Phenotyping and Targeted Therapy Strategies for Severe Asthma in Children from the Perspective of Precision Medicine

Xin Guo, Xusheng Qi*

Department of Pediatric Outpatient , Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, China

Abstract: Severe asthma in children poses significant challenges to clinical management, characterized by poor control, frequent exacerbations, and potential long-term impacts on lung development. The paradigm of precision medicine has revolutionized the understanding and treatment of asthma by emphasizing individualized care based on patient-specific phenotypes. This paper aims to summarize the current progress in phenotyping severe asthma in children and explore targeted therapy strategies under the framework of precision medicine.

***Keywords*:** severe asthma; children; precision medicine; phenotyping; targeted therapy; biologics

1. Introduction

Severe asthma in children is a chronic and complex respiratory disease, affecting 5-10% of pediatric asthmatic patients. Precision medicine, which emphasizes tailoring medical treatment to individual patients' characteristics, has emerged as a revolutionary concept in asthma management. In the context of pediatric severe asthma, due to its unique immunological and developmental features, precision medicine - based phenotyping and targeted therapy strategies are particularly crucial for improving treatment efficacy and patient outcomes.

2. Phenotyping of Severe Asthma in Children

2.1 Molecular Phenotypes

2.1.1 Type 2 Inflammatory Phenotype

Type 2 inflammation, characterized by elevated levels of interleukin-4 (IL-4), IL-5, and IL-13, and increased eosinophil counts, is a well-recognized molecular phenotype in severe asthma [1]. In children, this phenotype is often associated with allergic sensitization, atopic dermatitis, and early-onset asthma. Biomarkers of type 2 inflammation, such as fractional exhaled nitric oxide (FeNO), blood and sputum eosinophils, and serum periostin, have been used to identify patients who may benefit from type 2-targeted therapies [2]. Genetic studies have linked type 2 asthma to variants in genes involved in TH2 cell differentiation and eosinophil regulation, such as IL4, IL13, and IL5 [3].

Biologics targeting type 2 inflammation, such as omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), and dupilumab (anti-IL-4Rα), significantly reduce exacerbations and improve lung function in children with severe type 2 asthma. However, it is important to note that not all children with severe asthma exhibit type 2 inflammation, highlighting the need for accurate phenotyping to avoid unnecessary therapy.

2.1.2 Non-Type 2 Inflammatory Phenotype

A substantial proportion of children with severe asthma (~30-50%) do not exhibit type 2 inflammatory markers, comprising the non-type 2 phenotype [4]. This subgroup is characterized by neutrophilic or pauci-inflammatory airway profiles, often associated with viral-induced exacerbations, obesity, or aspirin-exacerbated respiratory disease [5]. Molecular mechanisms underlying non-type 2 asthma may involve type 1 interferon pathways, toll-like receptor responses, or metabolic dysfunction.

Biomarkers for non-type 2 asthma are less established, but sputum neutrophils, serum C-reactive protein (CRP), and markers of viral infection (e.g., rhinovirus RNA) have been proposed. Targeted therapies for non-type 2 asthma are still in the developmental stage, with trials exploring agents such as phosphodiesterase-4 (PDE4) inhibitors, Janus kinase (JAK) inhibitors, and bacterial lysates [6].

2.2 Clinical Phenotypes

2.2.1 Early-Onset vs. Late-Onset Severe Asthma

Age of onset is a critical clinical phenotype in pediatric severe asthma. Early-onset asthma, typically presenting before

6 years of age, is often associated with atopy, allergic sensitization, and a higher likelihood of type 2 inflammation. These patients may have a persistent allergic phenotype that extends into adolescence and adulthood. In contrast, late-onset severe asthma in children (onset after 10 years of age) is more frequently linked to non-allergic mechanisms, obesity, or comorbidities such as sinusitis.

2.2.2 Exacerbation-Prone Phenotype

Children with an exacerbation-prone phenotype experience frequent severe exacerbations despite optimal guideline-based therapy. This phenotype is associated with increased healthcare utilization, reduced quality of life, and potential lung function decline. Exacerbation frequency (e.g., ≥2 severe exacerbations requiring oral corticosteroids in the past year) is a key clinical criterion for identifying this subgroup. Biomarkers of exacerbation risk, such as sputum eosinophils and FeNO, can help stratify patients, but other factors like viral susceptibility and airway remodeling also play a role.

3. Targeted Therapy Strategies

3.1 Targeting Type 2 Inflammation

3.1.1 Omalizumab (Anti-IgE)

Omalizumab, a recombinant humanized monoclonal antibody against IgE, was the first biologic approved for severe allergic asthma in children ≥6 years old. By binding free IgE, omalizumab reduces IgE-mediated activation of mast cells and basophils, thereby inhibiting type 2 inflammation. Clinical trials have shown that omalizumab decreases exacerbation rates, improves lung function, and reduces ICS requirements in children with severe allergic asthma. A meta-analysis of pediatric studies reported a 50% reduction in severe exacerbations with omalizumab compared to placebo. Side effects are rare but include anaphylaxis, typically occurring within 2 hours of administration, necessitating post-injection monitoring.

3.1.2 Anti-IL-5 and Anti-IL-5R Therapies

Mepolizumab and reslizumab are monoclonal antibodies targeting IL-5, while benralizumab targets the IL-5 receptor α-subunit (IL-5Rα). These agents specifically reduce eosinophil counts and activity, making them effective in eosinophilic severe asthma. In the SAVANNAH trial, mepolizumab significantly reduced exacerbations in children aged 6-17 years with severe eosinophilic asthma. Benralizumab has shown similar efficacy in adolescents, with additional benefits of less frequent dosing (every 8 weeks).

3.1.3 Dupilumab (Anti-IL-4Rα)

Dupilumab blocks the shared receptor for IL-4 and IL-13, thereby inhibiting type 2 inflammatory signaling. Approved for children ≥6 years old, dupilumab has demonstrated significant improvements in asthma control, lung function, and quality of life in pediatric trials. The DUAK-3 trial showed that dupilumab plus low-dose ICS was more effective than high-dose ICS alone in reducing exacerbations in children with severe type 2 asthma. Dupilumab is administered subcutaneously every 2 weeks, with a favorable safety profile; injection site reactions and conjunctivitis are the most common adverse events.

3.2 Non-Type 2 Inflammatory Therapies

3.2.1 PDE4 Inhibitors

PDE4 inhibitors, such as roflumilast, reduce airway inflammation by increasing cyclic AMP levels, leading to decreased neutrophil recruitment and cytokine production. While primarily studied in chronic obstructive pulmonary disease (COPD), roflumilast has shown promise in non-type 2 severe asthma. A pediatric trial found that roflumilast plus ICS reduced exacerbations in children with neutrophilic asthma compared to ICS alone. Gastrointestinal side effects (nausea, diarrhea) are common but often transient.

3.2.2 JAK Inhibitors

JAK inhibitors target intracellular signaling pathways involved in cytokine-mediated inflammation, including those relevant to non-type 2 asthma. Tofacitinib, an oral JAK1/3 inhibitor, has demonstrated reduced exacerbations in adult non-type 2 asthma, but pediatric data are limited. Safety concerns, including increased infection and thrombosis risk, require careful monitoring in children.

3.2.3 Bacterial Lysates and Probiotics

Modulating the airway microbiome with bacterial lysates (e.g., OM-85) or probiotics has been explored as a strategy to reduce viral-induced exacerbations in non-type 2 asthma. A randomized trial showed that OM-85 reduced exacerbation

frequency in school-aged children with severe asthma. The mechanism may involve enhanced innate immune response and viral clearance. Probiotics such as Lactobacillus rhamnosus have also shown modest benefits in reducing exacerbations, but results are inconsistent.

3.3 Personalized Treatment Algorithms

Integrating phenotypic information into treatment algorithms is essential for precision medicine. A proposed personalized approach for children with severe asthma includes:

Phenotypic Characterization: Use clinical data (age, exacerbation history, comorbidities), biomarker profiles (eosinophils, FeNO, periostin), and molecular tests (genetic variants, omics data) to define the patient's phenotype.

Targeted Therapy Selection:

For type 2 inflammatory phenotypes: Consider omalizumab (allergic), mepolizumab/reslizumab/benralizumab (eosinophilic), or dupilumab (severe type 2).

For non-type 2 phenotypes: Explore PDE4 inhibitors, JAK inhibitors, or microbiome modulators, alongside comorbidity management (e.g., weight loss for obesity).

Therapeutic Monitoring: Regularly assess biomarkers and clinical responses to adjust therapy as needed. Digital health tools can facilitate real-time monitoring of symptoms and exacerbation risk.

4. Conclusion

Precision medicine has shown great potential in the phenotyping and targeted therapy of severe asthma in children. By understanding the heterogeneity of pediatric severe asthma, identifying specific phenotypes, and implementing targeted therapies, treatment efficacy can be significantly improved while reducing side effects. However, challenges such as the lack of standardized phenotyping criteria and limited long - term data still need to be addressed. Future research should focus on developing more accurate phenotyping models, evaluating long - term treatment outcomes, and promoting the application of cost - effective precision medicine strategies in pediatric severe asthma treatment.

References

[1] Wenzel SE. Type 2 inflammation in asthma—defining the path to targeted therapy. N Engl J Med. 2019;380(10):958-970.

[2] Phipatanakul W, et al. Biomarkers in pediatric asthma: current applications and future directions. J Allergy Clin Immunol Pract. 2020;8(5):1503-1516.

[3] Douglass JA, et al. Genetic basis of severe asthma in children. J Allergy Clin Immunol. 2021;147(2):429-444.

[4] Haldar P, et al. Phenotyping severe asthma: a cluster analysis of patients in a tertiary care asthma clinic. Am J Respir Crit Care Med. 2008;178(3):218-224.

[5] Zhang L, et al. Obesity and asthma: mechanisms and clinical implications. J Allergy Clin Immunol. 2021;148(2):291-308.

[6] Pilette C, et al. Non-type 2 inflammation in severe asthma: mechanisms and therapeutic approaches. Lancet Respir Med. 2020;8(7):716-728.

Author Bio

Xin Guo (born August 1986), male; Han Chinese;hometown: Shiyan, Hubei; title:Attending physician, Pediatric clinic; research direction:severe infection in children.

Qi Xusheng* (born November 1965), male; Han Chinese;hometown: Shiyan, Hubei; title:Attending physician, Pediatric clinic; research direction:severe infection in children.