

Mini Review

Severe asthma: comorbidities and new frontiers in therapy and management

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SUMMARY

Asthma is a heterogeneous inflammatory disease that affects around 5-10% of children globally. Up to 2% of pediatric asthmatic patients suffer from severe asthma, which leads to increased hospitalizations, higher healthcare costs, and poorer outcomes despite intensive standard treatment. Within this context, the endotype-driven approach and use of biologics have provided significant benefits in treating severe asthma and its associated comorbidities. Additionally, the emerging role of digital health may greatly reduce the global burden of asthma.

KEYWORDS: severe asthma, comorbidities, biologic therapies, mobile health

1.1 ASTHMA

Asthma is a chronic heterogeneous disease that affects around 5-10% of children globally. It is characterized by different airways inflammatory patterns and a history of symptoms such as shortness of breath, recurrent wheezing, chest oppression associated with airway hyperresponsiveness, variable airflow limitation with reversibility to bronchodilation, but this limitation, if left untreated, may become irreversible ¹⁻³.

The main goal of asthma management and treatment is to reduce underlying airway inflammation and monitor symptom control. The severity of asthma is mainly determined by the amount of treatment required to achieve and maintain adequate control and can be classified as mild, moderate, and severe ⁴.

1.2 SEVERE ASTHMA

The definition of severe asthma (SA) has evolved over the years; it is currently considered an umbrella term, which encompasses difficult-to-treat asthma and severe therapy-resistant asthma (STRA) ⁵.

According to the European Respiratory Society/American Thoracic Society (ERS/ATS) and GINA guidelines, SA refers to asthma that remains uncontrolled despite the use of medium or high doses of inhaled corticosteroids along with a second controller, or maintenance with oral corticosteroids (OCS), or that requires high-dose treatment to achieve and maintain control ^{2,6}. In addition, difficult-to-treat asthma includes all those concomitant and modifiable factors in asthma management that worsen the patient's condition, such as low adherence or inadequacy of treatment, incorrect inhalation technique, poor patient education, chronic exposure to tobacco smoke or allergens, unfavorable socio-cultural or psychological conditions, and comorbidities ⁶.

Indeed, it is crucial to rule out all the conditions that can resemble asthma and may require different treatments. These disorders, among others, include immunodeficiencies, cystic

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fibrosis, extrinsic compression of the airway (vascular rings, enlarged lymph nodes), inhaled foreign bodies, bronchopulmonary dysplasia, congenital respiratory malformations, and primary ciliary dyskinesia ⁷. Approximately 2% of pediatric patients with asthma suffer from SA, and within this group, only 5% experience true STRA. These individuals require additional therapeutic interventions, even though limited options are available ⁵.

1.3 COMORBIDITIES OF SEVERE ASTHMA

Comorbidities are more commonly associated with SA rather than mild or moderate asthma and can exacerbate the severity and intensity of symptoms, or make it difficult to manage. They can be classified into respiratory and non-respiratory comorbidities. Respiratory comorbidities include allergic and non-allergic rhinitis, chronic rhinosinusitis with or without nasal polyps, obstructive sleep apnea, inducible laryngeal obstruction, bronchiectasis, mycoses, and respiratory pattern disorders ⁵. The most common non-respiratory comorbidities observed are atopic dermatitis, gastro-esophageal reflux disease, obesity, anxiety, and depressive disorders ⁸.

1.4 PHENOTYPES AND ENDOTYPES OF ASTHMA

The complex heterogeneity of asthma arises from its multifaceted nature and a not fully understood pathogenesis. It has become evident that genetic susceptibility, atopy, respiratory infections, lung and gut microbiome, and environmental factors all play a significant role in asthma pathogenesis ⁹.

Over the last two decades, different phenotypes of asthma have been described, with the most common being allergic, non-allergic, late-onset asthma, exercise-induced, obesity-induced, and associated with lung function impairment. However, the clinical application of asthma phenotyping faces several challenges due to great clinical heterogeneity, potential overlapping features, evolving characteristics over time, and even the possible existence of subtypes within phenotypes.

Given the limits of clinical practice and the need for a personalized approach in the management and treatment of this highly prevalent non-communicable disease, where the 'one size fits all' approach has proven inadequate, the identification of the molecular, immunological and functional pathways underlying the different pathophysiological processes, known as endotypes, may allow the identification of the most appropriate therapy for each patient.

Endotype assessment is now considered crucial in the context of SA, especially to determine the best-tailored biological therapy. Currently, endotypes are still insufficiently known in pediatric asthma ⁵, but five different ones are described in pediatric STRA: an atopic eosinophilic endotype, promoted by T Helper (TH) 2 cells in the presence of allergic

sensitization; a non-atopic eosinophilic endotype, characterized by type 2 cytokines (such as IL-4, IL-5, and IL-13) produced by innate lymphoid type 2 cells, regardless of allergic status; a neutrophilic endotype, a mixed endotype, whose inflammation is both eosinophilic and neutrophilic; and a paucigranulocytic endotype, in which airway remodeling predominates over airway inflammation ¹⁰.

2.1 AVAILABLE BIOLOGIC THERAPIES IN PEDIATRICS

Choosing the most appropriate biological drug for asthma patients is a challenge for allergists. Omalizumab, mepolizumab, and dupilumab are the most widely used biologic drugs in severe pediatric asthma, which have proven to be safe and effective. Omalizumab was the first humanized monoclonal antibody against immunoglobulin E (IgE) approved for pediatric use and is indicated for children over 6 years of age with elevated total IgE (> 30 and < 1500 IU/mL). It is administered subcutaneously and its mechanism of action involves the selective binding of free IgE, preventing its binding to the IgE receptor on mast cells and basophils and thus inhibiting the release of inflammatory mediators. Omalizumab is particularly effective in asthmatic children with multiple allergic comorbidities. Patients with a high peripheral eosinophil count (> 300 cells/ μ L), elevated total IgE, fractionated exhaled nitric oxide (FeNO) > 20 ppb, and increased serum periostin are good candidates for treatment with omalizumab, although there are no validated biomarkers to predict treatment response.

Mepolizumab, a monoclonal antibody targeting IL-5, leads to eosinophil reduction and is indicated for pediatric patients affected by severe eosinophilic asthma from the age of 6 years. Mepolizumab is indicated in patients with blood eosinophils count > 300 cells/ μ m (or $\geq$ 150 cells/ μ L) in patients with well-characterized eosinophilic asthma or requiring several cycles with OCS.

Dupilumab, a fully human monoclonal antibody blocking IL-4 and IL-13 receptors, is indicated for patients over 6 years old affected by type 2 SA characterized by high blood eosinophils and/or FeNO. Dupilumab is a reliable and efficient medication; nevertheless, side effects have been reported, including temporary eosinophilia (without any organ damage), conjunctivitis, and oral herpes ⁹.

2.2 NEW FRONTIERS IN THERAPIES FOR PEDIATRIC SEVERE ASTHMA

Trials are currently being conducted in the pediatric population to assess the safety and efficacy of biologic drugs that are already available for the treatment of severe asthma in adults. Benralizumab is a monoclonal antibody that targets the α subunit of IL-5R, preventing IL-5 from exerting its effect on target cells (eosinophils, basophils, and ILC2) that induces an almost complete depletion of eosinophils. While approved by the Food and Drug Administration (FDA) to treat SA in patients aged 12 and older with a certain eosinophil

count, it is not yet approved by the European Medicines Agency (EMA) for use in children. The DOMINICA Study (NCT05692180) is currently ongoing to assess the drug's efficacy and safety in individuals 6 to 18 years of age ¹¹.

Tezepelumab is a human monoclonal antibody that binds specifically to thymic stromal lymphopoietin (TSLP), a key epithelial inflammatory cytokine involved in the pathogenesis of asthma. This groundbreaking treatment has recently received approval from both the FDA and the EMA for severe asthma patients over the age of 12 years ¹¹.

Research is also being conducted on the possibility of administering multiple biologic drugs simultaneously to target various inflammatory pathways. However, limited data are available regarding this approach, and guidelines for the dual use of biologic drugs are still lacking ¹¹.

2.3 NEW FRONTIERS IN ASTHMA CONTROL AND MANAGEMENT

The advent of digital technology is transforming the way chronic conditions with severe outcomes such as SA are managed and controlled. For example, mobile health and telemedicine can enable the remote monitoring of a patient with SA using a smartphone, leading to enhanced asthma control and management. This approach has the advantage of guiding the patient to effectively manage their condition, preventing severe exacerbations, avoiding unnecessary emergency room visits, and reducing costs for the public healthcare system.

3.1 SOCIO-ECONOMIC BURDEN OF SEVERE ASTHMA IN CHILDHOOD AND UNMET NEEDS

Asthma, particularly SA, has a significant socio-economic impact in terms of direct and indirect costs. Direct costs arise from medical expenses such as hospitalization, medication, and doctor visits, while indirect costs include decreased productivity at work or school due to absences. Furthermore, asthma places a burden on healthcare systems, resulting in increased allocation of resources for treatment and management.

The unmet needs in the field of SA outline the unresolved challenges that require immediate attention to enhance the management of the condition and promote better patient well-being. A deeper understanding of the underlying pathophysiology of asthma is necessary to develop oral therapies that may be both more effective and side-effects free. Additionally, there is a need to personalize treatment approaches and improve early diagnosis to address the specific needs of each patient.

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Conflicts of interest statement

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Ethical considerations

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Author's contribution

Tosca MA conceptualized and wrote the original draft; Naso M wrote, reviewed, and edited the original draft, Meleca V wrote the original draft; Olcese R reviewed and edited the original draft. All authors read and approved the final version of the manuscript.

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