Journal of Respiratory Medicine and Lung Disease

Review Article
Published: 13 Oct, 2018

# Severe Asthma

*Di Wu and Qian Zhang**

*Department of Respiratory Medicine, Nanjing Medical University, China*

## Abstract

Bronchial asthma is a chronic disease characterized by airway inflammation, hyperresponsiveness and remodeling. Most patients can achieve adequate control of asthma while the subgroup shows little reaction to current treatment is defined as 'severe asthma'. Efforts have been made by researchers to reveal a more exact definition, a more specific mechanism and an efficient individual therapy. This review will provide an update on the latest advancements with regard to all these domains.

**Keywords: Severe asthma; Definition; Diagnosis; Mechanism; Phenotypes; Treatment**

## Introduction

Severe Asthma shows little reaction to drugs in regular therapy like inhaled glucocorticosteroids in combination with long-acting $\beta_2$-agonists (LABA) and Long acting cholinergic receptor antagonist (LAMA) even in high doses [1]. The prevalence of severe asthma was estimated vary between 5% and 10%, although recent research implies it may be lower than estimated [2]. The difficulty of treating this subgroup still brings a challenge to clinicians to have severe asthma under control and also account for an considerable economic burden in overall asthma management on health care [3]. This review will focus on the most recent research developments of definition, mechanism, diagnose and treatment regarding severe asthma.

## Definition

Definitions of severe asthma have been refined and sharpened over the years. In 1999, ERS Task Force first described the definition of 'difficult/therapy-resistant asthma' as poorly controlled asthma and a continued requirement for SABA despite delivery of a reasonable dose of inhaled corticosteroids (ICS) and follow-up by a respiratory specialist for a period of >6 months, during this period, asthma management had to be carried out according to published asthma guidelines, however, this definition could also be due to other factors like poor adherence, incorrect use of inhaler, psychological problems and inherent comorbidities of patients[4]. In 2000, ATS raised the concept of 'refractory asthma' stressing the severity of asthma (1of 2 major criteria: continuous high-dose ICS or oral corticosteroids for>50% of the time during the previous year and ≥2 of 7 criteria: (1) Requirement for daily treatment with a controller medication in addition to ICS, eg, LABA, theophylline, or leukotriece antagonists. (2) Asthma symptoms requiring daily short-acting β2-agonists (SABA). (3) Persistent airway obstruction (FEV1 <80% predicted; diurnal PEF variability >20%). (4) One or more urgent care visits for asthma per year. (5) Three or more oral steroid 'bursts' per year. (6) Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose. (7) Near fatal asthma event in the past) [5]. Definitions proposed by the Paris Workshop in 2007 agreed that a diagnosis of 'severe asthma' should be reserved for those patients who have refractory asthma after an extensive re-evaluation of the correct diagnosis, aggravating comorbidities and environmental factors and an appropriate observation period of at least 6 months. The WHO Consultation adopted the definitions of 'severe' and 'difficult' asthma from the Paris Workshop in 2007 and extended it with a third group of patients with 'untreated' severe asthma, the third group is mostly in low-income countries. In 2011, the Innovative Medicine Initiative (IMI) proposed a more accurate definition of severe asthma. In this statement a clear distinction was made between 'difficult-to-control asthma' and 'severe refractory asthma' ,the former one is often caused by other factors than asthma itself, and for patients with severe refractory asthma, this disease remains uncontrolled though all possible factors that might aggravate the underlying disease have been dealt with [6]. In 2014, international ERS and ATS published a consensus definition of severe asthma, in this consensus, difficult-to-treat asthma is asthma that remains uncontrolled though clinicians treat patients with high-dose inhaled glucocorticoids or other controllers, or patients require such treatment to remain well controlled. Severe asthma is thought to be a subset of difficult-to-control asthma; this term

OPEN ACCESS

***Correspondence:***
*Qian Zhang, Department of Respiratory Medicine, Nanjing Medical University, 29 Xinlong Road, Changzhou 213003, China, Tel: 86-519-89621799; Fax: 86-519-88115560;*
*E-mail: kezhang0601@163.com*

**Received Date**: *08 Sep 2018*
**Accepted Date:** *06 Oct 2018*
**Published Date:** *13 Oct 2018*

***Citation:***
*Wu D, Zhang Q. Severe Asthma. J Respir Med Lung Dis. 2018; 3(2): 1039.*
***ISSN: 2475-5761***

**Table 1:** Definition of severe asthma for patients aged ≥6 years.

| |
|---|
| Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS# and LABA or leukotriene modifier/ theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled“ despite this therapy |
| Uncontrolled asthma defined as at least one of the following: |
| 1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or “not well controlled” by NAEPP/GINA guidelines) |
| 2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year |
| 3) Serious exacerbations: at least one hospitalisation9p--b, ICU stay or mechanical ventilation in the previous year |
| 4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) |
| Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics) |

LABA: Long-Acting β2-Agonists; CS: Cortico Steroids; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; NAEPP: National Asthma Education and Prevention Program.

**Table 2:** Definition of high daily dose of various inhaled corticosteroids in relation to patient age [7].

| Inhaled corticosteroid | Threshold daily dose in µg considered as high | |
|---|---|---|
| | Age 6–12 years | Age >12 years |
| Beclomethasone dipropionate | ≥800 (DPI or CFC MDI)<br>≥320 (HFA MDI) | ≥2000 (DPI or CFC MDI)<br>≥1000 (HFA MDI) |
| Budesonide | ≥800 (MDI or DPI) | ≥1600 (MDI or DPI) |
| Ciclesonide | ≥160 (HFA MDI) | ≥320 (HFA MDI) |
| Fluticasone propionate | ≥500 (HFA MDI or DPI) | ≥1000 (HFA MDI or DPI) |
| Mometasone furoate | ≥500 (DPI) | ≥800 (DPI) |
| Triamcinolone acetonide | ≥1200 | ≥2000 |

Notes: 1) Designation of high doses is provided from manufacturers' recommendations where possible. 2) As chlorofluorocarbon (CFC) preparations are being taken from the market, medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed by the clinician for the equivalent correct dosage. DPI: Dry Powder Inhaler; MDI: Metered-Dose Inhaler.

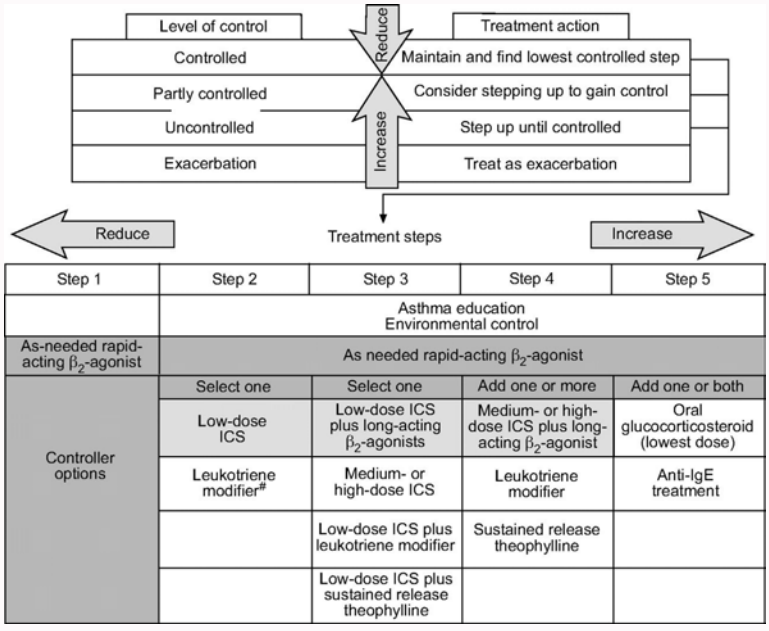


**Figure 1:** Global Initiative for Asthma [8].

is used to describe asthma that remains uncontrolled despite high-dose inhaled glucocorticoids combined with a LABA, a leukotriene modifier, or theophylline have been applied for the previous year or treatment with systemic glucocorticoids for at least half the previous year. Patients requiring such treatment in order to get asthma under control is also in the scope; it excludes patients in whom asthma is vastly improved with optimization of adherence, inhaler technique and treatment of coexisting conditions. The most recent definition of severe asthma for patients aged ≥6 years is showed in Table 1 [7].

#: the definition of high dose inhaled corticosteroids (ICS) is age-specific (Table 2). GINA: Global Initiative for Asthma (Figure 1).

## Diagnosis

The basic diagnostic procedures of severe asthma should include clinical history (Table 3), clinical examination and lung function testing followed by hyperactivity testing or reversibility testing, moreover , allergy testing should also be performed(skin prick tests, blood test clinical history), FeNO test is optional. After these basic

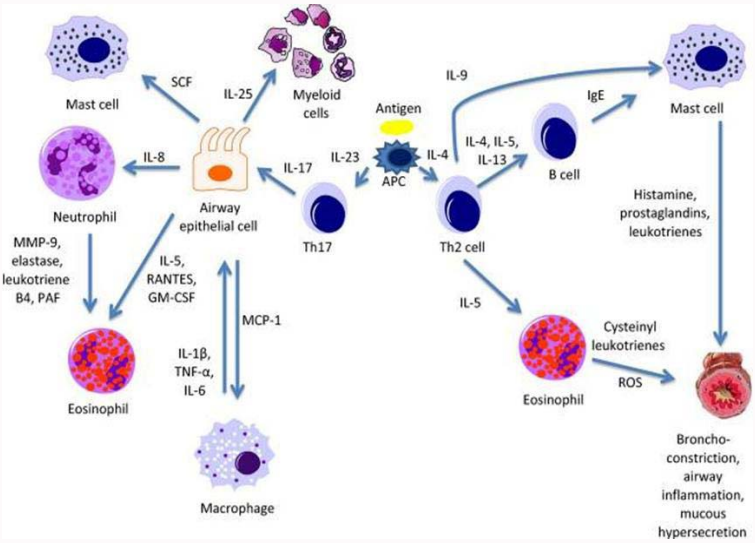


**Figure 2:** Th2 and Th17 allergen responses in the asthmatic airway [16].

procedures, the diagnosis of severe asthma is supposed to go through the following procedure.

### Confirmation of the diagnosis

Different diseases may mimic severe asthma (Table 4), these diseases should first be ruled out. At this moment, a detailed clinical history is very useful for clinician to confirm the right diagnosis. Reversibility testing is very helpful to distinguish severe from chronic obstructive pulmonary disease (COPD) considering both diseases may get controlled under systemic high –dose steroid therapy. Other tests such as computed tomography (CT) of the chest, CT can rule out many differential diseases (including malformations, bronchiolitis, tumors, dysplasias, bronchiectasis and various interstitial lung diseases), bronchoscopy to rule out endobronchial changes, for biopsy, or for diagnostic bronchoalveolar lavage, echocardiography to rule out heart failure or structural heart disease and 24-hour pH measurement to rule out gastroeso-phageal reflux [7-10].

### Ruling out diseases associated with asthma

Aspirin-exacerbated respiratory disease (AERD) is an intolerance of cyclooxygenase (COX) 1 inhibitors, which is often associated with hypersensitivity to severe asthma. It is reported to be with 4 to 21% of asthma patient. Using ASA provocation can confirm the diagnosis of AERD. Allergic bronchopulmonary aspergillosis (ABPA) is suspected when patients have very high total IgE levels, specific IgG and IgE antibodies to Aspergillus fumigatus, fleeting pulmonary opacities and central bronchiectasis. Churg–Strauss syndrome (CSS) is suspected when patients have blood eosinophils >10%, sinusitis**,** migrating pulmonary opacities and neuropathy [11-13].

### Comorbidities

Comorbidities that affect asthma severity, such as sleep-related breathing disorders, chronic rhinosinusitis, gastroesophageal reflux and heart disease, must be found. Obesity not only affects asthma control but also causes asthma misdiagnosis, because its symptoms and lung function results mimic asthma. The frequency of COPD and asthma co-occur is being studied under the term ACOS (asthma–COPD overlap syndrome). Depression or an anxiety disorder is present in up to 50% of asthmatic patients [14].

**Table 3:** Content of clinical history of severe asthma [9].

| **Content of clinical history:** |
|---|
| Nature, duration, and triggers of symptoms |
| Age at and circumstances of initial onset of symptoms |
| Relationship between symptoms and physical exertion and between symptoms and occupation |
| Seasonality and circadian variations in symptoms |
| Responsiveness of symptoms to asthma-specific therapies |
| Changes of symptoms on travels |
| Active and passive smoking |
| Allergies and comorbidities |
| Family history (asthma/allergic diseases) |
| Regular contact with animals |
| Occupational or private stress factors |
| Tolerance of cyclooxygenase (COX) 1 inhibitors |
| Long-term medication, adherence, inhalation technique |
| Exacerbations/hospitalizations in the last 12 months |

## Mechanism and Phenotypes

The mechanism of severe asthma is different from mild to moderate asthma, featuring in having a more heterogeneous pattern of inflammatory response, with greater involvement of neutrophils and the distal lung and increased airway remodeling, but it is still not totally clear to researchers how these differences mentioned above occur.

The classic model of asthma is a complicated interaction of cells and cell signaling molecules, that leads to an inflammatory response (Figure 2). A phenotype is defined as the "observable properties of an organism that are produced by the interactions of the genotype and the environment". Asthma has been classified as different phenotypes including persistent type 2 inflammation, neutrophilic inflammation, mixed inflammation and paucigranulocytic phenotype according to diverse pathobiologic processes, characterized by persistent symptoms, exacerbations , poor lung function, or a combination of these or we can simply classify them through Table 3. Most

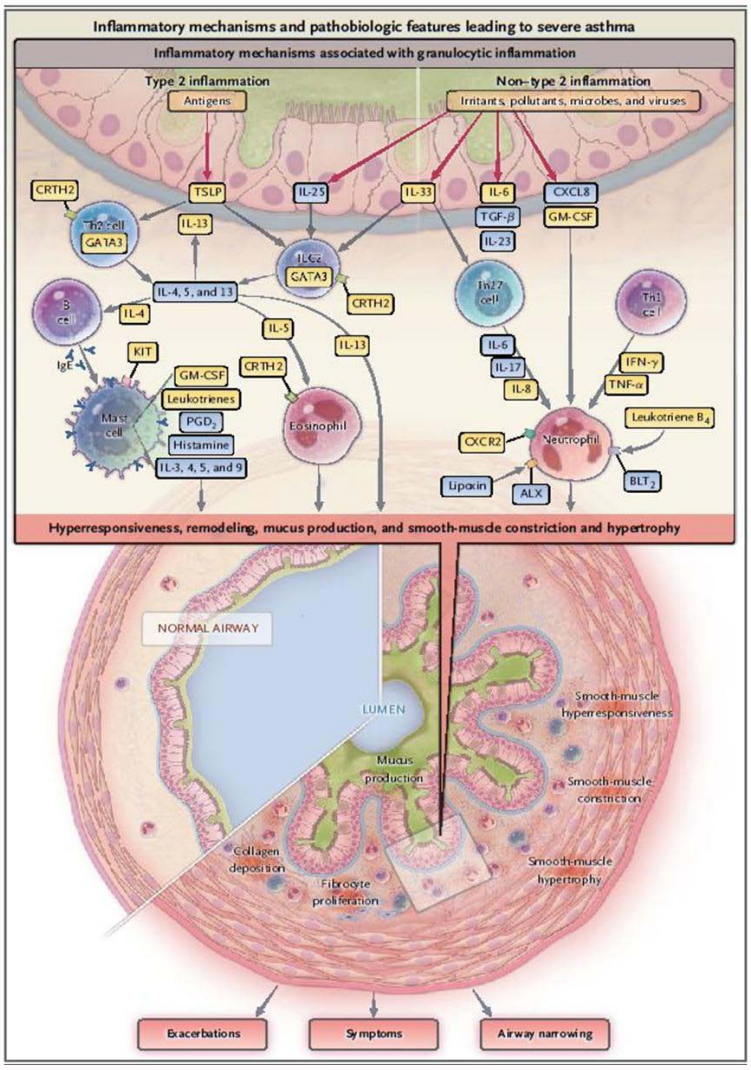


**Figure 3:** Inflammatory mechanisms and pathobiologic features leading to severe asthma [16].

**Table 4:** Diseases that may mimic asthma [10].

| **Diseases that may mimic asthma:** |
|---|
| Congenital or acquired immunodeficiency |
| Primary ciliary dyskinesia |
| Cystic fibrosis (CF) |
| Vocal cord dysfunction (VCD) |
| Central airway obstruction |
| Recurrent aspiration |
| Bronchiolitis |
| Gastroesophageal reflux disease (GERD) |
| Psychogenic hyperventilation |
| Chronic obstructive pulmonary disease (COPD) |
| Heart failure |
| Drug side effects (e.g. ACE inhibitor-induced cough) |
| Pulmonary embolism |

importantly, evidence of cellular inflammation in the airway underlie these phenotypes. The following Figure 3 shows inflammatory mechanisms and pathobiologic features leading to severe asthma [15,16].

## Type 2 inflammation

Type 2 immune response causes type 2 inflammation. Airway type 2 immune responses are mainly regulated by T helper 2 (Th2) cells, which is a subpopulation of $CD4^+$ T cells known as Th2 secreting cytokines IL-4, IL-5, IL-13 and stimulate type 2 immune response, apart from Th2 cells, basophils, eosinophils, mast cells, group 2 innate lymphoid cells (ILC2s) and IgE-producing B cells are also engaged in modulating type 2 immune responses (Figure 4). Type 2 immune responses are characteristic of allergic rhinitis in the upper airways and asthma in the lower airways and it often initiates in childhood with environment stimuli activating airway epithelial cells to produce IL-25, IL-33 or lymphopoietin resulting in increased production of type 2 cytokines, which leads to the development of asthma in children who are susceptible because of pre-existing atopy and genetic risk factors in regulating type 2 inflammation. Whereas, phenotypic heterogeneity is limited due to phenotypic traits can be caused by multiple disease mechanisms, the idea of endotype was introduced in 2008 to guide asthma research, an endotype is a disease subtype defined by a distinct functional or pathobiologic mechanism, there is only one proposed endotype of asthma, Th2-high asthma, which is characterized by increased levels of airway type 2 inflammation

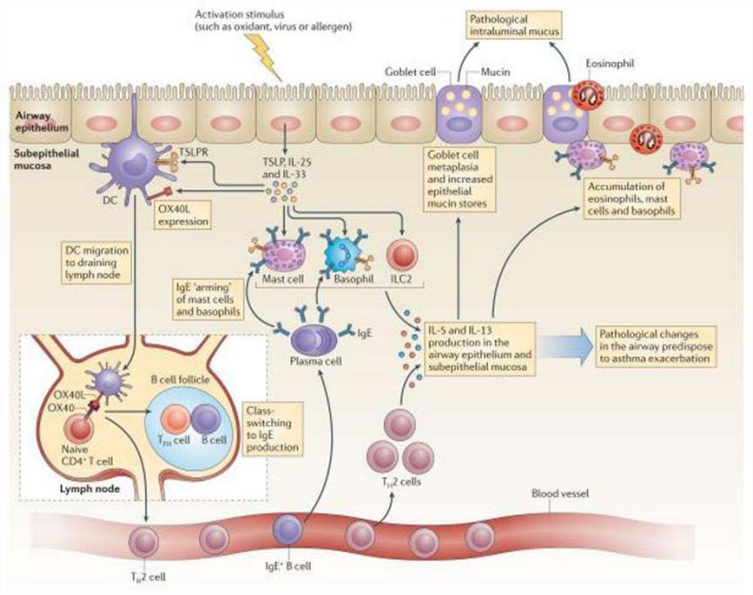


**Figure 4:** Type 2 immune response in asthma [20].

compared with healthy controls. Half patients with Th2-high asthma have eosinophilia and other signs of airway type 2 inflammation including a gene expression of periostin consistent with the activation of epithelial cells by IL-13, and the level of blood periostin can predict the expected result of IL-targeted treatment in patients with asthma. Another important characteristic of Th2-high asthma is its high responsiveness to inhaled corticosteroids, on the contrary, the current treatment approaches for Th2-low asthma is unsatisfactory, the reason why patients with Th2-low asthma shows little reaction to approaches may be a result of mechanisms of asthma uncovered other than type 2 inflammation. Though Th2-high asthma is generally considered as a corticosteroid-responsive endotype which make up about 50% of mild to moderate asthma and a large proportion of more severe asthma, there are still subgroups of patients with severe asthma requiring high doses of glucocorticoids to maintain control, which may be a direction for researching mechanisms of asthma [17-19].

### Neutrophilic inflammation

Facts aforementioned that Th2 lymphocytes are mainly involved in the development of eosinophilic allergic asthma, other subsets of the lymphocytes especially a lineage of $CD4^+$ effector the cells called Th17 for its expression of IL-17 induce airway neutrophilic inflammation. This subtype of inflammation is often related with severe asthmatic phenotypes. Study on asthmatic patients found that an significant overexpression of IL-17A and IL-17F in specimens of lung tissues, the levels of these cytokines are associated with asthma severity in particular in patients with steroid-resistant, neutrophilic asthma. The mechanism of neutrophilic is clear, stimuli like cigarette smoke, air pollution, microbes, microbial particles and other factors acting as pathogen-associated molecular patterns on skeptical patients get recognized by Toll-like receptors which then activate the transcription of NF-$\kappa$B (nuclear factor-$\kappa$B),the products induce the expression of pro-IL-1$\beta$ and pro-IL-18 cytokines, caspase-1 activated by NLRP3 (nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 activation) inflammasome cleaves pro-IL-1$\beta$ and pro-IL-18, converting them into mature forms, eventually active IL-1$\beta$ promotes Th17 cell-dependent inflammation leading to severe asthma. Besides, Th1 cells and the Th1-derived cytokines IFN-$\gamma$ and TNF-$\alpha$ are increased in patients with severe asthma, which was believed that may suggest Th1 cells participate in regulating neutrophilic inflammation until a study carried out in subjects with severe asthma received an unsatisfactory outcome [20-24].

### Mixed Inflammation and Paucigranulocytic Phenotype

Some patients with severe asthma have neutrophilic and eosinophilic inflammation in sputum at the same time, which naturally causes severe symptoms and more economic burdens. IL-6 and IL-17 may promote dual Th2 and type 17 helper T (Th2–Th17) cell presence in the airway, which then promoting both types of inflammation. Paucigranulocytic Phenotype often means well controlled or intermittent asthma, however, this phenotype is not as common as other phenotypes, so its findings should consider alternative diagnosis.

## Treatment

### Basic therapy

The first step to treat severe asthma is to confirm the diagnosis, clinician must exclude patients with uncontrolled asthma due to poor adherence, wrong inhaler technique and untreated coexisting conditions. While, exposure to persistent asthma triggers can also causes poor symptom control and frequent exacerbations, that indicates eliminating sources of allergen can be very effective for patients to get asthma under control [7].

### Additional treatment options

The treatment of severe asthma consists of high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications. High-dose inhaled glucocorticosteroids are used to treat patients with severe asthma in clinics, sometimes higher than maximal dosage recommended even without evidence that these ultra-high doses lead to better control of asthma, improvement of lung function or amelioration of asthma-

related quality of life. Clinicians need to realize that such high doses of inhaled steroids is highly associated with systemic side-effects in long time of application including adrenal suppression, skin thinning, ecchymoses, reduced bone mineral density, glaucoma and cataract. Therefore, additional treatment options is needed [7,25].

### Anti-IgE

For patients with severe allergic asthma, treatment of anti-IgE antibody omalizumab leads to a 50% reduction of frequency of severe asthma, better asthma control and quality of life. Besides the average daily usage of prednisolone falls from 15.5 mg to 5.8 mg. Omalizumab is approved when patients meet all the 3 following conditions: 1. Persistent symptoms and recurrent exacerbations despite high-dose ICS/LABA therapy. 2. FEV1 <80%.3. Total serum IgE between 30 and 1500 kU/L (although the upper limit is lower for body weights above 50 kg: see summary of product characteristics). If a total 4 months of every 2 to 4 weeks of this therapy sees no improvement of asthma control, a further application is not recommended. Though omalizumab if only approved for allergic asthma, it is also effective in intrinsic asthma, the application of omalizumab under this circumstances should be strictly evaluated in an experienced asthma center [16,26].

### Macrolides

Macrolide antibiotics not only possess anti-microbial activity but also have immunomodulatory and anti-inflammatory effects. Studies found that treatment with clarithromycin resulted in a decrease of IL-8 levels and neutrophil accumulation in the airway. Therefore, long-term macrolide therapy is considered a recommendation for non-eosinophilic asthma, especially there are no specific alternative treatment options for patients with non-eosinophilic asthma [27].

### Anti-IL-5 and anti-IL-5 receptor α (IL-5Rα)

IL-5 plays a key role in mediating eosinophil differentiation, proliferation and activation. Accordingly, targeting IL-5 (mepolizumab, reslizumab) and its receptor (benralizumab) is a good option to treat patients with severe asthma and eosinophilic inflammation. Anti-IL-5 and anti-IL-5Rα promotes programmed cell death of eosinophils, attenuate eosinophilic inflammation in systemic circulation and organ tissue. Studies show that anti-IL-5 treatment can result in reduction of acute exacerbations and improvement of pulmonary function and quality of life despite a reduction of systemic steroid treatment. Most common side effects of anti-IL-5 are mild, including headache, nasopharyngitis, and pharyngolaryngeal pain, this enables anti-IL-5 therapy a long-term treatment. Anti-IL-5Rα can directly inhibit IL-5 signaling and subsequently result in apoptosis of the eosinophil and have similar effect of anti-IL-5 [28,29].

### Anti-IL-4/13 and anti-IL-4 receptor α chain (IL-4Rα)

In type 2 inflammation, IL-13 is a central mediator for the development of mucus production and airway hyperresponsiveness because IL-13 acts on epithelial cells inducing the production of mucus and periostin. There are monoclonal antibody against IL-13 and inhibitor of the IL-4Rα, which can bind both IL-4 and IL-13. This means blocking IL-4Rα inhibits both IL-4 and IL-13. Studies show that lung function increases in patients with increased levels of periostin in serum following anti-IL-13 administration, however, patients with low levels of periostin shows no significant increase in lung function. Further studies is still ongoing. Anti- IL-4Rα block the binding of IL-4 and IL-13, group treated with an IL-4Rα antibody (dupilumab) experienced no exacerbation while reducing the inhaled treatment with LABAs and ICS [16,30,31].

### Anti-TSLP (thymic stromal lymphopoietin)

Epithelial cells play an important role in regulating immune responses in lung. When exposed to triggers, airway epithelial cells of patients with asthma produce TSLP, IL-25 and IL-33. TSLP and IL-33 directly act on innate lymphoid cells (ILCs) and then promote the production of Th2 cytokines. Anti-TSLP treatment attenuates airway inflammation in patients with allergic asthma [31,32].

### Targeting IL-17 pathways

When it comes to asthma featuring with neutrophilic inflammation, IL-17 is in the center of the development of neutrophilic inflammation. Brodalumab is a human monoclonal antibody against interleukin-17 receptor A (IL-17-RA), researches show it can improve in asthma control questionnaire (ACQ) in the high reversibility subgroup. We can also target IL-23 to affect the differentiation of Th17 and Th22 cells and then inhibit the production of IL-17 [33,34].

### Bronchial thermoplasty (BT)

These therapies mentioned above are possibly helpful to the temporary release of asthma's exacerbation, but fundamental change of construction of bronchus doesn't take a turn for the better, only worse by all means, to reach the goal of converting the process of refractory asthma. Bronchial thermoplasty (BT) was approved by US Food and Drug Administration in 2010 to treat severe asthma, not only has BT been shown to reduce airway smooth muscles but also the amount of the vascular smooth muscle, which offered the advantage of avoiding the major effect of steroids. This technology targets ASM by delivering a controlled specific amount of thermal energy (radio frequency ablation) to the airway wall through a dedicated catheter. Even if BT is a relatively new technology, BT does have a specific indications. Candidates for BT cover adults with severe persistent asthma who require regular maintenance medications of ICS (>1000 μg/day beclomethasone or equivalent) and a LABA (≥100 μg/day salmeterol or equivalent). In addition, these patients should have already received add-on therapies such as leukotriene modifiers, omalizumab, and oral corticosteroids 10 mg/day or less. These patients should be on stable maintenance asthma medications according to accepted guidelines, have a prebronchodilator $FEV_1$ of 60% or more of predicted, and have a stable asthma status ($FEV_1$ within 10% of the best value, no current respiratory tract infection, and no severe asthma exacerbation within the preceding 4 weeks). Patients are usually selected based on the AIR 2 trial. The patient should be stable in terms of his or her asthma status, defined as a post-bronchodilator $FEV_1$ within 15% of their baseline values, and no respiratory tract infection or asthma exacerbations within the past 14 days. For the time being, BT is still very limited due to its strict indications, however, in the coming days, this new method leaves enormous potential to scientists and clinicians to fulfill [35-37].

## Outlook

Severe asthma, taking a percentage of 5 to 10 of all asthma, draws much more attention due to its unrevealed mechanism and difficulty of treating [2]. In the coming future, more and more approaches will be found to deal with severe asthma. Based on today's limited application, new mechanism being found is crucial to novel drugs which put severe asthma under control. Besides, before that, BT is the one having the greatest potential because it has no similarity to other medicine used for asthma. It directly acts on the very beginning of

asthma and is going to play a very important role during the process.

## References


1. Ashton JC, Hancox RJ. The case for cannabinoid CB1 receptors as a target for bronchodilator therapy for β-agonist resistant asthma. Curr Drug Targets. 2018;19(11):1344-9.
2. Hekking PP, 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.
3. Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. Respir Res. 2017;18(1):129.
4. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur Respir J. 1999;13(5):1198-208.
5. Wener RR, Bel EH. Severe refractory asthma: an update. Eur Respir Rev. 2013;22(129):227-35.
6. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011;66(10):910-7.
7. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.
8. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J. 2015;46(3):622-39.
9. Lommatzsch M, Virchow JC. Severe asthma: definition, diagnosis and treatment. Dtsch Arztebl Int. 2014;111(50):847-55.
10. Amundson D, Seda G, Daheshia M. Recognizing asthma mimics and asthma complications. Mil Med. 2011;176(10):1162-8.
11. Erdogan T, Karakaya G, Kalyoncu AF. Comorbid diseases in aspirin-exacerbated respiratory disease, and asthma. Allergol Immunopathol (Madr). 2015;43(5):442-8.
12. Park MR, Nam YH, Lee SK, Kim KH, Roh MS, Lee HW, et al. Uncertain areas in the diagnosis of allergic bronchopulmonary aspergillosis in patients with asthma. Allergol Immunopathol (Madr). 2014;42(5):433-8.
13. Kim MY, Sohn KH, Song WJ, Park HW, Cho SH, Min KU, et al. Clinical features and prognostic factors of Churg-Strauss syndrome. Korean J Intern Med. 2014;29(1):85-95.
14. Stachler RJ. Comorbidities of asthma and the unified airway. Int Forum Allergy Rhinol. 2015;5 Suppl 1:S17-22.
15. Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. J Allergy Clin Immunol Pract. 2014;2(6):671-80.
16. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 2017;377(10):965-76.
17. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, et al. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. J Allergy Clin Immunol. 2014;133(6):1557-63.
18. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. Nat Rev Immunol. 2015;15(1):57-65.
19. Dunican EM, Fahy JV. The Role of Type 2 Inflammation in the Pathogenesis of Asthma Exacerbations. Ann Am Thorac Soc. 2015;12 Suppl 2:S144-9.
20. Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, et al. Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma. Mediators Inflamm. 2015;2015:879783.
21. Schatz M, Rosenwasser L. The allergic asthma phenotype. J Allergy Clin Immunol Pract. 2014;2(6):645-8.
22. Bhakta NR, Erle DJ. IL-17 and "TH2-high" asthma: Adding fuel to the fire? J Allergy Clin Immunol. 2014;134(5):1187-8.
23. Ota K, Kawaguchi M, Matsukura S, Kurokawa M, Kokubu F, Fujita J, et al. Potential involvement of IL-17F in asthma. J Immunol Res. 2014;2014:602846.
24. Oray M, Samra KA, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf. 2016;15(4):457-65.
25. Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. Eur Respir Rev. 2015;24(138):594-601.
26. Wong EH, Porter JD, Edwards MR, Johnston Sl. The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med. 2014;2(8):657-70.
27. Giannetti MP, Cardet JC. Interleukin-5 Antagonists Usher in a New Generation of Asthma Therapy. Curr Allergy Asthma Rep. 2016;16(11):80.
28. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-41.
29. Tabatabaian F, Ledford DK, Casale TB. Biologic and New Therapies in Asthma. Immunol Allergy Clin North Am. 2017;37(2):329-43.
30. van Buul AR, Taube C. Treatment of severe asthma: entering the era of targeted therapy. Expert Opin Biol Ther. 2015;15(12):1713-25.
31. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014;370(22):2102-10.
32. Linden A, Dahlen B. Interleukin-17 cytokine signalling in patients with asthma. Eur Respir J. 2014;44(5):1319-31.
33. Bauer E, Lucier J, Furst DE. Brodalumab -an IL-17RA monoclonal antibody for psoriasis and psoriatic arthritis. Expert Opin Biol Ther. 2015;15(6):883-93.
34. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Asthma Intervention Research 2 Trial Study Group. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013;132(6):1295-302.
35. Walsh GM. Mepolizumab-based therapy in asthma: an update. Curr Opin Allergy Clin Immunol. 2015;15(4):392-6.
36. Bonta PI, Chanez P, Annema JT, Shah PL, Niven R. Bronchial Thermoplasty in Severe Asthma: Best Practice Recommendations from an Expert Panel. Respiration. 2018;95(5):289-300.
37. Kanemitsu Y, Takakuwa O, Fukumitsu K, Asano T, Niimi A. Bronchial Thermoplasty for Severe Asthmatic Cough. Ann Intern Med. 2018;169(1):61-2.