¹Pulmonary Medicine and Critical Care, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, 2Department of Medicine. College of Medicine. King Saud Bin Abdulaziz University for Health Sciences, Rivadh, Saudi Arabia. ³Division of Pulmonary Diseases Lebanese American University Medical Center-Rizk Hospital, Beirut, Lebanon, ⁴Department of Pulmonary and Critical Care Medicine, Hotel Dieu De France Hospital Beirut, Lebanon, ⁵Department of Pulmonary Medicine, Rashid Hospital, Dubai Academic City, United Arab Emirates, 6 Respiratory Unit, Department of Internal Medicine, Al Sabah Hospital. Ministry of Health, Kuwait, ⁷Department of Chest Diseases, Faculty of Medicine, Alexandria University, Egypt, ⁸Department of Chest Diseases, Assuit University, Assuit, Egypt, °Clinic of Chest Diseases. Immunology and Allergic Diseases, Ankara Atatürk Chest Diseases and Chest Surgery Hospital, Ankara, Turkey, ¹⁰Department of Family Medicine, Samsun University, Samsun, Turkey, ¹¹Pulmonologist, Suite D2 Ahmed Kathrada Private Hospital, K43 Highway, Lenasisa Ext 8, 1827, South Africa, ¹²Physician, Fourth Floor Room 404 Fortis Suites, Hospital Road, 00100. Nairobi, Kenya, ¹³Chest Clinic, Faculty of Medicine, CHU ORAN University of Oran, Oran, Algeria, 14 Department of Pathology, CHU Abderrahmen Mami, Ariana, Tunisia Address for

correspondence:

Dr. Mohamed Omar Zeitouni, Pulmonary Medicine and Critical Care, King Faisal Specialist Hospital and Research Center, P.O. Box 3354, Riyadh 11211, Saudi Arabia. E-mail: mozeitouni@ yahoo.com

Submission: 20-10-2021 Accepted: 18-01-2022 Published: 19-04-2022



Challenges and recommendations for the management of asthma in the Middle East and Africa

Mohamed Omar Zeitouni¹, Mohamed Saad Al-Moamary², Marie Louise Coussa³, Moussa Riachy⁴, Bassam Mahboub⁵, Fatma AlHuraish⁶, Mohamed Helmy Zidan⁷, Mohamed Mostafa Metwally⁸, Kurtuluş Aksu⁹, Erdinç Yavuz¹⁰, Ismail Sikander Kalla¹¹, Jeremiah Chakaya¹², Snouber Abdelmadjid¹³, Habib Ghedira¹⁴

Abstract:

Clinical presentation of asthma is variable, and its diagnosis can be a major challenge in routine health-care practice, especially in low-and-middle-income countries. The aim of asthma management is to achieve optimal asthma control and to reduce the risk of asthma exacerbations and mortality. In the Middle East and in Africa (MEA), several patient- and physician-related factors lead to misdiagnosis and suboptimal management of asthma. A panel of experts comprising of specialists as well as general health-care professionals met to identify challenges and provide recommendations for the management of asthma in MEA. The major challenges identified for diagnosis of asthma were lack of adequate knowledge about the disease, lack of specialized diagnostic facilities, limited access to spirometry, and social stigma associated with asthma. The prime challenges for management of asthma in MEA were identified as overreliance on short-acting β -agonists (SABAs), underprescription of inhaled corticosteroids (ICS), nonadherence to prescribed medications, and inadequate insurance coverage for its treatment. The experts endorsed adapting the Global Initiative for Asthma guidelines at country and regional levels for effective management of asthma and to alleviate the overuse of SABAs as reliever medications. Stringent control over SABA use, discouraging over-the-counter availability of SABA, and using as-needed low-dose ICS and formoterol as rescue medications in mild cases were suggested to reduce the overreliance on SABAs. Encouraging SABA alone-free clinical practice in both outpatient and emergency department settings is also imperative. We present the recommendations for the management of asthma along with proposed regional adaptations of international guidelines for MEA.

Keywords:

Asthma, Global Initiative for Asthma, inhaled corticosteroids, management, overreliance, short-acting β -agonists

A sthma is a common chronic respiratory inflammatory disease defined by the Global Initiative for Asthma (GINA) as 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 that can become persistent.^[1,2] These symptoms are triggered

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms. by several environmental factors such as allergens, irritants, pollution, weather change, exercise, and viral respiratory infections.^[3-6] Although the symptoms are usually reversible spontaneously or by medications, some patients might experience exacerbations, which could be life-threatening. Exacerbations significantly increase the burden of the disease. The disability-adjusted life years attributed to asthma was 298 per 100,000 in 2017.^[7] The

How to cite this article: Zeitouni MO, Al-Moamary MS, Coussa ML, Riachy M, Mahboub B, AlHuraish F, *et al.* Challenges and recommendations for the management of asthma in the Middle East and Africa. Ann Thorac Med 2022;17:71-80.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

economic burden of asthma includes both direct medical costs (e.g., hospitalizations, emergency department [ED] visits, medical practitioner visits, and medications) and indirect nonmedical costs (e.g., time lost from work, decreased productivity or premature death).^[8,9] Several asthma studies showed that direct costs are higher than indirect costs and contribute to 50%–80% of the total costs.^[10] In the Middle East and in Africa (MEA), asthma presents a significant burden to the health-care systems and to individuals living with asthma. In a pediatric asthma study in Turkey, hospitalizations and interventions (58.9%) were identified as the main cost factor.^[11] However, the economic burden of asthma in the region has not been systematically explored and reported.

The main goal of asthma management is to achieve optimal asthma control and reduce the risk of asthma exacerbations and mortality. Although asthma care has improved over the years, the level of asthma control is not considered optimal in many countries.^[12,13] In MEA, asthma control is considered unsatisfactory as more than two-third of the patients have uncontrolled asthma.^[14] In an observational cross-sectional study of 939 asthma patients from Turkey, Egypt, Saudi Arabia, Kuwait, and the United Arab Emirates, 44.2% of patients had uncontrolled Asthma.^[15] In addition, the rate of adherence to asthma medications is poor, with about one-quarter of patient population reporting good medication adherence.^[16] A panel of experts met with an aim to address these unmet needs with a focus on the challenges faced by the health-care professionals (HCPs) in diagnosis and treatment and to provide practical recommendations for the management of asthma in MEA, which are presented in this manuscript.

Methodology

The MEA steering committee meeting that convened in January 2021 included a team of 14 members with expertise in the asthma diagnosis and management across MEA (12 pulmonologists: 1 each from Algeria, Kuwait, South Africa, Tunisia, Turkey, and United Arab Emirates and 2 each from Egypt, Lebanon, and Saudi Arabia; one general practitioner from Kenya and 1 family practitioner from Turkey).

The panel of experts discussed the clinical gaps and challenges in the management of asthma and provided practical recommendations based on their clinical experience to improve asthma care in MEA. For the review of evidence and development of recommendations, a literature search was conducted using MEDLINE and EMBASE databases. Several keywords including "asthma," "management," "leukotrienes inhibitors," "long-acting β -agonists," "inhaled corticosteroids," "short-acting β -agonists," "effectiveness," "survival,"

"Middle East," and "Africa" were used for in-depth literature search on the topic. The results presented in the literature were reviewed, and the recommendations were developed. The opinions and responses were integrated, and a thematic analysis was conducted to methodically categories the region-specific recommendations. This manuscript is an outcome of the expert group discussion with the recommendations for MEA.

Insights of Asthma Management in the Middle East and in Africa

Small regional surveys in patients with asthma in the MEA countries have reported prevalence in the range of 2%–32% [Table 1].^[17-23] The Evaluation of Asthma Management in Middle East North Africa Adult population (ESMAA) and SNAPSHOT studies provided an insight into the prevalence and control of asthma across all the assessed Middle Eastern countries and within the Gulf Cooperation Council Countries, with the highest prevalence of controlled asthma reported in Kuwait (42.6%) and Qatar (41.1%).[14,24] In MEA, the ESMAA study reported asthma as being uncontrolled in 41.5% of patients (95% confidence interval [CI]: 40.3%–42.6%), partly controlled in 29.1% (95% CI: 28.1%-30.2%), and controlled in 29.4% (95% CI: 28.4%-30.5%).^[14] The SNAPSHOT study reported a significantly lower EuroQol visual analog scale score in patients with asthma as compared to the general population (68.2 ± 22.9 vs. 78.1 ± 17.5; P < 0.0001).^[24]

Challenges and Recommendations for Management of Asthma

The challenges specific to MEA for management of asthma were discussed by the expert panel and recommendations to improve management were framed. Expert panel identified several gaps in the diagnosis and treatment of asthma in the region. Critical challenges for

Table 1: Country-wise prevalence of Asthma in the

Middle East and Africa		
Country/ study name	Patient population	Prevalence of asthma (%)
AIRGNE ^[17]	Children and adults (aged 7-39 years)	23-32
AIRET ^[18]	Children and adults (aged 7-66 years)	2.9
PARFAIT ^[19]	Adults	6.2-11.2
AIRMAG ^[20]	Adolescents and adults (aged 16-100 years)	3.45-3.89
Saudi Arabia ^[21]	Adolescents and adults (aged 15-75 years)	4
UAE ^[22]	Children (aged 6-14 years)	13.6
Kuwait ^[23]	Children (aged 13-14 years)	15.6

AIRGNE=Asthma Insights and Reality Gulf and Near East, AIRET=Asthma Insights and Reality in Turkey, PARFAIT=Prevalence and Risk Factors of Allergies in Turkey, AIRMAG=Asthma Insights and Reality in the Maghreb diagnosis of asthma include lack of awareness about the pathophysiology of the disease and treatment modalities in HCPs and patients, lack of specialized diagnostic facilities, limited access to spirometry, and social stigma associated with asthma. Region-specific factors affecting the asthma control are mentioned in Figure 1.

Poorly controlled asthma is associated with more exacerbations and emergency room visits.[12,25,26] Although asthma control is assessed by guideline-defined criteria, patients' perceptions of control are subjective. One major issue in assessing asthma control is the disconnect between physician-defined or guideline-defined asthma control and patients' perception of asthma control.^[27] Several real-world studies have reported that only about half of the patients meet criteria for well-controlled asthma.^[26,28-30] In the INSPIRE study, approximately 90% of 3415 patients had an average of 12 periods of asthma exacerbations per year, yet felt their asthma was well controlled.^[29] There is also a lack of awareness among patients on the description of controlled asthma.^[31,32] In another study, the percentage of patients with controlled asthma decreased from 58% to 33% after awareness of the definitions for asthma control.^[33]

The challenges for management of asthma in MEA are summarized in Table 2. The most common challenges in MEA are overreliance and overuse of short-acting β -agonists (SABAs), underprescription of inhaled corticosteroids (ICS), nonadherence to prescribed medications, and inadequate insurance coverage for its treatment.^[14,34] There are several factors contributing to overreliance of SABAs and underprescription of ICS such as over-the-counter purchase of SABAs, refilling of old prescription without consultation with physicians, using SABAs for rapid symptomatic relief at the time of exacerbations, and lack of knowledge and information about recent guidelines and treatment patterns. There is

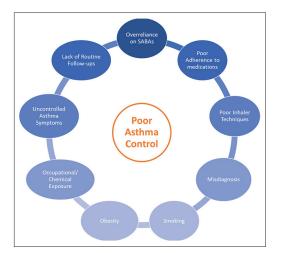


Figure 1: Factors Responsible for Poor Control of Asthma in the Middle East and Africa Region. SABA = Short-acting β -agonists

Table 2: Region-specific challenges and

recommendations for	optimal management of asthma
Challenges	Recommendations
Health-care system not well organized Limited pulmonologists	Establish specialized asthma polyclinics with the help from national health authorities across the country
treating asthma	Ensure availability of appropriate educational programs to enhance physicians' and patients' knowledge in asthma care
	Moderate/severe asthma patients to be managed by pulmonologists/specialists at the course of their management, while mild cases to be managed by GPs
	Develop a system where patients highly suspicious of having asthma are considered as priority and given an early care (e.g., appointment within 1 week and not exceeding 1 month)
	Enhance awareness of GPs on aspects of asthma diagnosis and management, especially the difference between reliever and controller therapies and the importance of maintenance medication for asthma treatment
Guidelines are old and not updated	Ensure standardization/harmonization of local guidelines with global guidelines
High prevalence of smoking in MEA	Enhance public awareness for decreasing smoking Support anti-smoking clinics and
	enhance access to these clinics
Pharmacists may handout asthma medications and even oral corticosteroids	Educate pharmacists to encourage patients to visit their physicians for appropriate treatment
without prescriptions Patients generally buy any medication without prescription	Consideration of strict mandate to allow SABA and other medications purchase only with the prescription from a specialist as SABA medication cannot be banned in the market but its overuse to be controlled
	Develop flowcharts/action plans for patients for adjusting their medications as-needed
	An individualized AAP developed for patient
Patients' overreliance on SABA	Patients to be instructed to avoid using SABA and to use with it low-dose ICS inhalers instead of SABA-only inhalers for exacerbations or use of formoterol/ICS on as-needed basis
Limited availability of combination therapy for asthma	Seek support from government/ regulatory authority ensuring easy accessibility of combination therapy of ICS/LABA
Inadequate asthma control due to poor adherence to asthma medications	Ensure availability of appropriate educational programs to enhance physician and patient knowledge in asthma care

Challenges	Recommendations
An overreliance of ED physicians on SABA as the patients with worsening symptoms often first go to the ED physicians and receive a prescription of SABA inhalers	Educate ED physicians on asthma treatments and avoidance of discharging patients on SABA alone
Use of multiple devices for asthma treatment	Asthma patients can be given an option of using smart devices that monitor their peak expiratory flow
	Specialized asthma centers with a focus on inhaler-use training, treatment adherence, smartphone application use, and transition to biological agents
	Having one device for reliever and controller medications will help
	Use artificial intelligence to identify medications adherence and prevent overuse of SABA
Inadequate coverage of asthma treatment by	Need to include asthma under insurance full coverage
insurance companies	There is a need to provide good quality asthma care and insurance facilities to all patients in this region

AAP=Asthma action plan, ED=Emergency department, GPs=General physicians, ICS=Intranasal corticosteroids, LABA=Long-acting β -agonists, MEA=Middle East and Africa, SABA=Short-acting β -agonists

an overreliance of ED physicians on the prescription of SABA inhalers, as patients with worsening symptoms often first present to the ED.

Several strategies need to be implemented to deal with these challenges aiming toward improving asthma control, reducing risks, and providing patients a long-term, effective and safe treatment for asthma. Other approach includes preparing country-level or regional guidelines for asthma, increasing awareness among the HCPs about the recent global and regional guidelines, and educating patients for improving their compliance to the prescribed medications.^[1,35] Incorrect inhaler technique is still a major problem in the region.^[36] Whenever control is not achieved despite adequate management and good inhaler technique and compliance, consultation with asthma specialists for further management of the disease should be recommended. It is also recommended to facilitate access to asthma care and enhance insurance coverage to improve accessibility to medications with special attention for biologics in the management of severe asthma. Development of professional groups to impart quality training to HCPs through certification courses, leveraging digital platforms to disseminate asthma guidelines, and adequate funding of education material were also recommended. The detailed list of challenges and recommendations for optimal management of asthma is summarised in Table 2.

Action Plan for Management of Asthma in the Middle East and in Africa

Asthma is a variable condition with symptoms and signs that are often not present during a routine health-care appointment, leading to difficulties in diagnosis. Optimal diagnosis is the cornerstone for ensuring patient-centric tailored treatment; however, misdiagnosis of asthma is a major challenge, especially in low-and middle-income countries.^[37] A national household survey from Saudi Arabia estimated the self-reported clinical diagnosis of asthma to be 4.05%.^[38] Evidence from the ESMAA study reported that diagnosis at least 5 years earlier was significantly associated with uncontrolled asthma (P < 0.001).^[13]

Comprehensive history taking, physical examination, and demonstration of variable airflow limitation by spirometry or peak flow measurement form the essential elements of asthma diagnostic process [Figure 2].[1,35,39] There are challenges for the implementation of guideline recommendations in all asthma management facilities due to the paucity of testing for airway obstruction, time limitations, and cost of introducing techniques such as fractional exhaled nitric oxide. In addition, fear of social stigma associated with asthma is a common deterrent among patients to accept a definite diagnosis. Experts opined that, in MEA, patients prefer using SABA inhalers for respiratory symptoms, which, in most countries, are available as over-the-counter medications. This causes underutilization of asthma clinics leading to missed diagnosis and increased risk of exacerbations, thereby increasing the severity of asthma.^[40]

Asthma guideline strategies focus on symptom control, risk reduction, minimizing medications side effects, and control of morbidities.^[1] Asthma control is based on assessing asthma symptoms, use of reliever medications, and impact on daily activities.^[1] The clinical status of a patient is described as controlled, partly controlled, or uncontrolled depending on the symptoms during the prior 4 weeks. The optimal control of asthma is freedom from troublesome respiratory symptoms during both day and night, needing minimal or no reliever medications (no more than two puffs SABA/week), maintaining daily activity, and maintaining normal or the best possible lung function.^[41] A composite measure of the diagnostic tests is required for the comprehensive assessment of asthma control.^[1] Several tools such as the GINA asthma symptoms assessment, the asthma control questionnaire, and asthma control test have brought forth validated control 'scores' that can be used in the treatment decisions.[1,42,43]

Asthma has long-term sequelae even in patients with mild-or-moderate disease and may experience airway

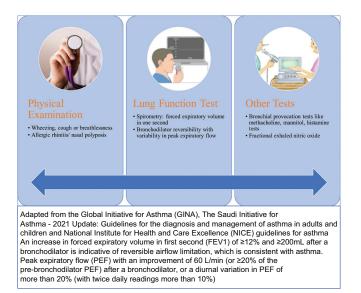


Figure 2: Cardinal Elements for Assessment of Asthma

remodeling leading to fixed airway obstruction over a period of time.^[1] If not controlled, patients may experience functional limitations, increased risk of exacerbations, deterioration in pulmonary function, and mortality. Thus, uncontrolled asthma has a major impact on the quality of life.^[21,44]

Multidisciplinary Approach to Asthma Management

Educating HCPs and increasing awareness of patients are critical to achieve optimal asthma control.^[33] HCPs are recommended to be made aware of the recent local and global guidelines for the management of asthma. The guidelines developed by the Saudi Initiative for Asthma (SINA) recommend a well-structured asthma education program with the goal for enhanced patient-health-care worker partnership, better understanding of clinical presentation and methods of diagnosis, and ability to differentiate between "reliever" and "controller" medications and their appropriate indications to improve quality of life and reduce cost and optimal utilization of health-care resources.[35] Several studies have shown improvement in asthma control with patient education about the disease, use of asthma management devices, lifestyle modifications, and routine consultation with the physicians.^[1,25,45,46]

The factors responsible for good adherence are higher age, presence of medical insurance coverage, smoking status history, level and frequency of exacerbations, high level of asthma control, and quality of life (mental or physical). Thus, increasing ICS prescription and bringing asthma into mainstream insurance coverage seem to be the foremost for improving the adherence of patients.^[47,48] Another vital element of effective management of asthma is a written asthma action plan. This personalized plan can act as a guide for self-medication and primary caregivers during the episodes of exacerbations. Several digital platforms are now available to aid self-management of asthma and aid HCPs track patients' exacerbation episodes.^[46-48] It is also important to review the action plan during regular consultation with HCPs to keep the plan updated as per the recent assessments.

Overreliance on Short-Acting β-Agonists in Asthma Management

For decades, the standard therapy for mild asthma has been as-needed SABA (GINA step 1) and low-dose ICS with as-needed SABA for symptomatic relief (GINA step 2).^[1] The overreliance of patients on SABAs stems from the rapid relief after inhalation;^[49] however, SABAs lack anti-inflammatory properties resulting in worse long-term outcomes and higher risk of asthma exacerbations and death compared with the outcomes when appropriate dose of ICS and other controllers are used.^[50-52] Regular use of SABA has also been associated with an increase in lung hyper-responsiveness, leading to increased sensitivity to asthma trigger factors.^[53] A population-based health data analysis from Canada reported a higher incidence of visits to ED (odds ratio [OR], 1.25; 95% CI: 1.18–1.33), hospitalization (OR, 1.45; 95% CI: 1.26-1.66), and use of oral corticosteroids (relative risk, 1.06; 95% CI: 1.04–1.08) with overuse of SABA.^[54] In an ED setting, SABA overreliance is also associated with transient lactic acidosis, tachycardia, arrhythmias, QTc interval prolongation, hypokalemia, hypomagnesaemia, muscle tremors and cramps, and anxiety. Suboptimal prescription of controller medications and overreliance on SABAs has contributed to asthma-related mortality.[55-57] According to a European survey-based study, approximately 39% of patients who received more than 12 canisters of SABA inhalers during the previous year died of asthma.^[58]

On the other hand, results of randomized controlled trials and observational studies report a significant reduction in the risk of severe exacerbations and asthma-related deaths with the use of ICS in mild asthma. $^{\scriptscriptstyle [51,52,59,60]}$ In one study, ICS reduced the risk of asthma exacerbations by 60% and increased the days with controlled asthma by 50%.^[59] In other studies, ICS with long-acting β -agonists (LABAs) prevented exacerbations and loss of lung function but were less effective at mitigating symptoms than regular ICS maintenance therapy.^[59,61,62] The efficacy and safety of budesonide/formoterol as reliever therapy in patients with asthma were evaluated in two randomized, double-blind, placebo-controlled trials.^[61,62] The outcomes of these trials indicated that as-needed budesonide-formoterol combination was superior to as-needed SABA and provided a noninferior

effect on annual rate of exacerbation reduction, with a less exposure to ICS, though was lower in controlling symptoms when compared with a maintenance ICS regimen. Similarly, the Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy) trial demonstrated the external validity of the pervious findings.^[63] In PRACTICAL study, the incidence of severe exacerbations was lower with as-needed budesonide–formoterol than with maintenance budesonide plus terbutaline as needed.^[64]

Therefore, it is recommended to optimize the use of ICS and SABA. The suboptimal use of ICS and overuse of SABA need to be discouraged. Patients requiring more than three canisters of SABAs per year are recommended to undergo detailed clinical assessment.^[1,58] It is recommended to use as-needed low-dose ICS and formoterol as the preferred rescue option when ICS/formoterol combination is used for the management of asthma or one of the options for mild cases.^[58] When ICS is combined with LABAs other than formoterol, SABA is the recommended option as a reliever.^[1]

Impact of Short-Acting β-Agonists Overreliance on Asthma Guidelines Updated in 2021

In clinical practice, asthma severity is assessed retrospectively based on the treatment step required to control symptoms and exacerbations.[1,65-67] 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 months or years, asthma severity level can be classified as follows: Mild asthma is controlled asthma at step 1 or 2, moderate asthma is controlled asthma at step 3, and severe asthma is that requires treatment at step 4 or 5.^[1] Recent guideline updates addressed the issues related to SABA overreliance and underutilization of anti-inflammatory therapy, especially in mild asthma. SABA is no longer recommended on an as-needed basis for mild asthma.[32,68,69] The recent GINA updates have recommended two tracks for asthma management based on the prescribed reliever therapy.^[1] Track 1 [Figure 3.1] is based on utilizing as-needed anti-inflammatory reliever therapy with low-dose ICS-formoterol combination for mild asthma (step 1–2). For moderate-to-severe asthma (step 3–5), ICS-formoterol is used as maintenance and reliever therapy (MART). For Track 2 [Figure 3.1], SABA is utilized as a reliever therapy on an as-needed basis. Step 1 requires ICS whenever SABA is needed, step 2 requires low-dose ICS, step 3 requires low-dose maintenance ICS in combination with LABA, and step

4 requires medium-to-high-dose maintenance ICS in combination with LABA. Uncontrolled patients at step 4 in both tracks may require additional therapy such as long-acting anti-muscarinic agent (LAMA). Biologics are considered for uncontrolled patients with moderate-to-severe asthma based on phenotype.

The expert panel recommends adapting the GINA strategies at country and regional levels. One of the examples of successful customization of these strategies is the SINA guidelines introduced by the Saudi Thoracic Society in 2009.^[70] The latest update by SINA-2021 has adopted a simple and friendly algorithm [Figure 3.2] which is similar to GINA for recommending avoidance of overreliance on SABA alone for mild cases. The preferred option for step 1 is as-needed low-dose ICS-formoterol combination or adding low-dose ICS when SABA is used. For step 2, low-dose ICS is used for compliant patients, otherwise as-needed low-dose ICS. For step 3, low-dose maintenance ICS in combination with LABA either as MART approach when formoterol is used or as a regular proactive regular dosing with other combination. For step 4, further escalation to medium-high-dose ICS is done with LABA. The once-a-day combination of ICSLABA is also available that has an adherence advantage over twice-a-day combination.[70-76] Uncontrolled patients at step 4 may require additional therapy such as LAMA. Biologics are considered for uncontrolled patients with moderate-to-severe asthma based on phenotype.

Short-Acting β-Agonists Alone-free Clinical Practice

Despite strong evidence suggesting an association of asthma exacerbations, increased risk of hospitalizations and ED visits, the inappropriate use of SABA is still prevalent. Besides safety issues, inappropriate use of SABA has been shown to be associated with a 6% increase in total asthma-related costs in the immediate 3-month period, and 5% and 6% increase in outpatient services and medications costs, respectively.^[54] With the recent recommendations to avoid prescribing SABA alone in the management of mild asthma (step 1) and the observed practice of discharging patients from EDs with SABA alone, the expert panel recommends SABA alone-free clinical practice. Patients with mild asthma are at risk of exacerbations as the triggers for exacerbations include environmental exposures (smoke, air pollution, or allergens), poor adherence to controller medications, prior history of exacerbations, and high SABA use.[40] However, in an ED setting, patients are often administered SABA inhalers for rapid relief of asthma exacerbations.[77-79] As per the recent GINA guidelines, while discharging patients from acute care centers, ICS-containing controller medications should be prescribed. If the patients are on Zeitouni, et al.: Management of asthma in MEA region

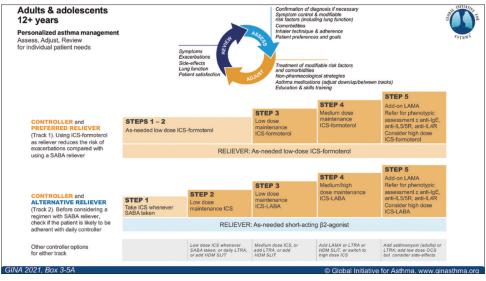


Figure 3: 1: Approach for Management of Asthma in Adults and Adolescents as per GINA Guidelines.^[1] HDM-SLIT = House dust mitesublingual immunotherapy, ICS = Inhaled corticosteroid, IgE = Immunoglobulin E, IL = Interleukin, LABA = Long-acting bronchodilator, LAMA = Long-acting muscarinic antagonist, LTRA = Leukotriene receptor antagonist, OCS = Oral corticosteroid, SABA = Short-acting beta-agonist

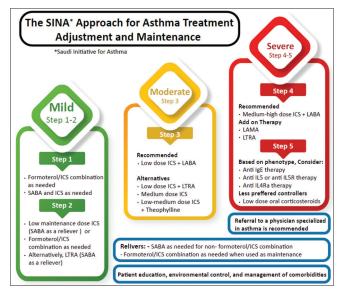


Figure 3: 2: Approach for Management of Asthma in Adults and Adolescents as per SINA Guidelines.^[69] ICS = Inhaled corticosteroid, IgE = Immunoglobulin E, IL = Interleukin, LABA = Long-acting bronchodilator, LAMA = Long-acting muscarinic antagonist, LTRA = Leukotriene receptor antagonist, SABA = Short-acting beta-agonist

ICS-containing controller, the dose should be increased for 2–4 weeks to reduce the future risk of exacerbations.^[1]

Besides ED, there are other avenues of inappropriate SABA use. In the United Kingdom, an asthma-related outpatient visit to a general practitioner in the previous year was associated with a higher likelihood of inappropriate SABA use.^[79] On the other hand, visiting a specialist and the use of ICS in the previous year were associated with lower likelihood of inappropriate use of SABA. Some patient-related factors also contribute to the overuse of SABA and suboptimal use of ICS. A qualitative study in six countries in Europe

and the United States showed that patients have a strong preference to SABA relievers because of their convenience of use prompted by symptoms and effectiveness in quickly alleviating asthma symptoms, allowing patients an uninterrupted routine. Conversely, patients do not perceive the benefits of ICS-based maintenance therapy, as they are not overtly apparent.^[80] Female patients having received pulmonary function tests and visited a specialist and those who are from higher socio-economic strata and have higher continuity of care were observed to be at lower risk of inappropriate SABA use.^[79]

Discouraging SABA overreliance requires a fundamental shift in the practice of recommending SABA alone for patients with milder forms of asthma to recommending as-needed low-dose ICS-formoterol or ICS controller medications with SABA. Collaborative efforts involving patients, caregivers, and policy makers are needed to encourage SABA alone-free clinical practice. The need is to identify practitioners and patients who are at risk of inappropriate use of SABA. Awareness programs to enhance understanding of the latest guideline recommendations among general physicians and ED care providers may help in eliminating SABA monotherapy prescription practice. The use of upcoming tools such as the SABA Reliance Questionnaire may help physicians to assess patients' beliefs about SABA.[81] It can also initiate a dialogue between patients and providers and may alleviate SABA monotherapy and overuse.

Conclusion

• We recommend adapting the GINA strategies

at country and regional levels, which essentially involves the following algorithm

- Avoidance of overreliance on SABA alone for mild cases
- Step 1: Low-dose ICS-formoterol combination or adding low-dose ICS when SABA is used
- Step 2: Low-dose ICS for compliant patients, otherwise as-needed low-dose ICS
- Step 3: Low-dose maintenance ICS in combination with LABA either as MART approach when formoterol is used or as a regular proactive regular dosing with other combination
- Step 4: Further escalation to medium-to-high-dose ICS with LABA.

This calls for fundamental shift in prescription practices in ED as well as in general practice settings. Considering the adverse effects of SABA's overreliance, the MEA experts recommend stringent regulations overprescription of SABA monotherapy. Over-the-counter availability of SABA should be discouraged and patients on SABA need to be monitored at regular intervals.

It is imperative to drive awareness of the adverse effects of SABA overreliance and exacerbation risks due to inadequate use of ICS among the treating physicians. Various patient-reported tools can help identify the overuse of SABA among patients with asthma.

In addition, patient awareness interventions should focus on differentiating in perceived symptomatic relief versus clinical control of asthma. Platforms such as social media, scientific societies, and patient advocacy groups could be utilized to educate the physicians, patients, and policymakers. Medical insurance coverage of asthma medications will help improve compliance. Furthermore, dissemination of simple tools for assessment and flowchart-based algorithms for management and referral of patients could play a key role in lowering the clinical and financial burden of asthma in the region. Generation and publication of local epidemiological data and current treatment practices can provide further insights and help in the development of robust regional treatment guidelines. The current manuscript identified the challenges and presents consensus recommendations for specialists as well as general practitioners for the management of asthma in MEA.

Financial support and sponsorship

The preparation of this consensus statement and funding of the journal's article processing charges were supported by AstraZeneca FZ LLC. All authors had full access to all the data in this study and took complete responsibility for the integrity of the data and accuracy of the data analysis.

Conflicts of interest

There are no conflicts of interest.

References

- Global Strategy for Asthma Management and Prevention: GINA; 2020. Available from: https://ginasthma.org/wp-content/ uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. [Last accessed on 2021 Mar 26].
- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5:691-706.
- 3. Subbarao P, Mandhane PJ, Sears MR. Asthma: Epidemiology, etiology and risk factors. CMAJ 2009;181:E181-90.
- de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, *et al.* Prognostic factors of asthma severity: A 9-year international prospective cohort study. J Allergy Clin Immunol 2006;117:1249-56.
- 5. Bener A, Abdulrazzaq YM, Al-Mutawwa J, Debuse P. Genetic and environmental factors associated with asthma. Hum Biol 1996;68:405-14.
- Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. Reprod Health 2009;6:17.
- WHO Fact Sheets Asthma; 2021. Available from: https://www. who.int/news-room/fact-sheets/detail/asthma. [Last accessed on 2021 Jun 28].
- Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: Executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.
- 9. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol 2001;107:3-8.
- 10. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract 2017;3:1.
- 11. Şekerel BE, Türktaş H, Bavbek S, Öksüz E, Malhan S. Economic burden of pediatric asthma in turkey: A cost of illness study from payer perspective. Turk Thorac J 2020;21:248-54.
- 12. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: The REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ Prim Care Respir Med 2014;24:14009.
- 13. Al-Jahdali H, Wali S, Salem G, Al-Hameed F, Almotair A, Zeitouni M, *et al.* Asthma control and predictive factors among adults in Saudi Arabia: Results from the Epidemiological Study on the Management of Asthma in Asthmatic Middle East Adult Population study. Ann Thorac Med 2019;14:148-54.
- 14. Tarraf H, Al-Jahdali H, Al Qaseer AH, Gjurovic A, Haouichat H, Khassawneh B, *et al.* Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study. Respir Med 2018;138:64-73.
- 15. Mungan D, Aydin O, Mahboub B, Albader M, Tarraf H, Doble A, *et al.* Burden of disease associated with asthma among the adult general population of five Middle Eastern countries: Results of the SNAPSHOT program. Respir Med 2018;139:55-64.
- Bassam M, Behbehani N, Farouk H, Alsayed M, Montestruc F, Al-Jahdali H, *et al.* Adherence to medication among adult asthma patients in the Middle East and North Africa: Results from the ESMAA study. Respir Med 2021;176:106244.
- 17. Khadadah M, Mahboub B, Al-Busaidi NH, Sliman N, Soriano JB, Bahous J. Asthma insights and reality in the Gulf and the near East. Int J Tuberc Lung Dis 2009;13:1015-22.

- Sekerel BE, Gemicioglu B, Soriano JB. Asthma insights and reality in Turkey (AIRET) study. Respir Med 2006;100:1850-4.
- Kurt E, Metintas S, Basyigit I, Bulut I, Coskun E, Dabak S, *et al.* Prevalence and risk factors of allergies in turkey (PARFAIT): Results of a multicentre cross-sectional study in adults. Eur Respir J 2009;33:724-33.
- Benkheder A, Bouacha H, Nafti S, Taright S, El Ftouh M, Yassine N, *et al.* Control of asthma in the Maghreb: Results of the AIRMAG study. Respir Med 2009;103 Suppl 2:S12-20.
- Al-Jahdali HH, Al-Hajjaj MS, Alanezi MO, Zeitoni MO, Al-Tasan TH. Asthma control assessment using asthma control test among patients attending 5 tertiary care hospitals in Saudi Arabia. Saudi Med J 2008;29:714-7.
- Bener A, Abdulrazzaq YM, Debuse P, Al-Mutawwa J. Prevalence of asthma among Emirates school children. Eur J Epidemiol 1994;10:271-8.
- Owayed A, Behbehani N, Al-Momen J. Changing prevalence of asthma and allergic diseases among Kuwaiti children. An ISAAC Study (Phase III). Med Princ Pract 2008;17:284-9.
- 24. Tarraf H, Aydin O, Mungan D, Albader M, Mahboub B, Doble A, et al. Prevalence of asthma among the adult general population of five Middle Eastern countries: Results of the SNAPSHOT program. BMC Pulm Med 2018;18:68.
- Levy ML, Andrews R, Buckingham R, Evans H, Francis C, Houston R, et al. Confidential Enquiry Report. Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD). London: Royal College of Physicians; 2014. Available from: https://www.rcplondon.ac.uk/sites/default/files/ why-asthma-still-kills-full-report.pdf. [Last accessed on 2021 Mar 26].
- Olaguibel JM, Quirce S, Juliá B, Fernández C, Fortuna AM, Molina J, et al. Measurement of asthma control according to Global Initiative for Asthma guidelines: A comparison with the Asthma Control Questionnaire. Respir Res 2012;13:50.
- O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: Time for a new approach? Eur Respir J 2017;50:1701103.
- Tuomisto LE, Ilmarinen P, Niemelä O, Haanpää J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinäjoki Adult Asthma Study. Respir Med 2016;117:223-9.
- 29. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: The INSPIRE study. BMC Pulm Med 2006;6:13.
- 30. Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. Respir Med 2002;96:142-9.
- Miles C, Arden-Close E, Thomas M, Bruton A, Yardley L, Hankins M, et al. Barriers and facilitators of effective self-management in asthma: Systematic review and thematic synthesis of patient and healthcare professional views. NPJ Prim Care Respir Med 2017;27:57.
- 32. Gruffydd-Jones K, Hansen K. Working for better asthma control: How can we improve the dialogue between patients and healthcare professionals? Adv Ther 2020;37:1-9.
- Haughney J, Barnes G, Partridge M, Cleland J. The living & breathing study: A study of patients' views of asthma and its treatment. Prim Care Respir J 2004;13:28-35.
- 34. Noibi S, Mohy A, Gouhar R, Shaker F, Lukic T, Al-Jahdali H. Asthma control factors in the Gulf Cooperation Council (GCC) countries and the effectiveness of ICS/LABA fixed dose combinations: A dual rapid literature review. BMC Public Health 2020;20:1211.
- Al-Moamary MS, Alhaider SA, Alangari AA, Idrees MM, Zeitouni MO, Al Ghobain MO, *et al.* The Saudi Initiative for Asthma – 2021 Update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2021;16:4-56.

- 36. Aksu F, Şahin AD, Şengezer T, Aksu K. Effect of training by a physician on dynamics of the use of inhaler devices to improve technique in patients with obstructive lung diseases. Allergy Asthma Proc 2016;37:98-102.
- Caminati M, Vaia R, Furci F, Guarnieri G, Senna G. Uncontrolled asthma: Unmet needs in the management of patients. J Asthma Allergy 2021;14:457-66.
- Moradi-Lakeh M, El Bcheraoui C, Daoud F, Tuffaha M, Kravitz H, Al Saeedi M, *et al.* Prevalence of asthma in Saudi adults: Findings from a national household survey, 2013. BMC Pulm Med 2015;15:77.
- National Institute for Health and Care Excellence (NICE), Asthma Diagnosis, Monitoring and Chronic Asthma; 2020. Available from: https://www.nice.org.uk/guidance/ng80/resources/ asthma-diagnosis -monitoring-and-chronic-asthma-management -pdf-1837687975621. [Last accessed on 2021 Mar 26].
- Kaplan A, Mitchell PD, Cave AJ, Gagnon R, Foran V, Ellis AK. Effective asthma management: Is it time to let the AIR out of SABA? J Clin Med 2020;9:E921.
- British Thoracic Society. Asthma: Better Lung Health for All. Available from: https://www.brit-thoracic.org.uk/ quality-improvement/guidelines/asthma. [Last accessed on 2021 Mar 29].
- Pollart SM, Elward KS. Overview of changes to asthma guidelines: Diagnosis and screening. Am Fam Physician 2009;79:761-7.
- Schuler M, Faller H, Wittmann M, Schultz K. Asthma Control Test and Asthma Control Questionnaire: Factorial validity, reliability and correspondence in assessing status and change in asthma control. J Asthma 2016;53:438-45.
- Zeru TG, Engidawork E, Berha AB. Assessment of asthma control and quality of life among asthmatic patients attending armed forces referral and teaching hospital, Addis Ababa, Ethiopia. Pulm Med 2020;2020:5389780.
- Tommola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Niemelä O, Nieminen P, et al. Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma. Eur Respir J 2019;54:1801580.
- Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest 2004;125:2046-52.
- Larsson K, Kankaanranta H, Janson C, Lehtimäki L, Ställberg B, Løkke A, *et al.* Bringing asthma care into the twenty-first century. NPJ Prim Care Respir Med 2020;30:25.
- Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. Cochrane Database Syst Rev 2017;4:CD012226.
- Grembiale RD, Pelaia G, Naty S, Vatrella A, Tranfa CM, Marsico SA. Comparison of the bronchodilating effects of inhaled formoterol, salmeterol and salbutamol in asthmatic patients. Pulm Pharmacol Ther 2002;15:463-6.
- Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, *et al.* Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991;325:388-92.
- 51. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax 2002;57:880-4.
- Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332-6.
- Beasley R, Bird G, Harper J, Weatherall M. The further paradoxes of asthma management: Time for a new approach across the spectrum of asthma severity. Eur Respir J 2018;52:1800694.
- FitzGerald JM, Tavakoli H, Lynd LD, Al Efraij K, Sadatsafavi M. The impact of inappropriate use of short acting beta agonists in asthma. Respir Med 2017;131:135-40.
- 55. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C.

Overuse of short-acting β 2-agonists in asthma is associated with increased risk of exacerbation and mortality: A nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55:1901872.

- Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. Emerg Med J 2005;22:404-8.
- 57. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: Recommendations for prescribing. Drugs Aging 2008;25:415-43.
- Kaplan AG, Correia-de-Sousa J, McIvor A; Global Policy Steering Group on Improving Asthma Outcomes. Global quality statements on reliever use in asthma in adults and children older than 5 years of age. Adv Ther 2021;38:1382-96.
- O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, *et al*. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.
- Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, *et al.* Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. Lancet 2003;361:1071-6.
- O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, *et al.* Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.
- 62. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, *et al.* As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
- 63. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, *et al.* Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.
- 64. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): A 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28.
- 65. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
- Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, *et al.* A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32:545-54.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
- 68. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, *et al.* GINA 2019: A fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and

adolescents. Eur Respir J 2019;53:1901046.

- 69. Cruz ÁA, Barile S, Nudo E, Brogelli L, Guller P, Papi A. ICS/formoterol in the management of asthma in the clinical practice of pulmonologists: An international survey on GINA strategy. Asthma Res Pract 2021;7:1.
- Al-Moamary MS, Al-Hajjaj MS, Idrees MM, Zeitouni MO, Alanezi MO, Al-Jahdali HH, *et al.* The Saudi initiative for asthma. Ann Thorac Med 2009;4:216-33.
- Furuhashi K, Fujisawa T, Hashimoto D, Kamiya Y, Yasui H, Karayama M, et al. Once-daily fluticasone furoate/vilanterol combination versus twice-daily budesonide/formoterol combination in the treatment of controlled stable asthma: A randomized crossover trial. J Asthma Allergy 2019;12:253-61.
- 72. Stanford RH, Averell C, Parker ED, Blauer-Peterson C, Reinsch TK, Buikema AR. Assessment of adherence and asthma medication ratio for a once-daily and twice-daily inhaled corticosteroid/long-acting β-agonist for asthma. J Allergy Clin Immunol Pract 2019;7:1488-96.e7.
- 73. Averell CM, Stanford RH, Laliberté F, Wu JW, Germain G, Duh MS. Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs. J Asthma 2021;58:102-11.
- 74. Busse WW, O'Byrne PM, Bleecker ER, Lötvall J, Woodcock A, Andersen L, *et al.* Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: A randomised trial. Thorax 2013;68:513-20.
- O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J 2014;43:773-82.
- 76. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, *et al.* Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: A randomized trial. Chest 2013;144:1222-9.
- Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2013;9:CD000052.
- 78. Newman KB, Milne S, Hamilton C, Hall K. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. Chest 2002;121:1036-41.
- Tavakoli H, Mark FitzGerald J, Lynd LD, Sadatsafavi M. Predictors of inappropriate and excessive use of reliever medications in asthma: A 16-year population-based study. BMC Pulm Med 2018;18:33.
- Blakeston S, Harper G, Zabala Mancebo J. Identifying the drivers of patients' reliance on short-acting I2-agonists in asthma. J Asthma. 2021;58:1094-1101. W
- Chan AH, Katzer CB, Horne R, Haughney J, Correia de Sousa J, Williams S, *et al.* SABA Reliance Questionnaire (SRQ): Identifying patient beliefs underpinning reliever overreliance in asthma. J Allergy Clin Immunol Pract 2020;8:3482-9.e1.