfunction, increased small airways resistance, and increased low frequency reactance area leading to increase lung stiffness.(257)

Treatment of obese asthma patients follows the same step approach for non-obese asthmatic; however, weight reduction, exercise and diet control are essential part of their management.(258) For morbidly obese patient with asthma, it is recommended to discuss the risks and benefits of bariatric surgery when other measures are failed.(259, 260)

Cough-variant asthma: Patients with cough-variant asthma may have chronic cough as their main symptom especially at night.(261, 262) 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.(263, 264) This condition may be confused with eosinophilic bronchitis which is characterized by cough and sputum eosinophilia with normal spirometry and airway hyper responsiveness.(265, 266)

Exercise-induced bronchoconstriction (EIB): 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.(267, 268) 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 or ICS/formoterol a few minutes before exercise.(269, 270) 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.(150, 269) Regular use of LTRA may also help in this condition, especially in children.(150, 267, 269)

Aspirin-exacerbated respiratory disease (AERD): is a special phenotype characterized by a triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to aspirin. (271) About 7% of adult asthma patients and 15% in those with severe asthma suffer from attacks in response to ASA or NSAIDs that inhibit cyclooxygenase-1 (COX-1). (272) Majority of patients experience first symptoms during their third or 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. (273) 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. (274) 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. (275) Prophylactic low-dose aspirin should also be avoided. However, referral to an allergy specialist for ASA desensitization is recommended in patients for whom aspirin is required as anti-platelet therapy, patients with difficult to manage polyposis, or patients with severe asthma. (276) Montelukast may help in the treatment of this type of asthma in some patients. (277)

Pregnancy: A study conducted in a tertiary care hospital in Saudi Arabia showed that almost half of the pregnant women had the desire to stop asthma medications during pregnancy as they believed that asthma medications would harm them and their babies more than asthma itself. (21) As such, a great effort should be directed towards the education of asthma in pregnancy in order to correct this misbe-

lief. The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics may have a worsening of their asthma control.(278, 279) Maintaining adequate control of asthma during pregnancy is essential for the health and wellbeing of both the mother and her baby, and the occurrence of poor asthma control 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 and 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) All asthma medications, including ICS, theophylline, antihistamines, β_2 -agonists, and LTRA are generally safe and have not shown to increase the risk of fetal abnormalities.(282, 283) However, prolonged use of systemic steroids may be associated with pregnancy-related complications, especially in the first trimester.(279)

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). (284-286) Fetal monitoring is recommended in severe asthma attack. If anesthesia is required during labor, regional anesthesia is recommended whenever possible (Evidence C).(287) The use of prostaglandin F₂ α may be associated with severe bronchospasm and should be avoided if possible.(288) If asthma is well controlled during pregnancy, acute asthma is rare during labor. Pregnant asthma patients should be encouraged to breastfeed after delivery and to continue their usual asthma medications during lactation.(289, 290)

Occupational asthma: All patients with asthma should be asked about their occupational history and exposures for possible related occupation-related allergens. A simple screening test is to ask the patient if their symptoms improve when they are away from work.(291) Once identified, early detection and elimination of occupational sensitizers and removal of patients from further exposure are an essential aspect of the management. Referral to an asthma for assessment and advice is recommended for patients with suspected or confirmed occupational asthma because of the legal implications of the diagnosis.(292, 293)

Asthma-COPD Overlap (ACO): Distinguishing asthma from COPD may be difficult in patients who show features of both diseases, hence the name Asthma-COPD Overlap.(294) ACO is a unique complex descriptive 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.(288) ACO has been estimated to account for approximately 15-25% of the obstructive airway diseases in adults and may carry worse outcomes compared with asthma or COPD alone.(288) Patients with ACO have the combined risk factors of smoking and atopy. They are generally younger, have more frequent exacerbation, worse quality of life, a more rapid decline in lung function, greater health care utilization, and higher mortality compared to patients with COPD alone.(295-297) Spirometry is required to confirm the diagnosis of chronic airflow limitation and document persistent airflow limitation, variability and reversibility.

If the initial assessment suggests the diagnosis of asthma or ACO, or there is uncertainty about the diagnosis of COPD, it is prudent to treat as asthma by starting ICS (with or without LABA) and to avoid using long acting bronchodilators (LABA and/or LAMA) as the only therapeutic option For ACO patients, we recommend considering smoking cessation, pulmonary rehabilitation, vaccinations, and treatment of comorbidities as additive therapeutic strategies.

Section 9: Management of Asthma in Children

Asthma represents the one of the commonest chronic illnesses of childhood with significant economic impact.(298) It is also a leading cause for childhood morbidity as measured by school absences, emergency department visits and hospitalizations.(299) From the prospective of both patient and society, the cost of not treating asthma is higher than the cost of asthma treatment.(300, 301) The sections related to asthma in children aims toward enhancing the multidisciplinary care of asthma patients with special attention to non-asthma specialists, including primary care and general practice physicians and other healthcare workers.(302)

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.(303, 304) 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 an asthma therapy. The diagnosis can be further supported by the presence of atopy, early sensitization, and a family history of atopy. Whenever possible, spirometry is recommended for children to be performed to show reversibility of airway obstruction after bronchodilator therapy.(298) Spirometry can generally 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	
Symptoms and signs	Remarks
History of multiple attacks of SOB or wheezing in a season	More than 3 attacks/season, recurrent, and worse during sleep with triggers such as physical activity, laughing, crying or exposure to tobacco smoke or air pollution.
Coughing	More than 2 weeks, not related to URTI, recurrent, and worse during sleep with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution.
Reduced activity	Not able to run, play, or laugh at the same intensity as other children and tires earlier during walks (wants to be carried).
Wheezing	Equal at both sides of the chest, during expiratory phase, especially on forced expiration.
Atopy	Eczema, environmental/food sensitization.
Family history	Atopy (allergic rhinitis, atopic dermatitis, food allergy) and asthma in first-degree relative.
Breath sounds	Prolonged expiratory phase.
Therapeutic trial	Trial of short-acting bronchodilator or corticosteroid therapy.
Spirometry	Typically, in children >6 years with bronchodilator response assessment.
Chest X-ray	May be considered in infants to rule out congenital causes.
Tests for hypersensitivity	Both skin testing or/and allergen specific IgE blood testing.

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.(305)

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.(306, 307)

Wheeze in pre-school children: Wheezing and shortness of breath in preschool children are among the most common presenting symptoms in paediatric practice. Approximately one third of children has at least one episode of wheeze before their third birthday.(308, 309) 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.(310) In addition to the diagnosis of asthma, wheezing in preschool children can be due to unique differential diagnoses such as 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 such as pulmonary function test or biomarkers. The use of “reactive airway disease”, as a diagnosis, is discouraged as it can restrain full clinical assessment and proper management of asthmatic children in this age group.(311-313)

Wheezing phenotypes in children: Wheezing phenotype in young children can be classified either symptom-based or age-based [Box 9.2].(309)

Box 9.2: Wheezing phenotypes in young children		
Symptom-based	Episodic	<ul style="list-style-type: none"> • Wheezing occurs during specific time periods. • Often associated with URTIs. • Absent between these episodes.
	Multi-trigger	<ul style="list-style-type: none"> • Episodic wheeze • Can occur between episodes, during sleep, and can be triggered by crying, laughing etc.
Age-based	Early transient	<ul style="list-style-type: none"> • wheezing starts before the age of 3 years with resolution by the age of 6 years.
	Persistent	<ul style="list-style-type: none"> • Wheezing starts before the age of 3 years and continues after the age of 6 years.
	Late-onset	<ul style="list-style-type: none"> • Wheezing begun between 3 and 6 years of age.

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.(309, 314) 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: (309, 315)

- 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.(316)

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 9.3].(317, 318). For children with a history of ≥ 4 wheezing attacks (at least one is diagnosed by physician) and either one major or two minor criteria at 3 years of age, there will be 4-10 fold 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.(319)

Box 9.3: Modified Asthma Predictive Index

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

≥ 1 of the major criteria:	Or	≥ 2 of the minor criteria:
• Parental history of asthma		• Eosinophilia ($\geq 4\%$)
• Skin test positive to aeroallergens		• Wheezing unrelated to colds
• Eczema (physician-diagnosed atopic dermatitis)		• Allergic sensitization to milk, egg, or peanuts

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].(320) Asthma management requires effective partnership between patients/caregivers and their healthcare providers.(321) Once established and strengthened, this relationship will positively impact asthma control.

Assessment of Asthmatic Patient: Asthma management requires careful evaluation of asthmatic patients at the individual level. Assessment of future risk of adverse outcomes, and assessment of symptom control represent a key element in the strategy of asthma management in children.

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Severe asthma with several hospitalizations. • History of bronchiolitis.
Medication side-effects	<ul style="list-style-type: none"> • Systemic: Frequent courses of oral corticosteroids or high-dose ICS; neuropsychiatric adverse reactions after the initiation of LTRA. • 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.

Assessing symptom control: 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.(322) Adherence to the prescribed medications and the proper use of their devices are recommended to be addressed before any modification of the treatment plan. 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.(323) In children, assessment of asthma control is recommended to cover the domains of physicians and patient/caregiver.

Physician Assessment of 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 assess disease. 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.(324)

Patient/caregiver Assessment of Control: 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):

The C-ACT is a validated test for children 5 to 12 years [Box 9.5]. 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.(325)

Box 9.5: The Childhood Asthma Control Test (C-ACT)

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

- Age group less than 5 years - The Respiratory and Asthma Control in Kids (TRACK):

The TRACK is a validated test for children <5 years [Box 9.6]. 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.(326)

Box 9.6: The Test for Respiratory and Asthma Control in Kids (TRACK)

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

Controller therapy: Controller therapy is a group of medications used on a regular basis to keep asthma under control and prevents future risk of adverse outcomes. The following are considerations for this category:

- ICS are considered the most effective first-line maintenance monotherapy for childhood asthma (Evidence A).(327, 328)
- Symptom-based or intermittent use of ICS as needed whenever SABA is required is an acceptable controller option for step 1, and is an alternative controller option for step 2 in children >5 years of age (evidence B).(111, 329)

- There are insufficient data to recommend short courses of high-dose ICS in children with mild intermittent asthma attacks (Evidence B).(330). 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).(331) 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. (332)
- The clinical benefits of intermittent inhaled or systemic steroid for children with intermittent and viral-induced wheezing remains controversial. This practice is recommended to be discouraged until clear evidence-based practices are available on this strategy of asthma management (Evidence C).(333, 334)
- 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).(335, 336) 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 the medication appendix.
- Children commenced on LTRA should be followed during the early phase of initiation for the development of neuropsychiatric adverse drug reactions (like anxiety, irritability, aggressiveness, and sleep disturbances) which warrant cessation of therapy in almost 1 out of 6 children. Patient and/or caregiver should be educated on this potential.(337-339)

Reliever therapy: Reliever therapy is a group of medications used to rescue asthmatic patient during exacerbation to relief acute symptoms of asthma. The following are considerations for this category:

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

Devices: It is important to select the best device for optimal treatment delivery [Box 9.7].

Box 9.7: Choosing an inhaler device for children*		
Age	Preferred Device	Alternative Device
Less than 4 years	MDI + spacer with face mask	Nebulizer with face mask
4 - 6 years	MDI + spacer with mouthpiece	Nebulizer with mouthpiece
More than 6 years	Dry powder inhaler, breath actuated pressurized MDI, MDI + spacer with mouthpiece	Nebulizer with mouthpiece

- Use of valved-holding spacer, with mouthpiece when possible, is recommended when an MDI is prescribed (Evidence B).(342) Breath-actuated devices (e.g. dry powder inhalers) represent an effective and simpler option for maintenance therapy in children 5 to 12 years of age (Evidence C).(343, 344) For more information about medications, refer to the medications appendix.
- Nebulizers are not superior to MDI delivered by spacer in both acute and chronic asthma management (Evidence A).(345)

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 patho-

physiology, 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.(346, 347) 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 [Box 9.8].(348)

Box 9.8: Goals and Objectives of caregiver to be covered during patient education session about asthma

Goals	Outcome
<ol style="list-style-type: none"> 1. Developing partnership and common goals. 2. Sharing understandable information. 3. Addressing relevant concerns and expectations. 4. Continuity and consistency in providing education. 	<ol style="list-style-type: none"> 1. Understand asthma risk by explaining in a simplified pathophysiology term. 2. Acknowledge role of prevention and importance of avoiding triggers. 3. Recognize difference between “controller” and “reliever” treatment. 4. Address adverse events of medications. 5. Explain devices use and importance of compliance with treatment plans 6. Recognize worsening asthma and explain action plan. 7. Define comorbid conditions and provide recommendations.

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 9.9]

Box 9.9: Components of asthma management action plan	
Item	Description
Patient identification	Name, medical record number, age, and weight
List of patient's medications	Dosage, frequency, controller versus rescuer medications
Recognition of asthma control status	In simple terms and colour coded
Suggested action based on asthma control status	
How to use inhalational devices	Use illustrations
When and how to seek medical advice	Access to emergency care or call centre
Others	How to clean and advices on environmental control inhalers and spacer.

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.(320, 349) 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.(350-352) A 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.(353) School-based programs that target asthma self-management are associated with improved asthma outcomes, fewer emergency department visits, fewer hospitalizations, fewer days of reduced activity.(354)

Precautions during viral pandemics: During the occurrence of viral infection pandemics, precautions related to infection control measures that include hand-washing, social distancing, optimizing asthma control, and minimizing use of nebulization as the mean of drug delivery to reduce the risk of droplet generation are of extreme importance. Referral to specific guidelines by local and international experts on this task is recommended. The SINA have released specific advices on asthma management of adult and children during the COVID-19 pandemic.(355, 356) Expert SINA panel advice to continue routine care for patient with acute exacerbation of bronchial asthma and to follow the regular clinical guideline including early

Outpatient Management of Asthma in Children

Management of asthma should be adjusted continuously based on asthma control. If current treatment did not achieve control, then treatment is recommended to 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. The SINA panel recommends ensuring consistency in the approach of asthma in adults, adolescents, and children. Therefore, outpatient treatment will be described in three phases: initiation, adjustment, and maintenance. The recommendations in the following sections are further stratified based on age groups: <5 years and ≥5 years.

Initiation of Asthma Treatment in Children:

Prior to initiating asthma treatment in children, it is recommended to ensure availability of initial clinical assessment data, such as the status of asthma control, assessing for risk factors, obtaining C-CAT score for children aged ≥ 5 years, and TRACK score for children <5 years. It is also recommended to provide teaching of inhalers technique, and action plan. The SINA panel recommends placing the child on one of the steps based on the common clinical scenarios described below:

- **Step 1:** The following are considerations to initiate asthma treatment at step 1:
 - SABA as needed (such as salbutamol) for a child with minimal symptoms (less than twice a week) that qualify for a controlled status based on physician assessment that is equivalent to a C-ACT score of ≥ 20 or TRACK score of >80 .
 - SABA on as needed basis for a child with intermittent viral-induced wheeze. (357-359)
 - An alternative option for children aged >5 years is as needed use of ICS whenever SABA is required or daily low dose use of ICS.(339)
- **Step 2:** Personalizing the treatment options for children in step 2 is stratified based on asthma-phenotype, assessment of aeroallergen sensitization, and determining the eosinophil count. Positive sensitization and high eosinophil count may favour ICS as a primary controller intervention.(360)
The following are recommended:
 - Low dose ICS for a child with more symptoms (more than twice a week) that qualify to partially controlled status based on physician assessment that is equivalent to a C-ACT score of ≤ 19 or TRACK score of ≤ 80 (Evidence A). (361-363) Different options of ICS are available in appendix 1.

- LTRA for a child who cannot or will not use ICSs, though it is a less effective option (Evidence B).(364-366)
- For child aged >5 years, daily low dose ICS is the preferred option; however, daily LTRA or as needed use of ICS whenever SABA is required is an alternative and less effective controller option for step 2.(111)
- 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.(367)
- 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 that is considered to be an uncontrolled status based on physician assessment, it is recommended to commence treatment on double dose of ICS.(368, 369)

Adjustment of Asthma Treatment in Children:

Before treatment adjustments, it is recommend to assess adherence to treatment, proper device use, control of environment, and confirmation of the diagnosis especially if there is a failure to respond to therapy.(370) 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. Based on clinical assessment and the level of asthma control, the following are recommended:

- A child with uncontrolled asthma: escalation of treatment to at least the next step.
- 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.

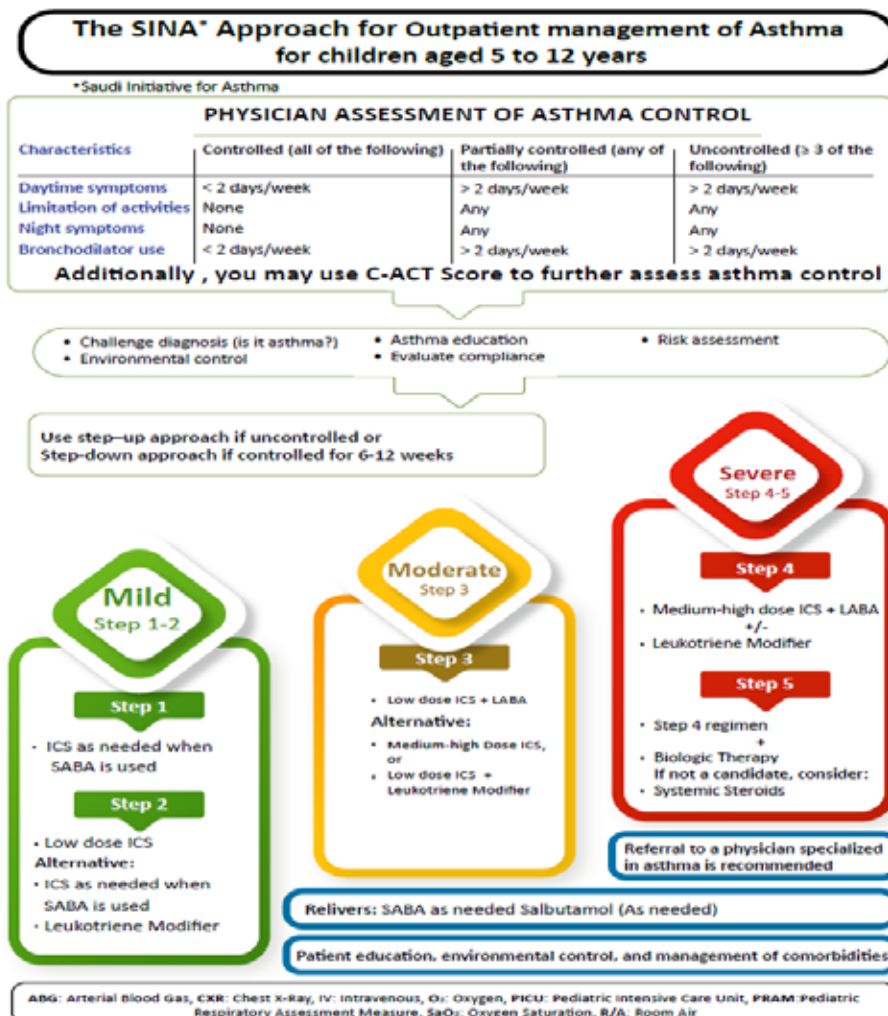
The SINA panel recommends the following concepts of treatment adjustment based on age in the following section.

Children aged 5 to 12 years: If control is not achieved after initiation of therapy for a child aged 5 – 12 years, the following are recommended [Box 9.10]:

- **Uncontrolled asthma at step 1:** The preferred option is escalating to step 2 with low dose ICS (step 2) (Evidence A).(327, 328) Alternatively, either daily LTRA or as needed, use of ICS whenever SABA is required are less effective option for step 2 in this age group.(111)
- **Uncontrolled asthma at step 2:** Escalation of treatment to step 3 by adding LABA to low dose ICS (Evidence A).(137) Alternatively, LTRA can be added to low dose ICS or the dose of ICS escalated to moderate dose (Evidence A).(371-376)
- **Uncontrolled asthma 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.

- **Uncontrolled asthma at step 4:** At this step, it is recommended to refer the child to a physicians specialized in asthma as there are growing evidence to support other lines of biological therapy for children with uncontrolled asthma at step 4.(377, 378) The following are the SINA recommendations for biological therapy at step 5 for this age group:
 - Anti-IgE therapy is a well-established therapy in children aged ≥ 6 years with uncontrolled asthma at step 4 who fulfil the following criteria: severe persistent allergic asthma with frequent daytime symptoms or night-time awakenings, and who have multiple documented severe asthma attacks despite daily combination of high-dose ICS and LABA (Evidence A).(379, 380) However, this line of management is recommended to be restricted to physicians specialized in asthma (Evidence C).(377, 378)
 - Mepolizumab is an anti-IL-5 agent approved for children aged ≥ 6 years (Evidence A)(381, 382) that is indicated when eosinophil level is ≥ 150 cells/uL at treatment initiation or ≥ 300 cells/uL at any time in the prior 12 months. The dose 40 mg for patients 6-11 years of age subcutaneously every four weeks.
- Specific immunotherapy in pediatrics: They are limited data, but it can be used for children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV₁ as detailed in immunotherapy subsection.(196) It should be initiated by an asthma and allergy specialist.

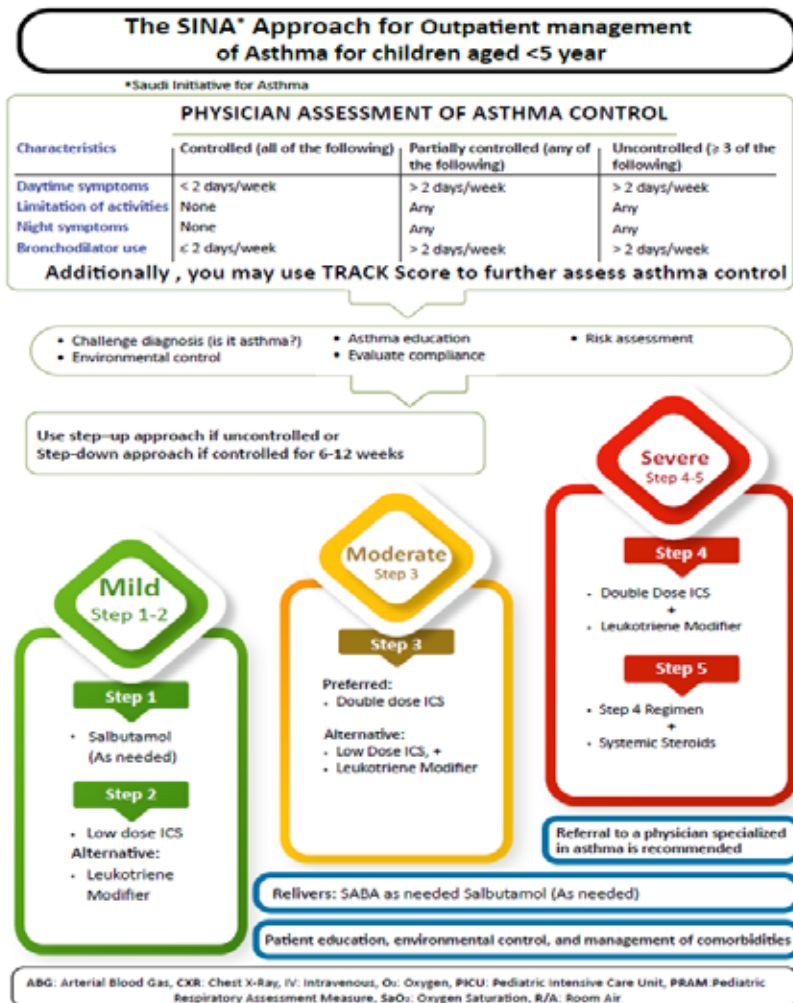
Box 9.10: Outpatient management of Asthma for children aged 5 to 12 years



Children aged <5 years: If control is not achieved after initiation of therapy for a child aged 5 – 12 years, the following are recommended [Box 9.11]:

- **Uncontrolled asthma at step 1:** The preferred option is to escalate to step 2 with low dose ICS (Evidence A).(327, 328)
- **Uncontrolled asthma at step 2:** It is recommended to escalate treatment to step 3. The recommended option is to double the dose of ICS (Evidence A).(374, 383, 384) Alternatively, adding LTRA to low dose ICS is another option, although this is considered as less effective.(368, 369)
- **Uncontrolled asthma at step 3:** It is recommended to escalate treatment to step 4 by the addition of LTRA to moderate dose ICS (Evidence B).(385-387) There is no evidence to support the use of LABA for patients younger than 5 years.
- **Uncontrolled 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. However, to date, there is no evidence to support the use of either LABA or biological therapy 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.

Box 9.11: Outpatient management of Asthma for children aged <5 year



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. Patient is recommended to be clinically assessed regarding medications and doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors. Based on clinical assessment and asthma control status, the SINA 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.
- 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 is recommended to 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 9.10]: 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),(183, 184) .(185) It should be clearly explained to the patient and/or caregiver that asthma control may deteriorate if treatment is abruptly discontinued.(186) 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.(187)
- If the patient is on a combination of ICS with LABA or LTRA, taper ICS to the lowest possible dose (Evidence B).(188, 189) If control is maintained, LABA or LTRA may then be discontinued (Evidence D).(188)
- 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.(190)
- 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 9.11]

- The need for continuation of ICS should be regularly assessed as wheeze improves in a significant portion of children.(388)

- 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),(183, 184) It is recommended to be clearly explained to the caregiver that asthma control may deteriorate if treatment is abruptly discontinued.(186) 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. Consultation with a healthcare provider is recommended if control is not achieved.
- 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.(190)
- 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.
- Biological therapy or Immunotherapy are 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.

Section 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 includes (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.(389) 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 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. 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 is recommended to 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.

Immediate transfer to hospital: If the child does not adequately improve within or after the initial period, urgent medical care is recommended. Box 10.1 shows the indications for immediate transfer to hospital for children with acute asthma exacerbation.

Box: 10.1 Description of indications for immediate transfer to hospital for children with acute asthma exacerbation

Indications	Description
Features of severe symptoms	<ul style="list-style-type: none"> • Unable to speak and/or risk to choke with food or drink • Bluish discoloration of lips and tongue (Cyanosis) • Rapid breathing >40 per minute for children <5 years of age • Silent chest
Lack of response to rescuer treatment	<ul style="list-style-type: none"> • Lack of response after 1-2 hrs. of proper technique and dosage
Limitation to deliver acute treatment	<ul style="list-style-type: none"> • Social, family, or environmental reasons

During the transfer to hospital, rescuer treatment (inhaled SABA) should be provided as well as oxygen supply (to maintain saturation >94%). In addition to consideration to give the first dose of systemic corticosteroid, instant communication with specialized call center is recommended to provide the required consultations.

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, 103, 390-393) 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.(394)

*Box 10.2: The paediatric respiratory assessment measure (PRAM) score				
Sign	0	1	2	3
Suprasternal retraction	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry	Normal	Decreased at bases	Widespread decreased	Absent/minimal
Wheezing	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	95%≤	94%–92	92%>	

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.(394, 395) The PRAM represents a useful means to record clinical signs in a standardized fashion [Box 10.2].(68) The PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing.(392) 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.(396, 397) The SINA 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: Management of acute asthma exacerbation in the emergency department should target the following goals:(398)

- Rapid reversal of bronchospasm
- Correction of hypoxemia if present
- Reducing the need for hospitalization
- Preventing recurrence of the attack after discharge

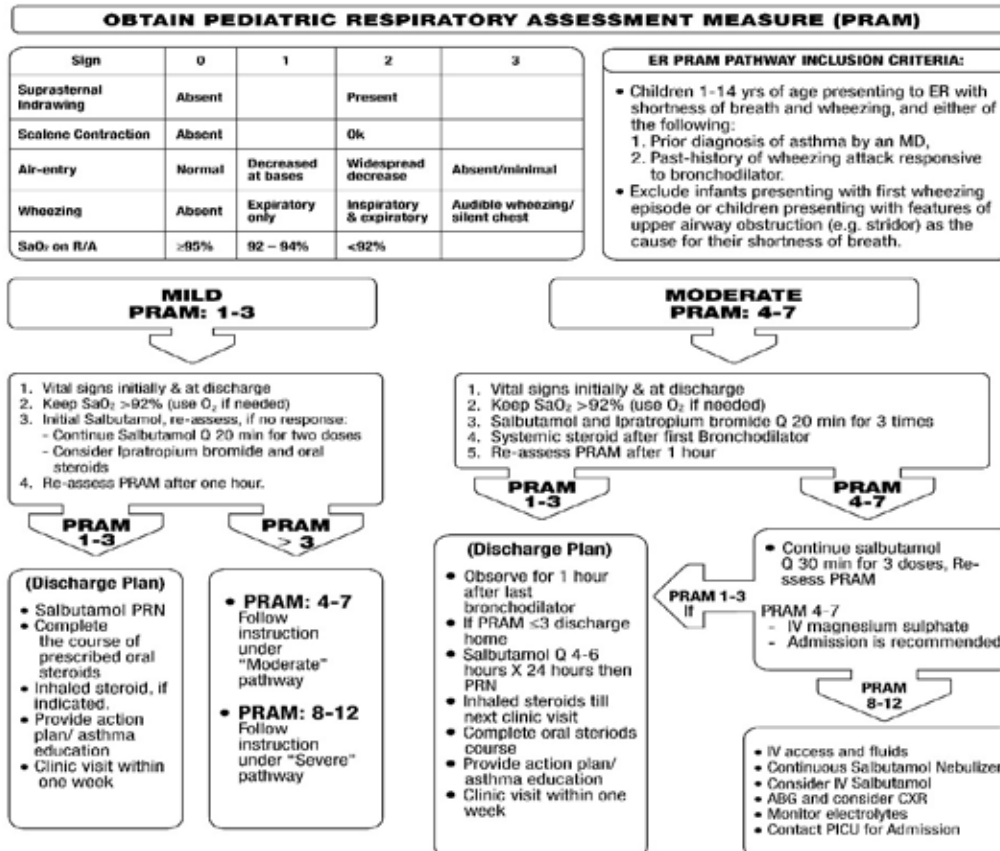
After performing the necessary clinical assessment, the SINA expert recommends the utilization of PRAM as a tool to assess patients in the emergency department and guide further management as well. The PRAM score should be obtained at the initial assessment and after initiation of treatment as well. 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 (399):

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

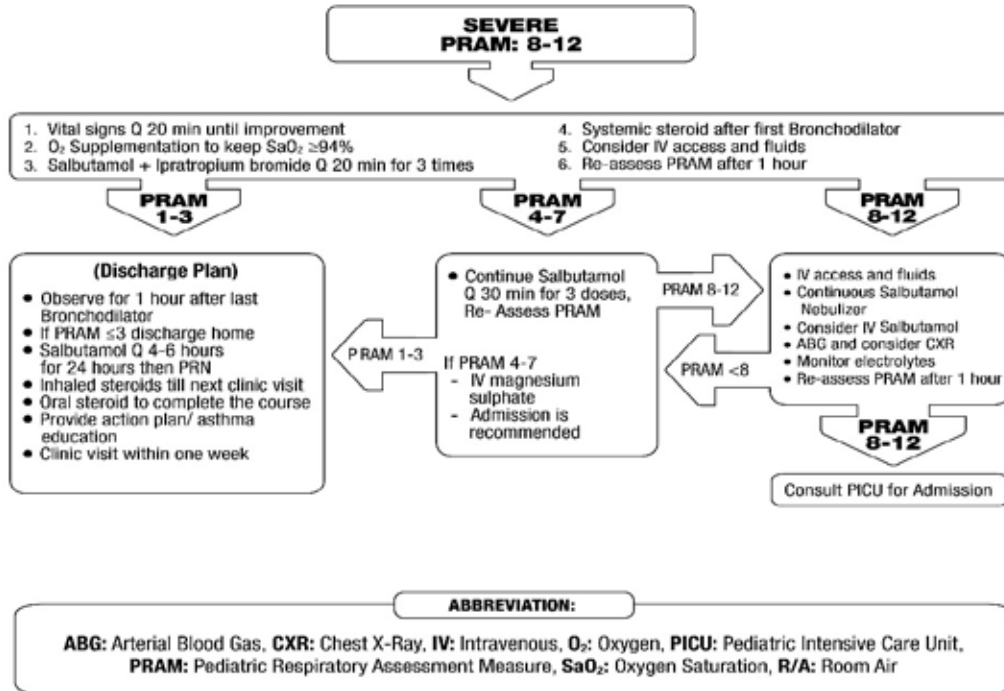
In addition, managing physician is recommended to be aware of the following clinical features of severe or life-threatening asthma that require immediate medical attention:

- 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

Box 10.3: Assessment and treatment of acute asthma in children



← **PRAM 1-3** If



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 10.3]. (397, 400-402) 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. (395) Ancillary investigation that includes chest- X-ray and ABG are not routinely recommended.(399) 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 $>39^{\circ}\text{C}$ 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.(403) Antibiotics are recommended when bacterial pneumonia is clinically suspected. (400, 401)

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

- I- **Mild - PRAM score of 1–3:** the initial management includes
 - Obtain vital signs initially and at discharge.
 - Prescribe appropriate oxygen dose to keep Saturation $\geq 92\%$.
 - Salbutamol dose based on weight: (345, 404)
 - 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 with spacer or 250 mcg by nebulizer every 20 minutes for the first hour only.(405)
 - 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. (406)
 - Re-assess PRAM after 1 hour.

- Management after initial treatment based on PRAM score:
 - **PRAM score is 1-3:** The management includes:
 - 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).
 - II- **Moderate - PRAM score of 4–7:** The management includes:
 - Obtain vital signs.
 - Prescribe appropriate oxygen dose to keep Saturation $\geq 92\%$.
 - Salbutamol dose based on weight: (345, 404)
 - 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 (404, 405, 407).
 - The combination of salbutamol and ipratropium bromide has been shown to be effective in this situation (Evidence B).(404)

- 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. (406, 408)
- 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. (409-411)
 - PRAM score is 8-12: treat as severe asthma attacks (see below)
- III- **Severe - PRAM score of 8 – 12:** The management includes:
- Obtain vital signs every 20 minutes until improvement.
 - Prescribe appropriate oxygen dose to keep Saturation $\geq 94\%$.
 - 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. (404, 405, 407, 412) This combination has been shown to be effective in this situation (Evidence B). (404)
 - 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. (406, 408)
 - 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. (406, 408)
 - 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. (409-411)
 - 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 >20 kg. (413, 414)
- 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).(410, 411)
- ABG, CXR and electrolyte are recommended to be obtained and the paediatrics critical care or equivalent service must be consulted.

Advice related to COVID-19 pandemic: Based on the available evidence at the time of preparing this document, asthma is not considered to be a strong risk factor for severe COVID-19 disease.(415, 416) The Expert SINA panel advises to continue routine care for patient with acute exacerbation of bronchial asthma and to follow the regular clinical guideline including early administration of systemic glucocorticoid therapy if indicated. The SINA expert panel recommends the avoidance of nebulization unless clinically indicated as it is considered an aerosol-generating procedure that may lead to disease spread.(416) It is recommended to commence therapy with MDI with spacer and switch to nebuliser therapy only if child has moderate to severe disease with poor response to MDI under strict precaution measures as per hospital.

Section 11: Medications Used in Asthma Treatment

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.(417) Relievers are medications used on an “as-needed basis” that act quickly to reverse bronchoconstriction and relieve symptoms.

Anti-inflammatory Controller medications

Inhaled corticosteroids: ICS are currently the most effective anti-inflammatory medications for the treatment of asthma.(48, 108, 418). 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.(126) 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 [Box 11.1 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.(146, 419)

Box 11.1: List of inhaled corticosteroids for adults and adolescent and daily recommended doses *

Drug (Doses in mcg)**	Low dose	Medium dose	High dose
Beclomethasone dipropionate (Standard particles, HFA)	200–500	>500–1000	>1000
Beclomethasone dipropionate (Extra fine particles, HFA)	100-200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (Extra fine particles, HFA)	80–160	>160–320	>320
Fluticasone propionate (DPI & HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	100	100	200

DPI: Dry powder inhaler; HFA: chlorofluoroalkane propellant

*Adapted from reference (1)

**Based on availability in the Saudi market for children

Box 11.2: List of inhaled corticosteroids inhalers and daily recommended doses*

Drug (Doses in mcg)**	Less than 5 years	Children above 5 years		
	Low dose	Low dose	Medium dose	High dose
Beclomethasone dipropionate (Standard particles, HFA)	100	200-500	>500–1000	>1000
Beclomethasone dipropionate (Extra fine particles, HFA)	50	100-200	>200–400	>400
Budesonide	200	200-400	>400–800	>800
Budesonide (Nebules)	500	250–500	>500–1000	>1000
Ciclesonide	Not applicable	80-160	>160–320	>320
Fluticasone propionate (DPI)	Not applicable	100–250	>250–500	>500
Fluticasone propionate (HFA)	50	100–250	>250–500	>500
Mometasone furoate	100	200-400	200-400	>400

DPI: Dry powder inhaler; HFA: chlorofluoroalkane propellant

* Adapted from reference (1)

**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.(420) Therefore, low-medium dose of ICS is generally safe and well tolerated in adults and 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.(421, 422) Some studies have shown that ciclesonide had relatively lower local and systemic side effects especially in children.(423) Systemic side effects are occasionally reported with high doses and long-term treatment.

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.(424) Though this effect was statistically significant and sustained during adult life, it is not clear if that will be of significant clinical impact.(425, 426) For instance, use of moderate-dose ICS resulted in 1.2 cm reduction in the final adult height after more than 4 years use.(427) Moreover, more studies demonstrated the negative impact of medium-to-high doses ICS on bone mineralization. (428-430) 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.(431) 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.

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.(432, 433) LTRA are generally well tolerated, however; it is recommended to be aware of the FDA warning about serious behaviour and mood-related changes with montelukast.(166) 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.(434-437) There are no clinical data to support their use under the age of 6 months.(166)

Other controller medications

Long-acting inhaled β_2 -agonists: The commonly used long-acting inhaled β_2 -agonists, formoterol and salmeterol, are used on a twice daily basis. Vilanterol, indacaterol, and olodaterol are LABA agents with a 24-hour duration of action .(438-444) 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).(445) Their side effects are limited to tachycardia, tremor, headaches, muscle cramps,

and sometimes hypokalemia. Regular use of LABA combined with ICSs 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.

Long-Acting Anti-Muscarinic Agents: Long-acting anti-muscarinic (cholinergic) agents (LAMA) inhibit the effect of acetylcholine on M3 receptors, thus producing bronchodilation. LAMA agents are classically used for the treatment of COPD patients. When studies in asthma patients, the users of LAMAs (Tiotropium bromide, aclidinium bromide, Umeclidinium bromide, glycopyrronium) were found to be of higher age at asthma onset, higher annual exacerbation rates, and worst asthma control.(446, 447) Tiotropium bromide is the first LAMA extended for use in asthma. Its bronchodilatation duration of action of more than 24 hours allows for single daily dosing.,(448, 449) The earlier studies on tiotropium were conducted using the handihaler® device, while the more recent studies were conducted using the new Respimat device. To date, tiotropium is mainly available in the Saudi Market in the handihaler device in an 18-mcg capsule format while the Respimat device has not been widely available. Tiotropium was shown to be an effective stepping up strategy when added to a combination of ICS/LABA,(450) and not inferior to LABA as an add on to a medium dose ICS.(152, 153, 162, 451) Adding LAMA can significantly improve lung function in uncontrolled cases and reduce attacks (Evidence A).(151, 161, 162) Recently, once a day, triple therapy of umeclidinium bromide, fluticasone bromide and vilanterol received the USA FDA approval for the treatment of asthma.(452) The main side effect of LAMA is dryness of mouth, although mild prostatic symptoms have been reported.

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 a role in improving steroid resistance in patients with severe asthma requiring high-dose ICS.(453, 454) 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. Currently, it is very rarely used in treating asthma.

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

Cromones: Cromones (sodium cromoglycate and nedocromil sodium) are not recommended for pre-school 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.(455). They are no longer available as an option to treat asthma.

Combination therapy with 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.(139) 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.(113, 139). Recent studies compared as-needed budesonide-formoterol with as needed SABA alone or in combination with daily maintenance budesonide in mild asthmatics showed that budesonide-formoterol used as needed was non-inferior to budesonide maintenance therapy for severe exacerbations but at 17% to 25% the dose of ICS in the maintenance therapy at the expense of a small, but significant, change in asthma control score in favour of budesonide maintenance therapy. ICS are now recommended to start from step 1 either as ICS (evidence mainly in Budesonide) formoterol combination on as needed basis or in a separate inhaler every time rescue treatment SABA is needed.(116, 117, 456) Fixed combination inhalers of ICS and LABA are available in different devices in the Saudi Market [Box 11.3].(457-460) 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.(144, 145) The dose of fluticasone furoate of 100 mcg is approximately equivalent to fluticasone propionate 250 mcg.(461) Such a combination has a potential adherence advantage while maintaining the same safety as the combination of fluticasone propionate and salmeterol.(462)

Box 11.3: List of fixed combinations of inhaled steroid and long acting β 2 agonists

Inhaled Steroid (Doses in mcg)	Long Acting β 2 agonist (Doses in mcg)	Brand name	Device Type	Device Name
Beclomethasone (100)	Formoterol (6)	Foster [®]	MDI	
Budesonide (80,160, 320)	Formoterol (4.5, 9)	Symbicort [®]	DPI	Turbuhaler [™]
Budesonide (200, 400)	Formoterol (6, 12)	Pulmoton [®]	DPI	Elpenhaler [™]
Fluticasone propionate (50, 125, 250)	Salmeterol (25)	Seretide [®]	MDI	Evohaler [™]
Fluticasone propionate (100, 250, 500)	Salmeterol (50)	Seretide [®]	DPI	Diskus [™]
Fluticasone furoate (100, 200)	Vilanterol (25)	Relvar [®]	DPI**	Ellipta [™]
Fluticasone propionate (50,125,250)	Formoterol (5,10)	Flutiform [®]	MDI	
Fluticasone propionate (250, 500)	Salmeterol (50)	Rolenium [®]	DPI	Elpenhaler [™]
Mometasone furoate (100)	Formoterol (5)	Dulera [®]	MDI	

MDI: Metered dose inhaler, DPI: Dry powder inhaler

*Based on availability in the Saudi market for children

**Once a day combination

Triple therapy with ICS, LABA, and LAMA: Fixed combination inhalation devices are considered more convenient for patients.(463) Triple therapy of ICS, LABA and LAMA were first introduced for COPD treatment. The first approved triple therapy for asthma is the once-a-day combination of fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta[®]). It is available in two formats where 1 inhalation contains fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg or 1 inhalation contains fluticasone furoate 200 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg. In patients with uncontrolled moderate or severe asthma on a combination of ICS/LABA, adding umeclidinium was

found to be an effective treatment option with favourable risk-benefit profile as it led to improved FEV₁ and asthma symptoms but did not result in significant reduction in moderate and/or severe exacerbations.(160)A higher dose of fluticasone furoate (200 mcg) primarily reduced the rate of exacerbations, particularly in patients with raised biomarkers of type 2 airway inflammation. Other triple therapy combinations are approved for COPD treatment and not yet for asthma, such as the combination of budesonide 320 mcg, glycopyrronium 14.6 mcg, and formoterol Fumarate 9.6 mcg (Breztri Aerosphere®) and the combination of mometasone furoate 160 mcg, glycopyrronium bromide 63 mcg, and indacaterol 150 mcg (Enerzair Breezhaler®).

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 when biological agents cannot be used. 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. Sudden withdrawal can elicit adrenal failure, therefore gradual withdrawal is recommended. In patients prescribed long-term systemic corticosteroids, prophylactic treatment for osteoporosis is recommended. If available biological therapy should be considered in these patients to decrease the corticosteroid burden.

Reliever medications

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

Rapid onset inhaled β_2 -agonists: Short acting bronchodilators, such as salbutamol, have been traditionally used for relief of symptoms of acute attacks of asthma and for the pre-treatment 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.(464) Regular long-term use of SABA is not recommended. ICS/Formoterol combination inhalers can be used alone on as needed basis in patients with mild asthma or in combination with regular regimen in as needed maintenance and reliever therapy approach in more symptomatic patients.(113-115) 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.(144, 145) In acute asthma, inhaled salbutamol is the preferred choice.(465, 466) 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 one hour 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.(467) 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.(468) IV therapy

should not be considered routinely if ever 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.(404) They 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.(469, 470) A systematic review showed the combination therapy has an added benefit in reducing hospitalizations.(471) Combining both agents led to reduction in hospital admission rates by 38-57%, improvement in lung function, and substantial cost saving.(470, 472, 473) 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.(474) The adult dosing of nebulized ipratropium bromide is 500 μ g 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 μ g) every 20 minutes, then as needed for up to three hours.

Theophylline: There is no evidence supporting the routine use of theophylline in treating acute asthma and its routine use is discouraged. Similarly, routine use of intravenous aminophylline in acute asthma is strongly discouraged, as there is no evidence to show added benefit and the drug has high levels of toxicity and side effects.(475).

Intravenous magnesium sulphate: In a systematic review, magnesium sulphate was shown to reduce hospitalizations in patients with severe or life-threatening asthma attacks that failed to respond to initial treatment.(476) A single dose of IV magnesium sulphate at a dose of 1–2 g over 20 minutes is safe and effective in acute severe asthma.(477)

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, hydrofluroalkane (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, Easyhaler, and Nexthaler 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.(478-481)

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. To date, there are no head-to-head studies to compare the available biologics with each other, neither between those with different targets nor between anti-IL5 therapies themselves. In addition, due to the wide variability of the published clinical trials' inclusion criteria and analysis methodologies, it is also difficult to compare the efficacy of these therapies based on existing studies. This section describes the biologic agents that received appropriate approvals.(482)

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 ³⁶ 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.(483, 484) Baseline IgE level does not predict response, but is necessary, in addition to the weight, to calculate the dose that is administered every two or four weeks.(485) However, the higher eosinophil count or FeNO, the better the response. Omalizumab also significantly reduces exacerbation rate in patients with severe eosinophilic asthma.(486) Repeating IgE level is not recommended to monitor the response as the level could go higher upon commencing anti IgE therapy. Anti IgE therapy is recommended to be stopped if no clinical response is observed in four months. 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 eosinophils maturation, survival, and movement from the bone marrow to systemic circulation. Anti-IL5 monoclonal antibodies treatment is directed to patients with severe eosinophilic asthma with two or more exacerbations in the past year and who have peripheral blood eosinophils count according to the specific anti-IL5 agent. Anti-IL5 therapy reduces

exacerbations by 40-60%, improves lung function, and allows for about 50% reduction in oral glucocorticoids maintenance treatment.(487-489). Patients with more severe disease and higher eosinophil counts are expected to benefit more.(490) Anti-IL-5 and anti-IL-5 receptor therapy reduced attacks by almost half and improved lung function in patients with severe, uncontrolled eosinophilic asthma regardless of the serum IgE concentrations and atopy status.(491) As there is currently no data to guide when to stop anti-IL5 therapy, the treatment may be continued for at least 4 months to judge efficacy and if effective at least 12 months prior to stopping and re-evaluation (Evidence D).(177) These medications should be avoided in patients with active helminthic infection. There is insufficient data regarding its use during pregnancy. There are currently 3 different Anti-IL5 medications in clinical use:

- **Mepolizumab** binds circulating IL5. Based on clinical trials, blood eosinophils should be $>150/\mu\text{L}$ within the last 6 weeks or $>300/\mu\text{L}$ within the last 12 months before starting. It is given as subcutaneous injections every four weeks at doses of 100 mg for patients ≥ 12 years and 40 mg for patients 6-11 years of age. Severe herpes zoster has been reported very rarely in some patient. Consider varicella vaccine before starting if clinically indicated.
- **Reslizumab** binds circulating IL5. Based on clinical trials, blood eosinophils should be $>400/\mu\text{L}$ before starting. It is approved for patients ≥ 18 years. It is given as monthly IV infusion at a dose of 3 mg/kg over 20-50 min.(492) Oropharyngeal pain and elevated CPK were reported in less than 10% and anaphylaxis was reported in 0.3% of patients. Since the dose is weight adjusted, reslizumab could be more efficacious when fixed dose mepolizumab is not adequate.(493)
- **Benralizumab** binds to the α chain of IL5 receptor leading to eosinophil apoptosis.(494) In addition, it induces antibody mediated cell cytotoxicity and, therefore, has a prolonged effect in reducing eo-

sinophils. Based on clinical trials, blood eosinophils counts is recommended to be $>300/\mu\text{L}$.(495) OCS reduction up to 75% from baseline was demonstrated in patients with baseline eosinophils counts $>150/\mu\text{L}$.(496) When there is suboptimal response to mepolizumab, evidence showed that benralizumab therapy may lead to significant clinical benefit in patients with severe eosinophilic asthma with reductions in exacerbation frequency and OCS exposure, alongside improvements in patient reported outcome measures.(497, 498) It is given at a dose of 30 mg subcutaneously once every 4 weeks for the first 3 doses and once every 8 weeks thereafter. It is indicated for patients ≥ 12 years. For patients with prolonged OCS use with baseline eosinophils counts $>150/\mu\text{L}$, it is indicated when in a patient ≥ 18 years.

Anti-interleukin 4 receptor α (Anti-IL4R α): 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 IgE producing B-cells, induction of airway smooth muscle hyper-reactivity, eosinophil tissue chemotaxis, airway mucus production and subepithelial fibrosis. Dupilumab is indicated in severe eosinophilic asthma (blood eosinophils $\geq 150/\mu\text{L}$ or FeNO ≥ 25 ppb) and oral steroids dependent severe asthma regardless of blood eosinophils count, although patients with eosinophil count $>300/\mu\text{L}$ had significantly more benefit. It is approved for patients ≥ 12 years of age. It improves asthma control, quality of life, lung function, and reduces the use of OCS and the rate of asthma attacks.(499) The dose is 400 mg SC once, then 200 mg every two weeks for the eosinophilic asthma phenotype and 600 mg once then 300 mg every two weeks for the oral steroid dependent asthma, or if there are comorbid conditions responsive to dupilumab such as moderate to severe atopic dermatitis or chronic rhinosinusitis with nasal polyposis.(180) Adverse effects include upper respiratory tract infections and injection site reaction. Transient eosinophilia has

been observed in some patients in the first 3 months of treatment. It is recommended not to start dupilumab in patients with blood eosinophil count $>1500/\mu\text{L}$. Also, conjunctivitis has been noted in 10% of patients in the atopic dermatitis studies, but not in the asthma studies.(500) Patients on dupilumab should avoid live vaccines.

Thymic stromal lymphopoietin (TSLP) Inhibitors: Tezepelumab is a human monoclonal antibody specific for the epithelial-cell-derived TSLP that is studied for the treatment of asthma and atopic dermatitis. Phase II randomized controlled trials showed that tezepelumab led to lower rates of clinically significant asthma exacerbations than those who received placebo, independent of baseline blood eosinophil counts.(501, 502) It is not yet approved for asthma treatment ; however, there are ongoing phase III trials to assess its safety in adults and adolescents with severe, uncontrolled asthma and also to assess its efficacy in reducing OCS use in adults with oral corticosteroid dependent asthma.(503, 504) Pre-publication data showed that tezepelumab was well tolerated and met the primary end point of a statistically significant and clinically meaningful reduction of annualized asthma exacerbation rate for patients on medium-high ICS with or without OCS.(505)

References

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