

# Etiology, pathophysiology, and management of Allergic Asthma in Children's

## Abstract

Many young toddlers experience frequent chest discomfort, wheezing, and coughing. Before the age of six, one-third of preschoolers experience these symptoms, yet only 40% of these wheezing preschoolers go on to develop asthma. The majority of youngsters in older school-aged children suffer asthma. Controlling asthma affects quality of life. Only a small portion of patients who receive asthma therapy succeed in controlling their condition. Even if co-morbidities, an erroneous diagnosis, or subpar inhaling technique could be to blame, non-adherence is frequently the main factor in therapy failures. Non-pharmacological interventions focus on avoiding cigarette smoke and avoiding allergens when a child is allergic. The GINA and the British Guideline for the therapy of asthma are two international standards for pharmacological management.

**Keywords:** allergens, etiology, management, pathophysiology

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**Abbreviations:** GINA; global initiative for asthma, AR; allergic rhinitis, HDM; house dust mites, IgE; immunoglobulin E, IL; interleukins, SHS; second hand exposure, TH; t helper, LABA; long-acting beta agonist, ICS; inhaled corticosteroid, AIT; allergen immunotherapy, SCIT; subcutaneous immunotherapy, SLIT; sublingual immunotherapy

## Introduction

A common condition known as asthma is caused by persistent lower respiratory tract irritation<sup>1</sup>. Healthcare professionals who treat inflammation of the upper or lower airways should be aware of recent developments in our knowledge of the definition and causes of asthma. But the physical and psychological changes that the adolescent with asthma goes through have an impact on their health and happiness. Asthma-related morbidity and mortality are often more likely to affect adolescents with asthma. Contextual variables like race, ethnicity, and living circumstance have an impact on the prevalence, morbidity, and mortality of adolescent asthma. How well teenagers transition to receiving adult medical care depends on these factors. A review of the unique characteristics of adolescents with asthma is given, along with tips on how medical professionals can encourage good asthma management and improved asthma control. Children with severe asthma are more likely to experience significant morbidity. Children with severe asthma are more likely to encounter adverse outcomes, including potentially fatal exacerbations, drug side effects, and a reduced quality of life. It's critical to distinguish between severe therapy-resistant asthma and concomitant asthma that makes treatment difficult.<sup>1</sup>

The most frequent problems that need to be fixed before a diagnosis of severe asthma is made are inadequate medication adherence, inappropriate medication delivery, or an asthma misdiagnosis. As long as comorbidities are treated clearly and succinctly, difficult-to-treat asthma, which is a far more frequent source of chronic symptoms and exacerbations, can be managed. The most frequent causes of paediatric hospital admissions are acute asthma or wheeze attacks, and the UK has one of the highest rates of severe attacks in all of Europe. Although illnesses are the main cause of the majority of attacks, the pathophysiology of asthma and wheeze in preschoolers and school-aged children vary substantially. Preschoolers' phenotypes can vary and frequently include non-atopic episodes brought on by neutrophilic

infection, even if type 2 inflammation, airway eosinophilia, and allergen sensitization are more prevalent in older children.<sup>2</sup>

Although the management strategy is common, for outcomes to improve, objective evaluations of airway function, inflammation, and infection are needed, both during the attack and during stable times, in order to identify treatable components and focus medicine. Prior to 2000, the term "severe asthma" lacked a clear agreement definition. A task committee supported by the European Respiratory Society and the American Thoracic Society changed the definition of severe asthma in paediatric patients aged 6 and older in 2014.<sup>3</sup> The definition and diagnosis of asthma are topics of discussion because of things like the challenge of performing objective pulmonary function testing or the frequent remission of symptoms in childhood. This debate is particularly vehement in the case of infants and young children. Since there is no universally accepted diagnosis for asthma in pre-school children.

## Allergen Immunotherapy (AIT)

Allergen immunotherapy is the process of administering an allergen injection to reduce allergy inflammation and symptoms (AIT). Since AIT induces long-term immunological and clinical tolerance to the etiological allergen, it has been utilised for more than a century and is regarded as the only way of disease-modifying therapy for IgE-mediated allergic disorders.<sup>4</sup> Both subcutaneous AIT (SCIT) and sublingual AIT (SLIT) are used and recognised as effective treatments for adults and children with allergic rhinitis (AR), whether they have asthma or not.<sup>1,2</sup> SCIT has been advocated as the primary route for AIT administration since the initial report. Despite its proven efficacy, the use of SCIT is still constrained by the necessity of routine injections administered by a physician for a minimum of three years and the potential for severe systemic reactions. As a result, SCIT should be delivered in a medical environment by doctors who are trained to handle anaphylaxis. Furthermore, people with uncontrolled asthma and faster dose regimens are at a higher risk of systemic responses to SCIT.

Effective AIT may influence the normal course of allergy illness by developing immunological tolerance through complex molecular and cellular pathways, reducing the establishment of new sensitizations as well as clinical disease progression (from rhinitis to asthma). As a long-lasting benefit after discontinuance, AIT may also be used to

manage allergy symptoms that are resistant to avoidance measures and medications, as well as to reduce medication use and improve quality of life. AIT's effectiveness and safety for the treatment of allergic asthma have been demonstrated in recent studies, and updated asthma guidelines now endorse SLIT as an add-on therapy for asthma in adults and adolescents with HDM allergy, under specific circumstances.<sup>5</sup>

## Etiology

Asthma prevalence trends have changed over time; while they are on the rise globally in low- to middle-income nations, they appear to have reached a plateau in some industrialised nations. It has been hypothesised that sex hormones may be implicated in the aetiology of particular types of asthma since boys are more prone than girls to develop asthma as youngsters. Asthma and mental health are linked; however, it is unknown what causes this. Due to inflammation or because having a chronic condition exerts physical strain on the body, it's likely that asthma increases mental health problems like depression. The link between asthma and mental health may be challenging due to common etiological factors such as SHS exposure, prenatal smoking, and dysfunctional households. In conclusion, it is unclear whether there is a link between asthma and outcomes in terms of mental health.<sup>6</sup>

This understanding has not resulted in a widespread immunologic focus on the diagnosis and management of asthma. Using historical data, skin tests, and more current research using in vitro test to look at new subject groups, this review summarises prior epidemiologic evidence linking IgE-mediated events with asthma. It reveals that an allergic aetiology can sometimes be present in up to 75% to 100% of chronic asthma cases and many acute episodes. It is therefore advocated to abandon the outdated categorization of asthma into intrinsic and extrinsic asthma in favour of a thorough investigation of allergic variables in almost every asthmatic patient.<sup>7</sup>

## Asthma in toddlers (0–6 Years)

Over 80% of asthma cases are diagnosed in the first six years of life, according to studies on the disease's natural history.<sup>4</sup> It can be challenging to diagnose paediatric asthma in children in age range because the symptoms are varied and not all caused by asthma. The symptoms of asthma in infants and young children include coughing, both productive and dry (although young children rarely expectorate), wheezing, shortness of breath, and struggle in breathing. Airway inflammation, bronchospasm, edoema, and expansion of the mucous glands are all asthma symptoms. It's interesting that comparable symptoms can also be present in a number of other paediatric illnesses, including congenital airway problems and respiratory tract infections, making a diagnosis challenging. It is well known that asthma in this age group is.<sup>8</sup>

In this age group, especially in children aged 0–3 years, symptoms are typically brought on by viruses rather than being allergically induced. Before developing an upper respiratory infection, which can cause a catastrophic inflammatory cascade, infants occasionally show little symptoms.

Children's first few years following an asthma diagnosis are crucial. The number of kids who had a second asthma encounter, including doctor visits and hospital stays, peaked at three years after diagnosis and then stabilised. It is believed that it takes three years to stabilise and control asthma episodes because, overall, 75% of children had a second attack within three years of their diagnosis. Asthma attacks are common right after diagnosis, which emphasises

the value of aggressive therapy, close monitoring, and early childhood education methods. Depending on the frequency or severity of wheezing symptoms, wheeze therapy is the cornerstone in this age group. Children who have many emergencies room visits, oral steroid regimens, or hospitalizations who have recurrent wheezing or significant morbidity are typically treated with inhaled corticosteroids. There is an issue with the evidence base for paediatric asthma care because there are few researches on the pathophysiology of asthma in children under the age of five.<sup>8</sup>

## Asthma in toddler (6-12 years)

Children at this age are more capable of doing spirometry with more accuracy, and reversible airway blockage on spirometry can be a helpful diagnostic tool. However, it is important to emphasise that spirometry findings in children with asthma can be normal despite significant disease and morbidity. Spirometry is widely employed as a monitoring technique for asthma symptoms in children as a result, following the confirmation of the diagnosis by other testing.<sup>4</sup>

In this age group, symptoms change from discrete wheezing episodes brought on by viral infections to allergy flare-ups. Since sports and exercise have become more of a discrete activity for kids of this age, caregivers can recognise the symptoms of dyspnea or cough with exertion, exercise-induced symptoms appear more clearly in this age group. This could be due to a true change in the clinical presentation of asthma in this age group.<sup>1</sup> When a child avoids or loses interest in physical activity, it is critical to look at asthma as a potential underlying cause. When exposed to certain triggers, such as cold temperatures, cigarette smoke, or seasonal allergens, some children in this age group may show little daily symptoms but suffer from severe asthma attacks. Although less common than in the 0–6-year age group, viral asthma flare-ups do occur in this age range. As a result, healthcare utilisation in this age range may be lower than in the 0–4-year age range.<sup>8</sup>

## Pathophysiology

GINA's classification of asthma phenotypes includes allergic, non-allergic, late-onset, asthma with fixed airflow limitation, and asthma linked to obesity.<sup>9</sup> Phenotypes are categorised by observable traits without any relation to the underlying disease process, which limits their usefulness. Tobacco smoke, allergies, hormones, and infections some of the known causes of persistent airway inflammation, which can result in airway blockage and hyper responsiveness, include cold air, obesity, exercise, systemic eosinophilia, and genetic mutations.<sup>10</sup>

Innate and adaptive immune systems must both be activated in the immunological pathophysiology of asthma for persistent airway inflammation to occur. Sub-basement membrane thickening, sub epithelial fibrosis, angiogenesis, increased smooth muscle mass in the airways, and mucous gland hyperplasia are some of the structural changes to the airways that result in long-lasting changes. Through a combination of T helper (Th) 1, 2, and 17 responses as well as underlying genetic susceptibility, these recognised variables cause long-lasting structural alterations in the different asthma endotypes. This suggests that the majority of asthmatics are affected by Type 2 inflammation, which was named after the type-2 TH cell lymphocyte. Along with inflammatory cells including eosinophils, mast cells, basophils, type 2 TH lymphocytes, and IgE, interleukin IL4, 5, and 14 have all been connected to type-2 inflammation. If they do not have a strong propensity for type-2 inflammation, asthmatics typically respond poorly to corticosteroids and can be challenging to treat.<sup>4,6</sup>

## Immunologic tolerance mechanisms during allergen immunotherapy

Upper and lower respiratory allergy symptoms are treated by AIT by reducing the IgE-mediated response to allergen exposure. AIT regulates T- and B-cells by many pathways involving both innate and adaptive immunity, changing antibody isotypes, reducing mediator release, and boosting inflammatory cell migration to tissues.<sup>1,2</sup>

A key factor in the development of immunologic tolerance is the overexpression of allergen-specific T-regulatory (Treg) and B-regulatory (Breg) cells, which primarily block the Th2 response. With the release of cytokines including interleukin (IL)-10 and transforming growth factor (TGF), regulatory cells control allergic inflammation, inhibit allergen-specific Th2 lymphocyte activation, and eventually advance toward a Type 1-mediated immune response. After high-dose allergen delivery by AIT, dendritic cells (DCs) produce and activate two types of Treg cells: natural (nTreg) and inducible (iTreg) cells. Both nTreg and iTreg cells block allergic reactions by secreting regulatory cytokines (IL-10, TGF-, and IL-35), directly inducing tolerogenic DC subsets, preventing the activation of allergen-specific Th2 lymphocytes, downregulating the expression of FC-RI receptors on mast cells, reducing the production of allergen-specific IgE, and encouraging allergen-independent B-cell production of IgG4. Directly inhibiting cytokines linked with T cells, such as IL-4 and IL-5, mast cells' and eosinophils' production of proinflammatory cytokines, the production of allergen-specific IgE, and the levels of IgA and IgG4 are all affected by IL-10. IgG4 competes with IgE for the same epitopes, acting as a "immunologic blockade" that lowers mast cell and basophil degranulation. It has also been proposed that IgG4 can co-stimulate the inhibitory IgG receptor FcRIIb, which can adversely regulate FcRI signalling and, as a result, reduce effector cell activation. Additionally, IgG4 prevents IgE from enhancing allergen presentation to T cells. TGF- reduces the production of Th2-cytokines (IL-4, IL-5, IL-9, and IL-13) and innate lymphoid cells type 2 (ILC2), which in turn reduces the activation of eosinophils, basophils, mast cells, and IgE-secreting B lymphocytes.<sup>5</sup>

## GINA Recommendations for Asthma

GINA does not advise treating adult and adolescent asthma with short-acting beta 2-agonists (SABA) alone, without inhaled corticosteroids, for safety reasons (ICS). Strong evidence exists to support the claims that regular or frequent use of SABA increases the likelihood of exacerbations, despite the fact that SABA alone can temporarily relieve asthma symptoms in certain people. Instead, GINA advises that ICS-containing controller therapy be given to all adults and adolescents with asthma in order to lower their risk of severe exacerbations and to control symptoms. The following asthma treatments are available for both adults and teenagers:

- Low dose ICS formoterol as needed (recommended), or
- Regular low-dose ICS combined with SABA as needed.<sup>14</sup>

## Why did GINA change its recommendations?

The new GINA 2019 guidelines marked the completion of GINA's 12-year work to gather evidence for novel ways for treating moderate asthma. Our objectives were to decrease the risk of asthma-related exacerbations and death, including in patients with so-called mild asthma; to communicate consistently about the goals of treatment, such as exacerbation prevention, across the asthma severity spectrum; and to prevent patients from developing a pattern of reliance on SABA early in the course of the disease.<sup>11</sup>

## Management

Children who have frequent flare-ups and persistent symptoms despite using their inhalers correctly and following the step asthma recommendations should be referred to an asthma expert with experience managing severe asthma. Step-up medicine is indicated if asthma symptoms have been identified, inhaler technique and adherence are sufficient, and modifiable risk factors including exposure to allergens or smoke have been addressed. Most of the young children's, however, require distinct approaches to managing acute wheeze attacks due to differences in the pathophysiology and therapeutic response. Because the management of severe wheezing attacks in pre-school children has not advanced in over two decades, this knowledge gap is crucial. The cornerstones of treatment for acute asthma attacks in school-aged children remain to be systemic corticosteroids & bronchodilators with the latter being given as a brief course to target airway eosinophilia and type-2 inflammation.<sup>12</sup> Asthma can be managed by some pharmacological and non-pharmacology therapy which are discussed below:

## Pharmacological therapy

The two primary parts of asthma pharmacological therapy are maintenance and relieving drugs. The mainstay of asthma management is maintenance therapy, and the purpose of treatment is to reduce or completely eliminate the requirement for rescue drugs. The usage of painkillers is a sign that asthma control is.

## Non-pharmacological therapy

Education of caregivers about modifiable risk factors and comorbidities as well as yearly asthma evaluations to gauge control and future risk are non-pharmacological aspects of asthma management.

It is impossible to emphasise the value of education in improving caregiver and child understanding of asthma and its management. Risk factors that can be changed, such smoking, indoor air pollution, and obesity, should be openly discussed. Drug adherence, symptom control, and mortality have all been shown to improve with short-term self-management education programmes.<sup>12</sup>

At least once a year, all young people with asthma should have their condition examined. These evaluations ought to focus on current symptom management and therapy, previous episodes, triggers, modifiable risk factors, and individual action plans for asthma (PAAPs). Asthma evaluations offer an opportunity to assess a child's and caregiver's knowledge of the condition and, if necessary, offer education. Annual asthma examinations provide a chance to review inhaler technique, including the use of spacers, and, if necessary, provide instruction. Ineffective inhaler technique is common in juvenile asthmatics and is associated with ineffective disease treatment.<sup>13</sup>

Investigating such attitudes may increase involvement during consultations, leading to improved results for young people. Understanding young people's and caregivers' opinions concerning asthma diagnosis and management is essential.

One management strategy that could increase adherence, particularly in teenagers, is the use of a single inhaler device for both maintenance and emergency medication (SMART approach). Eosinophilic airway inflammation measurements have been incorporated into management algorithms by a number of researches. A child's care must be reviewed after an asthma attack, and the family must be informed and involved to ensure that it never happens again.<sup>14</sup>

On World Asthma Day, May 3, 2022, the Forum of Worldwide Respiratory Societies (FIRS) encourages international respiratory communities to work together with peers, patients, communities, and healthcare professionals to close any gaps in asthma care. Even though there is no known treatment for asthma, symptoms can be controlled, and asthma attacks or exacerbations can be minimized or prevented.

Critical care gaps need to be filled in order to reduce needless suffering and the costs related to uncontrolled asthma. There are currently gaps in asthma care, in addition to unequal access to diagnosis and treatment, such as:

- disparate treatment between socioeconomic groups, populations, and age groups There are currently gaps in asthma care, in addition to unequal access to diagnosis and treatment, that include:
- Inequitable treatment of various socioeconomic groups, populations, and age groups
- Access to and affordability of prescribed inhalation medications worldwide
- Primary, secondary, and tertiary care coordination of care
- Quality asthma care plans and education for asthma sufferers
- Knowledge and awareness of asthma
- Asthma patient care delivery based on scientific evidence.<sup>15</sup>

## Diagnosis

Children under the age of six need a comprehensive medical history, physical exam, & an objective evaluation of pulmonary function to be diagnosed with asthma (spirometry is advised, both before and after bronchodilator therapy). Confirm the diagnosis and record fluctuating expiratory airflow restriction. The Broncho provocation challenge tests and evaluates for airway indicators. When objective assessments of pulmonary function test are normal but asthma symptoms are present, inflammation may also be useful for illness diagnosis.<sup>9,16</sup>

## Treatment

The main objective of managing asthma is to achieve and maintain disease control in order to prevent exacerbations, which are sudden, progressive worsening of asthma symptoms that frequently require immediate medical attention and/or the use of oral steroid therapy, as well as to lower the risk of mortality and morbidity. Treating the asthma medication can be a first line of treatment after that therapy can be last option. Regular ICS therapy has been shown to improve quality of life, minimise symptoms and exacerbations, and improve lung function. Only ICS therapy should be used in combination with LABA administration. It has been demonstrated that a LABA and ICS combination is quite efficient.<sup>16,17</sup>

## Anti-leukotrienes

An inflammatory condition is asthma. Utilizing anti-inflammatory medications is the foundation of an effective treatment intervention. Steroids are currently utilised parenterally, orally, and in aerosol form. Corticosteroid medication comes with intrinsic administration challenges and side effects. As a result, researchers are looking into a newer class of medications known as ALT, LA, or leukotriene modifiers. The ALT are a new family of anti-inflammatory, asthma-specific medications that target particular mediators. The ALT are extremely promising as new asthma treatments. Cys LT1 receptor antagonists and the 5 LO inhibitors have shown to be helpful in the

treatment of asthma. The FLAP, Cys LT2, and BLT receptor antagonists have little bearing on the treatment of asthma. The management of asthma and broncho-constriction brought on by exposure to allergens, exercise, aspirin, cold air, and inhaled LTs has been found to benefit from the use of the selective Cys LT receptor antagonists such as Zafirlukast, Pranlukast, and Montelukast as well as Zileuton, a direct inhibitor of 5-LO.<sup>18</sup>

## Allergy-specific immunotherapy (AIT)

In allergy-specific immunotherapy (AIT), the patient's relevant allergens are subcutaneously or sublingually administered in steadily increasing doses until an effective dose is reached that successfully induces immunologic tolerance to the allergen.<sup>19</sup> The current gold standard for treating allergic rhinitis is AIT. People who have asthma are more likely to develop allergic rhinitis. In patients with allergic rhinitis, nasal allergen exposure results in eosinophil infiltration into the lower respiratory tract, smooth muscle spasm, and AHR. Conversely, in asthmatics without rhinitis, direct bronchial allergen exposure enhances nasal eosinophilic inflammation. It is commonly accepted that airway allergy inflammation can increase nasal allergy inflammation and vice versa. This idea is known as "one airway, one disease." Treatment for allergic rhinitis eases asthma symptoms, lowers AHR, and lessens aggravation in asthmatics. We discovered that patients with uncontrolled asthma are aware that asthma symptoms tend to get better after rhinitis treatment and that asthma symptoms get worse when rhinitis symptoms are worse. As a result, if asthma is exacerbated by rhinitis, treating rhinitis is essential, and AIT is a suitable way to manage both rhinitis and asthma.<sup>20</sup>

## Future improvements in health care

The treatment of paediatric asthma changes over time as a result of improvements in technology and service delivery, to name just two examples:

**Technology:** The use of technology in the treatment of asthma has the potential to considerably improve clinical outcomes. Users of smartphone apps may receive medication reminders, which have been shown to increase ICS adherence. In addition to storing PAAPs, applications can be used to provide educational material to kids and their careers. Smart inhalers—not to be confused with SMART inhalers—are electronic devices that can record when they are used and provide users with auditory reminders. One paediatric study found that utilising smart inhalers increased medication adherence to 84% from 30% in the control group.<sup>18</sup>

**Hubs for diagnostics:** In the United Kingdom, NHS England's Long Term Plan has called for the establishment of regional diagnostic centres for the treatment of asthma. Diagnostic centres are anticipated to lead to earlier and more precise asthma diagnoses by improving access to objective testing and specialised interpretation. Hubs are designed to improve asthma outcomes by providing the best possible initiation and monitoring of the therapy. The clinical value of diagnostic hubs in the treatment of paediatric asthma is not currently supported by literature.<sup>21</sup>

## Conclusion

The risk of asthma morbidity and mortality is significantly increased by asthma, the most prevalent respiratory disease in the world. Patients who experience persistent coughing, wheezing, chest tightness, or dyspnea should be suspected of having asthma, and objective lung function tests should be used to confirm the diagnosis (spirometry preferred). Finding potential causes of asthma symptoms

may also involve performing an allergy test. With the majority of patients, asthma management can be obtained with the right pharmaceutical treatment and avoidance techniques. A potentially disease-modifying treatment, allergen-specific immunotherapy should only be administered by doctors who have received the necessary allergy training. All asthma patients should receive regular follow-up care so that the appropriate inhaler strategies, therapy compliance, and asthma control criteria can be reassessed. The most effective anti-inflammatory drugs for treating asthma and other inflammatory conditions are ICSSs.

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