



Review on Moderate To Severe *Asthma*

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ABSTRACT :

Asthma is chronic condition characterized by wheezing , coughing ,and shortness of breath due to airway inflammation and hyper-responsiveness. Severe asthma accounts for a considerable amount of asthma

-related costs , although being less common than milder asthma .the current pharmacologic approach to the treatment of asthma includes the use of glucocorticoids and beta-agonists mainly . however ,these conventional therapies have poor controllability of moderate-to-severe asthma and also produce several side effects on their long-term use. Asthma is a chronic condition with great variability. It is characterized by intermittent episodes of wheeze, cough, chest tightness, dyspnea and backed by variable airflow limitation, airway inflammation and airway hyper-responsiveness. Asthma severity varies uniquely between individuals and may change over time. Stratification of asthma severity is an integral part of asthma management linking appropriate treatment to establish asthma control. Precision assessment of severe asthma is crucial for monitoring the health of people with this disease. The literature suggests multiple factors that impede the assessment of severe asthma, these can be grouped into health care

professional, patient and organizational related barriers. These barriers do not exist in isolation but interact and influence one another. Recognition of these barriers is necessary to promote precision in the assessment and management of severe asthma in the era of targeted therapy. In this review, we discuss the current knowledge of the barriers that impede assessment in severe asthma and recommend potential strategies for overcoming these barriers. We highlight the relevance of multidimensional assessment as an ideal approach to the assessment and management of severe asthma.

Keywords:

Allergic asthma, Asthma, House dust mite allergic asthma, Asthma exacerbation, Exacerbation, Quality of life, Utility, Severe asthma; position paper; phenotypes; biologic therapies; macrolides

Introduction:

Asthma is a chronic condition characterized by wheezing, coughing, and shortness of breath due to airway inflammation and hyper-responsiveness. Depending on the age of onset, clinical signs might indicate one of several phenotypes of diagnostic, management and therapy problems. A subspecialized severe asthma services provides the benefit of an organized, variety of approaches to validate the diagnosis, asthma inflexibility and phenotype, and risk factors and comorbidities operation. This multimodal approach constantly comprises a team of respiratory croakers nurses, and support health specialists, nutritionists, and clinical psychologists. In addition to evaluation and monitoring for common comorbidities. they give croaker review, lung function testing, blood tests, inhaler optimization, and general illness mindfulness.

A breakthrough in the understanding of asthma pathogenesis was made with the recognition that chronic inflammation of the conducting airways characterizes the disease, even during asymptomatic periods.

Severe asthma has been recognized as a distinct from of asthma that responds poorly to currently available medication; it is the asthma group with the greatest unmet need.

In the introduction to the ERS Monograph on Difficult-to-Treat Severe Asthma published 8 years ago, "the disease is heterogeneous, and the challenge for the next 10 years would be to understand the different types of severe asthma"

This Monograph is comprehensive in its coverage of all aspects of severe asthma. including its definition evaluation epidemiology, diagnosis, pathology, treatable traits, clinical and molecular phenotype, mechanisms, treatment and management. Asthma a chronic inflammation respiratory disease, is among the most common noncommunicable disease, affecting millions of lives and causing numerous morbidities around the world. According to the world Health Organization, around 100 to 200 milion people experience asthma, and annul deaths have reached 180,000 worldwide.

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DEFINITION AND PATHOGENESIS OF SEVERE ASTHMA

Historically, asthma was thought to be a condition caused by increase in the activity of the airway smooth muscle, or bronchoconstriction, in reaction to environmental stimuli. Even in people with just occasional symptoms or new-onset asthma, chronic airway inflammation is now regarded a characteristic of the condition.

Various definitions for severe asthma have been proposed, with most clinicians adopting the consensus definition developed by the European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force on Severe Asthma."

These characteristics make severe asthma the primary target for new treatments, However, to achieve effective treatment outcomes with the greatest precision, it is essential to have a definition of severe asthma that encompasses its key features and characteristics.

It is now well recognised and appreciated that asthma is not one disease but rather comprises multiple phenotypes . Although not explicitly stated previously, the multiple presentations of asthma have long been appreciated. For example, differences in asthma were recognised between children and adults, differences that also extend into characteristics of severe disease in these age groups. It has also been recognised that among asthma patients were those with severe disease.

Asthma patients with these characteristics had the greatest unmet medical needs and incurred the greatest costs, making severe asthma of considerable public health importance and the primary target for new therapeutics.

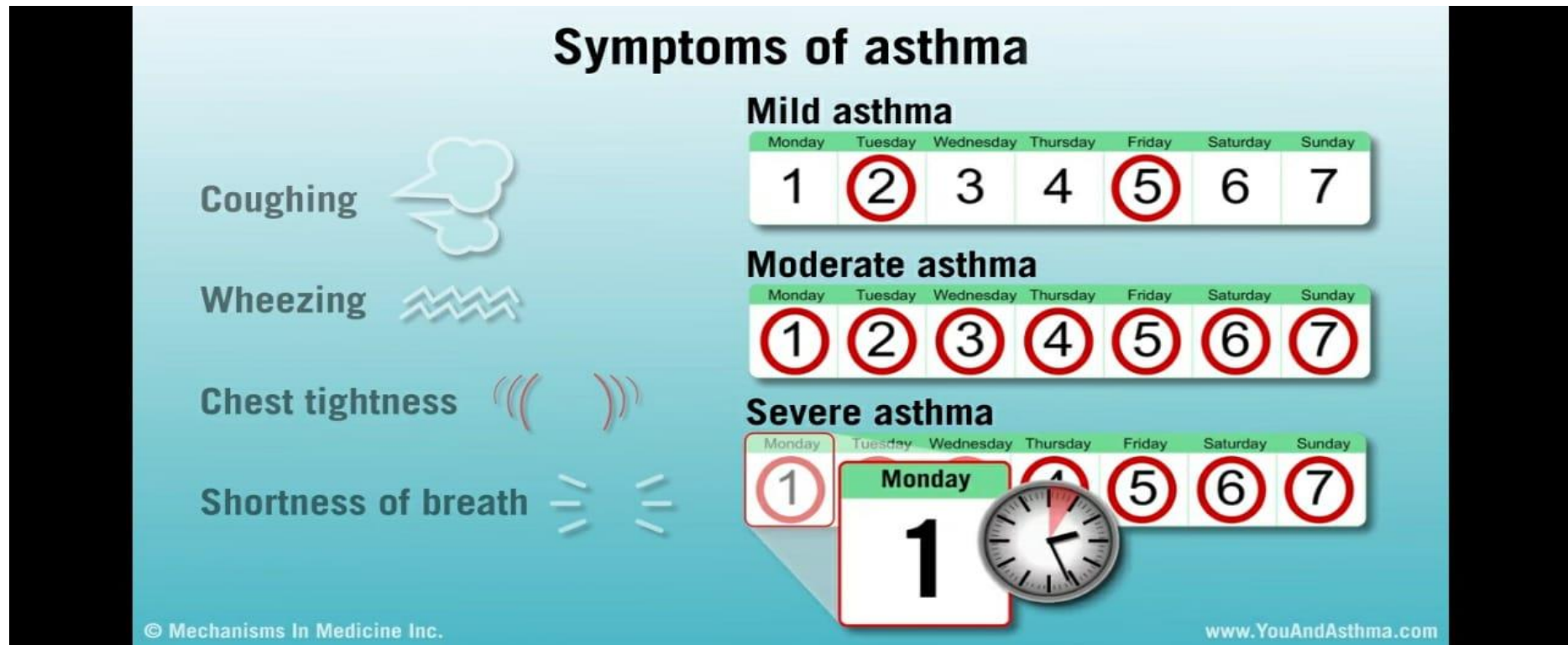
A first step towards gaining a better understanding of the pathogenesis, pathophysiology and potential therapeutic targets for improved outcomes in patients

In 1981, CARMICHAEL et al. reported on 58 cases of corticosteroid resistant asthma. The resistance to SCSs was defined by lack of improvement in airflow obstruction with >20 mg of oral prednisolone daily for 7 days.



Components of severity		Classification of asthma severity (youths ≥12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV ₁ /FVC: 8–19 years: 85% 20–39 years: 80% 40–59 years: 75% 50–80 years: 70%	Symptoms	≤2 days·week ⁻¹	>2 days·week ⁻¹ but not daily	Daily	Throughout the day
	Night-time awakenings	≤2 times·month ⁻¹	3–4 times·month ⁻¹	>1 time·week ⁻¹ but not nightly	Often 7 times·week ⁻¹
	SABA use for symptom control (not prevention of EIB)	≤2 days·week ⁻¹	>2 days·week ⁻¹ but not >1 time·day ⁻¹	Daily	Several times·day ⁻¹
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV ₁ between exacerbations FEV ₁ >80% pred FEV ₁ /FVC normal	FEV ₁ >80% pred FEV ₁ /FVC normal	FEV ₁ >60% but <80% pred FEV ₁ /FVC reduced 5%	FEV ₁ <60% pred FEV ₁ /FVC reduced >5%
Risk	Exacerbations (consider frequency and severity)	0–2/year	← >2/year →		
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV ₁			





ASSESSMENT And Evaluation of Asthma The combination of patient symptoms is required and respiratory function testing is required for a reliable diagnosis of asthma

The assessment of severe asthma is complex. This is because the disease is heterogeneous in nature and associated with many comorbidities; therefore, a multidimensional evaluation is essential.

This section focuses on the evaluation of adults and children with difficult-to-control asthma. It will address:

- 1) the evaluation required to determine that the patient with "difficult asthma" has asthma
- 2) the appropriate assessment of confounding factors and co-morbidities
- 3) the initial determination of phenotypes which may be useful in optimizing therapy.

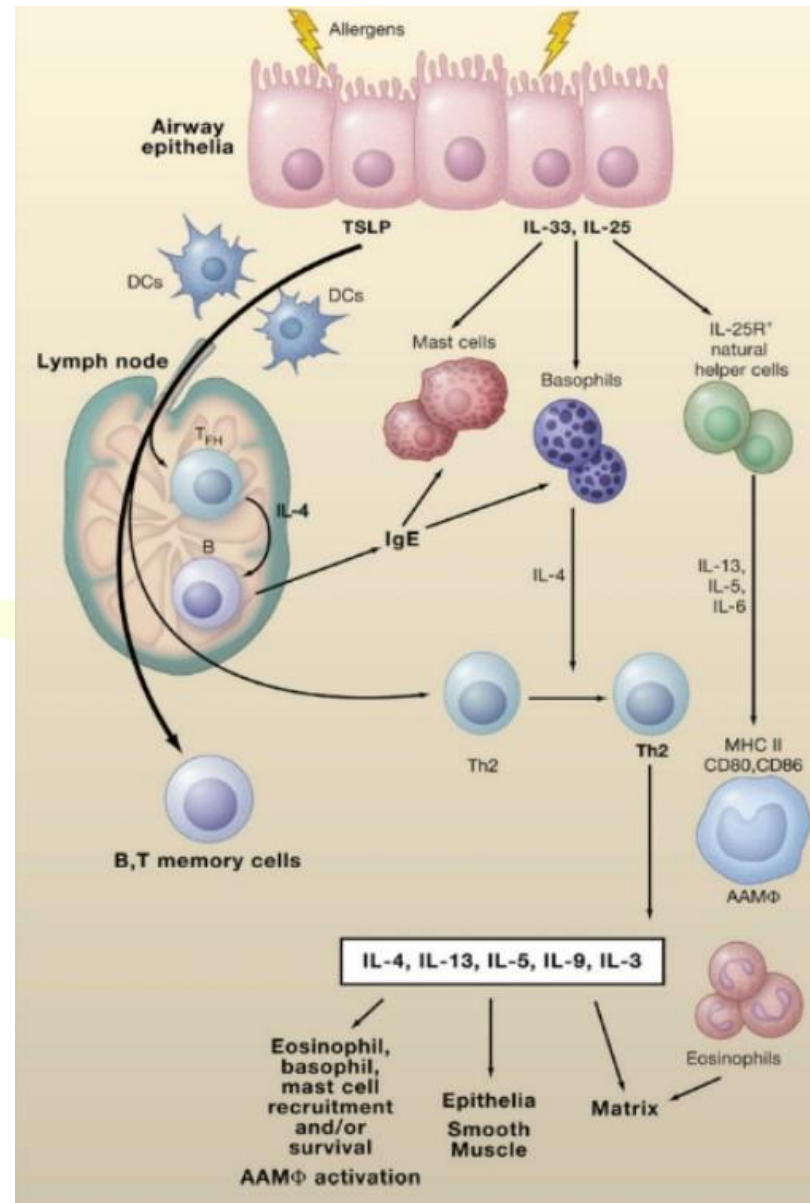
HISTORY: Asthma symptoms include wheezing tightness Of the chest and coughing. These symptoms are frequently recurrent in nature & can vary in strength .The Presence of chest tightness as the Primary Presenting symptom should raise Suspicions of Heart illness .Dust mites , cockroaches, molds. and animal dander from are example of Perennial allergies. Cigarette smoking , secondhand smoke exposure, Perfumes at heat or strong scents excess heat or cold, exercise or psychosocial strain are among non-allergic triggers.

IMMUNUNOMODULATORS:

Initiation of allergic immunity is mediated through interactions of allergens with epithelia that result in release of the cytokines thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. TSLP mediates migration of dendritic cells (DCs) and their maturation, which primes the IL-4 competency of T helper (Th) cells. These competent Th cells move into follicular areas of lymph nodes and mature into IL-4-secreting T cells. They mediate isotype switching in B cells in the germinal center reaction in lymph nodes. The B cells then produce igE antibody (and IgG1 in the mouse). IgE, in turn, binds to mast cells and basophils, extending their survival and facilitating allergen-specific activation of these cells. IL-33 promotes IL-4 release from basophils, and IL-33 and IL-25 promote IL-13 and IL-5 release from IL25R natural helper cells . in tissues (these cells also release IL-6, which supports B cell maturation and impairs T regulatory cells). 1L25R natural helper cells and basophils together produce IL-4, IL-5, and IL-13, which promote terminal differentiation and/or recruitment of T helper 2 (Th2) cells to tissues, as well as alternative activation of macrophages (AAM) and eosinophil recruitment. These effects are greatly augmented by activation of tissue Th2 cells, which contribute a diverse set of cytokines that feed back to facilitate the survival and

activation of innate immune cells and the effects of Th2-associated cytokines on epithelia, smooth muscle, and the stromal matrix. Memory T and B cells are generated that can facilitate more rapid responses to repeated stimulation, particularly if the regulatory T cell response is impaired. **Fig**





Research Through Innovation

In individuals with asthma who are on chronic systemic corticosteroid medication, mepolizumab improves exacerbation frequency, asthma symptoms, and the requirement for systemic corticosteroid therapy.

According to data from clinical studies, effectiveness is achieved when blood absolute eosinophil counts are more than 150/microl (0.15 $10^9/L$); however, the efficacy threshold for patients on prolonged systemic corticosteroid treatment is unknown. Every four weeks, 100 mg of mepolizumab is given subcutaneously.

Reslizumab also appears to lessen the number of asthma exacerbations and symptoms. Patients had blood absolute eosinophil concentrations of about 400/microl (0.4 $10^9/L$) in clinical studies. The eosinophil count threshold for effectiveness in individuals treated with prolonged systemic corticosteroids is unknown. Every four weeks, patients are given 3 mg/kg of Reslizumab IV over 20 to 50 minutes.

Treatment

The details of standard therapy can be found in the asthma guidelines and the German National Disease Management Guideline. Basic therapy consists of an inhaled corticosteroid (ICS), to which additional controllers are added if asthma control is inadequate: an inhaled long-acting beta 2 agonist (LABA), montelukast, and/or theophylline. If this does not adequately control asthma, oral corticosteroids (e.g. prednisolone)

Although patients with severe asthma are often deficient in vitamin D, current evidence does not support a universal recommendation of vitamin D therapy. There are specific treatment principles for the diseases associated with asthma. Below we outline basic measures and additional treatment options following a diagnosis of severe asthma.

A typical target is the allergic inflammatory pathway. Omalizumab is an anti-IgE antibody that interacts with mast cells, eosinophils, and basophils in the allergic pathway. It's approved for people with mild to

severe asthma who don't respond to ICS and have confirmed allergen sensitivity. It's given every 2 to 4 weeks. Antibodies such as mepolizumab, reslizumab, and benralizumab target the interleukin-5 pathway, which is implicated in eosinophil recruitment and activation. Bronchial thermoplasty (BT) is an endoscopic technique that uses radiofrequency heat radiation to ablate airway smooth muscle, diminishing its ability to cause bronchoconstriction. In people with severe asthma, data shows that BT lowers exacerbations, minimizes asthma-related health-care utilization, and enhances the quality of life.

Patients with poorly controlled asthma at Step 3 require review by a respiratory physician. 2 Treatment options that might be recommended include: 2 Increasing ICS beyond standard dosing may be considered for patients with asthma that is poorly controlled despite lower dose treatment taken optimally. 3 This is only appropriate for a small number of patients. 3 High dose ICS treatment, e.g. > 400 micrograms per day of budesonide, > 250 micrograms day of fluticasone propionate

Oral corticosteroids taken at the lowest effective dose for maintenance treatment, e.g. prednisone < 7.5 mg/day, may be considered for limited periods for patients with severe asthma

Tiotropium, an inhaled long-acting muscarinic antagonist (LAMA), may be an appropriate additional treatment for people with features of asthma and COPD, i.e. asthma COPD overlap syndrome (ACOS). Although tiotropium is indicated as an adjunctive treatment for patients with asthma

PHARMACOLOGICAL MANAGERMENTS

Medication for controlling asthma The main goal of such medications is to block the inflammatory process that causes asthma and thus preventing any non-reversible airway remodeling. The backbone of controller therapy is inhaled corticosteroids.

Long-acting muscarinic antagonists, which are routinely used to treat COPD, do not appear to be superior to LABA and are normally reserved for patients with severe disease. LABA mono-therapy is unsuitable and should never be given for a patient with asthma, as it was associated with an elevated asthma-related mortalities

Beta-2 agonists help mucociliary clearance by relaxing bronchial smooth muscle, reducing mast cell degranulation and histamine release, inhibiting microvascular leakage into the airways, and increasing mucociliary clearance.

Long-acting beta-2 agonists (e.g. indacaterol) are used for moderate to severe asthma, and ultra-long-acting beta-2 agonists (e.g. indacaterol) are used for moderate to severe asthma, but should never be taken alone. They work in tandem with inhaled corticosteroids, allowing for lower corticosteroid doses. The safety of using beta-2 agonists on a regular basis for an extended period of time is unknown. When administered as monotherapy, long acting beta-2 agonists may raise the risk of asthma –related mortality.

Conclusions

Asthma is one of the most known respiratory disorders that require long-term managements. The diagnosis and treatment of severe asthma is time consuming and requires special experience. Diagnosis of asthma is complicated by the common features between asthma and other respiratory diseases.

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