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SHORT REPORT

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# Turkish Severe Asthma Program (TSAP)

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## ABSTRACT

Severe asthma (SA) is defined as asthma that is uncontrolled under high-dose ICS+LABA treatment or can only be controlled with this high-dose treatment, with a differential diagnosis from difficult asthma. It has been known that severe asthmatics with poor symptom control were reported as 3.7% (range between 3.6-6.1%). Although SA constitutes a very small proportion of all asthmatics, it causes a significant social and psychological burden on patients and on social reimbursement systems. The Turkish Severe Asthma Program (TSAP) was established by stakeholders that include the Turkish National Society of Allergy and Clinical Immunology (TNSACI), representatives from national severe asthma centers, and those from the pharmaceutical industry to develop standards to diagnose and treat patients with SA and to monitor their treatments at the national level. Here we present the TSAP organization and vision.

**Keywords:** Asthma, severe asthma, national data, TNSACI, TSAP

## INTRODUCTION

Severe asthma (SA) is a disease that is characterized by frequent attacks, and frequent emergency visits and hospitalizations, and seriously impairs the quality of life. As a result of long-term steroid treatment given to ensure disease control, patients develop serious side effects, sometimes reaching life-threatening levels. With the introduction of new biological agents in the treatment of SA, it has been possible to control asthma in these patients, and decreased attacks and long-term systemic steroid use has been also observed. Moreover, additional treatments beyond biologicals and non-pharmacological treatment options should also be evaluated thoroughly (1). However, severe asthma patients in our country cannot access these treatments sufficiently.

Severe asthmatics, who constitute around 5–10% of asthmatics, place a burden on society by requiring advanced healthcare facilities and a high economic cost (2, 3). It is recommended that asthmatic cases who are followed by specialists and who have difficulty in diagnosis and in Steps 4-5 treatment should be referred to centers experienced in SA, especially in terms of phenotypic evaluation (4-6).

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Here, the organization and vision of the TSAP, which was established to follow up pediatric and adult severe asthma patients with standard diagnosis and treatment methods, will be explained.

### Program Objectives

#### Short-Term Goals

Establishing severe asthma clinics and using a standardized approach to be used in these centers:

1. Identification and phenotyping of severe asthmatic patients,
2. Decision-making on an effective diagnostic algorithm,
3. Drawing up a treatment and follow-up roadmap (control, stepping up/down, treatment/biologicals selection and switching, non-biological treatment options, non-pharmacological treatments),
4. Identification of attack risks,
5. Determination of disease burden,
6. Detection and improvement of patient compliance,

#### Long-Term Goals

1. Collection of data for severe asthma database records,
2. Publication of national data,
3. Ensuring that the centers in the program have the necessary equipment to become a "severe asthma center of excellence", apply for accreditation, and be accredited,
4. Encouraging participation of new centers that meet the standards,
5. Establishment of transitional units between childhood and adulthood

The timeline and action taken during the formation of TSAP are summarized in Figure 1.

### Definition of Severe Asthma

The severity of asthma is based on retrospective assessment of at least 2-3 months of asthma treatment required for good asthma control. This assessment identifies patients with SA that may benefit from add-on therapies such as biologics. The definitions related with SA are given in Table I. First, assess asthma control, and if it is well controlled after 3 months of therapy, determine asthma severity according to the treatment step. If the patient has uncontrolled asthma, it is referred as "difficult to treat asthma" because of insufficient or improper treatment, recurrent unresolved comorbidities, and it is called "severe asthma" if there is optimal treatment and resolved issues (1).

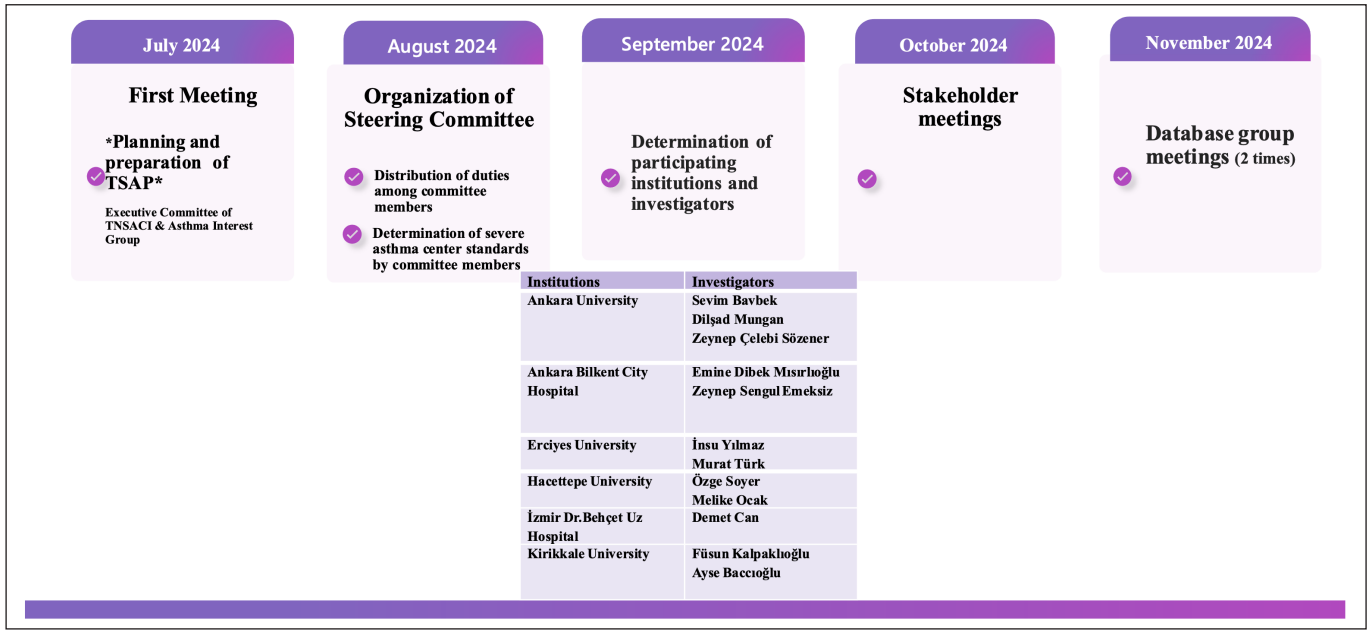


**Figure 1:** The timeline and actions of the TSAP Organization.

**Defining of Asthma Control**

Asthma control contains two parts, as symptom control and risk of outcomes. The tools for asthma control are listed in Supplementary file Table I. Symptom control shows past the situation of asthma and lung function is an important part of the assessment of future risk. Symptom control includes the frequency of day and night-time asthma symptoms, night waking, activity limitation due to asthma, and ≥2/week frequency of reliever (short acting beta2-agonist; SABA) use. At least one yes to any question suggests not well controlled asthma. Furthermore, among the numeric asthma control tools, uncontrolled asthma is scored as less than 20 in the Asthma Control Test (ACT) and >0.75 in the Asthma Control Questionnaire.

**Table I. Definitions of severe asthma and related conditions in adults, adolescents, and children aged 6-11 years (1)**

| | |
|---|---|
| **Uncontrolled asthma** | Uncontrolled asthma is diagnosed if at least one of the criteria below exists;<br>a. Poor symptom control: frequent symptoms or reliever use, activity limitation, night awaking due to any asthma symptom<br>b. History of frequent exacerbations, defined as >2 attacks/year that require OCS or one that necessitates hospitalization |
| **Difficult to treat asthma** | "Difficult to treat asthma" is asthma that is uncontrolled despite using a medium to high dose of ICS with a second controller (usually a LABA) or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.<br>In many cases, asthma may appear to be difficult to treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking, or comorbidities, or because the diagnosis is incorrect. |
| **Asthma severity** | "Asthma severity" is assessed retrospectively due to the patient's level of asthma treatment that is required to control asthma. To assess asthma severity, the minimum effective dose of treatment step must be taken at which good asthma control has been achieved. So, this assessment cannot be applied to patients with uncontrolled asthma.<br>- Moderate asthma: is well controlled with low or moderate dose ICS+LABA (step 3 or 4).<br>- Mild asthma: is well controlled with as-needed low-dose ICS+formoterol or low dos≥e ICS plus as-needed SABA (step 1 or 2). |
| **Severe asthma** | "Severe asthma" is described as;<br>-Having uncontrolled asthma even after receiving at least 3-6 months of optimal treatment with high-dose ICS+LABA and/or LTRA and/or OCS<br>- Adjustment of managing contributing factors such as comorbidities and inhaler technique, adherence.<br>- Asthma is not classified as severe if it improves when contributory factors such as inhaler technique and adherence are addressed. |
| **Severe asthma phenotypes**<br>**Type 2 inflammation** | Type 2 inflammation of bronchial mucosa in asthma is characterized by eosinophilic or allergic status proven by the following tests with no systemic CS treatment.<br>a. Allergic asthma: Allergen sensitivity in skin prick tests or serum specific IgE that correlates with asthma symptoms.<br>b. Eosinophilic asthma:<br>(In patients with high dose ICS or OCS)<br>- Blood eosinophils ≥150/uL (check at least 3 times), and/or<br>- FeNO ≥20 ppb (check at least 3 times), and/or<br>- Sputum eosinophils ≥2%. |
| **Non-type 2 inflammation** | Type 2 inflammation is driven by cytokines such as interleukin (IL)-4, IL-5, and IL-13. This type of inflammation has a good response to corticosteroids.<br>In cases where the type 2 inflammatory requirements are not met, it is referred to as non-type 2 asthma. The amounts of neutrophils are elevated in non-type 2 inflammation. |

**OCS:** Oral corticosteroid, **ICS:** Inhaled corticosteroid, **LTRA:** Leukotriene receptor antagonist

**Prevalence of Severe Asthma and Disease Burden in Children and Adult Patients with Asthma**

Asthma is an important health problem all over the world, with an increasing prevalence in low- and middle-income countries (7). Geographical location, age, ethnicity, and the definitions implemented by various organizations all contribute to the substantial variation in the prevalence of SA (8).

Currently, there are still few studies on the prevalence of SA in children because of its low prevalence, the use of various definitions, and the lack of whole-population studies. The proportion of severe asthmatics in pediatric asthma appears to be lower than that of adult asthma (9). The Swedish BAMSE birth cohort of 3015 children aged 12 years reported an estimated SA prevalence of 0.23% of the population or 2.1% of children with asthma (10). In the NORDSTAR cohort, the prevalence of SA was 0.4%, 1.0%, and 0.3% in children in Sweden, Norway, and Finland, respectively (11). The current Danish cohort, which comprises 29,851 children between the ages of 2 and 17, with a median age of 8.0 years, exhibits a SA rate of 4.8%, which is higher than that of other cohorts (12). Nevertheless, few studies have examined the prevalence of SA cases within the pediatric demographic in Türkiye. Research including 618 children aged 6 to 18 years across 12 asthma outpatient clinics indicated that 1.6% of the patients had severe asthma (SA) (13). Further research is required about SA in children, with the primary inquiry being the prevalence of SA among children in Türkiye.

The PARFAIT Study yielded the most comprehensive epidemiological data regarding adult asthma patients. In this study, prevalence of asthma in the adult age group was 7.1% in males and 9% in females nationwide (14). The epidemiological studies conducted in our country, presenting data from several cities, have indicated that the incidence of asthma among adults ranged from 0.7% to 13.5%, while the prevalence of asthma-like symptoms varied from 7.1% to 38% (15-21). Although variable rates are reported in various studies from different countries regarding the prevalence of SA, the study conducted in Netherlands by Hekking et al. is the most widely accepted one in this context.

Severe refractory asthma was defined as the proportion of patients with difficult-to-manage asthma exhibiting both high adherence and effective inhalation technique. As a result, the prevalence of severe asthma was found to be 3.7% among all adult asthmatics and 10.4 per 10000 adult inhabitants (22). The national data for the prevalence of severe asthma in Türkiye is unfortunately limited. A single-center study has reported that 7% of 300 adult patients with asthma were identified as having severe asthma (23). A multicenter study conducted at tertiary care centers revealed the prevalence of severe asthma as 12% (2). In a further investigation involving 2,336 patients from 28 tertiary hospitals, this rate was shown to be 7.7% (24). The Turkish Adult Asthma Registry recently reported a severe asthma prevalence of 32.6%. It is important to acknowledge that this rate, much exceeding those observed in prior national and international research, pertains specifically to patient data from tertiary facilities specializing in asthma treatment and does not represent the prevalence of SA in the general patient population (4).

Previous studies have shown that severe asthma increases health expenditures and severely reduces patients' quality of life (6, 25). A study in asthmatic children has indicated that total asthma expenses were over twice as high in the very poorly controlled group compared to the not well controlled or well controlled groups (baseline: $7,846, $3,526 and $3,766, respectively; month 12: $7,326, $2,959 and $2,043, respectively; month 24: $8,879, $3,308, and $1,861, respectively (P<0.001) (26). A study conducted in Türkiye has revealed that the annual cost per asthmatic patient amounted to $991.7, with outpatient expenses constituting the predominant share of direct costs at 48.5%, while the average inpatient cost per patient was $955.5 (27). Children with severe asthma frequently experience significant exacerbations linked to decreased lung function, poor quality of life, and a greater likelihood of medication side effects and interactions. All these factors contribute to higher expenses as well as an increase in unscheduled visits, emergency department admissions, hospitalizations, school absences, and workdays lost due to caring responsibilities (28, 29).

Regarding SA in adult patients, most patients with SA experience loss of labor force and this leads to economic losses (6). In our country, it has been shown that the annual per capita direct cost of adult asthma is 830.2-1467.5 USD, the cost of emergency department admission is 125.2-306.2 USD, and the cost of hospitalization is 513.2-1066 USD (30-33). The annual per capita cost of patients with severe asthma is 4369.8 USD (5). The direct and indirect costs impose a substantial burden on the state and insurance systems, indicating that severe asthma is a health issue requiring careful assessment. In a study with controlled and uncontrolled asthmatics according

to the existence of symptoms despite the GINA step 4 or 5 treatment, patients expressed a variety of activities that they were unable to do including routine daily activities, exercise, hanging out with friends, and even having pets (3). It is evident that SA imposes a significant burden on economic, individual, and societal scales. In this context, a comprehensive health policy with effective treatment strategies must be implemented to mitigate the socioeconomic consequences of severe asthma.

### Team Members to Diagnose and Follow-Up Severe Asthma in Specialized Severe Asthma Clinics and to Participate in the Implementation of This Program

Team members working in severe asthma clinics should have experience in the diagnosis and treatment of severe asthma, as well as use and follow-up of biological therapies. The presence of an intensive care unit in the same building is not required for a severe asthma clinic to be eligible. However, referral and rapid transport to an intensive care unit should be available if necessary. The health care team in a severe asthma clinic should include:

- Pediatric/Adult Allergy-Clinical Immunology Specialist
- Pediatric/Adult Asthma nurse
- Lung function testing technician
- Physiotherapist
- Dietician
- Clinical psychologist

In order to achieve a multidisciplinary approach, on-site assessment of different specialists such as pulmonologist, otorhinolaryngologist, dermatologist, rheumatologist, endocrinologist, cardiologist, physical medicine and rehabilitation specialist, and psychiatrist should be feasible.

### Requirements to Diagnose and Follow-Up Severe Asthma in Specialized Severe Asthma Clinics

To correctly diagnose and treat patients in severe asthma centers, there are required diagnostic facilities to accurately identify and treat patients in addition to having staff members with the right equipment. These are listed in the Table II. Firstly, even though the history is suggestive of asthma, the diagnosis of asthma needs to be confirmed. The test needed to confirm asthma diagnosis is spirometry that can show airway obstruction and reversibility. Furthermore, bronchial provocation tests and peak flowmeter may be useful if spirometry is normal or cannot be used. To make the differential diagnosis, some specific tests and consultation to Departments other than Allergy may be appropriate on clinical suspicion.

### Data Collection

As already pointed out in the Introduction part, and based on the defined short-term and long-term goals, the collection of data for severe asthma database records leading to publication of national data, electronic case report forms, and an electronic data capture system will be used to collect and extract anonymized data from the enrolled subjects (Table III).

**Table II: Recommended tests to diagnose and follow-up for severe asthma in specialized severe asthma clinics**

| Category | Test or Facility | Indication |
|---|---|---|
| **Diagnosis** | Spirometry | Suggestive history of asthma |
| | Bronchodilator responsiveness (Reversibility) test | |
| | Bronchial provocation test (BPT) | Negative reversibility and high FEV1 |
| | Peak expiratory flow (PEF) meter | Spirometry is normal or unavailable. |
| | Impulse oscillometry (IOS) | To identify and predict loss of control of asthma in children that cannot cooperate for spirometry. Unlike spirometry, IOS doesn't require cooperation and can be used before 5 years old. IOS has been noted to be more useful than spirometry and to identify both the asthma and predict loss of control and exacerbations. |
| | | To evaluate peripheral small airways either alone or in combination with FeNO measurement |

**Table II continue**

| | | |
|---|---|---|
| **Phenotyping** | **Hemogram: Eosinophil count**<br>>= 150/μL shows type 2 inflammation | To diagnose type 2 inflammation.<br>If blood eosinophil count is <150/μL, at least 3 hemograms should be analyzed at least 2-week intervals or at the minimum OCS dose. |
| | **Fractional exhaled nitric oxide (FeNO)**<br>A threshold of ≥20 ppb (at least 3 times) | To diagnose type 2 inflammation |
| | **Sputum eosinophils** | To diagnose type 2 inflammation. A level of ≥2% eosinophils in the sputum shows type 2 inflammation |
| | **Allergy testing**<br>Skin prick test (SPT)<br>Serum allergen specific IgE | To diagnose type 2 inflammation and the presence of atopy |
| **Additional investigations for differential diagnosis** | | |
| **Spirometry** | Flow volume curve | To differentiate lower and upper airway obstruction |
| **Blood tests** | C-reactive protein | Suspicion of infection or chronic inflammatory diseases |
| | Immunoglobulin (Ig)A-G-M | In cases with frequent infection and a prediagnosis of immune deficiency |
| | Alpha1-antitrypsin | If there is a family history of early emphysema |
| | Total IgE | To diagnose allergic bronchopulmonary aspergillosis (ABPA)<br>Before omalizumab treatment (dose adjustment) |
| | Fungal precipitant | Suspicion of ABPA |
| | B-natriuretic peptide (BNP) | Suspicion of hypervolemic state and renal failure, heart failure, hepatic diseases |
| | Auto-immune markers; Anti-neutrophil cytoplasmic antibodies (ANCA), ANA, anti-dsDNA | If the level of blood eosinophils is greater than 1500/μl, consider diagnosing vasculitis |
| **Parasitic investigation;** | Serology / Stool examination | If blood eosinophils ≥300/μl, exclude parasitic infection |
| **Special tests** | Sweat test (measure salt) | Cystic fibrosis (recurrent chest infections, weight loss, diarrhea, wheezing and shortness of breath) |
| | Tuberculin skin test (Mantoux /PPDs) | To detect the presence of Mycobacterium tuberculosis, if the patient is exposed to a TB patient or has symptoms of active TB disease like coughing, chest pain, fever, weight loss, or tiredness. |
| **Imaging** | Chest x-ray; PA graph | It is not a routine test, but an initial graph at the first visit may be helpful to exclude other lung diseases in the diagnosis of asthma |
| | High resolution thorax computed tomography (HRCT) | To diagnose suspicious image in chest-x ray<br>To eliminate other lung diseases (emphysema, bronchiectasis….) if there is a clinic of them such as productive cough. |
| | Paranasal sinuses computed tomography (PNCT) | To detect chronic rhinosinusitis with or without polyposis |
| | Diffusing capacity of the lungs for carbon monoxide (DLCO) | To investigate reasons of hypoxemia |
| **Comorbidity assessment with consultation to** | **Tests** | **Indication** |
| Pulmonology | Sleep test | Sleep apnea (Snoring, daytime sleeping, apnea, obesity) |
| | Bronchoscopy | Unilateral/localized wheezing (foreign antibody, mass) |
| | DLCO | Hypoxemia |
| | Plethysmography (lung volumes) | To evaluate restrictive lung diseases (interstitial lung diseases, neuromuscular disorders, chest wall abnormalities including pectus excavatum and severe scoliosis)<br>To determine the ability of a patient to tolerate surgery |

**Table II continue**

| | | |
|---|---|---|
| Physical treatment | Bone density (DEXA) | To diagnose osteoporosis as an adverse event of frequent OCS or long-term high dose ICS use |
| Ear, nose, throat | Flexible endoscopic evaluation | To diagnose and perform surgery of nasal polyposis and chronic rhinosinusitis |
| Internal medicine | Blood tests | Obesity and thyroid evaluation tests |
| Gastroenterology | Esophageal pH test<br>Upper gastrointestinal system endoscopy | To diagnose acid reflux or gastro-esophageal reflux diseases (GERD) |
| Psychiatry | Face to face meeting | Anxiety and depression |
| Social/psychological support | Face to face meeting | If the patient has no health insurance or is homeless |
| Cardiology | Echocardiography<br>Electrocardiography | Cardiac failure<br>Congenital heart diseases (cardiac murmur) |

**Table III: Main categories of data collection**

| Category | Details |
|---|---|
| **General information**<br>*Demographics*<br>*Social history*<br>*Childhood history*<br>*Family history* | Age, gender, weight, height, BMI<br>Smoking history, occupation, educational status<br>Mode of delivery, prematurity, breast milk intake, childhood diseases and more<br>Family history of atopic diseases |
| **Diagnosis**<br>*Phenotype information*<br>*Endotype information* | Age at onset, diagnostic tests, clinical course<br>Allergy, eosinophilia, obesity, NERD, attack status, low PFT<br>T2 high, T2 low |
| **Comorbidities**<br>*Allergic comorbidities*<br>*Other comorbidities* | Information on diagnosis, duration, treatment history, treatment response<br>Allergic rhinitis, atopic dermatitis, drug allergy, food allergy, CRSwNP, eosinophilic lung diseases<br>Obesity, GERD, depression, OSA and all other chronic diseases |
| **Laboratory** | Allergen sensitization profile, quantitative Ig levels, blood eosinophil count, induced sputum eosinophilia, FeNO and more |
| **Pulmonary function tests** | Spirometry, bronchodilator response, lung volumes, diffusion capacity |
| **Medical imaging** | Chest X-ray, thorax CT, paranasal sinus CT, bone densitometry |
| **Treatment**<br>*Maintenance*<br>*Reliever*<br>*Biologic*<br>*Other* | Compliance, response and side effect information regarding all treatments received<br>All main and alternative maintenance therapies<br>Reliever type and frequency<br>Detailed history of biological use<br>Oral corticosteroids, antibiotics, immunotherapy |
| **Disease control and exacerbations** | Level of symptom control, categorical classification, ACT, C-ACT, impact on quality of life<br>Emergency admission, hospitalization, intubation history<br>Attack frequency, attack triggers |

### Treatment in Adult Asthma Patients

The current GINA report recommends adding LTRA and/or LAMA to the medium-dose ICS+LABA combination before advancing to high-dose ICS. Phenotype-directed biological treatments can be considered as "add-on" treatments in severe asthma. Long-term azithromycin treatment (6 months), regardless of phenotype, and low-dose oral corticosteroid (OCS) (more effective in Type 2 severe asthma phenotype but should be preferred as a last resort due to serious side effects) treatments can be considered as add-on treatment in appropriate patients if biological treatments cannot be reached in step 5 treatment. Bronchial thermoplasty can be considered as non-pharmacological treatment for some adult patients with severe asthma (evidence is limited and selected patients) (Table IV) (1).

**Table IV: Asthma treatment in adult with severe asthma (1)**

| | | Explanations |
|---|---|---|
| **Standard Treatment** | High dose ICS + LABA + LTRA* + LAMA* | ← *Treatments recommended to be added to medium-dose ICS+LABA before increasing to high-dose ICS.<br>← It is recommended that high-dose ICS not be used for more than 6 months because of the possibility of systemic side effects. |
| **Add-on Treatments** | | |
| **Biologicals** | | |
| | Omalizumab (anti-IgE) | ← It has an allergic (atopic) asthma indication.<br>← It is covered by reimbursement in Türkiye |
| | Mepolizumab (anti-IL5) | ← It is indicated in eosinophilic asthma.<br>← It is covered by reimbursement in Türkiye. |
| | Reslizumab (anti-IL5) | ← It is indicated in eosinophilic asthma.<br>← It is not available in Türkiye |
| | Benralizumab (anti-IL5Rα) | ← It is indicated in eosinophilic asthma.<br>← It is covered by reimbursement in Türkiye. |
| | Dupilumab (anti-IL4Rα) | ← It is indicated for asthmatics who meet T2 asthma criteria or are OCS-dependent. There is no license or reimbursement for use in asthma in Türkiye. |
| | Tezepelumab (anti-TSLP) | ← It has indications for both T2 (more effective in this group) and non-T2 asthma.<br>← It is not available in Türkiye. |
| **Azithromycin** | 500 mg, 3 days a week, for 6 months | ← QT length should be checked before and 1 month after treatment.<br>← Sputum should be checked for atypical mycobacteria beforehand.<br>← Treatment for at least 6 months is suggested.<br>← Diarrhea is one of the most common adverse drug reactions. |
| **Low dose OCS** | ≤7.5 mg prednisolone or equivalent | ← It has serious cumulative side effects.<br>← It can only be considered in patients with poor symptom control and/or frequent attacks and who cannot be given biological therapy.<br>← The patient should be informed about the potential side effects of the drug. |
| **Bronchial thermoplasty** | It requires 3 bronchoscopy sessions, each lasting less than 1 hour, approximately 2-3 weeks apart.<br>The first session targets the right lower lobe, the second session targets the left lower lobe, and the final procedure targets both upper lobes. | ← Biological treatment may be recommended after independent institutional review board approval in selected patients who do not have an indication and who do not benefit from azithromycin treatment.<br>← Long-term consequences are uncertain. |

**ICS:** Inhaler corticosteroid, **LABA:** Long acting beta2-agonist, **LAMA:** Long-acting muscarinic antagonists, **LTRA:** leukotriene receptor antagonist, **OCS:** Oral corticosteroid

### Treatment in Children with Asthma

Although most children with asthma can be managed with low to medium doses of ICSs, some children are left with troublesome symptoms, frequent and severe asthma attacks—which can be fatal—and decreased lung function, despite the use of high doses of medication (7). In children with poorly controlled asthma, even after addressing potentially modifiable factors, increasing pharmacological treatment is necessary to manage symptoms and prevent complications. The recommended stepwise treatment for these children according to the GINA report is given in Table V (1). High doses of ICS or OCS can effectively control asthma but may lead to significant side effects such as adrenal suppression, growth failure, and non-specific symptoms like lethargy and nausea (34). On the positive side, biological therapies offer a promising way to reduce the need for corticosteroids, potentially lowering these

risks. However, selecting the right treatment requires careful evaluation of the clinical and inflammatory phenotypes to ensure the best outcome. During the past decade, much progress has been made in the development of monoclonal antibodies against several key players in asthma pathogenesis. Five monoclonal antibodies, or biologics (the term widely used for these agents), are currently available for the treatment of uncontrolled severe asthma in children. A summary of the biologics approved for children and adolescents with asthma is given in Table VI (7).

## CONCLUSION

The Turkish Severe Asthma Program is a project of the Turkish National Society of Allergy and Clinical Immunology (TNSACI), in which the Adult and Pediatric Immunology and Allergy Departments in our country

**Table V: Asthma treatment in children with severe asthma (1)**

| | Children 5 years and younger (Step 4) | Children 6-11 years (Step 5) | Explanations |
|---|---|---|---|
| **Preferred Controller** | Continue controller & refer for specialist assessment. | Refer for phenotypic assessment + higher dose ICS-LABA, or add on therapy.<br><br>e.g., Anti IgE, Anti-IL4Rα, Anti-IL5s | Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures |
| **Other controller options (limited indications, or less evidence for efficacy or safety)** | Add LTRA, or increase ICS frequency, or add intermittent ICS | As a last resort, consider add-on low-dose OCS, but consider side-effects | |

**Table VI: Summary of biologics approved for children and adolescents with asthma.**

| | Therapeutic target | Indications | Age range | Dosing / Frequency / Route of administration | Side effect |
|---|---|---|---|---|---|
| **Omalizumab** | Anti-IgE | Severe allergic asthma (Perennial)<br><br>IgE: 30-1500 IU | ≥6y*<br><br>(*approved in our country) | Based on total IgE & weight.<br><br>75-375 mg every 2-4 weeks<br><br>Subcutaneous | Anaphylaxis<br>Serum sickness<br>EGPA |
| **Mepolizumab** | Anti–IL-5 | Severe asthma with an eosinophilic phenotype (Eosinophil count≥150/μL) | ≥6y<br>≥12y*<br>(*approved in our country) | 6-11y: 40 mg every 4 weeks<br>>12y: 100 mg every 4 weeks<br><br>Subcutaneous | Hypersensitivity<br>Herpes zoster infection<br>Helminth infection<br>EGPA |
| **Benralizumab** | Anti–IL-5Rα | Severe asthma with an eosinophilic phenotype (Eosinophil count≥300/μL) | ≥12y<br>≥18y*<br><br>(*approved in our country) | 30 mg every 4 weeks<br><br>Subcutaneous | Hypersensitivity<br>Helminth infection |
| **Dupilumab** | Anti–IL-4Ra | Moderate-severe asthma with an eosinophilic phenotype (Eosinophil count≥150-300/μL) | ≥6y | 6-11y: <30 kg: 100 mg every 2 weeks<br>6-11y: >30 kg: 200 mg every 2 weeks<br>≥12y: 200 mg or 300 mg every 2 weeks<br><br>Subcutaneous | Hypersensitivity<br>Transient eosinophilia<br>Helminth infection |
| **Tezepelumab** | Anti–TSLP | Severe asthma | ≥12y | 210 mg every 4 weeks<br><br>Subcutaneous | Hypersensitivity<br>Arthralgia<br>Pharyngitis<br>Back pain |

will participate. The stakeholders of this program are the TNSACI, national severe asthma centers, and the pharmaceutical industry representatives. This program has been initiated with the participation of a limited number of centers, and after all conditions for implementation are met, it will be opened to the participation of other centers and moved to the national level. The program aims to establish standards to diagnose and treat patients with SA and to monitor their treatments at the national level. With the start of this project, data will be collected from the SA patients registered to this program regarding epidemiological and clinical features of SA including phenotypes, burden, and costs. This data will be compiled in a database and published alongside national severe asthma statistics. In the long term, the aim is to ensure that the centers within this program are accredited as "severe asthma centers of excellence". Once accreditation is achieved and the goal of severe asthma excellence centers is met, these centers will be mapped across the country.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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**Author Contributions**

Concept: **All authors,** Design: **All authors,** Data collection or processing: **All authors,** Analysis or Interpretation: **All authors,** Literature search: **All authors,** Writing: **All authors,** Approval: **All authors.**

## REFERENCES

1. Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024. Available from: www.ginaasthma.org
2. Yildiz F, Mungan D, Gemicioglu B, Yorgancioglu A, Dursun B, Oner Erkekol F, et al. Asthma phenotypes in Turkey: a multicenter cross-sectional study in adult asthmatics; PHENOTURK study. Clin Respir J 2017;11(2):210-23.
3. Bavbek S, Misirligil Z. A breath for health: an exploratory study in severe asthma patients in Turkey. Allergy 2008;63:1218-27.
4. Celik GE, Aydin O, Gokmen D, Koycu Buhari G, Celebi Sozener Z, Gemicioglu B, et al. Picturing asthma in Turkey: results from the Turkish adult asthma registry. J Asthma 2023;60(11):1973-86.
5. Bavbek S, Malhan S, Mungan D, Misirligil Z, Erdinc M, Gemicioglu B, et al. Economic burden of severe asthma in Turkey: a cost of illness study from payer perspective. Eur Ann Allergy Clin Immunol 2021;53(3):128-37.
6. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax 2015;70(4):376-8.
7. Pijnenburg MW, Fleming L. Advances in understanding and reducing the burden of severe asthma in children. Lancet Respir Med 2020;8(10):1032-44.
8. Håkansson KEJ, Guerrero SC, Backer V, Ulrik CS, Rastogi D. Burden and unmet need for specialist care in poorly controlled and severe childhood asthma in a Danish nationwide cohort. Respir Res 2023;24(1):173.
9. Rusconi F, Fernandes RM, Pijnenburg MWH, Grigg J. The Severe Paediatric Asthma Collaborative in Europe (SPACE) ERS Clinical Research Collaboration: enhancing participation of children with asthma in therapeutic trials of new biologics and receptor blockers. Eur Respir J 2018;52(4).
10. Nordlund B, Melén E, Schultz ES, Grönlund H, Hedlin G, Kull I. Prevalence of severe childhood asthma according to the WHO. Respir Med 2014;108(8):1234-7.
11. Hansen S, von Bülow A, Sandin P, Ernstsson O, Janson C, Lehtimäki L, et al. Prevalence and management of severe asthma in the Nordic countries: findings from the NORDSTAR cohort. ERJ Open Res 2023;9(2).
12. Renzi-Lomholt M, Ulrik CS, Rastogi D, Stæhr Jensen JU, Håkansson KEJ. Impact of family socioeconomic position on childhood asthma outcomes, severity, and specialist referral - a Danish nationwide study. Chron Respir Dis 2024;21:14799731241231816.
13. Soyer OU, Beyhun NE, Demir E, Yildirim S, Boz AB, Altinel N, et al. A multicenter survey of childhood asthma in Turkey. II: Utilization of asthma drugs, control levels and their determinants. Pediatr Allergy Immunol 2009;20(2):172-9.
14. 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(4):724-33.
15. Ozdemir N, Uçgun I, Metintas S, Kolsuz M, Metintas M. The prevalence of asthma and allergy among university freshmen in Eskisehir, Turkey. Respir Med 2000;94(6):536-41.
16. Kalyoncu AF, Demir AU, Ozcakar B, Bozkurt B, Artvinli M. Asthma and allergy in Turkish university students: Two cross-sectional surveys 5 years apart. Allergol Immunopathol (Madr) 2001;29(6):264-71.
17. Teke T, Özer F. Selçuk Üniversitesi öğrencileri arasında astım ve astım semptom prevalansı. Genel Tıp Dergisi 2008;18(1):13-21.
18. Uğurlu E, Oncel SB, Evyapan F. Symptom prevalence and risk factors for asthma at the rural regions of Denizli, Turkey. J Thorac Dis 2014;6(5):452-8.
19. Baççıoğlu A, Söğüt A, Kılıç Ö, Beyhun E. The Prevalence of Allergic Diseases and Associated Risk Factors in School-Age Children and Adults in Erzurum, Turkey. Turk Thorac J 2015;16(2):68-72.
20. Kurtuluş Ş, Sak ZHA, Can R. Chest Diseases in Refugees Living in a Tent Camp and in Turkish Citizens Living in the District: Ceylanpınar Experience. Turk Thorac J 2018;19(3):117-21.

21. Sengoren Dikis O, Demirci H, Sezgin B, Haberal MA, Akar E, Kaya H. What is the emergency application differences concerning diseases pertinent to the chest between Turkish citizens and Syrian refugees: A cross-sectional study. Clin Respir J 2020;14(8):725-31.
22. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015;135(4):896-902.
23. Bavbek S, Celik G, Ediger D, Mungan D, Sin B, Demirel YS, et al. Severity and associated risk factors in adult asthma patients in Turkey. Ann Allergy Asthma Immunol 2000;85(2):134-9.
24. Turktas H, Mungan D, Uysal MA, Oguzulgen K. Determinants of asthma control in tertiary level in Turkey: a cross-sectional multicenter survey. J Asthma 2010;47(5):557-62.
25. Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. Can Respir J 2010;17(2):74-80.
26. Szefler SJ, Zeiger RS, Haselkorn T, Mink DR, Kamath TV, Fish JE, et al. Economic burden of impairment in children with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2011;107(2):110-9.e1.
27. Beyhun NE, Cilingiroğlu N, Sekerel BE. The cost of childhood asthma and its determinants in Ankara, Turkey. Turk J Pediatr 2007;49(2):179-88.
28. Fleming M, Fitton CA, Steiner MFC, McLay JS, Clark D, King A, et al. Educational and health outcomes of children treated for asthma: Scotland-wide record linkage study of 683716 children. Eur Respir J 2019;54(3).
29. Montalbano L, Ferrante G, Montella S, Cilluffo G, Di Marco A, Bozzetto S, et al. Relationship between quality of life and behavioural disorders in children with persistent asthma: a Multiple Indicators Multiple Causes (MIMIC) model. Sci Rep 2020;10(1):6957.
30. Çelik GE, Bavbek S, Paşaoğlu G, Mungan D, Abadoğlu Ö, Harmancı E, et al. Direct medical cost of asthma in Ankara, Turkey. Respiration 2004;71(6):587-93.
31. Serinken M, Dursunoğlu N, Cimrin AH. [Therapy costs of adult patients admitting to emergency unit of a university hospital with asthma acute attack]. Tuberk Toraks 2009;57(2):198-204.
32. Bavbek S, Mungan D, Türktaş H, Mısırlıgil Z, Gemicioğlu B. A cost-of-illness study estimating the direct cost per asthma exacerbation in Turkey. Respir Med 2011;105(4):541-8.
33. Emre JÇ, Özdemir Ö, Baysak A, Aksoy Ü, Özdemir P, Öz AT, et al. Cost of asthma hospitalizations in a pulmonary clinic of a state hospital. Asthma Allergy Immunology 2022;12(3):140-5.
34. Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. N Engl J Med 2018;378(10):891-901.

**Supplementary Table I: Tools for asthma control in adults, adolescents, and children**

| **Symptom Control** | | | |
|---|---|---|---|
| | **Component** | **Result Assessment** | |
| GINA symptom control tool | Asthma-related symptoms or medication use, activity limitations brought on by the condition, and insomnia.<br><br>Ask the patient if the patient had any of the following in the past 4 weeks:<br>-Daytime asthma symptoms ³ 2 /week?<br>-Any night waking due to asthma?<br>-SABA* reliever use ³ 2 /week?<br>-Activity limitation due to asthma? | Well controlled: No to all questions<br>Partly controlled: 1 or 2 yes answers<br>Uncontrolled: 3 or 4 yes answers | |
| **Numerical asthma control tools** | | | |
| Asthma Control Test (ACT) | The ACT has 4 symptom/reliever (except ICS-formoterol) questions plus patient self-assessed control.<br>The minimum clinically important difference is 3 points. | Scores (5-25) of;<br>- 20-25: well controlled<br>- 16-19: not well controlled<br>- 5-15: very poorly controlled | |
| Asthma Control Questionnaire (ACQ) | The ACQ has 5 symptom questions.<br>The minimum clinically important difference is 0.5 points. | Scores (0-6) of;<br>- ≤ 0.75: well controlled<br>- 0.75-1.5: grey zone<br>- ≥ 1.5: poorly controlled | |
| Childhood Asthma Control Test | 4-11 years | Scores (0-27) of;<br>0 (poorest asthma control) to 27 (optimal asthma control).<br>≤ 19 indicates uncontrolled asthma | |
| Lung function (% of predicted FEV1) | At the diagnosis<br>3-6 months after treatment<br>At least once a year | -Personal best | |
| **Future risk factors** | | | |
| At the diagnosis<br>- Periodically | **a- For exacerbations**<br>Poor asthma control<br>SABA over-use: ≥ 3x200 dose-canisters/ year or ≥1 canister/month<br>Inadequate ICS<br>Comorbidities: obesity, chronic rhinosinusitis, GERD, pregnancy, food allergy<br>Exposures: Smoking, air-pollution, allergens<br>Socioeconomic problems<br>Low FEV1 (<60%) or high reversibility<br>Type 2 inflammation: high blood eosinophilia, high FeNO, allergy<br>Exacerbation history: ≥1 exacerbation/ year, ever intubated or intensive care unit for asthma. | **b- For persistent airflow limitation**<br>- History: preterm birth, low birth weight, high infant weight, chronic mucus hypersecretion, nontreated asthma exacerbations<br>- Medications: lack of ICS<br>- Exposure to smoke/chemicals<br>- Investigations: Low initial FEV1, High blood eosinophilia | **c- For side effects**<br>**Systemic CS;**<br>- Easy bruising<br>- Osteoporosis<br>- Fragility fractures<br>- Cataracts<br>- Glaucoma<br>- Adrenal suppression<br><br>**Local**<br>Long Term-High dose -Potent ICS:<br>Oral candidiasis<br>Dysphonia<br>Drug interreactions with asthma medications: ketoconazole, ritonavir, itraconazole, erythromycin/clarithromycin may increase side effects of ICS (adrenal suppression) and LABA (cardiovascular adverse events) |

**FEV1:** Forced expiratory volume in the first second, **ICS:** Inhaler corticosteroid, **LABA:** Long-acting beta2-agonist, **OCS:** Oral corticosteroid, **SABA:** Short-acting beta2-agonist, ***:** As-needed ICS-formoterol reliever not included.