Thorac Res Pract. 2023; 24(6): 309-324 DOI: 10.5152/ThoracResPract.2023.23035

Review

Stepwise Approach in Asthma Revisited 2023: Expert Panel Opinion of Turkish Guideline of Asthma Diagnosis and Management Group

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Cite this article as: Çelik GE, Aydın Ö, Damadoğlu E, et al. Stepwise approach in asthma revisited 2023: Expert panel opinion of Turkish guideline of asthma diagnosis and management group. *Thorac Res Pract.* 2023;24(6):309-324.

Abstract

Introduction of inhaled corticosteroids (ICS) has been the cornerstone of the long-term management of asthma. ICSs either alone or in combination with long-acting beta-2 agonists have been shown to be associated with favorable asthma outcomes. However, asthma control is still reported to be below expectations all around the world. Research in the last decades focusing on the use of ICS/formoterol both as maintenance and as needed (maintenance and reliever therapy approach) showed improved asthma outcomes. As a result of recent developments, Turkish Asthma Guidelines group aimed to revise asthma treatment recommendations. In general, we recommend physicians to consider the risk factors for poor asthma outcomes, patients' compliance and expectations and then to determine "a personalized treatment plan." Importantly, the use of short-acting beta-2 agonists alone as a symptom reliever in asthma patients not using regular ICS is no longer recommended. In stepwise treatment approach, we primarily recommend to use ICS-based controllers and initiate ICS as soon as possible. We define 2 different treatment tracks in stepwise approaches as maintenance and reliever therapy or fixed-dose therapy and equally recommend each track depending on the patient's risks as well as decision of physicians in a personalized manner. For both tracks, a strong recommendation was made in favor of using add-on treatments before initiating phenotype-specific treatment in step 5. A strong recommendation was also made in favor of using biologic agents and/or aspirin treatment after desensitization in severe asthma when indicated.

KEYWORDS: Asthma, long-term management, reliever, controller, severe asthma
Received: *March 26, 2023* ***Accepted:*** *July 25, 2023* ***Publication Date:*** *October 27, 2023*

INTRODUCTION

Since its first publication in 1996, Turkish Asthma Guidelines: Diagnosis and Treatment has been updated regularly. The last update was published in December 2020 and was carried out under the auspices of the Turkish Thoracic Society and Turkish National Society of Allergy and Clinical Immunology. However, owing to dramatical changes in the management of asthma recently, particularly in stepwise approach in terms of treatment arms, a revision is needed in our recent recommendations. In this context, online meetings were held with an author group of the guidelines team. All of the authors were experts on asthma. For the updating process, a careful review of MEDLINE, PubMed, and Cochrane databases, after the last update in 2020, was carried out. The panel discussions were held via online meetings during which treatment goals and strategies as well as treatment steps were discussed in line with current literature data.

While making the recommendations, the relevant existing evidence, the current situation and evidence and health legislation in our country, and the clinical experiences of the experts were taken into consideration. The decision on recommendations were made based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method.[1] The quality of evidence was decided based on Global Initiative for Asthma (GINA) A, B, C, and D criteria.[2] In brief, when the benefit of the patient is high, a strong recommendation was issued. If the risk–benefit ratio

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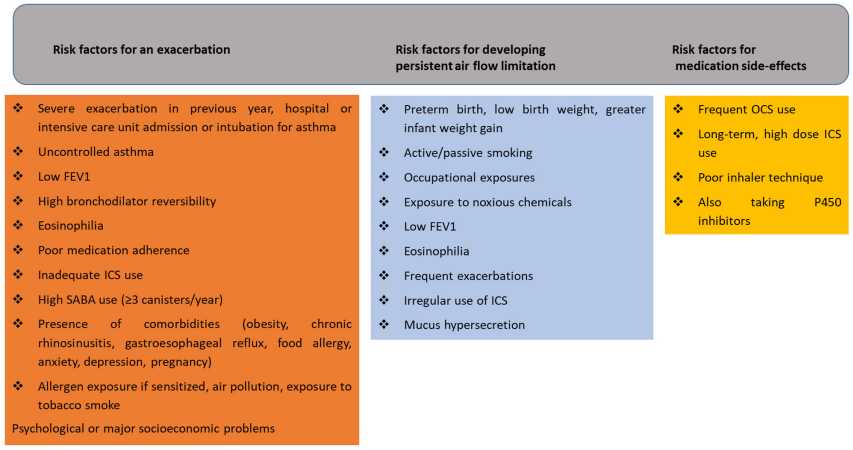

Figure 1. Risk factors for poor prognosis of asthma. FEV1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid; OCS, oral corticosteroid; P450, cytochrome P450; SABA, short-acting beta-2 agonist.

was not clear enough, a weak recommendation was made. The word "recommended" was used for strong recommendation in a positive sense, while "not recommended" indicated a strong recommendation in a negative sense. Weak recommendation was made as "suggestion" or as "could benefit."

After several meetings, recommendations were finalized. Recommendations were sent to all members of the expert panel via Google Forms and voting was performed confidentially. Recommendations were interpreted as "strong consensus" if there was more than ≥90% agreement, as "consensus" when there was 70%-89% agreement, and as "majority agreement" if the agreement was between 51% and 69%.[2] Each recommendation was numbered in order to be easily followed up by the readers. The final version of the manuscript including the voting results was shared with the expert panel, and the last version was established. The update includes 7 sections, 116 recommendations for treatment, and 9 recommendations created by the expert panel to improve asthma management in the country. The details of each section are provided here.

MAIN POINTS

- Using short-acting beta-2 agonists alone as a symptom reliever in asthma patients not using regular inhaled corticosteroids (ICS) is no longer recommended.
- We recommend using ICS-based controllers and initiating ICS therapy as soon as possible in stepwise treatment approach.
- Two different treatment tracks are defined in stepwise approaches as maintenance and anti-inflammatory reliever therapy or fixed-dose therapy and each track is equally recommended. Decision should be made according to the patient's risks as well as choice of physicians in a personalized manner.
- We recommend using add-on treatments before initiating phenotype-specific treatments in step 5.
- We recommend using biologic agents and/or aspirin treatment after desensitization in severe asthma when indicated.

CLINICAL AND RESEARCH CONSEQUENCES

Section 1: Goals of Asthma

Achieving asthma control is the target in the long term-management of asthma. Within the scope of this, we recommend daily symptom control and prevention for future risk factors that will adversely affect the course of the disease [Evidence A/strong recommendation] [Recommendation 1, strong consensus].[2,3] In order to minimize future risks, we recommend to reduce/prevent exacerbations to prevent persistent airflow limitation and to keep the drugs used within safe limits in terms of side effects (Figure 1) [Evidence A/strong recommendation] [Recommendation 2, strong consensus].[2,3] Therefore, we recommend that patients with asthma should be reviewed in terms of these risk factors in their initial evaluation and during the annual follow-up [Evidence A/strong recommendation] [Recommendation 3, strong consensus].

Section 2: General Principles of Asthma Treatment

Considering the treatment goals in asthma, we urge physicians to consider the need for "biopsychosocial strategic approaches" that will provide success in patient care in the long term.[2,3] We recommend that physicians take care of patients from a biopsychosocial point of view and exhibit the necessary attitudes in terms of both medical treatment and psychosocial support. [Evidence A/strong recommendation] [Recommendation 4, strong consensus].[2,3] A multimodality approach that consists of medications, nonmedical therapies, treatment of risk factors, and ensuring patient compliance is recommended (Figure 2) [Evidence A/strong recommendation] [Recommendation 5, strong consensus].[2,3] It is essential to ensure patients' compliance with the treatment.[2,3] We recommend to determine the conditions/factors that will lead to poor compliance of the patients with the treatment and to take an approach toward this [Evidence A/strong recommendation] [Recommendation 6, strong consensus]. We recommend that these evaluations be made at the first visit as the initial evaluation and be reviewed annually [Evidence A/strong recommendation] [Recommendation 7, strong consensus].[2,3]

One of the main factors that will affect the compliance of patients with the treatment is the effective communication

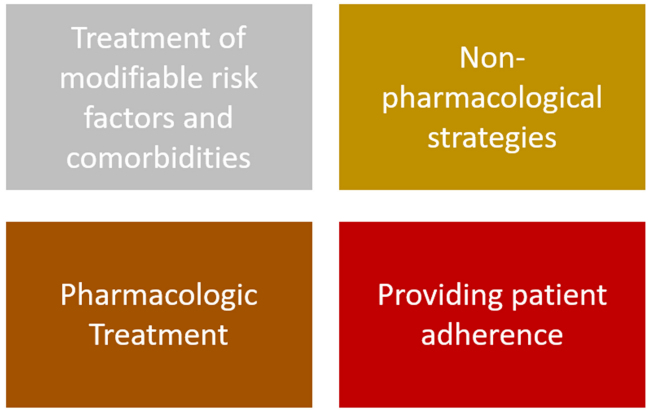

Figure 2. General treatment strategies for adjusting chronic follow-up of asthma.

of physicians with patients and family members. We recommend physicians to use effective communication skills, as it will increase the patient's compliance with the treatment and cause positive effects in the treatment outcomes [Evidence A/strong recommendation] [Recommendation 8, consensus].[2,3] We recommend patient-centered approaches as it has been shown that the participation of patients and, if necessary, their family members in the treatment processes increases the success of the treatment [Evidence A/strong recommendation] [Recommendation 9, strong consensus].[2,3]

The chronic nature of the disease requires patients to have knowledge and skills related to disease management. In this context, we recommend patients to be informed about asthma and to be guided in terms of the health resources they can access, to improve their inhaler device use skills, to increase their health literacy level, and to learn to use a written asthma action plan [Evidence A/strong recommendation] [Recommendation 10, strong consensus].[2,3]

Section 3: General Principles of Pharmacological Treatment

ASTHMA MEDICATIONS

We recommend controller medications, reliever medications, and add-on therapies for the long-term management of asthma [Evidence A/strong recommendation] [Recommendation 11, strong consensus].[2-5] **Controller medications** are medications that are used on a regular basis or as needed in the form of inhaled corticosteroid (ICS)/formoterol (FOR) in step 1 and 2 treatments. Inhaled corticosteroid-based medications are the main controllers that suppress airway inflammation and consequently symptom control is achieved, exacerbations are prevented, and respiratory function loss is reduced.[2,3]

Reliever medications are used in order to relieve the symptoms only when the patient has a symptom or assumed to have symptoms (i.e., before exercise). Frequent need for reliever medications is an indication of insufficiency or lack of proper usage of controller medications.[2,3] **Add-on medications** are added to the current treatment for patients in whom good symptom control cannot be achieved despite ICS/long-acting beta-2 agonists (LABA) combination or for patients with exacerbations despite steps 3-5 treatment, and they are not used alone.[2,3,6] These include phenotype-specific and not phenotype-specific treatments.

Using "controller" medications in order to control symptoms and prevent future risks and using "symptom reliever" medications when the patient has symptoms forms the basis of pharmacological treatment of asthma.

TREATMENT STRATEGY [STEPWISE APPROACH]

We recommend long-term introduction of the pharmacological treatment in the context of "Stepwise approach" (Figure 3) [Evidence A/strong recommendation] [Recommendation 12, strong consensus].[2,3] Stepwise treatment is an approach to adjust pharmacological therapy according to asthma control level, in which steps are dynamic (up and down) and are changed based on asthma control level.

CHOICE OF CONTROLLER MEDICATIONS

We primarily recommend to use ICS-based controllers and initiate their use as soon as possible in the stepwise treatment approach [Evidence A/strong recommendation] [Recommendation 13, strong consensus]. It has been reported that initiating ICS use early in asthma provided good outcomes in terms of preventing disease progression.[4] Delayed initiation of controller medications resulted in reduced response rates and may cause to use higher doses of medications for similar treatment response.[4] More frequent exacerbations and increased pulmonary function loss over the years may be seen in patients who are not on ICS treatment.[5] For this reason, ICS-based treatments are recommended to be initiated starting from step 1.[2-5]

Leukotriene receptor antagonists (LTRAs) are not recommended as the first option at step 2 [Evidence A/strong recommendation] [Recommendation 14, strong consensus].[6] Compared with ICS-based treatments at step 2 and ICS/LABA combination treatments at steps 3-4, LTRAs have been shown to have a limited effect in preventing exacerbations.[6] Moreover, caution should be exercised in terms of neuropsychiatric adverse effects while using this treatment.[2,3] However, they are recommended when ICS-containing medication cannot be given at this step [Evidence A/strong recommendation] [Recommendation 15, Consensus].[2,3,6]

CHOICE OF SYMPTOM RELIEVERS

We do not recommend to use short-acting beta-2 agonist (SABA) alone as a symptom reliever in adult patients not using regular ICS-based controller therapy [Evidence A/strong recommendation] [Recommendation 16, strong consensus].[2,3,7-9] For this reason, we recommend taking ICS whenever SABA is taken for mild asthmatic patients who are not using regular controller therapy [steps 1-2] [Evidence B/strong recommendation] [Recommendation 17, strong consensus] (Box 1).[2,3,10]

Box 1. Rationale for not using SABA alone.

Severe exacerbations may occur in mild asthmatic patients and for this reason this group of patients need ICS-based therapies. However, it has been showed that ICS usage is irregular,[2-3] and SABA usage is inappropriately high in patients with mild asthma.[2-3,8]

SABA usage-related deaths have been reported in patients not using ICS treatment regularly.[9] Because of this, patients who are not using regular controller medications should use ICS-containing medication whenever SABA is taken, as ICS/SABA combination therapy if it is possible or as taking SABA and ICS-containing medication consecutively.[10] This recommendation is primarily for primary care physicians.

This treatment may be administered as ICS/SABA combination therapy in fixed-dose preparation or using the 2 drugs consecutively at the same time. However, the use of a fixed combination of ICS/SABA as a symptom reliever could be safer and more effective in the management of asthma when available. As-needed ICS/FOR is preferentially recommended as a reliever medication by the expert panel [Evidence A/strong recommendation] [Recommendation 18, strong consensus] (Box 2).[10-17]

Box 2. Rationale for recommending ICS/FOR as a reliever.

It is strongly recommended because this treatment method ensures patients receive ICS. In step 2, it has been shown that this treatment is similarly effective in preventing exacerbations and symptom control and more effective in preventing severe exacerbations compared to regular low-dose ICS and as-needed SABA.[11-13]

In other steps (steps 3-4), it has been shown that it prevents exacerbations and provides similar symptom control compared to treatments including as-needed SABA as a reliever.[14-17]

ADD-ON THERAPIES

Add-on therapies are additional therapies that can be applied in both tracks at steps 3-5 and are given in addition to current ICS-based medications.[2,3] [Evidence B/strong recommendation] [Recommendation 19, strong consensus]. These therapies are not recommended to be used alone. Add-on therapies include phenotype-specific and not phenotype-specific treatments (Boxes 3 and 4).[2,3]

Box 3. Phenotype specific add-on therapies.

- Anti-IgE (step 5)
- Anti IL-5, IL-5R (step 5)
- Anti-IL-4/IL-13 (step 5)
- Aspirin treatment after desensitization (step 5)

Box 4. Add-on therapies that are not phenotype specific.

- Add-on LAMA (steps 4-5)
- Add-on LTRA (steps 3-5)
- Low-dose OCS (steps 4-5)
- Azithromycin (step 5)

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Subcutaneous allergen immunotherapy with house dust mite [SCIT] could be beneficial in patients with mild-to-moderate allergic asthma accompanied by allergic rhinitis who are sensitized to house dust mites and whose asthma is under control. Subcutaneous allergen immunotherapy with house dust mite is added to regular treatment to reduce symptoms and medication use, provided that forced expiratory volume in the first second of expiration (FEV1) is ≥70% [Evidence B/weak recommendation] [Recommendation 20, majority agreement].[18]

Sublingual allergen immunotherapy with house dust mite [SLIT] could be beneficial in patients with allergic asthma accompanied by allergic rhinitis, who are sensitized to house dust mites and whose asthma is under control or partially controlled with low–medium-dose ICS and FEV1 ≥70% predicted, when added to the regular treatment to reduce exacerbations and improve symptom control [Evidence B/weak recommendation] [Recommendation 21, consensus].[18] House dust mite sublingual tablets are not currently available in our country and are not covered by reimbursement.

Allergen-specific immunotherapy is recommended to be performed primarily by immunology and allergy specialists in allergy clinics when indicated [Evidence D/strong recommendation] [Recommendation 22, strong consensus].

TRACKS IN STEPWISE APPROACH

The stepwise approach includes 2 different arms. The main discrepancy in the both arms is the preferred reliever medication. In the first track, the reliever consists of a fixed combination of ICS/formoterol, whereas SABA is the recommended reliever in the second track. The main idea in the first track is to prevent SABA use alone due to high risks for morbidity and mortality and guarantee to administer ICS in combination with formoterol.[10]

In the first track, ICS/FOR combination in a single inhaler is used only as needed in steps 1 and 2 in the context of "Anti-inflammatory reliever" and both in maintenance and as-needed treatment, which is called the ''maintenance and reliever (MART) approach'' at steps 3-5.[11-17] This includes using low-dose ICS/FOR containing medications as maintenance treatment and as needed.[11-17] Contrary to fixed-dose approach, the dose of ICS is flexible in the MART approach. The patient can take a certain number of extra doses daily according to his/her needs in addition to the regularly used

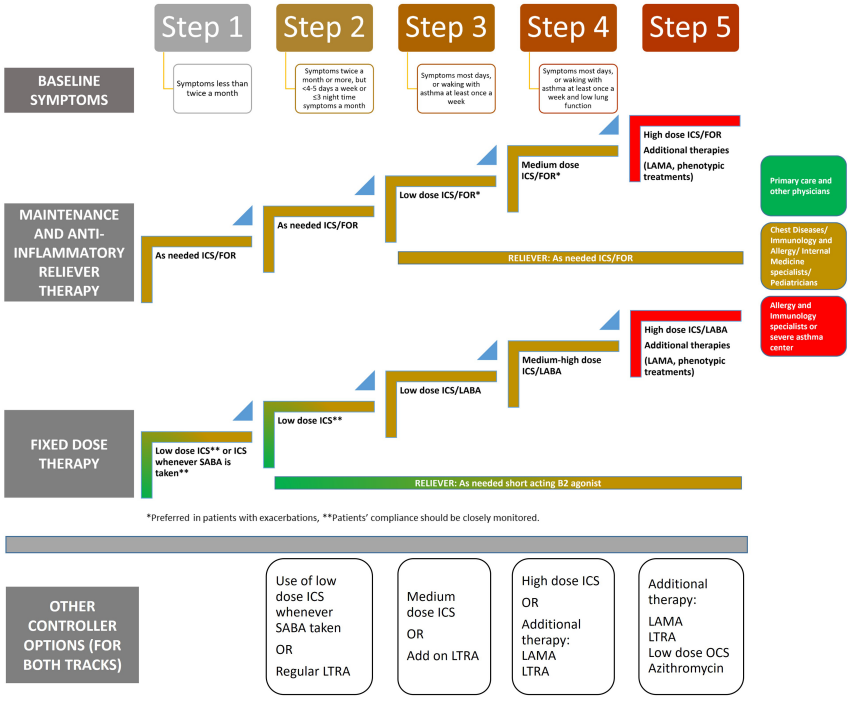

Figure 3. Stepwise approach for chronic treatment of asthma based on treatment tracks. ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting beta-2 agonist.

maintenance dose; by this way, daily ICS dose taken may change.[15-17]

In the other track, SABA is used as a reliever.[19-22] The applied ICS dose in this track is fixed, and ICS is given alone (steps 1-2) or in combination with LABA (steps 3-5) depending on the treatment step.[19-22] This approach is called the "fixed-dose approach" as the dose of ICS is fixed and determined by physicians.[2,3,19-22]

In the stepwise treatment approach, we equally recommend to apply ICS-based therapies in 2 different treatment tracks as MART or fixed-dose therapy (Figure 3) [Evidence A/strong recommendation] [Recommendation 23, strong consensus].[2,3] The choice of either treatment track is affected by not only available current evidence but also other risk factors, factors related to patients' compliance and expectations, and opinion of the treating physician; therefore, a "personalized treatment" is determined accordingly [Tables 1-4] [Evidence

Table 1. Initiation of Step 1 Therapy [Recommendations 26-29]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Patients with asthma symptoms less than twice a month [Recommendation 26, strong consensus]	As-needed low-dose ICS/FOR[11,12] [Recommendation 27, strong consensus]	B	Strong	This treatment method ensures patients to receive ICS while using reliever medication. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Regular low-dose ICS and as-needed SABA [Recommendation 28, majority agreement]	D	Strong	It is recommended to prevent SABA-related adverse events, as the rate of taking SABA alone in patients with mild asthma is high in our country. It is recommended for patients at risk for poor prognosis of asthma. Close monitoring of patient adherence to treatment is recommended. Recommended for primary care physicians.
	Concomitant low-dose ICS whenever SABA is needed[20-22] [Recommendation 29, strong consensus]	B	Strong	Recommended for primary care physicians. Close monitoring of patient adherence to treatment is recommended.

FOR, formoterol; ICS, inhaled corticosteroid; SABA, short-acting beta-2 agonist.

Table 2. Initiation of Step 2 Therapy [Recommendations 30-33]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Two or more daytime symptoms per month but less than 4-5 days per week OR Reliever use 2 or more per month but less than 4-5 days per week OR Patients with complaints of ≤3 nights per month [Recommendation 30, strong consensus]	As-needed low-dose ICS/FOR[12] [Recommendation 31, strong consensus]	A	Strong	It is recommended because it is a treatment type that allows the patient to receive ICS in the use of rescue medication. It is recommended for respiratory diseases, allergy and immunology, internal medicine, and pediatrics physicians.
	Regular low-dose ICS* and as-needed SABA[21] [Recommendation 32, consensus]	A	Strong	It is recommended in patients with risk for poor prognosis of asthma. Close follow-up of the patient's adherence to treatment is recommended. It is a priority recommendation for physicians working in primary health care.
	Additional low-dose ICS with each SABA use[20-22] [Recommendation 33, consensus]	B	Weak	Regular low-dose ICS can be considered in patients with treatment adherence problems.
	Regular LTRA use[6] [Recommendation 15, strong consensus]	A	Strong	It is not the primary treatment in the treatment of asthma.
			Strong	Recommended in patients who cannot use ICS-based therapy. Recommended for respiratory diseases, allergy and immunology, internal medicine, and pediatrics physicians.

FOR, formoterol; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SABA, short-acting beta-2 agonist.
*Low-dose ICS is lower than budesonide 400 µg/day or equivalent.

Table 3. Initiation of Step 3 Therapy [Recommendations 34-37]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Symptoms on most days OR Patients with at least 1 nighttime awakening in a week [Recommendation 34, strong consensus]	MART approach: Maintenance and reliever use of low-dose ICS/FOR[14-17] [Recommendation 35, strong consensus]	A	Strong	It is a priority recommendation for patients with an asthma exacerbation in the previous year. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Fixed-dose approach: Regular low-dose ICS/LABA, as-needed SABA[2,3,19] [Recommendation 36, strong consensus]	A	Strong	Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Regular medium-dose ICS*/as-needed SABA[2,3] [Recommendation 37, strong consensus]	A	Strong	It is a priority recommendation for physicians working in primary health care. Recommendation for primary care physicians; to patients who are candidates for step 3 therapy. Initiation of this therapy and referral to a specialist is recommended.

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; OCS, oral corticosteroid; MART, maintenance and reliever therapy; SABA, short-acting beta-2 agonist.
*Low-dose ICS is lower than budesonide 400 µg/day or equivalent.

A/strong recommendation] [Recommendation 24, strong consensus].

Section 4: Initiation of Pharmacological Therapy

The treatment is commenced with determination of the appropriate treatment step in previously untreated patients. In this context, the frequency of the patient's daytime and nighttime symptoms in the last 4 weeks and the presence of risk factors for poor prognosis of asthma are recommended to be considered [Evidence B/strong recommendation] [Recommendation 25, strong consensus], (Figure 3, Tables 1-4) [Recommendations 15, 26-41].[2,3]

Table 4. Initiation of Step 4 Therapy [Recommendations 38-41]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Asthma symptoms most days OR Nocturnal asthma symptom at least once a week OR Low PFT values [Recommendation 38; strong consensus]	MART approach: Maintenance: medium-dose ICS/FOR As-needed low-dose ICS/FOR[14-17] [Recommendation 39, strong consensus]	A	Strong	It is a priority recommendation for patients with an asthma exacerbation in the previous year. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Fixed-dose approach: Regular medium-dose ICS/LABA, as-needed SABA[2,19] [Recommendation 40, strong consensus]	A	Strong	Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
Patients with quite uncontrolled asthma symptoms or patients with an exacerbation	Short-term use of OCS [Recommendation 41, strong consensus]	A	Strong	

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; MART, maintenance and reliever therapy; OCS, oral corticosteroid; PFT, pulmonary function test; SABA, short-acting beta-2 agonist.

Maintenance and reliever therapy is recommended to be applied with low-dose ICS/FOR [160/4.5 µg for BUD/FOR or 100/6 µg for BDP/FOR [Evidence A/strong recommendation] [Recommendation 42, strong consensus].[2,3] Care should be taken not to exceed the maximum daily dose of formoterol in MART approach [Evidence A/strong recommendation] [Recommendation 43, strong consensus]. In patients with asthma 12 years of age and older, the maximum recommended daily dose is a total of 54 µg formoterol (delivered dose) including doses used for maintenance for BUD/FOR [Total maximum number of dose/days: 12].[2] The maximum recommended daily dose is a total of 36 µg formoterol (delivered dose) including doses used for maintenance for BDP/FOR [Total maximum number of dose/days: 8].[2]

Section 5: Monitorization of Treatment

We recommend to achieve good asthma control and to prevent and/or control future risks in the follow-up of the asthmatic patient [Evidence A/strong recommendation] [Recommendation 44, strong consensus].[2,3] In this regard, treatment is monitored, the response is assessed, and the treatment is reviewed in line with the data obtained.[2]

FOLLOW-UP SCHEDULE

Regular follow-up at certain intervals is recommended for asthmatic patients [Evidence A/strong recommendation] [Recommendation 45, strong consensus].[2,3] After initiation of asthma treatment for the first time, a control visit is recommended to schedule within 4 weeks after the initial evaluation [Evidence A/strong recommendation] [Recommendation 46, strong consensus]. During this visit, accuracy of the diagnosis, exposure to environmental triggers and their control, response to treatment, patient's acceptance/perception of the disease, and factors related to adherence are recommended to be assessed (Box 5) [Evidence A/strong recommendation] [Recommendation 47, strong consensus].[2,3]

Box 5. Maintenance and reliever treatment (MART) approach

This includes using low dose ICS/FOR containing medications as maintenance treatment and as-needed.[14-17] It is a flexible treatment approach. The ICS dose used by the patient is not fixed. The patient can take a certain number of extra doses daily according to his/her needs in addition to the regularly used maintenance dose, by this way daily ICS dose taken may change.

Afterward, it is recommended to evaluate the patient's asthma every 4 weeks until the control is achieved, and then every 3-12 months according to the clinical features as well as underlying severity of the disease [Evidence A/strong recommendation] [Recommendation 48, strong consensus].[2,3] A follow-up visit is recommended 2-4 weeks after an exacerbation [Evidence D/strong recommendation] [Recommendation 49, strong consensus].[2,3]

ASSESSMENTS PERFORMED AT FOLLOW-UP

Initial characteristics of asthma should be recorded while commencing initial treatment [Evidence A/strong recommendation] [Recommendation 50, strong consensus]. Assessing symptom control during the last 4 weeks, risk factors, FEV_1, treatment adherence, exacerbation history, and factors like patient's satisfaction is recommended at each control visit (Figure 4) [Evidence A/strong recommendation] [Recommendation 51, strong consensus].[2,3] Monitoring the course of the disease with recording annual follow-up of certain parameters of patients regularly is recommended in order to determine individual asthma progress of patients (Figure 4) [Evidence A/strong recommendation] [Recommendation 52, strong consensus].

Reviewing Treatment

Pharmacological treatment is routinely reviewed during follow-up visits. In this regard, pharmacological therapy can be

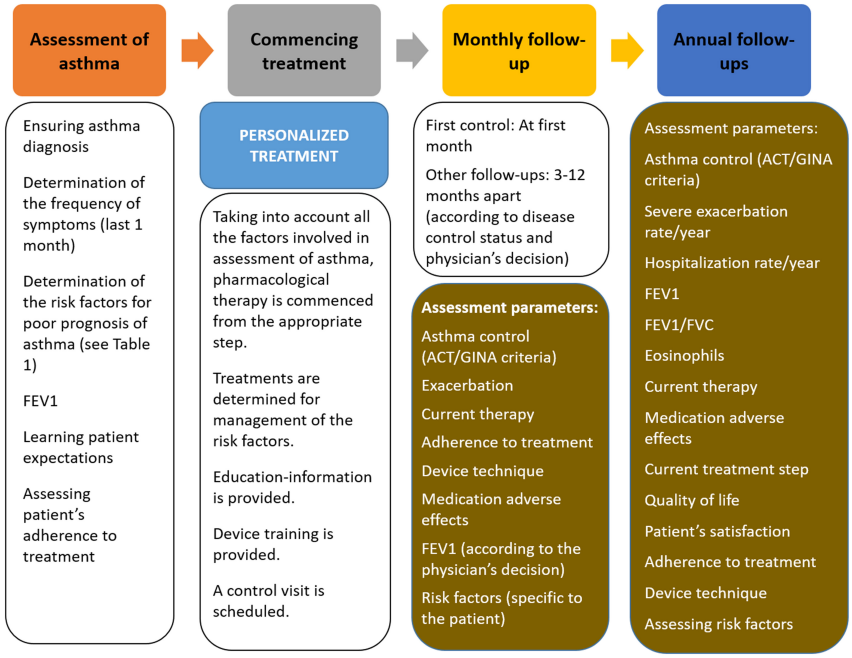

Figure 4. Monitoring parameters of asthma at initial diagnosis and follow-up. ACT, asthma control test; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; GINA, Global Initiative for Asthma.

continued as it is, and medications used can be changed or their doses can be increased or decreased.

If Asthma Is Not Controlled with Current Therapy

First of all the reasons for uncontrolled asthma should be clarified (Figure 5). In this context, confirmation of the diagnosis may be needed; treatment adherence should be checked, comorbidities are treated, and environmental control measures are taken [Evidence A/strong recommendation] [Recommendation 53, strong consensus].[2,3] In case of treatment nonadherence or an adverse event requiring discontinuation of the medication, change of therapy is recommended [Evidence A/strong recommendation] [Recommendation 54, strong consensus].

If asthma control is still not achieved after assessing and controlling each of these conditions and providing an appropriate/effective approach, then asthma is considered uncontrolled. In this case, a step-up may be considered or if in steps 4-5 initiating add-on therapies may be considered before stepping up (Figure 5) [Evidence A/strong recommendation] [Recommendation 55, strong consensus].[2,3,23-26]

Adjustment of Treatment in Case of Poor Medication Adherence and/or Increased Risk of Medication Side Effects

Patients should be trained and checked for inhaler device technique at each visit [Evidence D, strong recommendation] [Recommendation 56, strong consensus].[2,3] If there is a difficulty in inhaler device technique that cannot be corrected, switching to another device by considering the patient's opinion as well is recommended [Evidence D/strong recommendation] [Recommendation 57, strong consensus].

We recommend to make changes in the treatment if side effects are observed with current medications that necessitate changing [Evidence D, strong recommendation] [Recommendation 58, strong consensus]. In this context, other controllers can be used [Evidence A, strong recommendation] [Recommendation 59, consensus].[23-26]

If ICS-based therapies cannot be used in step 2 treatment [poor adherence or side effect], LTRA use can be considered [Evidence A/strong recommendation] [Recommendation 15, strong consensus].[25,26]

It is recommended to initiate another LABA-containing combination therapy in patients if side effects of LABA are observed using ICS/LABA in fixed-dose approach tracks of step 3-5 treatments [Evidence D/strong recommendation] [Recommendation 60, majority agreement].[2,3,19] We recommend to initiate LTRA in addition to low-dose ICS treatment in patients with side effects of LABA on low-dose ICS/LABA in fixed-dose approach in step 3 treatment [Evidence A/strong recommendation] [Recommendation 61, majority agreement].[25,26] In patients who have side effects of LABA on low-dose ICS/LABA use in step 3 treatment, it may be beneficial to discontinue LABA and start theophylline in addition to low-dose ICS treatment [Level of evidence B/weak recommendation] [Recommendation 62, strong decision].[2,3]

If there is a poor medication adherence in either fixed-dose or MART therapy and cannot be corrected, introduction of other track is recommended to be considered [Evidence D/strong recommendation] [Recommendation 63, strong consensus].[2,3]

Stepping Up in Uncontrolled Asthma

Stepping up is recommended in patients whose symptom control cannot be achieved and who are at risk of an asthma exacerbation despite current treatment and appropriate measures to control environmental factors, comorbid conditions, adherence to treatment, with a definiteasthma diagnosis

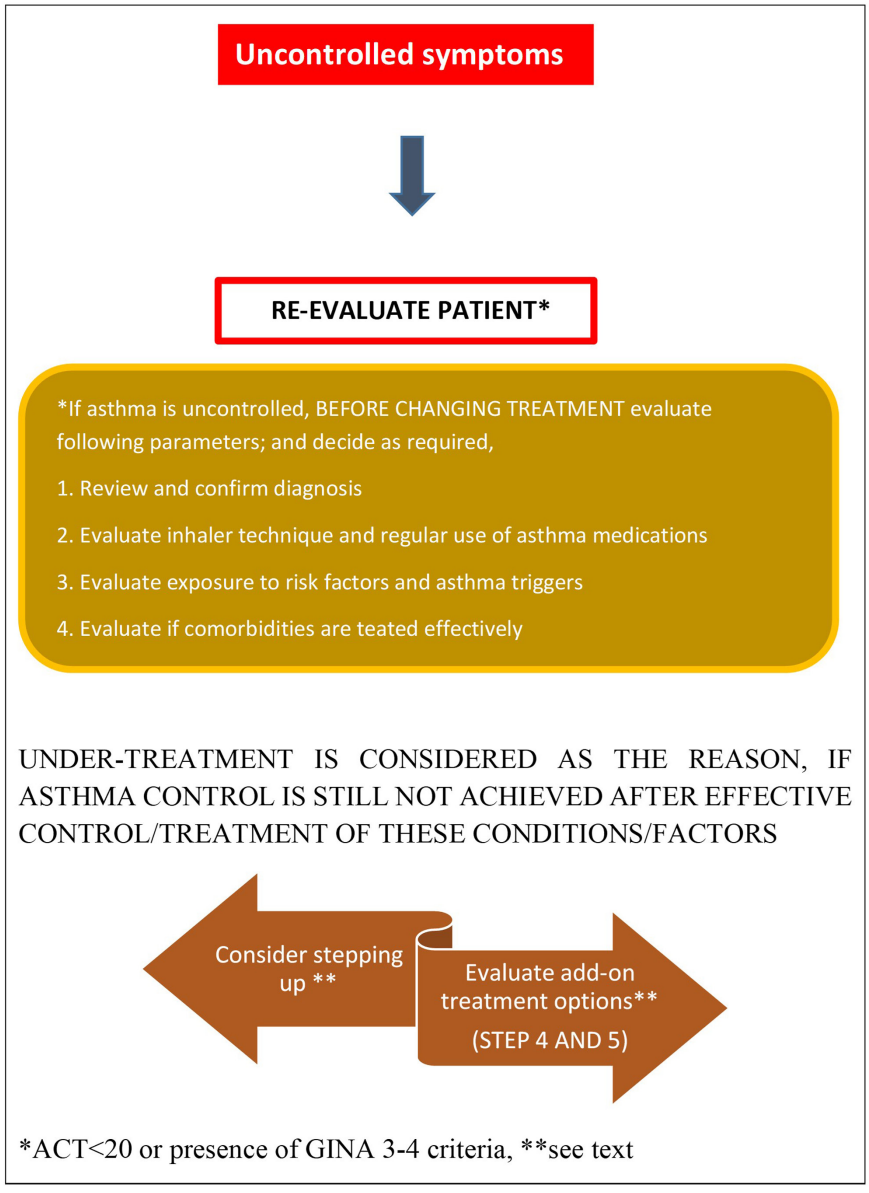

Figure 5. Approach to patient whose asthma is not well controlled under treatment. ACT, asthma control test; GINA, Global Initiative for Asthma. *ACT < 20 or presence of GINA 3-4 criteria. **See text.

[Evidence C/strong recommendation] [Recommendation 64, strong consensus].[2,3] We recommend to step up the treatment at the track in which the patient is currently on [Evidence A/strong recommendation] [Recommendation 65, strong consensus].

Stepping up the treatment is recommended in 2 different ways:[2]

- *Sustained step up under chronic treatment:* In patients whose asthma is uncontrolled for at least 1 month on treatment, a step-up in treatment is done (Figure 3) [Recommendation 66, strong consensus].[14,15]
- *Short-term step up [for 1-2 weeks]:* The ICS dose is increased in patients with loss of asthma control during viral respiratory tract infections or allergen exposure. This application is recommended for 1-2 weeks [Evidence C/strong recommendation] [Recommendation 67, strong consensus].[16,17]

Initiation of "Add-On Treatments" in Uncontrolled Asthma

In uncontrolled asthma at step 4, initiation of add-on treatments may be considered before stepping up (Figures 3 and 5) [Evidence D/weak recommendation] [Recommendation 68, consensus].[2,3] However, at step 5, we strongly recommend to initiate add-on non-phenotype-specific treatments before phenotype-specific treatment (Figures 3 and 5) [Evidence D/strong recommendation] [Recommendation 69, consensus].[2,3,23-26] These therapies can be used in both tracks [Evidence A/strong recommendation] [Recommendation 70, strong consensus].

Addition of LAMA therapy may be beneficial in patients who are not under control with medium-dose ICS/LABA in step 4 [Evidence B/weak recommendation] [Recommendation 71, consensus].[23,24]

Adding LTRA to medium-dose ICS/LABA therapy in step 4 may provide benefit [Evidence A/weak recommendation]

[Recommendation 72, consensus].[2] We recommend to add LTRA to ICS/LABA therapy in both tracks in patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease in steps 3-5 [Evidence B/strong recommendation] [Recommendation 73, strong consensus].[25,26]

Stepping Down in Controlled Asthma Under Current Treatment

The aim of stepping down is to find the minimum effective dose that maintains good control of symptoms and prevents exacerbations, the risk of persistent airflow limitation, and progression of the disease while minimizing drug side effects and the costs of treatment.[2,3] There is not enough evidence about optimal timing of step-down, which drugs and how much dose should be reduced first.[27-31] For this reason, we recommend to make a decision individually by taking into account personal and environmental risks of the patients. Therefore, if asthma is under control with the treatment initiated, stepping down the treatment should be considered, by taking into account individual risks (Figure 6) [Evidence D/strong recommendation] [Recommendation 74, strong consensus].[27]

Stepping down is not recommended based on symptom control alone [Evidence D/strong recommendation] [Recommendation 75, strong consensus]. The mainstay of stepping down is well asthma control that is composed of control of symptoms, risks for asthma exacerbations or persistent airflow limitation, and development of side effects.[27-31]

We recommend going 1 step down in patients who have remained under control for at least 3 months after asthma symptom control has been achieved, and if there is no risk for an asthma exacerbation or persistent airflow limitation [Evidence B/strong recommendation] [Recommendation 76, strong consensus].[2] This period can be extended up to 6 months. If there is a risk factor for the development of asthma exacerbation or persistent airflow limitation, the current treatment is recommended to continue for at least 1 year with observation of no exacerbation.[27] If there is no asthma exacerbation in the last year, in this case, in line with the decision of the physician, 1 step-down can be considered with close follow-up of the patient [Evidence D/strong suggestion] [Recommendation 77, strong consensus].[27-31] However, if the side effects pose a risk for the use of the drug, the treatment is adjusted according to the profit–loss ratio.

Step-down approach may differ from patient to patient, depending on their actual treatment, the presence of risk factors, and the patient's preferences. Pulmonary function test values, symptom scores, and exacerbation risks are recorded before stepping down.[27-31] The patient is provided clear instructions. The patient's active participation is ensured, and the patient is closely followed up. Patients should be closely monitored for symptom control and exacerbation risk, following step-down.[22,23] [Recommendation 78, strong consensus]. Stepping down too quickly in a short time can lead to an increased risk of symptoms and asthma exacerbations.[27,28] Complete cessation of ICS therapy in adult and

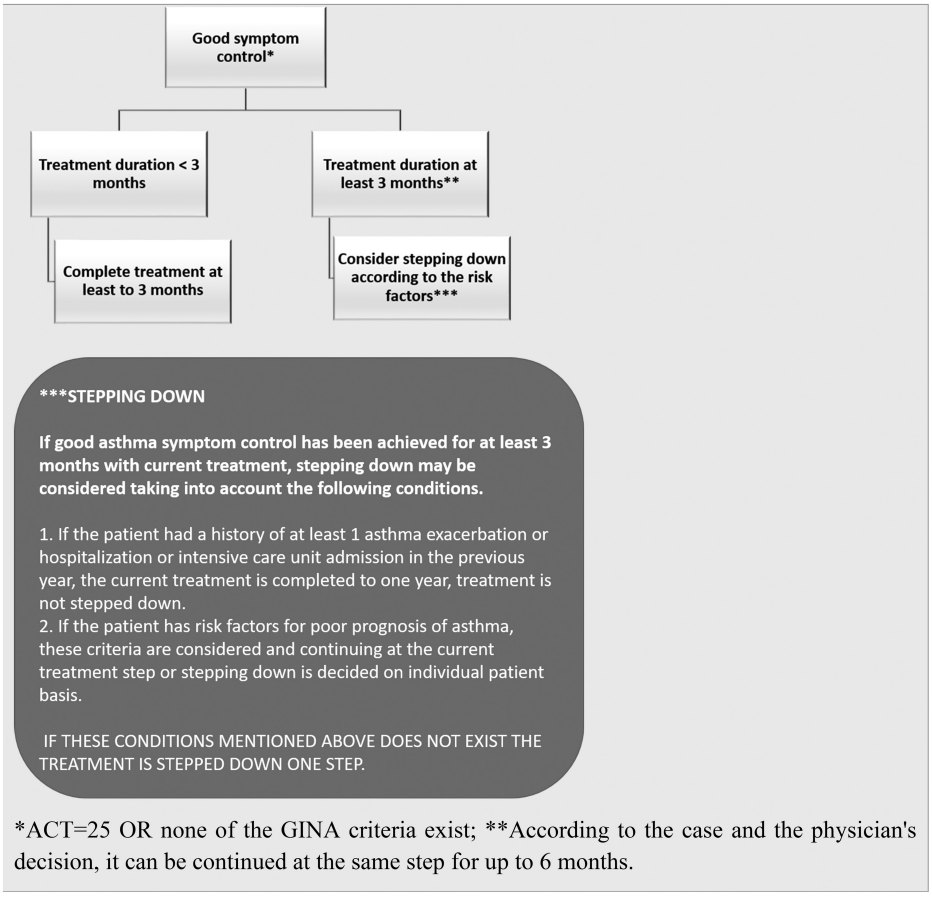

Figure 6. Approach to stepping down treatment. ACT, asthma control test; GINA, Global Initiative for Asthma. *ACT = 25 OR none of the GINA criteria exist. **According to the case and the physician's decision, it can be continued at the same step for up to 6 months.

adolescent patients is not recommended because it is associated with a significantly increased risk of asthma exacerbations [Evidence B/strong recommendation] [Recommendation 79, consensus].[29-31]

SPECIFIC COMMENTS FOR STEPPING DOWN OPTIONS IN TRACKS

Maintenance and Reliever Therapy Approach

In maintenance treatment of MART approach, first the dose of ICS and then its frequency are reduced (Figure 7) [Recommendation 80, consensus].[2,10-17] When stepping down, as-needed use of low-dose ICS/FOR is recommended in the lowest steps (steps 1 and 2)[Recommendation 81, strong consensus].[2,27]

Fixed-Dose Approach

We recommend first a 25%-50% reduction in ICS doses at 3-month intervals for the fixed-dose approach (Table 5) [Evidence B/strong recommendation] [Recommendation 82, strong consensus].[2,10,11,27,30,31]

Step Movements in Tracks

We recommend to perform stepping up or down through the same track from any of the conventional fixed-dose or MART approaches (Figure 7) [Evidence D/strong recommendation] [Recommendation 96, strong consensus].[2] If there is no response and/or poor adherence to treatment at any step, switching from one track to another is considered (Figure 7) [Evidence D/strong recommendation] [Recommendation 97, strong consensus].[2]

Section 6: Special Conditions

Asthma Treatment and Management for Primary Care Physicians

Asthma cases requiring primary and secondary care can be treated in primary health care settings (Figure 3, Tables 1 and 2) [Evidence D/strong recommendation] [Recommendation 98, consensus].[2,3] Because of the risks of SABA-only treatment, these patients should be closely monitored for adherence to ICS therapy as recommended [Evidence D/strong recommendation] [Recommendation 99, strong consensus].[7-9]

Primary care physicians are expected to refer adult patients for expert assessment in the presence of certain conditions [pulmonologists, allergy and immunology, and internal medicine specialists] [Evidence D/strong recommendation] [Recommendation 100, strong consensus].[2,3] These conditions are patients with diagnostic difficulties; patients in whom asthma and COPD cannot be differentiated or suspicion of overlap (ACO); need for use of ICS/LABA combination, LABA, LTRA, or LAMA that specialist prescription is required in Turkey; patients whose asthma is difficult to

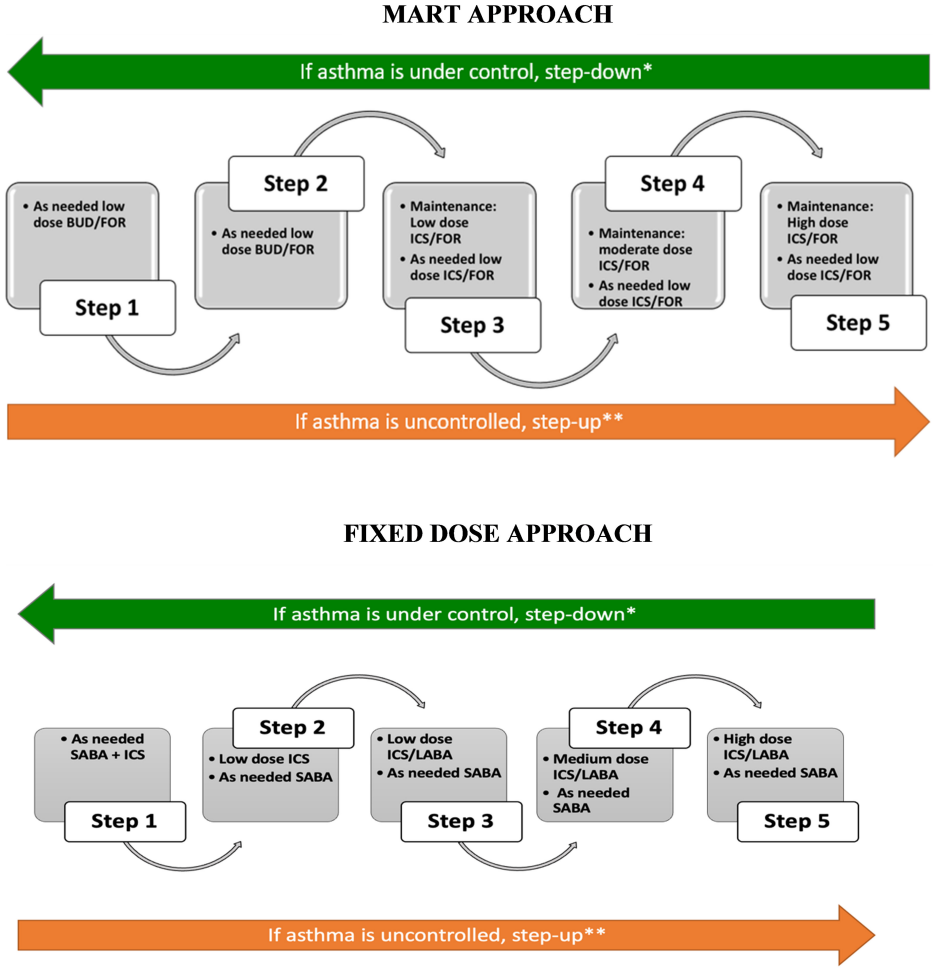

Figure 7. Step-up and step-down based on tracks. BUD, budesonide; FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; SABA, short-acting beta-2 agonist. *See Table 5. **See Figure 3.

control; suspicion of occupational asthma; patients with allergen-induced asthma who require allergy testing (referral to an allergy and immunology specialist); and patients who require specialist care, follow-up, and treatment in terms of comorbidities.[2,3] Before referral of patients to a secondary or tertiary care center from primary care centers, we recommend to initiate an appropriate treatment [Evidence D/strong recommendation] [Recommendation 101, strong consensus].[2,3,20-22] Before referral, we recommend initiation of an appropriate dose of ICS according to the patient's treatment step (Figure 3, Tables 1 and 2) [Evidence A/strong recommendation] [Recommendation 102, strong consensus].[20-22]

When considering referral of patients whose asthma remains uncontrolled despite step 2 treatment, we recommend increasing the ICS daily dose to moderate dose and then referral of the patient to specialist care [Evidence D, strong recommendation] [Recommendation 103, strong consensus].[2,3] Avoidance measures are recommended against asthma triggers that patients are exposed to [Evidence D/strong recommendation] [Recommendation 104, strong consensus].

REFERRAL OF SEVERE ASTHMA

Before the diagnosis of severe asthma, we recommend to ensure the accuracy of the diagnosis of asthma, evaluate adherence to treatment, and improve any existing problems, treat comorbidities, and control triggers appropriately [Evidence A/strong recommendation] [Recommendation 105, strong consensus].[2,32] Despite having these conditions under control, the patients whose asthma remains uncontrolled with high-dose ICS/LABA therapy or is becoming uncontrolled when this treatment is reduced is defined as severe asthma.[2,32]

We recommend referral of patients receiving step 4-5 treatment and followed by specialists who have difficulty in diagnosis and treatment, to the centers experienced in severe asthma, especially for phenotypic evaluation [Evidence D/strong recommendation] [Recommendation 106, strong

Table 5. Recommendations for Stepping Down Treatment for Fixed-Dose Approach [Recommendations 83-90]

Treatment Step	Current Medications	Options for Stepping Down	Evidence
Step 5	High-dose ICS/LABA and OCS	High-dose ICS/LABA is continued, OCS dose is reduced [Recommendation 83, strong consensus]	D
		Following up with sputum eosinophils to reduce OCS dose [No consensus was reached on the form of the recommendation.]	B
		Alternate day OCS [Recommendation 84, consensus]	D
		Using higher-dose ICS instead of OCS [Recommendation 85, strong consensus]	D
		Get expert opinion [Recommendation 86, strong consensus]	D
Step 4	Medium–high-dose ICS/LABA maintenance	ICS dose of the ICS/LABA combination is reduced by 50% [Recommendation 87, strong consensus]	B
		Discontinuation of LABA is not recommended [Recommendation 88, strong consensus]	A
	High-dose ICS and another controller	ICS dose is reduced by 50% while continuing the other controller [Recommendation 89, strong consensus]	B
Step 3	Low-dose ICS/LABA maintenance	ICS/LABA dose is reduced to once a day [Recommendation 90, consensus]	D
		Discontinuation of LABA is not recommended [Recommendation 91, strong consensus]	A
	Medium–high-dose ICS	ICS dose is reduced by 50% [Recommendation 82, strong consensus]	B
Step 2	Low-dose ICS	Switch to once-daily dose [budesonide, ciclesonide, mometasone] [Recommendation 92, consensus]	A
		Switch to as-needed low-dose ICS/FOR treatment [Recommendation 93, Consensus]	A
		Adding LTRA (weak recommendation) [Recommendation 94, consensus]	B
	Low-dose ICS	Switch to as-needed low-dose ICS/FOR treatment [Recommendation 93, consensus]	A
		Discontinuation of ICS totally is not recommended [Recommendation 95, majority agreement]	A

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

Table 6. Non-Phenotype-Specific and Phenotype-Specific Treatments in Step 5 [Recommendations 109-115]

Non-Phenotype-Specific Treatments			
Recommendation	**Evidence**	**Strength of Recommendation**	**Comment**
High-dose ICS/LABA[2,19]	A	Strong [Recommendation 109, strong consensus]	• In most patients increasing ICS dose provides minimal benefit; however, it is recommended before phenotype-specific therapy. • Be careful for systemic side effects of high-dose ICS.
Add-on LAMA[34,35]	A-B	Strong [Recommendation 110, strong consensus]	• Recommended for uncontrolled patients on high-dose ICS/LABA. • LAMA can be prescribed in a separate inhaler [tiotropium] or as a combination in triple therapy [beclomethasone–formoterol–glycopyrronium, fluticasone furoate–vilanterol–umeclidinium, mometasone–indacaterol–glycopyrronium]. • Add-on LAMA moderately affects pulmonary functions and delays exacerbations. • Combination therapy should include at least medium-dose ICS. • Recommended in ACO. • Recommended before initiation of phenotype-specific therapy.
Add-on azithromycin[36]	B	No consensus	• 500 mg/day 3 times a week for at least 6 months was shown to be beneficial in patients taking high-dose ICS/LABA with persistent asthma symptoms. • Prolongation of QT interval and development of antimicrobial resistance are concerns. • Used in eosinophilic and noneosinophilic asthma. • Consultation with an infectious diseases specialist regarding development of antimicrobial resistance is required.
Low-dose oral corticosteroids[2,37,38] [<7.5 mg prednisolone equivalent]	D	Weak [Recommendation 111, majority agreement]	• Can be beneficial in some severe asthma patients. • Can be tried with close monitoring for severe side effects in patients taking step 4-5 treatment with inadequate response to other treatment options
Phenotype-Specific Treatments			
Recommendation	**Evidence**	**Strength of Recommendation**	**Comment**
Anti-IgE[39]	A	Strong [Recommendation 112, strong consensus]	• It is recommended in patients with uncontrolled asthma despite step 5 treatment and has perennial allergy [compatible clinical symptoms with diagnostic tests] and has a total IgE level between 30 and 1500 IU/mL.
Anti-IL-5 and IL-5R[40-43]	A	Strong [Recommendation 113, strong consensus]	• It is recommended in patients with uncontrolled eosinophilic asthma despite step 5 treatment.
Anti-IL-4/-13[44]	A	Strong [Recommendation 114, strong consensus]	• It is recommended in patients with uncontrolled eosinophilic asthma despite step 5 treatment.
Aspirin treatment after desensitization[45]	B	Strong [Recommendation 115, Strong consensus]	• It is recommended in patients with a diagnosis of NERD and uncontrolled disease despite Step 5 treatment. It has been shown to prevent recurrence of nasal polyps. • Close monitoring is required for adverse effects. • It is recommended to be performed by allergy and immunology specialists in cooperation with ENT physicians. • Doses of 100 mg-1300 mg are used in aspirin desensitization. The experiences in our country show that 300 mg dose is usually sufficient. The effects are mostly related to reduction of inflammation in rhinitis/rhinosinusitis and nasal polyps. It has been shown to prevent exacerbations and reduce OCS usage in asthma.
Bronchial thermoplasty[46]	B	No consensus	• Long-term consequences are not known. It can be performed on a clinical trial basis. • It may be beneficial in experienced centers in selected patient groups.

ACO, asthma-COPD (chronic obstructive pulmonary disease) overlap; ENT, ear–nose–throat; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; NERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroid.

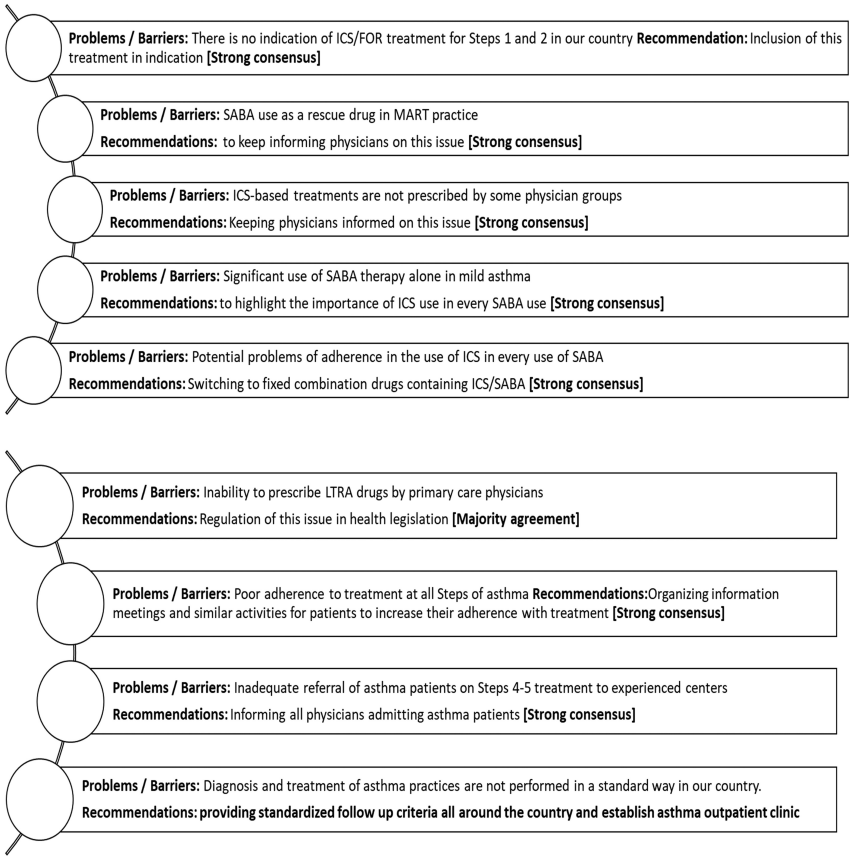

Figure 8. Problems and barriers in Turkey and recommendations provided by expert panel [recommendations 1-9]. ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; OCS, oral corticosteroid; SABA, short-acting beta-2 agonist.

consensus].[32,33] Referral criteria are as follows: cases where diagnostic difficulties are experienced and/or interventional procedures and tests are required for differential diagnoses which cannot be performed, history of a life-threatening exacerbation or intensive care unit admission and mechanical ventilation because of an asthma exacerbation, any suspicion of severe asthma and/or presence of referral criteria for severe asthma, patients who are candidates for a biologic agent, presence of marked eosinophilia, suspicion of occupational asthma, presence of a history of anaphylaxis, venom [bee], food and drug allergies, allergic bronchopulmonary aspergillosis, and exacerbation with nonsteroidal anti-inflammatory drugs.[32,33]

In patients with severe asthma, we strongly recommend to use non-phenotype-specific add-on treatments in steps 4-5 before initiation of phenotype-specific treatments (Table 6) [Evidence A/strong recommendation] [Recommendation 107, consensus] [Recommendations 109-111].[23-26,32,34-38] In these cases, phenotyping studies are performed and evaluated in terms of eligibility for treatment options available in our country (Table 6) [Evidence D/strong recommendation] [Recommendation 108, strong consensus] [Recommendations 112-115].[33,39-46]

COUGH VARIANT ASTHMA

The type of asthma with the only or principal symptom as cough is defined as "cough variant asthma."[47] Although these cases have been shown to benefit from medium-dose ICS/LABA, adding LTRA, and short-term OCS treatment in case of no response was recommended [Recommendation 116, majority agreement].[47] Patients have been reported to benefit from codeine 20-30 mg capsules [red prescription] when added to their treatment, up to 6 times daily.[47]

Conclusion and Recommendations

Asthma management in our country is an up-to-date treatment process because of its high prevalence, an important reason of health service admission, and a high cost especially in patients with severe asthma. It is anticipated that some of the recommendations in our updated treatment approach may cause difficulties in the field. In this context, there is a need for some arrangements and initiatives to be done by individual, social, and country managers in order to reduce and control the burden of asthma in our country. Our suggestions for problems in this regard are given below (Figure 8).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Design – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Supervision – A.F.K., A.F.K., A.Y., B.G., D.E.,F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B.; Resources – G.E.Ç., Ö.A.; Materials – G.E.Ç., Ö.A.; Data Collection and/or Processing – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Analysis and/or Interpretation – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K.,

Ö.A., S.B., S.K.Ö., S.R.I.; Literature Search – A.B., E.D., F.Ö.E., G.E.Ç., Ö.A., S.K.Ö., S.R.I.; Writing – A.B., E.D., G.E.Ç., Ö.A., S.K.Ö.; Critical Review – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.

Declaration of Interests: A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., F.Ö.E., F.Y., G.K., İ.Y., M.K., Ö.A., S.B. have no conflict of interest to declare. B.G. reports the following interests: grants or contracts from AstraZeneca, Sanofi, GSK, Chiesi, Abdi İbrahim, Deva, Sandoz; honoraria for lectures from GSK, Chiesi, Abdi İbrahim, Deva, Sandoz; participation on a Data Safety Monitoring Board or Advisory Board for GSK, Chiesi; participation to clinical studies for Sanofi, AstraZeneca. E.D. reports the following interests: honoraria for lectures from Novartis, GSK. G.E.Ç. reports the following interests: honoraria for lectures from GSK, Novartis; leadership or fiduciary role in other board, society, committee or advocacy group for EAACI Executive Committee (representative for working groups). İ.K.O. reports the following interests: honoraria for lectures from GSK, AstraZeneca, Novartis, Chiesi, Deva, Abdi İbrahim Pharmaceuticals; participation on a Data Safety Monitoring Board or Advisory Board for GlaxoSmithKline, Deva, Abdi İbrahim Pharmaceuticals; leadership or fiduciary role in other board, society, committee or advocacy group for GINA, Turkish Thoracic Society. S.K.Ö. reports the following interests: honoraria for lectures from Novartis, GSK. S.R.I. reports the following interests: leadership or fiduciary role in other board, society, committee or advocacy group for Turkish Thoracic Society.

Funding: This study received no funding.

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