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REVIEW

A Brief Review of Severe Asthma

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ABSTRACT

Severe asthma describes an asthma condition that requires a substantial amount of inhaled corticosteroid and bronchodilators to keep it under control including the frequent additional need for oral steroid to avoid exacerbations. The incidence of severe asthma in Malaysia is unknown but data elsewhere shows that it is around 5 to 10 % of asthmatics. This category of asthmatic patients has considerable morbidity, is disproportionate cost-wise to the number of sufferers and requires specialised and focused care. The management of severe asthma should be undertaken at a severe asthma clinic led by a physician with a special interest in its management. The diagnosis needs confirmation, comorbidities identified and triggering factors addressed. Inhaler technique and compliance are major contributing issues and must be addressed at all consultation opportunities. Once the diagnosis of severe asthma is confirmed, the disease needs phenotyping to plan for the most appropriate treatment, termed as a personalised approach to severe asthma care. The advances in biologics have changed the landscape of treatment of this disease but in Malaysia especially, there are many limitations namely the cost. This article briefly explores the current understanding of severe asthma, the assessment including phenotyping and possible treatment options.

KEYWORDS: Severe asthma, assessment, phenotyping, Type 2 High, non-Type 2, biologics, severe asthma clinic, registry, cost limitation, research opportunities

INTRODUCTION

Definition

Asthma is defined as a heterogeneous condition that is characterised by chronic airway inflammation. Associated with this process is a history of symptoms related to the inflamed airways such as variable cough, chest tightness, wheezing, dyspnoea, and demonstrable variable airflow limitation necessary for diagnosis [1].

Severe asthma has been defined on a few occasions over the years and it is a more nuanced definition with emphasis on symptoms. In 2014, both the American Thoracic Society (ATS) and European Respiratory Society (ERS) collaborated on a widely used definition until today [2]. Global Initiative for Asthma (GINA) had also published guidelines on severe asthma in 2019 [3] and the latest guideline to its treatment including the most recent in 2021 that has included the segment on severe asthma [4]. Clinical features of severe asthma include frequent and persistent symptoms, repeated exacerbations, fixed loss of lung function, impairment of quality of life and the presence of comorbidities such as anxiety or depression [3].

An asthma is said to be uncontrolled when either of these two conditions is present; the symptom control is poor, or the patient has frequent exacerbations (at least twice in a year), and if the exacerbation ended up with an admission, a single episode represents poor control. A difficult-to-treat asthmatic is a patient who has poor control despite treatment corresponding to stage 4 or 5 of the GINA guideline as in Table 1. And it is often accounted for by factors such as poor compliance, poor technique, smoking, or the presence of unrecognised comorbidities. Severe asthma is present when despite addressing modifiable risk factors (compliance to adequate therapy, correct inhaler technique, comorbidities, smoking and correct diagnosis) the disease remains uncontrolled or worsens

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if the treatment is reduced. The diagnosis is therefore a retrospective one and at times termed severe refractory asthma. This definition is incorporated in the latest GINA guideline in 2021 [4]. For referencing, Table 1 compares the two widely used definitions in severe asthma.

Table 1 The two widely used definitions in severe asthma

European Respiratory Society/American Thoracic Society 2014 [2]	Global Initiative for Asthma [4]		
Asthma which requires treatment with high-dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy	A difficult-to-treat asthmatic has poor control despite treatment at stage 4 or 5 of the GINA guideline. Severe asthma is present when despite addressing modifiable risk factors (compliance to adequate therapy, inhaler technique, comorbidities, smoking and correct diagnosis) the disease remains uncontrolled or worsens if the treatment is reduced.		
		Step 4	Step 5
	Preferred controller	Med dose maintenance ICS/formoterol	Add on LAMA Refer for phenotypic assessment ±anti IgE, anti-IL-5/5R, anti-IL4R Consider high dose ICS/formoterol
	Other controller options	Med dose maintenance ICS/LABA	Add on LAMA Refer for phenotypic assessment ±anti IgE, anti-IL-5/5R, anti-IL4R Consider high dose ICS/LABA
	Reliever	Preferred is as needed low-dose ICS/formoterol Or the alternative is as-needed SABA	

Note: (ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; LAMA, long-acting muscarinic agent)

Burden of Asthma

Globally, asthma is a very common chronic disease. It affects about 339 million people worldwide with the highest prevalence in countries like Australia and New Zealand [5,6]. Acute asthma attacks cause about 1150 deaths daily [7]. In 2016 for example, the World Health Organisation (WHO) estimated a worldwide death estimate due to asthma of about 420,000. Most of the asthma deaths unfortunately had occurred in low or low-middle income countries. In Malaysia in 2014, WHO estimated that asthma deaths were 1,642 or 1.29% of total deaths in the year [7].

In terms of disability, asthma is the 16th commonest cause of years lived with disability, and the 28th as a cause of burden of disease as measured by disability adjusted life years [8].

In Malaysia, based on our 3rd National Health and Morbidity Survey 2006 [9], the prevalence of asthma based on respondent survey was about 4.2%, against a backdrop of the rate between 5.2% and 9.4% worldwide [4]. A large study on asthma control conducted in Asia Pacific, the Asthma Insights and Reality in Asia-Pacific (AIRIAP) study [10], showed that the rate of persistent asthma among asthmatics in the region was about 23% and in Malaysia, only about half of that proportion of asthmatics was on inhaled corticosteroid (ICS). In the study persistent asthma was defined as the presence of symptoms (nocturnal, daytime or exacerbations) of more than twice in a week. The study also confirmed that the prevalent of symptoms among the Asia Pacific asthmatics with 51.4% had daytime symptoms, 44.3% had sleep disturbances, and 43.6% had a hospitalisation and attending an ER in previous 12 months [10].

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How Common is Severe Asthma?

Data from a Dutch population survey [11] shows that nearly a quarter of asthmatics are on asthma treatment at stages 4 and 5 of the GINA guidelines. From that quarter, only about 33% of the patients have well controlled asthma [4], the rest of about two thirds is troubled by on-going symptoms with accompanying reduced lung functions. With assessment and specialised intervention only about 20% or a fifth of this group remains symptomatic and this is the group that we are dealing with. In other words, severe asthma is a subset of difficult-to-treat asthma. The Dutch data also shows that this is about 3.7% [11] of all asthmatics. Other estimates vary but has sometimes been quoted to be around 5 to 10% of total asthmatics [12].

Evolving Understanding of Asthma

The knowledge of asthma has gone through phases of understanding that have influenced the way the disease is treated [13]. In the 60s and 70s, we know that asthma was a disease with significant bronchoconstriction from the action of the bronchial smooth muscles which led to the widespread use of sympathetic beta 2 agonist (B2 Agonist) as treatment with reduction in symptoms. A decade or so later our knowledge expanded to the understanding of bronchial inflammation as the cause of symptoms and reduction in lung function [4,13]. Together with B2 Agonist, the use of Inhaled Corticosteroid (ICS) became the standard treatment to control asthma. In the early 2000, the cohorts of asthmatic who remain symptomatic led to the understanding of clinical phenotypes or clusters in asthma. Deeper analysis into these clusters opened the way to understand the endotypes or processes that explain these different clinical manifestations (phenotypes) which led to the understanding of the spectrum of high T Helper cells or the other end of low T Helper cells [14]. Identification of specific cells and proteins paved the way for precision medicine in the management of severe asthma that we see today. Asthma was previously viewed as a single entity diagnosis and a treatment that fits all patients, but science and our clinical experience have shown that it is a disease that needs stratification because treatment is variable to different clusters. In severe asthmatic cells identification allow for the application of precision medicine, a medicine that is tailored to the specific individual patient to increase the chances of symptoms control [15].

Phenotypes and Endotypes

Phenotype is the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment, and an endotype is a specific biologic mechanism that explains observable properties of an organism. For example, studies such as severe asthma research programs [14,16] conducted in the US have identified at least three distinct phenotypes associated with severe asthma: late-onset allergic, late-onset minimally atopic eosinophilic and late-onset non-eosinophilic with their accompanying clinical and physiologic characteristics. To illustrate this further, Table 2 summarizes the important clinical and the physiological features of some these phenotypes [13,14].

Table 2 Severe asthma phenotypes including clinical and physiological characteristics

Phenotype	Clinical/Physiologic Characteristics
Early-onset allergic	History of food allergy, atopic dermatitis and allergic rhinitis
Late-onset minimally atopic eosinophilic	Chronic rhinosinusitis/nasal polyps Severe airway obstruction Subset = AERD
Late-onset non-eosinophilic	Poorly characterized May have significant lower respiratory tract infection and/or GERD

Note: AERD is aspirin exacerbated respiratory disease and GERD is gastro-oesophageal reflux disease

Assessment of Severe Asthma

The assessment of patients with severe asthma must be systematic and done in a comprehensive manner. The most important step is to confirm the diagnosis of asthma [4] which involves demonstration of a significant variable airflow obstruction of more than 15% because up to a third of presumed difficult to control asthmatics may have other diagnosis to account for their symptoms [16]. Next step is to exclude the presence of comorbidities and if any is present, it requires an appropriate treatment to minimise its impact on asthma control. Evaluation of patients with severe asthma from uncontrolled asthma involves assessment of comorbidities versus the contributing factors for asthma control. Table 3 lists features of factors that contribute to poor asthma control against comorbidities that may also be present causing asthma to be uncontrolled.

Once asthma severity is established, GINA step appropriate treatment recommendation should be promptly commenced, and treatment adherence is monitored and maintained. Should asthma control remain an issue, the disease should be endo-typed. Based on its type of inflammation, a more personalised treatment should be commenced to the individual patient [17].

Studies [14,15] on asthma endotypes with inflammatory pathways and biomarkers have identified two types of asthma, Type 2, and non-Type 2. The former is more common (up to 70%) whilst the former could vary between 30 to 50%. Type 2 asthma is also called an eosinophilic variety and manifests itself with high fraction of exhaled nitric oxide (FeNO) and is often associated with allergic asthma and therefore often have an accompanying high serum IgE. This pathway is often mediated by interleukin 4, 5 and 13 [18,19]. The non-Type 2 is neutrophilic in nature and is mediated by other interleukins; 1,6 and 17 with contribution from tumour necrosis factor [14,15]. Table 4 lists the severe asthma phenotypes and its associated clinical and pathological features. These features are useful guide to phenotyping individual with severe asthma patient in practice.

Table 3 Evaluation of Severe asthma versus uncontrolled asthma

Comorbidities	Contributing Factors
Rhinosinusitis/(adults) nasal polyps	Poor treatment adherence
Psychological factors	Poor inhaler technique
Vocal cord dysfunction	Environmental exposure
Obesity	
Smoking and related diseases	
Obstructive sleep apnea	
Hyperventilation syndrome	
Hormonal influences	
Gastroesophageal reflux disease	
Medications	
Rhinosinusitis/(adults) nasal polyps	

Table 4 Severe asthma phenotypes with its clinical and pathological features

Phenotype	Associations
Early-onset severe allergic	Blood and sputum eosinophils
	High serum IgE
	High FeNO
Late-onset eosinophilic	Blood and sputum eosinophils
	Recurrent exacerbations
	High FeNO
Late-onset non-atopic steroid-dependent asthma with fixed airways obstruction	Airway wall remodeling as increased airway wall thickness
Frequent exacerbators	Sputum eosinophils in sputum
	Reduced response to ICS and/or OCS
Late-onset obese (primarily women)	Moderate FEV_1 reduction
	Frequent OCS use

Note: Fraction of exhaled nitric oxide (FeNO), Inhaled corticosteroid (ICS), Oral corticosteroid (OCS), Forced Expiratory Volume in One Second (FEV1)

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To personalize therapy and maximize drug response it is important to endotype severe asthma with biomarkers to identify the asthma phenotype. Endotype is a distinct biological mechanism that links clinical characteristic with a molecular pathway that may represent a phenotype and the phenotype may have more than one endotype linkages. Current available methods involve utilising proteins such sputum eosinophils, circulating blood eosinophils, exhaled nitric oxide, IgE and allergen skin testing [18]. Sputum eosinophils is very difficult to perform and consequently is not often done in practice except in research setting. In the clinic, blood eosinophils and serum total IgE including allergen skin testing are usually done and in some centres the test fraction of exhaled nitric oxide (FeNO) if available. If used properly with the stringent technological specification and the appropriate clinical context, FeNO is very helpful to guide treatment adequacy but it is only available in a few centres in Malaysia. It however requires very specific technical validation. In the future, endo-typing includes the use of other proteins such as periostin, dipeptidyl peptidase-4 (DPP-4), eosinophil peroxidase and urinary bromotyrosine in phenotyping severe asthma [20].

Management of Severe Asthma

The first step is to optimize the dose of inhaled corticosteroid/long-acting beta 2-agonist (ICS/LABA) as some may respond to higher doses of ICS than routinely used but be mindful of the risk of systemic side effects with higher ICS doses. In the usual way, ICS dose should be stepped down slowly once asthma control is achieved at 3-6 months intervals. In some, an even higher doses of ICS than routinely used may be beneficial. For those who need oral steroid, this may also be used but again the risk of systemic side effects is higher. Many guidelines [1,2,3] cautiously remind the possibility of using oral steroid but patients must be monitored for weight gain, blood pressure, blood glucose, glaucoma, and bone density. There should also be low threshold for adding prophylactic measures to prevent loss of bone density.

These add-ons may be considered in selected patients with uncontrolled symptoms and persistent airflow limitation despite moderate-/high-dose ICS and LABA: tiotropium, theophylline or LTRA. At this point treatment should be biomarker-guided or adjusted by FeNO or sputum eosinophils count. Biomarkers are proteins that can be used to phenotype severe asthmatic. The next step is the individualize treatment based on phenotype by using biologics. Table 5 lists the selected biomarkers used in asthma phenotypes and the suitable biologics that can be considered by the attending clinicians [23].

Bronchial thermoplasty can also be considered in selected patients which works by decreasing the smooth muscle mass by application of excess heat to the bronchial muscles in the airways with radiofrequency energy ablation during bronchoscopy. Typically, a patient may need at least 3 bronchoscopy sessions to achieve a significant improvement on symptoms. But overall, the procedure still lacks convincing evidence of safety over benefits, especially in the long term [21,22].

The possible biologics that can be given for suitable patients are numerous and are selected based on the isolated biomarkers and the symptoms frequency and severity. Table 6 highlights the biomarkers and their actions in relation to the inflammatory pathways involved in the biologic therapy.

Table 5 Biomarkers and their phenotype including suitable biologics

Biomarker	Source	Phenotype	Associated Biologic
Immunoglobulin E	Serum	Allergic (early onset)	Omalizumab
Eosinophil	Blood, sputum	Eosinophilic (late onset)-allergic and non-allergic	Benralizumab Mepolizumab Reslizumab Dupilumab
Exhaled nitric oxide	Breath	Type 2 inflammation	Omalizumab Dupilumab Librikizumab Tralokinumab
Periostin	Serum, sputum	Type 2 Inflammation	Omalizumab Dupilumab

Note: Type 2 inflammation refers to Type 2 asthma or Type 2 high that includes allergic asthma, exercise-induced asthma, and late-onset eosinophilic asthma.

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Table 6 Targeted Pathways for Biologic Therapies

Type 2 Inflammatory Pathways		Non-Type 2 Inflammatory Pathways	
IgE	Inhaled allergens stimulate production of IgE by B lymphocytes and bind to mast cells degranulation	IL-17	Cytokine produced by Th17 cells; plays important role in the immunologic responses seen in asthma
IL-5	Pro-eosinophilic cytokine, cytokine that regulates proliferation, maturation, migration, and effector functions of eosinophils	CXCR2	Potent chemo-attractant for neutrophils; under investigation in asthma and COPD
IL-4 IL-13	Cytokine found in increased levels in airways and sputum of asthma patients and involved in eosinophil trafficking and B cell production of IgE Cytokine associated with eosinophil trafficking and production of FeNO from epithelial cells		
TSLP	Novel target; epithelial-cell-derived cytokine; drives allergic inflammatory responses by activating dendritic cells and mast cells		

Note: CXCR2, Chemokine receptor 2; IgE, Immunoglobulin E; Th2, T helper 2 cells; TSLP, Thymic stromal lymphopoietin

Table 7 Summaries of most of the approved biologics, their targets, and data on their efficacy

Target Antigen	Agent	Clinical Data	Trial Results on Efficacy
IL-5R*a*	Benralizumab (Fansera)	Eosinophil count of at least 300/mL.	CALIMA trial (n=1306) shows two regimens (4 and 8-week cycles) that decrease exacerbations by 36% and 28% respectively and lowered blood counts [24] SIROCCO trial (n=1,205) for 48 weeks showed exacerbations reduced by 45% & 51%. Exacerbations decreased 17%–30% in patients with >300 blood eosinophils/μL [25]
IL-5	Reslizumab (Cinqair)	Eosinophil count of at least 400/mL.	BREATH program [25]: 4 studies (n=1656), serum eosinophil counts reduced (mean diff vs placebo: −476.83, 95% CI −499.32 to −454.34) Reduced number of eosinophils in the blood and lungs; decreased blood eosinophils. [26]
IL-5	Mepolizumab (Nucala)	Eosinophil count of at least 150/mL.	COLUMBA trial (n=347), 61% decrease in exacerbation rate, 78% reduction in blood eosinophils by week 4, sustained; 1/3 experienced no exacerbations; ACQ5 improved. [27] Dream study showed reduced exacerbations by 40-60%; 50% reduction in oral steroid. Blood eosinophil counts decline by 75% within a month, failure to achieve decrease raises questions about biologic efficacy in patient; FeNO minimally reduced. [28]
	Omalizumab (Xolair)	Total serum IgE level >30 IU/ mL; for moderate-to-severe persistent allergic asthma	Hanania et al. (n=850) showed in 48 weeks, it decreased exacerbations by 25%; improved asthma QoL scores. Overall trial showed reduced asthma exacerbations, serum-free IgE, ICS dose; QOL improved. [29]
Anti-IL-4/ -13	Dupilumab	Patients with allergies, elevated IgE, eosinophilia, or high FeNO levels.	Quest trial (n=1902) showed 60–80% reduction in exacerbations; reduced FeNO and IgE levels; improved lung function and reduced dependence on OCS. [30]

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In Malaysia, there are now two biologics available for use, Omalizumab and Benralizumab with trade name Xolair and Fasenra, respectively. The latter has been available for use for nearly 2 decades but has only been present for prescriptive use in the country in the last 5 years. Benralizumab, an anti-interleukin 5 receptor antibody is approved within the last 12 months and therefore local experience in clinical use is limited. Omalizumab has more than 10 years data from randomized control trials, post-marketing, real-life studies as well as pharmacovigilance data, and is well known to decrease the rates of exacerbation and improves quality of life by improvement in lung function and asthma symptom control. The use of this medication also leads to reduction in healthcare utilization such as emergency room visit and use of oral steroid. And importantly it is safe and well tolerated in adults. Detailed review of all biologics is beyond this brief summary, but Table 7 provides a brief summary data for a quick reference for further read up on the subject.

The major trials for new biologics had limitations, including their sample size issues and therefore additional studies with larger groups of patients are needed to confirm findings. There is the problem of a short treatment period which limits the data on durability of response. Other unmet needs include the determination of most effective biomarkers to select responsive patients and there is also limited data on which biologic to try first. There is also no data on combination therapy with two biologics [31].

Opportunities in Malaysia

Knowledge of asthma in general and severe asthma in particular is rapidly expanding and this presents an exciting opportunity for new treatment strategies and understanding of the pharmacology. The care for severe asthma should develop in centres specifically designed for patients with the disease because it is costly and labour intensive. The centres will further develop and adapt the latest knowledge and expertise to ensure right patients get the right treatment with continuous networking between similar centres in Malaysia. They are then able to collaborate with regional or international centres to ensure continuity, research work, and quality assurance. This prospect is further boosted by the emergence of many academic health centres across the country, which can potentially develop into specific clinical care centres. The issue of cost of the new treatment with biologics is a real one because the public healthcare budget is shrinking and the need for effective but expensive treatment is not confined to only asthma, every disease has therapeutic budget needs.

CONCLUSION

Finally, personalised medicine in severe asthma is here to stay and the best initiative for this to work would be a top-down evidence-based approach which would allow for severe asthma clinic longevity, training, and research to prosper over the longer term.

Conflict of Interest

Authors declare none.

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