Insight view of Bronchial Asthma: Phenotypes, Classification and Management in Children

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Abstract

Asthma remains a global public health problem and is a common chronic respiratory disease. It is characterized by airway inflammation related to variable airflow obstruction, airway hyper-responsiveness, and airway wall remodeling. Smoking, obesity and age are an important risk factor for asthma morbidity. During the last decades bronchial asthma has become the most common disease of childhood. Accordingly, many epidemiological and genetic studies have dealt with its origin. Clinically important patient subgroups can be found via phenotypic clustering, which has implications for the development of specialized therapy approaches and clinical trial designs. Shared goals for asthma management can be achieved in various ways, taking into account different healthcare systems, medication availability, and cultural and personal preferences. The aim of the current study to review the phenotypes of bronchial asthma, classfication and different modalities of management.

Keywords: Bronchial Asthma; Phenotypes; Management

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Introduction

Asthma is a complex and heterogeneous disease with a wide range of clinical characteristics, varying disease progression, and response to treatment **(1)**.Allergic asthma is thought to result from aeroallergen-induced inflammation driven by TH2 cytokines, including interleukin (IL) 4, IL-5, and IL-13. Release of these cytokines leads to recruitment of immune cells, such as eosinophils and basophils **(2,3)**.

Among children with asthma, persistent cough is also a positive finding on physical examination since not all children with asthma wheeze. Physicians should also examine the upper respiratory tract and skin for signs of concurrent atopic conditions such as allergic rhinitis, dermatitis, and nasal polyps **(4)**.

In pediatric patients, a scoring rubric called the Pediatric Respiratory Assessment Measure (PRAM) has been developed to assess a patient's acute asthma severity using a combination of

scalene muscle contraction, suprasternal retractions, wheezing, air entry and oxygen saturation. (5).

Although bronchial thickening, hyperinflation, and focal atelectasis suggest asthma when they are present, chest radiographs obtained during asthma exacerbations can demonstrate normal findings, which reduce its sensitivity as a diagnostic tool. Similarly, identical findings may be observed with chronic bronchitis and viral bronchopneumonia, among other conditions, and these similarities limit the specificity of chest radiography (6).

Before considering a step up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (7).

The step-algorithm provides for step-up options, it is important to reduce (step down) the therapy after the corresponding controls after approximately (2–3 months) with good asthma control. The goal should be to use the lowest ICS concentration that can guarantee optimal therapeutic success (8).

- **Endotypes and phenotypes of asthma:**

The model of asthma as a single entity is now obsolete due to an increased understanding of its underlying heterogeneity. The traditional dogma of asthma is that of excessive T-helper cell type 2 (Th2) cell responses and specific IgE driving airway hyper responsiveness. While this accurately conveys the dominant mechanisms of allergic asthma, the term "asthma" is now considered an umbrella diagnosis for a collection of several other distinct diseases (endotypes) and varying phenotypes (young atopic, obese middle aged, and elderly), all of which manifest with symptoms of wheezing and shortness of breath to cough and chest tightness, and are accompanied by variable airflow obstruction (9).

Table (1): Endotypes and phenotypes of asthma (Kuruvilla et al.,2019)

Endotype	Phenotype	Clinical characteristics	Molecular mechanism	Biomarkers	Natural history
T2 high	Atopic	Well defined, early onset, steroid sensitive	Allergic sensitization	Blood/sputum eosinophil count, serum specific allergen IgE, high FeNO, high total IgE	Identifiable and treatable, preserved lung function
	Late onset	± concomitant CRSwNP, steroid refractory	*Staphylococcus aureus* enterotoxin	Blood/sputum eosinophil count, high FeNO	Severe from onset, more frequent exacerbation

Endotype	Phenotype	Clinical characteristics	Molecular mechanism	Biomarkers	Natural history
	AERD (Aspirin-Exacerbated Respiratory Disease)	Adult onset	Dysregulated arachidonic acid metabolism	Blood/sputum eosinophil count, urinary LTE4	Severe from onset, more frequent exacerbation
Non-T2	Non-atopic	Adult onset—paucigranulocytic or neutrophilic	NLRP3/1L-1β, altered micro-RNA expression, Thl7	Induced sputum neutrophil count, MMP-9 in BAL	Variable course and lung function
	Smokers	Older adults	Oxidative stress, mixed Th2 high/Th2 low	Induced sputum neutrophil count	More frequent exacerbation, lower lung function
	Obesity related	Female sex	Oxidative stress, neutrophils, increased innate immune activation	Serum IL-6	Severe symptoms, preserved lung function
	Elderly	> 50 to > 65 years at onset	Immunosenescence, Thl/Thl7 inflammation	Induced sputum neutrophil count	Steroid resistant

I. Type 2 (T2)-High Endotype:

The type 2 immune response-driven endotype consists of an intricate interplay of several individual pathways. A dysregulated epithelial barrier facilitates translocation of allergens, air pollution, and viruses, leading to release of alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP primes dendritic cells to induce the differentiation of naïve T cells into Th2 cells. Th2 cells activate B cells via IL-4 to differentiate into plasma cells that generate IgE required for mast cell responses to allergens. The alarmins IL-25 and IL-33 can activate group 2 innate lymphoid cells (ILC2s), mast cells, eosinophils, and basophils. Activated ILC2s, like Th2 cells, produce IL-5 and IL-13. IL-5 promotes eosinophil differentiation and survival. IL-13, IL-4, and inflammatory mediators from mast cells, basophils, and eosinophils have effects on airway hyper-responsiveness, smooth muscle hypertrophy, and airway

remodeling. CysLT, cysteinyl leukotrienes; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPx, eosinophil peroxidase; MBP, major basic protein; PGD2, prostaglandin D2 **(9)**.

- ***Early-Onset Allergic Asthma:***

Early onset or "extrinsic" allergic asthma is the archetypal asthma phenotype. The presentation ranges from mild to severe, and it has not been elucidated whether severe asthma is the result of evolution from a milder form or instead arises de novo as a severe type during childhood **(10).** This phenotype is distinguished from T2-high nonatopic asthma by positive allergy skin tests and increased serum-specific IgE. It is important to note that the presence alone of elevated total or specific IgE are specific biomarkers for allergic asthma, as allergy testing may be positive in up to 50% of the general population. Otherwise, little is known regarding precise roles of innate and adaptive immune cells specifically in early-onset allergic asthma as compared to other forms of Th2-high non-atopic asthma **(9).**

- ***Late-Onset Eosinophilic Asthma:***

A subset of T2-high asthmatics has a distinct steroid-resistant eosinophilic phenotype of unknown molecular mechanism. Airway T2 inflammation is not ameliorated by ICS therapy in approximately half of asthmatics, and these patients are older and have more severe asthma with fixed airflow obstruction **(11)**.

There is generally no evidence of atopy, but is characterized by an intense, ILC2-driven production of IL-5 and IL-13. A recent cluster analysis identified an endotype of asthma with chronic rhinosinusitis with nasal polyps CRSwNP that highly expresses *Staphylococcus aureus* enterotoxin (SE) specific IgE and high levels of IL-5 and IgE **(12)**.

- ***Aspirin-Exacerbated Respiratory Disease (AERD):***

A subset of the above-described late-onset phenotype is AERD, characterized by asthma, CRSwNP, and COX-1 inhibitor-induced respiratory reactions. Although the mechanisms underlying AERD are not fully elucidated, its development appears to be contingent upon dysregulated arachidonic acid (AA) metabolism and cysLT production. Baseline levels of prostaglandin E2 (PGE2) levels are markedly deficient along with its receptor EP2. PGE2 is critical in inhibiting the activation of ILC2s, mast cells, and eosinophils. The loss of homeostatic PGE2 expression removes negative feedback on the 5-lipoxygenase (5-LOX) pathway and thus upregulates constitutive cysLT synthesis **(9)**.

II. Non-T2 or T2-Low Asthma Phenotypes:

The prototypical patient with obesity-associated asthma is the non-atopic, middle-aged woman with severe symptoms despite a moderately preserved lung function. While the obese-asthma syndrome is complex and multifaceted, the bulk of evidence points toward non-eosinophilic inflammatory mechanisms at the molecular level. Innate immune responses involving Th17

pathways and ILCs have been implicated. Uniquely, it is the type 3 ILCs (ILC3) that express both IL-17 and IL-22 that have been associated with obesity-related asthma **(13)**. Another important cytokine, IL-6, has also been recently shown to cause systemic inflammation in a subgroup of asthma patients with obesity and severe disease **(9)**.

The mechanisms underlying smoking-associated asthma is unclear, but it has been considered a T2-low neutrophilic, steroid-resistant phenotype. Putative mechanisms include oxidative stress that mediates epigenetic modifications causing neutrophil and macrophage activation **(14)**. However, smoking also increases the risk of sensitization to allergens and increases total IgE demonstrating the link between asthma and COPD. The recently described term "asthma-COPD overlap syndrome (ACOS)" demarcates those patients with a significant smoking history and consequent airflow obstruction but also have overlapping features of asthma (bronchodilator reversibility, eosinophilia, atopy). The current joint task force of the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) published a consensus document outlining diagnostic criteria for ACOS **(9)**.

- **Classification of asthma**

The 2022 Global Initiative for Asthma (GINA) guidelines categorize asthma severity as mild, moderate, or severe. Severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations, as follows **(7,15)**:

(1) Mild asthma: Well-controlled with as-needed reliever medication alone or with low-intensity controller treatment such as low-dose inhaled corticosteroids (ICSs), leukotriene receptor antagonists, or chromones.

(2) Moderate asthma: Well-controlled with low-dose ICS/long-acting beta2-agonists (LABA).

(3) Severe asthma: Requires high-dose ICS/LABA to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment.

Also, GINA **(7)** classify asthma according to the level of asthma symptoms control into controlled, partly- controlled and uncontrolled.

- **Management of asthma:**

The long-term goals of asthma management from a clinical perspective are to achieve good control of symptoms and maintain normal activity levels. To minimize the risk of asthma-related death, exacerbations, persistent airflow limitation and side-effects. It is also important to elicit the patient's own goals regarding their asthma, as these may differ from conventional medical goals **(7)**.

The adjustment of asthma therapy is based on asthma control, and follows a step-up/step-down algorithm to increase or reduce the medication. Regular follow-up should occur in a period of 2-3 months to optimize the treatment strategy. It is important to record symptom control, lung function, risk factors, inhalation technique, adherence, and non- pharmacological strategies on a regular basis **(16)**.

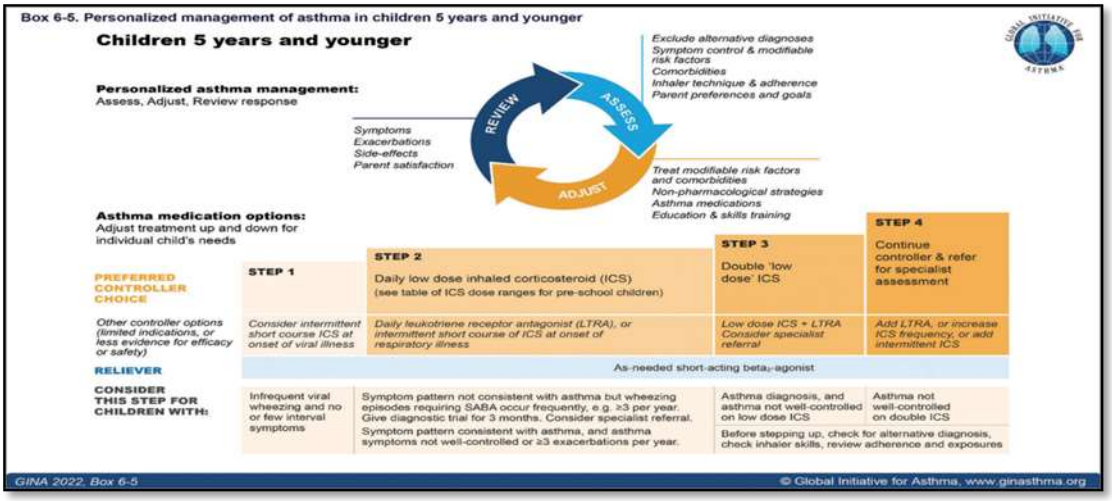

Figure (1): Personalized asthma management for children 5 years and younger. ICS: Inhaled corticosteroids, LTRA: Leukotriene receptor antagonist, SABA: Short-acting beta2 agonist **(7)**.

➢ *Categories of asthma medications:*

When compared with medications used for other chronic diseases, most of the medications used for treatment of asthma have very favorable therapeutic ratios. The pharmacological options for long-term treatment of asthma fall into the following three main categories.

I.Controller medications: used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.

II.Reliever (rescue) medications: provided to all patients for as-needed relief of break through symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction.

III.Add-on therapies for patients with severe asthma: may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors **(7).**

I. Controller medications:

Controller medications for children include inhaled corticosteroids (ICS), combination ICS/long-acting beta2-agonists (ICS/LABA), leukotriene receptor antagonists (LTRA) and chromones **(15)**.

✓ **Inhaled corticosteroids (ICS):**

Inhaled corticosteroids (ICS) are the FDA-indicated treatment of choice in preventing asthma exacerbations in patients with persistent asthma **(16)**. If inhaled corticosteroids alone are not adequate in controlling a patient's asthma symptoms, other controller medications such as long-acting beta-agonists or leukotriene receptor antagonists may also be started. Asthma controller

medications often are used in conjunction with short-acting beta-agonists such as albuterol as part of an asthma action plan to address acute and chronic symptoms **(17)**.

Inhaled corticosteroids have potent glucocorticoid activity and work directly at the cellular level by reversing capillary permeability and lysosomal stabilization to reduce inflammation. The onset of action is gradual and may take anywhere from several days to several weeks for maximal benefit with consistent use. Metabolism is through the hepatic route, with a half-life elimination of up to 24 hours **(18)**.

These drugs are administered through the inhalation route directly to their sites of action. This mode of administration decreases the dose required for the desired effect as it bypasses the first-pass metabolism in drugs taken orally. The reduced systemic bioavailability also minimizes side effects **(19)**.

Inhaled corticosteroids come in liquid capsule formulations given through a nebulizer machine, metered-dose inhalers (MDI) administered through spacers, and dry powder inhalers (DPI) **(20)**. Many different brands of inhaled corticosteroids are available on the market with similar efficacy between the formulations. Widely used inhaled corticosteroids include budesonide, fluticasone, beclomethasone, flunisolide, mometasone, and triamcinolone **(21)**.

✓ Combination ICS/LABAs:

In patients who are not controlled on low- or medium-dose ICS, addition of an inhaled long-acting β_2-adrenergic receptor agonist (LABA) such as salmeterol or formoterol has been shown to be more efficacious than increasing the dose of ICS **(22).** ICS/LABA combination formulations, such as fluticasone/salmeterol and budesonide/formoterol, have helped achieve good asthma control in a large proportion of patients **(23).**

Corticosteroids can interact with β_2-agonists in a beneficial way, since they prevent desensitization at various levels including an increased β_2-receptor transcription, an increased G-stimulatory protein expression, and decreased phosphorylation by reducing the level of β-adrenergic receptor kinases **(22).**

Therapy with LABAs may be associated with headache or cramps, but systemic adverse effects such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia, are less common than with oral beta-agonist therapy **(15).**

✓ leukotriene receptor antagonists:

Leukotriene receptor antagonists are indicated in the prophylaxis and chronic treatment of asthma and the prevention of exercise-induced bronchospasm **(24).** Leukotriene modifiers include cysteinyl-leukotriene 1 (CysLT1) receptor antagonists (LTRA) (montelukast, pranlukast, and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton) **(15).**

Leukotrienes (LTs) are a group of inflammatory mediators that belong to the eicosanoid family. Their synthesis, primarily by leukocytes, is spurred by a variety of immunologic and nonimmunologic stimuli, including antigens, immune complexes, complement, cytokines,

osmotic challenges, and pollutants, among others. These molecules collectively serve a variety of purposes aimed at furthering the inflammatory cascade via alterations in vascular permeability, effects on leukocytes, and constriction of smooth muscle. including the bronchoconstriction that plays a vital role in the pathophysiology of asthma, asthma and similar diseases **(25).**

There are some reports of serious adverse events due to angioedema, hypersensitivity, fatigue, confusional state, abnormal dreams, epilepsy, aggression, immune system disorder, hemorrhage, excoriation, eosinophil count increase, pain in extremity, and abdominal pain **(7).**

✓ **Chromones:**

Sodium cromoglycate and nedocromil sodium have potent effects in preventing both early and late asthmatic responses to inhaled allergens, such as pollen, and reducing airway reactivity to a range of inhaled irritants, such as sulfur dioxide and cold air **(26)**.

The chromones block the degranulation and the release of proinflammatory mediators from several cell types. The most detailed studies involve inhibition of the release of histamine and leukotrienes from pulmonary mast cells by cromoglycate **(27)**.

Cromoglycate and nedocromil are remarkably free of adverse reactions. Transient bronchospasm and cough can occur. Severe hypersensitivity reactions (e.g., hypotension and angioedema) have been reported but are very rare. Systemic overdose has not been recorded **(28)**.

II Reliever medications:

- **Short-acting beta-agonists (SABA):**

Short-acting β-agonist (SABA) drugs have been mainstays of asthma therapy for many decades and are recommended treatment at all levels of asthma severity, as they provide prompt relief of asthma symptoms through smooth muscle relaxation and, thereby, bronchodilatation **(29).**

Although SABA provides quick relief of symptoms, SABA-only treatment is associated with increased risk of exacerbations and lower lung function. Regular use increases allergic responses and airway inflammation. Over-use of SABA (e.g. ≥3 canisters dispensed in a year) is associated with an increased risk of severe exacerbations, and dispensing of ≥12 canisters in a year is associated with increased risk of asthma-related death **(15).**

Tremor and tachycardia are commonly reported with initial use of SABA. Tolerance develops rapidly with regular use. Excess use, or poor response indicate poor asthma control **(7).**

- **Low-dose ICS-formoterol:**

Low dose budesonide-formoterol or BDP formoterol is the reliever for patients prescribed as-needed controller therapy for mild asthma, where it substantially reduces the risk of severe exacerbations compared with SABA-only treatment. It is also used as the reliever for patients with moderatesevere asthma prescribed maintenance and reliever treatment, where it reduces the risk of exacerbations compared with using asneeded SABA, with similar symptom control **(15).**

- **Short-acting anticholinergics:** e.g. ipratropium bromide, oxitropium bromide

Anticholinergics antagonise the parasympathetic effects of acetylcholine, thus providing therapeutic benefit *via* a supplementary mechanism to ICS and LABA effects in asthma **(30)**.
The most common adverse reactions are bronchitis, nausea, mouth dryness, skin flushing, dyspnea, symptoms of a common cold, dizziness, sinusitis, dyspepsia, back pain, UTI, tachycardia, arrhythmias, severe adverse reactions:, hypersensitivity reaction, paradoxical bronchospasms, anaphylaxis and closed-angle glaucoma **(31).**

III Add-on controller medications:

For patients with severe asthma. These may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors **(7).**

- **Add-on tiotropium (long-acting muscarinic antagonist):**

In patients aged ≥6 years whose asthma is not well controlled with ICS-LABA. Add-on tiotropium (mostly 5μg once daily by mist inhaler) modestly improves lung function and modestly increases the time to severe exacerbation requiring oral corticosteroids **(31).**

- **Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment:**

For patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4-5 treatment **(32).**

- **Add-on anti-interleukin-5/5R treatment:**

Subcutaneous mepolizumab for patients aged ≥12 years; or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4-5 treatment **(33).**

- **Add-on anti-interleukin-4R α treatment** (subcutaneous dupilumab)

For patients aged ≥12 years with severe Type 2 asthma, or requiring treatment with maintenance oral corticosteroids OCS **(34)**.

- **Add-on oral corticosteroids:**

Typically, a short course of OCS is used (e.g. 40–50 mg/day usually for 5–7 daysfor patients who (i) fail to respond to an increase in reliever and controller medication for 2–3 days, (ii) deteriorate rapidly or who have a PEF or FEV1 <60% of their personal best or predicted value; or (iii) have a history of sudden severe exacerbations **(7)**.
For children 6–11 years, the recommended dose of OCS is 1–2 mg/kg/day to a maximum of 40 mg/day (Evidence B), usually for 3–5 days. Patients should be advised about common side-effects, including sleep disturbance, increased appetite, reflux, and mood changes **(35).**

* ***Other therapies:***

✓ **Allergen immunotherapy:**

Allergen-specific immunotherapy may be a treatment option where allergy plays a prominent role, including asthma with allergic rhinoconjunctivitis (36). There are currently two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

1- Subcutaneous immunotherapy (SCIT): involves the identification and use of clinically relevant allergens, and administration of extracts in progressively higher doses to induce desensitization and/or tolerance. In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and non-specific airway hyperresponsiveness (37).

2- Sublingual immunotherapy (SLIT) for house dust mites (HDM) in patients with asthma and HDM allergic rhinitis demonstrated a modest reduction of ICS with high dose SLIT (38).

✓ Vaccinations:

Influenza causes significant morbidity and mortality in the general population, and contributes to some acute asthma exacerbations. The risk of influenza infection itself can be reduced by annual vaccination. However, a recent systematic review and metanalysis that included observational studies with a wide range of study designs suggested that influenza vaccination reduced the risk of asthma exacerbations, although for most of the studies, bias could not be excluded (39).

People with asthma, particularly children and the elderly, are at higher risk of pneumococcal disease but there is insufficient evidence to recommend routine pneumococcal vaccination in people with asthma (40).

✓ Bronchial thermoplasty:

Bronchial thermoplasty involves treatment of the airways during three separate bronchoscopies with a localized radiofrequency pulse (41).

For adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center, bronchial thermoplasty is a potential treatment option at Step 5 in some countries (7).

✓ Vitamin D:

Several cross-sectional studies have shown that low serum levels of Vitamin D are linked to impaired lung function, higher exacerbation frequency and reduced corticosteroid response (42).

Vitamin D supplementation may reduce the rate of asthma exacerbation requiring treatment with systemic corticosteroids in asthma patients with baseline 25(OH)D of less than 25 nmol/L (43).

Non-pharmacological strategies:

In addition to pharmacological treatments, other strategies may be considered where relevant, to assist in improving symptom control and/or reducing future risk (7).

✓ **Avoidance of environmental tobacco smoke**

In people with asthma (children and adults), exposure to passive smoke increases the risk of hospitalization and poor asthma control. Active smoking is associated with increased risk of poor asthma control, hospital admissions and, in some studies, death from asthma; it increases the rate of decline of lung function and may lead to COPD; and it reduces the effectiveness of inhaled and oral corticosteroids **(44)**.

After smoking cessation, lung function improves and airway inflammation decreases **(45)**.

Reduction of passive smoke exposure improves asthma control and reduces hospital admissions in adults and children **(46)**.

Conclusion:

Childhood bronchial asthma and allergic disease is raised in the recent years. T2-high phenotypes have been classified into early-onset allergic asthma, late-onset eosinophilic asthma, and AERD. T2-low phenotypes have been classified according to clinical characteristics that include obesity, smoking, and age

Despite considerable interest in monitoring asthma in children, for many aspects of monitoring asthma in children there is a substantial lack of evidence. Therefore further studies are needed in this topic.

For severe asthma, licensed therapeutic approaches include high-dose inhaled steroids, the Symbicort maintenance and reliever regimen (with budesonide and formoterol fumarate), and anti-IgE therapy.

Paediatric data are needed on cytokine-specific monoclonal antibody therapies and bronchial thermoplasty. However, despite the interest in innovative approaches, getting the basics right in children with apparently severe asthma will remain the foundation of management for the foreseeable future.

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References:

1- **Dharmage, S. C., Perret, J. L., & Custovic, A. (2019).** Epidemiology of asthma in children and adults. *Frontiers in pediatrics*, *7*, 246.

2- **Lemanske Jr, R. F., & Busse, W. W. (2010).** Asthma: clinical expression and molecular mechanisms. *Journal of allergy and clinical immunology*, *125*(2), S95-S102.

3- **Pijnenburg, M. W., Baraldi, E., Brand, P. L., Carlsen, K. H., Eber, E., Frischer, T., ... & Carlsen, K. C. L. (2015).** Monitoring asthma in children. *European Respiratory Journal*, *45*(4), 906-925.

4- **Bush, A., & Saglani, S. (2010).** Management of severe asthma in children. *The Lancet*, *376*(9743), 814-825.

5- **World Health Organization (WHO). (2022).** Asthma fact sheets. Updated 11 May 2022.

6- **Tarraf H, Aydin O, Mungan D, et al. (2018).** Prevalence of asthma among the adult general population of five Middle Eastern countries: Results of the SNAPSHOT program. BMC Pulm Med.; 18(1): 68.

7- **Global Asthma Network. The Global Asthma Report 2022**. Int. J. Tuberc. Lung Dis. 26, S1–S102 (2022).

8- **Shastri MD, Chong WC, Dua K, et al. (2021).** Emerging concepts and directed therapeutics for the management of asthma: regulating the regulators. Inflammopharmacology.;29(1):15-33.

9- **Kuruvilla, M. E., Lee, F. E. H., & Lee, G. B. (2019).** Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clinical reviews in allergy & immunology, 56, 219-233.

10- **Miranda, C., Busacker, A., Balzar, S., Trudeau, J., & Wenzel, S. E. (2004).** Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. Journal of Allergy and Clinical Immunology, 113(1), 101-108.

11- **Kaur, R., & Chupp, G. (2019)**. Phenotypes and endotypes of adult asthma: moving toward precision medicine. Journal of Allergy and Clinical Immunology, 144(1), 1-12.

12- **Popović-Grle, S., Štajduhar, A., Lampalo, M., & Rnjak, D. (2021)**. Biomarkers in different asthma phenotypes. Genes, 12(6), 801.

13- **Fitzpatrick, A. M., Chipps, B. E., Holguin, F., & Woodruff, P. G. (2020).** T2-"low" asthma: overview and management strategies. The Journal of Allergy and Clinical Immunology: In Practice, 8(2), 452-463.

14- **Samitas, K., Zervas, E., & Gaga, M. (2017)**. T2-low asthma: current approach to diagnosis and therapy. Current opinion in pulmonary medicine, 23(1), 48-55.

15- **Global Initiative for Asthma (GINA). (2017)**. Global strategy for asthma management and prevention. GINA reports.

16- **Papi, A., Blasi, F., Canonica, G. W., Morandi, L., Richeldi, L., & Rossi, A. (2020)**. Treatment strategies for asthma: reshaping the concept of asthma management. Allergy, Asthma & Clinical Immunology, 16, 1-11.

17- **Williams, L. K., Peterson, E. L., Wells, K., Ahmedani, B. K., Kumar, R., Burchard, E. G., Pladevall, M. (2011)**. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. Journal of Allergy and Clinical Immunology, 128(6), 1185-1191.

18- **Loymans, R. J., Gemperli, A., Cohen, J., Rubinstein, S. M., Sterk, P. J., Reddel, H. K., ter Riet, G. (2014)**. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. Bmj, 348.

19- **FitzGerald, J. M., & Gibson, P. G. (2006).** Asthma exacerbations· 4: prevention. Thorax, 61(11), 992-999.

20- **Teach, S. J., Gill, M. A., Togias, A., Sorkness, C. A., Arbes Jr, S. J., Calatroni, A., Szefler, S. J. (2015)**. Preseasonal treatment with either omalizumab or an inhaled

corticosteroid boost to prevent fall asthma exacerbations. Journal of Allergy and Clinical Immunology, 136(6), 1476-1485.

21- **Jackson, D. J., & Bacharier, L. B. (2021)**. Inhaled corticosteroids for the prevention of asthma exacerbations. Annals of Allergy, Asthma & Immunology, 127(5), 524-529.

22- Wu, A. C., Butler, M. G., Li, L., Fung, V., Kharbanda, E. O., Larkin, E. K., ... & Soumerai, S. B. (2015). Primary adherence to controller medications for asthma is poor. Annals of the American Thoracic Society, 12(2), 161-166.

23- **Liang, Y. R., Tzeng, I. S., Hsieh, P. C., Kuo, C. Y., Huang, S. Y., Yang, M. C., Lan, C. C. (2022)**. Transcriptome analysis in patients with asthma after inhaled combination therapy with long-acting β2-agonists and corticosteroids. International Journal of Medical Sciences, 19(12), 1770.

24- **Capra, V., Ambrosio, M., Riccioni, G., & Rovati, G. E. (2006)**. Cysteinyl-leukotriene receptor antagonists: present situation and future opportunities. Current medicinal chemistry, 13(26), 3213-3226.

25- **Graf, R., Ascenço, A. S., Freitas, R. D. S., Balbinot, P., Peressutti, C., Costa, D. F., Kulchetscki, R. M. (2015)**. Prevention of capsular contracture using leukotriene antagonists. Plastic and reconstructive surgery, 136(5), 592e-596e.

26- **Edwards, A. M. (2014).** Chromones. In History of Allergy (Vol. 100, pp. 317-322). Karger Publishers.

27- **Beckett, P. A., & Howarth, P. (2003)**. Pharmacotherapy and airway remodelling in asthma?. Thorax, 58(2), 163-174.

28- **Hall, M. (2012)**. Chronic obstructive pulmonary disease and asthma. Home Healthcare Now, 30(10), 603-612.

29- **de Las Vecillas, L., & Quirce, S. (2023).** Landscape of short-acting beta-agonists (SABA) overuse in Europe. Clinical & Experimental Allergy, 53(2), 132-144.

30- **Rodrigo, G. J. (2018).** Anticholinergics for asthma: a long history. Current Opinion in Allergy and Clinical Immunology, 18(1), 38-43.

31- **Price, D., Kaplan, A., Jones, R., Freeman, D., Burden, A., Gould, S., ... & Thomas, M. (2015).** Long-acting muscarinic antagonist use in adults with asthma: real-life prescribing and outcomes of add-on therapy with tiotropium bromide. Journal of asthma and allergy, 1-13.

32- **Holgate, S. T., Djukanović, R., Casale, T., & Bousquet, J. (2005).** Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clinical & Experimental Allergy, 35(4), 408-416.

33- **Jat, K. R., & Gupta, A. (2022)**. Recent advances in long-term management of asthma. Indian Journal of Pediatrics, 89(4), 378-386.

34- **Thanisulas, M. (2020)**. Factors Influencing Control in Bronchial Asthma in Children Aged between 5 to 12 years at a Tertiary Care Teaching Hospital (Doctoral dissertation, Madras Medical College, Chennai).

35- National Asthma Education and Prevention Program (NAEPP) (2007). Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol.; 120 (5 Suppl):S94-138.

36- To T, Stanojevic S, Moores G, et al. (2012). Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health.;12:5.

37- Gans, M. D., & Gavrilova, T. (2020). Understanding the immunology of asthma: Pathophysiology, biomarkers, and treatments for asthma endotypes. Paediatric respiratory reviews, 36, 118-127.

38- Sze, E., Bhalla, A., & Nair, P. (2020). Mechanisms and therapeutic strategies for non-T2 asthma. Allergy, 75(2), 311-325.

39- Glezen, W. P. (2006). Asthma, influenza, and vaccination. Journal of allergy and clinical immunology, 118(6), 1199-1206.

40- Schwarze, J., Openshaw, P., Jha, A., Del Giacco, S. R., Firinu, D., Tsilochristou, O., ... & Skevaki, C. (2018). Influenza burden, prevention, and treatment in asthma-A scoping review by the EAACI Influenza in asthma task force. Allergy, 73(6), 1151-1181.

41- Mitzner, W. (2006). Bronchial thermoplasty in asthma. Allergology International, 55(3), 225-234.

42- Paul, G., Brehm, J. M., Alcorn, J. F., Holguín, F., Aujla, S. J., & Celedón, J. C. (2012). Vitamin D and asthma. American journal of respiratory and critical care medicine, 185(2), 124-132.

43- Jolliffe, D. A., Greenberg, L., Hooper, R. L., Griffiths, C. J., Camargo, C. A., Kerley, C. P., Martineau, A. R. (2017). Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. The lancet Respiratory medicine, 5(11), 881-890.

44- Gerald, L. B., Gerald, J. K., Gibson, L., Patel, K., Zhang, S., & McClure, L. A. (2009). Changes in environmental tobacco smoke exposure and asthma morbidity among urban school children. Chest, 135(4), 911-916.

45- Beasley, R., Semprini, A.,Mitchell, E. A. (2015). Risk factors for asthma: is prevention possible?. The Lancet, 386(9998), 1075-1085.

46- Gautier, C., Charpin, D. (2017). Environmental triggers and avoidance in the management of asthma. Journal of asthma and allergy, 47-56.