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EXPLORING NOVEL THERAPEUTIC APPROACHES FOR ALLERGIC RHINITIS IN CHILDREN: CURRENT TRENDS AND FUTURE PERSPECTIVES

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Abstract

Allergic rhinitis is the most common chronic disease affecting children and is frequently undiagnosed and untreated due to their limited ability to express symptoms. This condition significantly impacts psychosocial well-being, learning capacity and quality of life and is associated with potential complications like asthma, sinusitis and otitis media. Recognizing signs such as allergic shiners, creases and salute is vital for identification. Allergic rhinitis arises from an immune overreaction to environmental allergens, triggering the release of inflammatory mediators. Symptoms include congestion, sneezing, itching and rhinorrhea. Treatment options emphasize environmental control, although complete allergen avoidance may not be feasible. Initial therapy comprises nonsedating second-generation oral antihistamines, while intranasal corticosteroids offer effective relief with fewer systemic side effects. Decongestants may be necessary and allergen immunotherapy injections can be considered for persistent cases. Clinicians must consider factors influencing compliance in pediatric patients. Rapid intervention and tailored management are crucial for improving outcomes and minimizing the allergic rhinitis impact in children.

Keywords: Allergen immunotherapy, allergic rhinitis, antihistamines, pediatrics

1. INTRODUCTION

The prevalence of allergic rhinitis (AR) is on the rise worldwide, creating a serious challenge for patients, healthcare workers and economies across all age groups [1]. Cutting-edge technology, such as mobile devices for e-health, offers the potential to gather valuable insights from real-world data, symptoms, patient adherence and epidemiological characteristics. Early identification of disease onset and implementation of preventive measures is particularly crucial for the infant population [2]. Sensitization patterns, risk factors for the allergic rhinitis development and biomarkers predicting disease courses are the focus of many investigations in the infant population [3], [4]. In addition, the MeDALL framework [5] aims to encourage customized, predictive, preventive and participative methods in treating allergy diseases by analyzing data from birth cohort studies. The development of infant asthma/wheeze, infantile eczema, early adult asthma and allergic rhinitis has been associated with food sensitization during the first 2 years [6]. It is predicted that the persistence or reoccurrence of fatal type 2 signaling

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is associated with specific IgE production and sensitization in childhood, which offers a significant risk of developing multimorbidities, including asthma and allergic rhinitis in late childhood and at stage of adolescence. However, specific IgE production can be used to predict disease in up to 25% of children by examining IgE reactivity to PR-10 proteins in early infancy [7], [8], [9]. Nearly half of pediatric AR patients have their first symptoms by age 6 and the prevalence of symptoms increases with age [10], [11], [12]. Therefore, the development and spread of allergy disorders may be slowed or stopped by early-life prevention, diagnosis and medication [13]. Children who were exposed to an urban environment at a young age had a higher prevalence of asthma sensitization, aeroallergy and AR than children who were exposed to a rural environment [14]. In older children, rhinitis associated with hormonal changes, rhinitis associated with immunologic disorders, chronic non-allergic rhinitis, acute infectious rhinitis, rhinitis medicamentosa, atrophic rhinitis, nasal polyps or unilateral rhinitis, chronic rhinosinusitis and rhinitis due to systemic medications are all possible [15], [16]. This article objective is to provide an up-to-date and comprehensive overview of the current treatment options for allergic rhinitis. In addition, it provides a summary of the most recent research on the diagnosis, pathophysiology and appropriate management or treatment strategies of pediatric allergic rhinitis.

2. NATURAL HISTORY

Allergic rhinitis is a common respiratory condition in which the nasal mucosa is inflamed by an allergen [17]. It affects a significant portion of the global population and has a significant impact on quality of life [2], [18]. Worldwide, allergic rhinitis affects 10 to 30 percent of the population, with differences between regions and age groups. The condition can occur at any age but most often occurs in childhood or adolescence, with early allergen sensitization increasing the likelihood of later onset [19]. After being diagnosed with allergic rhinitis, between 40% and 60% of patients continue to experience symptoms into adulthood [20]. Allergic rhinitis is primarily caused by allergens like mold spores, pollen, pet dander, house dust mites and mold, with sensitization patterns influenced by individual susceptibility and location [19]. The condition can be classified as seasonal or perennial based on symptoms throughout the year [21]. The former is typically associated with pollen exposure, while indoor allergens cause the latter. As part of the "allergic march" or "atopic march," in which atopic dermatitis precedes allergic rhinitis and possibly asthma later in life, allergic rhinitis frequently coexists with other allergic conditions. Sleep, work productivity, academic performance and overall well-being are negatively impacted, as is the likelihood of developing comorbid conditions like otitis media, sinusitis and asthma [22]. Depending on the severity of the symptoms, treatment options include pharmacotherapy (antihistamines, intranasal corticosteroids), allergen avoidance and immunotherapy [22], [23].

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3. PATHOPHYSIOLOGY

3.1 Early and Late Phase of Allergic Rhinitis

When an allergen triggers a type I hypersensitivity reaction, the antibody IgE plays a mediating role [24]. Type I hypersensitivity responses typically begin within 20 minutes after allergen exposure and entail the rapid activation of inflammatory and mast cells and subsequent infiltration into tissues [25]. The allergic reaction in AR includes two distinct stages: the acute and the chronic stages. The initial stage of an allergic response often begins within 20 minutes. Antigen-presenting cells, such as mucosal surface dendritic cells, take in peptides produced from allergens, break them into smaller pieces and then present them on the major MHC class II molecule. Naive $CD4^+$ T cells transform into allergen-specific Th2 cells when their T cell receptors attach to an antigen complex presented by an MHC class II molecule. Activated Th2 cells generate cytokines, including IL-4, IL-3 and IL-5, which stimulate B cells to create IgE (allergen-specific). The high-affinity Fc receptor for IgE (FcR) on mast cells is required for allergen-specific IgE to activate mast cells [25] [26], [27]. Mast cells release histamine and other allergic mediators after FcR cross-linking, resulting in vascular leakage, inflammation, bronchoconstriction and intestinal hypermotility [28], [29], [30], [31]. Other lipid mediators, such as prostaglandin D2 (PGD2), cyclooxygenase (C4) and leukotriene (LT), are also released. Watery rhinorrhea and mucosal edema are classic symptoms of AR, both caused by these mediators causing blood vessels to leak. AR is characterized by plasma leakage and vascular engorgement (nasal congestion) caused by histamine action on H1 and H2 receptors on blood vessels of mucosa. Reflex secretory reactions manifest as sneezing, pruritus and similar symptoms [32]. After being exposed to allergens, the late allergic response often occurs between four and six hours later. During this stage of nasal mucosal inflammation, inflammatory cells such as eosinophils, T lymphocytes, monocytes, neutrophils and basophils enter and activate in the nasal mucosa [32]. Interleukins 4 (IL-4) and 5 (IL-5) are cytokines that attract these inflammatory cells. For inflammatory cells to enter, the endothelium must first produce adhesion molecules such as vascular cell adhesion molecule 1 (VCAM1), which these cytokines stimulate [33]. Activated nasal mucosa structural cells can generate chemokines (such as eotaxin, RANTES and TARC) that promote cellular inflow from the peripheral circulation [34]. Fig. 1 shows a condensed version of the AR pathophysiology.

3.2 T Helper 2 Responses in Allergic Rhinitis

Th2 cells produce IL-5, IL-4, IL-6 and IL-13, stimulating B cell proliferation and differentiation into plasma cells and activating type 2 responses [35]. IgE-producing B cells are largely derived from Th2 cells and Th2 cells are crucial to the pathophysiology of AR [36], [37]. In the late phase of an allergic reaction, Th2 cells join eosinophils and basophils in infiltrating the nasal mucosa tissue [38]. For naive CD4+ T cells to differentiate into effector Th2 cells, IL-4 is a critical cytokine [39]. The process relies on the IL-4 receptor complex activating signal transducer and transcription 6 (STAT6) signaling activator. In allergic disease (such as eosinophilic esophagitis, AR, asthma and

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chronic rhinosinusitis), Th2 cytokines may deregulate epithelial cell barrier integrity and increase inflammatory cell activation [39, 40-43]. The cytokines may also be produced by cells inside the sinonasal milieu, leading to enhanced permeability of the sinonasal epithelium [44], [45]. Inflammation and continued exposure to inflammatory antigens may be maintained by Th2 cytokines [44].

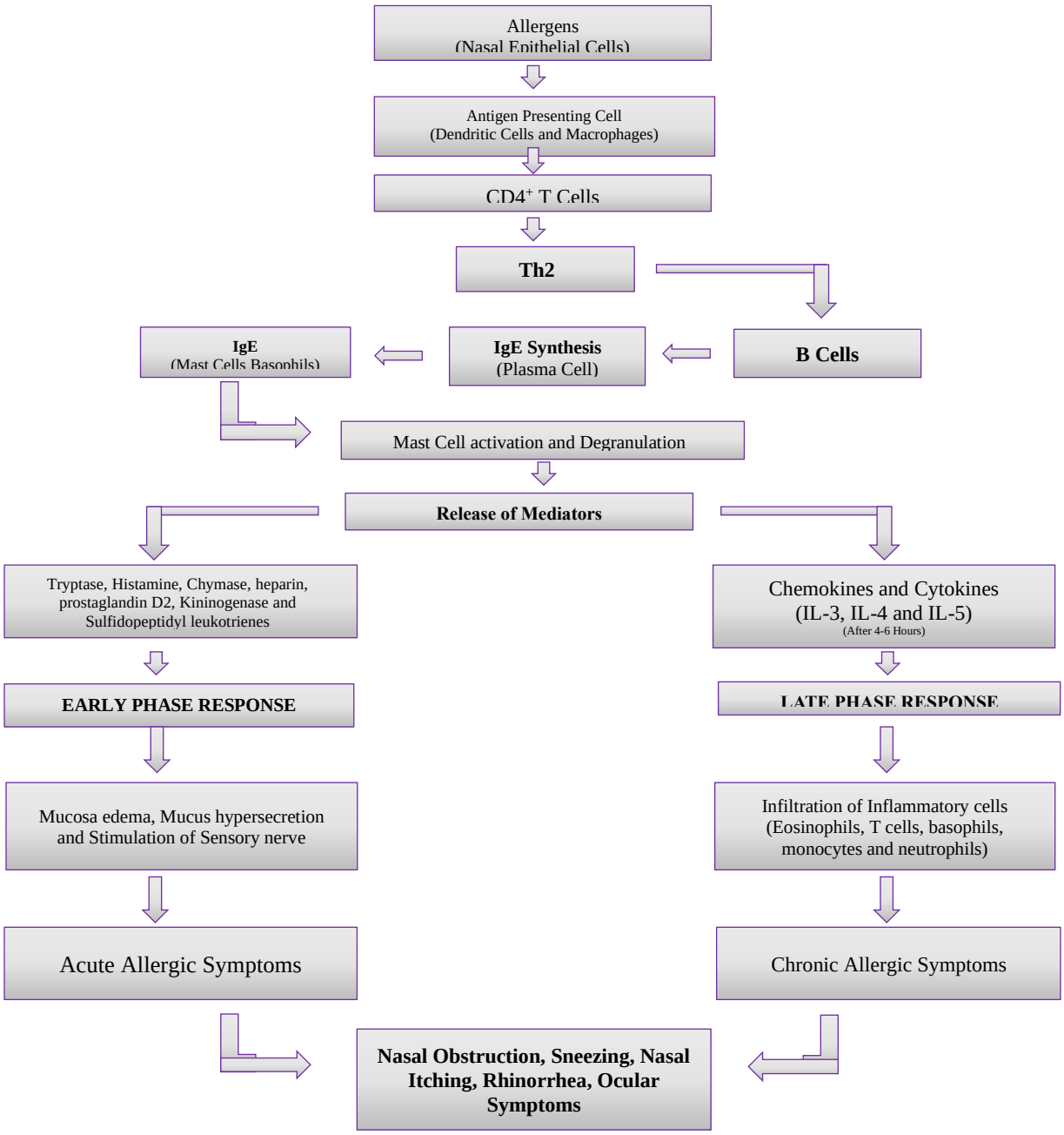

Figure 1: Allergic Rhinitis Pathophysiology

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4. CAUSES AND CLASSIFICATION OF ALLERGIC RHINITIS

Allergic rhinitis (AR) is a common condition characterized by inflammation of the nasal mucosa due to an immune response triggered by environmental allergens [46]. There are several potential causes of allergic rhinitis. Saini et al. [46] claim that the condition is mainly caused by the immune system reacting too much too harmless things like dust mites, pollen, mold spores and animal dander. The body recognizes these substances as foreign invaders and releases inflammatory mediators like histamine. These substances are referred to as allergens. There are two types of allergic rhinitis: seasonal and perennial Seasonal allergic rhinitis is typically brought on by pollen from trees, grasses, or weeds and manifests itself at specific times of the year. Contrarily, perennial allergic rhinitis occurs throughout the year and is typically brought on by allergens found in indoor environments such as dust mites, pet dander, or mold [47]. Additionally, genetic factors have been linked to allergic rhinitis development. According to research, people who have allergies in their families are more likely to develop the condition. Long et al. [48] stated that, there are some genetic variants that make allergic rhinitis more likely. These genetic factors influence the immune system and the production of antibodies involved in allergic reactions.

Table 1: Causes and Classification of Allergic Rhinitis

Causes and Classification	Explanation	Ref.
Genetic Predisposition	Allergic rhinitis, which may have a genetic component, is more likely to occur in those with allergies in their families. Numerous genes are linked to an increased risk of allergic diseases like allergic rhinitis. The immune system's response to allergens, which can be influenced by genetic factors, can influence the likelihood of developing allergic rhinitis.	[48]
Hormonal Changes	Hormonal changes, particularly during pregnancy or puberty, can impact the frequency or severity of allergic rhinitis. The immune system and the nasal mucosa can be affected by changes in hormone levels, making people more sensitive to allergens and making allergy symptoms worse.	[49]
Occupational Allergens	In some cases, allergic rhinitis can be caused by exposure to specific allergens in the workplace. Certain occupations, such as farming, animal handling, or laboratory work, may expose individuals to allergenic substances like animal proteins, chemicals, or dust particles, leading to the development of work-related allergic rhinitis.	[50]
Environmental Allergens	Environmental allergens, including dust mites, pollen, pet dander, certain foods and mold spores trigger allergic rhinitis. When a person with allergic sensitivity meets these allergens, their immune system releases histamine and other chemicals, leading to inflammation of the nasal passages and typical allergy symptoms.	[46]
Air Pollution	Exposure to air pollutants, such as vehicle exhaust, industrial emissions and particulate matter, has been linked to an increased risk of allergic rhinitis. Air pollutants can exacerbate the body's inflammatory response and may interact with allergens, intensifying the symptoms of allergic rhinitis.	[47]

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5. SIGNS AND SYMPTOMS OF AR IN CHILDREN

Many symptoms are associated with allergic rhinitis; some common symptoms as listed in Table 2. However, many children with allergic rhinitis have difficulty expressing discomfort and their condition often goes undiagnosed. Consequently, recognizing the symptoms is crucial in the pediatric population. Children with allergic rhinitis often exhibit distinct physical signs, including the presence of an "allergic shiner" which causes lower eyelid darkeness due to suborbital edema and chronic nasal obstruction. The development of an "allergic crease," or a horizontal line on the skin above and below the nose bridge due to frequent rubbing, is another obvious sign. Additionally, children may display the "allergic salute," a behavior in which they repeatedly rub their nose upwards with their palm to temporarily open the nasal passages and alleviate itching [51], [52]. Many allergic rhinitis children experience systemic symptoms, such as fatigue, malaise, weakness, poor appetite and irritability [53]. However, Children may struggle to articulate these symptoms and mistakenly attribute them to other causes. If these symptoms are not actively sought out, it is unlikely that their presence will be detected. Children and adolescents with allergic rhinitis typically have trouble sleeping, feel unwell and look unattractive, all of which can have a negative impact on their academic performance and confidence [53, 54]. Nasal and extra-nasal symptoms are seen in patients with AR [55]. Mucosal inflammation is brought on by allergen contact and mucosa becomes more sensitive to allergens and non-allergic stimuli [7]. Ocular symptoms, such as allergic rhinoconjunctivitis (eye irritation, redness and watering), are common in people with AR [56]. Other symptoms include postnasal drip, cough and palate itching [55]. More than 30% of AR patients experience life-threatening allergic reactions, including anaphylaxis and other serious disabilities [57]. Symptoms are considered persistent for more than four days per week and more than four weeks in a row, whereas they are considered irregular when they occur for less than four days per week or fewer than four weeks in a row [58].

Table 2: Signs and Symptoms in Children

Symptoms	Signs
Runny nose	Watery or itchy eyes
Itchy nose	Pale or bluish skin under the eyes
Sneezing	Nasal congestion
Nasal itching	Swollen or blue-colored skin under the eyes
Nasal congestion	Constant mouth breathing
Postnasal drip	Dark circles under the eyes
Coughing	Fatigue or irritability
Sore throat	Impaired sense of smell or taste
Headache	Poor concentration or decreased school performance
Fatigue	Snoring or sleep disturbances

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6. PREVALENCE OF ALLERGIC RHINITIS IN CHILDREN

In this study, data included from 17,110 children under 18, found that AR was present in 59.7/1000 children. This makes allergic rhinitis the most common chronic condition affecting children today. Asthma was the second most common disease affecting children (42.5 cases per 1000) [59]. However, it is crucial to recognize that the reported prevalence of allergic rhinitis is probably underestimated as it solely considers children with seasonal AR, thereby excluding the likely presence of children experiencing perennial AR.

A study was conducted in Tucson, Arizona, with 747 children and evaluated the natural history of physician-diagnosed allergic rhinitis in the early years of life and found that 42% of all children had this condition by the age of six years [60]. This demonstrates even more how frequently allergic rhinitis affects children. Approximately 50% of these children had suffered the onset of symptoms within their first year. Children who had allergic rhinitis before the age of one were more likely to acquire a diagnosis of asthma by the time, they were six. Risk factors of allergic rhinitis included the early introduction of formula or foods, cigarette smoking by maternal (1 pack/day) in 1st year, higher IgE serum levels at 9 months to 6y, parental allergic disorders and the presence of dogs at home [61]. Studies on the prevalence of AR in children have been conducted primarily in some regions (Asia-Pacific, Africa, Australia, Latin America, Eastern Europe, Turkey and the Middle East), with results showing large inter- and intraregional variations, from 2.9% in Turkish children aged 10–18 to 54.1% in Nigerian adolescents aged 13–14 [62]. In addition, the incidence of AR has risen dramatically over the past decade, most noticeably in several middle eastern and rich African countries. Compared to Western populations (the United States and Europe), where the disease is more homogeneous, the AR variability in these areas is striking. Severity and prevalence of allergic diseases vary with age and there are significant gender variations in the predictive power of specific IgE and the degree to which allergies manifest at age 10 [63].

The incidence of allergic rhinitis has skyrocketed since the 1990s [64-66]. About 40% of adults and 25% of children are estimated to be affected worldwide. About 80% of people with AR experience their first symptoms before age 20 [67] and symptoms tend to be most severe between the ages of 20 and 40 [67, 68]. Reports indicate that the peak age of diagnosis for AR in children is between 24 and 29 months (2.5%) [26], with an overall incidence rate of 17.2% in the first 5 years of life. Males have a higher incidence of AR in childhood, whereas females have a higher prevalence in adolescence [69, 70]. 29% found daily living was "impaired a lot" due to allergies during peak allergy season [71]. Daytime fatigue and reduced quality of life directly result from the sleep disruption caused by AR symptoms [26]. Sixty-six percent of adults and 43 percent of children in 100 patients with moderate/severe AR reported experiencing sleep disturbances [72]. Multiple studies comparing the frequency of AR in urban settings with that in rural regions demonstrate that AR prevalence has grown over time due to global urbanization [73], [74]. Increased pollution levels [such as those from traffic and PM 2.5] can aggravate pollen-sensitive AR [76], [77]. It has been found that the incidence of AR is higher in cities than in rural regions

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[74]. Over the past three decades, increasing seasonal allergy symptoms and a lengthening pollen season have been linked to European climate change [78].

According to the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire, the prevalence of AR in children worldwide has been examined extensively [79], [80], [81], [82], [83]. Significant differences in the prevalence of rhinoconjunctivitis, childhood asthma and eczema were found worldwide in the ISAAC phase-I study [84]. More than 700,000 kids were enrolled in the research; specifically, 257,800 kids aged 6–7 and 463,801 kids aged 13–14. The reported prevalence of rhinoconjunctivitis symptoms varied substantially among geographic regions, with up to a 25-fold range in the 13- to 14-year-old age group [83], [85]. Eastern Europe and several regions of Southern and Central Asia had the lowest incidence levels across both age groups. China and Portugal both have relatively low prevalence levels in the older population. Phase II of the ISAAC used a more in-depth approach to evaluate potential etiological variables in children aged 9 to 11. Dermatology evaluation, bronchial challenge, skin prick testing, blood collection for genetic investigations and dust collection were all part of the standardized modules employed. The population attributable fraction (PAF) for a positive prick test to seasonal allergens varied between 0% and 71%, while for perennial allergens it ranged from 0% to 41%. Similarly, the prevalence of rhinoconjunctivitis symptoms showed a comparable variation across the globe, ranging from 1.5% to 24.5%. Centers in developed countries had an estimated prevalence at risk (PAF) of 36 and 25% for sensitization to seasonal and perennial allergens, respectively, compared to those in less developed countries, where the PAF was 13% and 13%. In less developed nations, atopy was responsible for a smaller share of reported rhinitis symptoms [80].

A case-control study conducted in the United Kingdom shows that AR influences academic achievement. Current AR symptomatic students performed worse on summer exams than winter ones [86]. Several studies have quantified the monetary impact of AR. According to a Swedish study, the average yearly direct expenditures associated with AR were 210 Euros and the average indirect costs were 750.8 Euros. Presenteeism accounted for 70.0% of the expenses, whereas absenteeism accounted for 8.1% of the overall expenditures [87]. Untreated or insufficiently treated AR is predicted to cost European Union nations between 55 and 151 million Euros annually in lost productivity owing to absenteeism and presenteeism [88]. Many people don't realize how common AR is and many who have it have never been properly diagnosed. AR consequences include sleeping problems, worse quality of life and financial strain. For healthcare providers, politicians and society to effectively manage AR and allocate appropriate resources.

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7. ENVIRONMENTAL FACTORS

Clinical symptoms of allergic rhinitis include nasal itching, rhinorrhoea, nasal itching, nasal obstruction and sneezing [89]. The guidelines for allergic rhinitis and asthma categorize allergic rhinitis (AR) as either an intermittent disease with symptoms occurring less than four days a week or lasting less than four weeks, or a persistent disease with symptoms occurring more than four days a week or lasting more than four weeks. Recent research has observed that various allergens are abundant in different places, with outdoor allergens like tree and grass pollens being the major sensitizing allergens for seasonal AR (SAR) and interior allergens like dust mite allergens being the main sensitizing allergens for perennial AR (PAR). For instance, in Denmark, grass and birch pollen are the two most common allergens [90], in Japan, Japanese cedar pollen (JC) is the most common allergen [91], [92], in northern China, artemisia pollen is the main allergen [93, 94] and in some regions, ragweed is the most common sensitizing allergen [95]. To define AR and confirm the allergen-specific diagnosis of AR, it is necessary to identify the appropriate allergens based on the findings of these studies [92], [96], [97]. Sometimes, environmental factors may not only induce AR but may also aggravate AR [98]. Particularly, an increase in environmental air pollutants has been linked to an increase in the prevalence of allergic respiratory conditions [99]; One study on children found that these children had a higher risk of developing AR when they were exposed to oxidizing air pollutants [100]. There is scientific evidence suggesting that environmental exposure to particulate matter (PM2.5) may contribute to increased DNA methylation levels in the body [101], [102]. Furthermore, changes in phenotypic genetics can also be caused by environmental factors, which can increase the incidence of allergic diseases.

8. DIAGNOSING ALLERGIC RHINITIS IN CHILDREN

Typically, allergens are proteins in nature with a molecular weight between 10-40 kDa that trigger hypersensitivity (type I) when they react with certain IgE antibodies [26], [103]. Food allergies (such as shrimp, soy, clam, crab, wheat, yolk egg, peanut and milk of cow), animal allergens (such as dander of dog and cat) and house dust mites (HDMs) are common examples of allergens [104], [105]. The main risk factor for AR has been shown time and time again to be exposed to common indoor allergens (such HDMs, cockroaches, cat and dog dander) [106]. A comprehensive history is crucial to the diagnosis of allergic rhinitis. If asked the right questions, children, especially the older ones, maybe a reliable source of knowledge. However, the physician must rely heavily on information supplied by parents or other caretakers when evaluating younger children. The doctor may find it helpful to inquire about allergens in the home environment [46] and query about the signs and symptoms. AR symptoms in a child are a crucial diagnostic signal and nonspecific [14]. The traditional indications of allergy shiners and an allergic crease can identify children with nasal obstruction, although this does not always imply an underlying allergic cause [56].

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Allergic rhinitis should be diagnosed with absolute confidence with allergen testing. While inhalant allergens are the most common cause of allergic rhinitis in children, just as they are in adults, the possibility of a food allergy in infancy or early childhood should not be discounted. Until around 2 years, food allergies are the most common type [105]. Since sensitization to pollen requires exposure over two or more seasons, testing for seasonal allergens such as trees, weeds and grasses is often sought around 2 or 3 years of age. However, after months or weeks of regular contact, an allergy to permanent inhalant allergens, including home dust mites, dogs, cats, cockroaches and feathers, might develop. Children ≤2 years of age may undergo allergy testing for perennial inhalant allergens and probable food allergens if clinically warranted. If an allergy skin test returns positive, young kids will have milder swelling and flare than older kids and adults [46], [106], [107].

9. TREATMENTS

Treatment for pediatric allergic rhinitis follows the same general principles as treatment for adult allergic rhinitis. Environmental management, medication and immunotherapy are all viable choices for allergy avoidance. The major objective of treatment for allergic rhinitis in children is to alleviate symptoms without impairing the child capacity to function and the secondary objective is to avoid the onset of allergic rhinitis complications.

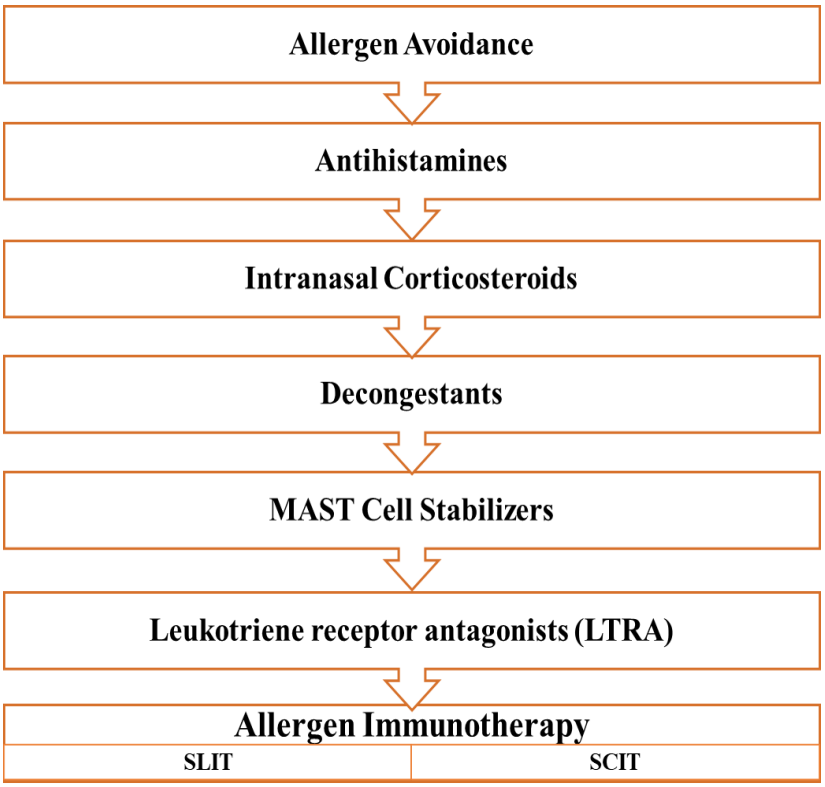

Figure 2: A Stepwise Process for Allergic Rhinitis Treatment

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9.1 Allergen Avoidance

Avoiding relevant allergens (such as home dust mites, pollens, pets and molds) and irritants (such as cigarette smoke) is the primary line of therapy for allergic rhinitis. It is recommended that patients with a house dust mite allergy use allergen-proof bedding and maintain a relative humidity level in the home of less than 50%. Using windows filter, keeping windows closed, using AC and spending less time outside during peak pollen seasons are all ways to lessen exposure to outdoor mold and pollen. Patients sensitive to animal dander often find relief from their symptoms within four to six months after the animal is no longer in the home. Unfortunately, few people follow this advice; therefore, it may be necessary to reduce allergy levels by using HEPA filters and keeping the animal out of the bedroom. Dehumidification to less than 50%, cleaning with fungicides, HEPA filtration and repair of any water damage are all steps that may be taken to reduce exposure to mold allergens. Patients suffering from allergic rhinitis should be counseled to employ a mix of these avoidance methods for the best benefits [108], [109].

9.2 Antihistamines

Even though novel antiallergy medicines have been developed, oral antihistamines remain the backbone of therapy for allergic diseases. It is reasonable to assume that these agents will have the same effect on children as adults [110]. First-generation (sedating) antihistamines are over-the-counter, but second-generation (nonsedating) medicines are only accessible with a doctor's prescription. Second-generation medications have virtually eliminated many of the side effects of first-generation antihistamines, such as drowsiness and the need for frequent dosage. Preferential binding to peripheral H1 receptors (less CNS penetration; less anti-serotonin, α-adrenergic activity of blockage and anticholinergic; fewer sedative effects) is just one of how second-generation agents improve upon their predecessors [111].

All individuals with allergic rhinitis should initially be treated with second-generation oral antihistamines (such as fexofenadine [Allegra], desloratadine [Aerius], cetirizine [Reactine] and loratadine [Claritin]). Canada has released two new second-generation antihistamines, rupatadine (Rupall) and bielastine (Blexten). These antihistamines are currently only accessible with a doctor's prescription. Children are just as dependent on a lack of cognitive and sedative effects as adults are. Vuurman et al. [112] found that in a study involving 52 children of primary school who had a previous medical record of SAR, along with 21 children who had no history of allergies. On the other hand, children with allergic rhinitis treated with the second-generation oral antihistamine loratadine significantly outperformed those with allergies treated with the first-generation agent diphenhydramine across the board. Diphenhydramine-treated kids routinely performed poorly across the board. Due to the significant performance difference, the authors recommended that non-sedating oral antihistamines be provided to school-aged children with AR [112].

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Table 3: Oral antihistamines (second generation)

Oral antihistamines (second generation)	Usual pediatric dose	Ref
Cetirizine (Reactine)	The recommended dosage for the children's formulation is 5–10 mL (equivalent to 1–2 teaspoons) to be taken once daily.	[114]
Rupatadine (Rupall)	For children aged 12 years and older, the recommended dosage is 1 tablet (10 mg) to be taken once daily. For children between the ages of 2 and 11 years with a body weight of 10-25 kg, the recommended dosage is 2.5 mL (equivalent to 0.5 teaspoons) to be taken once daily. For children between the ages of 2 and 11 years with a body weight greater than 25 kg, the recommended dosage is 5 mL (equivalent to 1.0 teaspoon) to be taken once daily.	
Loratadine (Claritin)	The recommended dosage for the children's formulation is 5–10 mL (equivalent to 1–2 teaspoons) to be taken once daily.	[116]
Bilastine (Blexten)	For children aged 12 years and older, the recommended dosage is 1 tablet (20 mg) to be taken once daily.	[113]
Desloratadine (Aerius)	The recommended dosage for the children's formulation is 2.5–5 mL (equivalent to 0.5–1.0 teaspoon) to be taken once daily.	[115]

9.3 Intranasal Corticosteroids

Apart from fluticasone propionate, which is approved for use in children as young as 4 years of age and mometasone furoate, which is approved for use in children as young as 12 years of age, intranasal corticosteroid sprays are generally approved for children starting from the age of 6 years (Table 4). They effectively relieve various allergic rhinitis symptoms, including rhinorrhea, itching, nasal congestion and sneezing. Systemic corticosteroids have been linked to negative consequences, including stunted development, inhibition of the hypothalamic-pituitary-adrenal axis and behavioral problems [118]. However, locally acting on the nasal mucosa, intranasal corticosteroids are rapidly metabolized, have a long half-life, do not have the same adverse effects as systemic medications and do not cause clinically significant side effects [119]. A review of MANY studies shows that beclomethasone does not produce systemic side effects, even with prolonged use of up to 6 years [120]. There have been many case reports demonstrating the Current medical consensus suggests that children on inhaled corticosteroids or low-dose corticosteroids should have the varicella vaccine [121].

Table 4: Intranasal corticosteroids

Intranasal corticosteroids	Usual pediatric dose	Ref
Budesonide (Rhinocort)	For once-daily use: 1 spray administered intranasally; For twice-daily use: 2 sprays (each spray delivering 64 µg) administered intranasally. However, the total daily dose should not exceed 256 µg.	[122], [123]
Beclomethasone (Beconase)	The recommended dosage is to administer 1 spray (each spray delivering 50 µg) intranasally twice daily.	[124]

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Fluticasone furoate (Avamys)	The recommended dosage is to administer 1 spray (each spray delivering 27.5 µg) intranasally once daily.	[124], [125]
Triamcinolone acetonide (Nasacort)	The recommended dosage is to administer 1 spray (each spray delivering 55 µg) intranasally once daily.	[126]
Mometasone furoate (Nasonex)	The recommended dosage is to administer 1 spray (each spray delivering 50 µg) intranasally once daily.	[127]
Fluticasone propionate (Flonase)	The recommended dosage is to administer 1 to 2 sprays (each spray delivering 50 µg) intranasally once daily.	[125]

9.4 Decongestants

Decongestants are useful in alleviating the symptoms of nasal obstruction because they promote vasoconstriction inside the nasal mucosa by activating α-adrenergic receptors. However, these medications have little impact on symptoms like runny nose, itchy eyes, or sneezing; therefore, they may work best when combined with antihistamines or other medications [128], [129]. Prescribing nasal decongestants (alpha-sympathomimetic) should be limited to a few days at most, as prolonged use can lead to rebound effects on the nasal mucosa and habituation [130]. The main substances used are oxymetazoline, pseudoephedrine, phenylephrine or xylometazoline [131], [132], [133].

Table 5: Decongestants with pediatric dose

Decongestants	**Usual pediatric dose**	**Ref.**
Phenylephrine	This medication is not recommended for children under 4 years of age. The recommended dosages for children in different age groups are as follows: For children aged 4-5 years: 2.5 mg to be administered every 4 hours. For children aged 6-11 years: 5 mg to be administered every 4 hours. For children aged 12 years and older: 10 mg to be administered every 4 hours.	[128], [129]
Pseudoephedrine	This medication is not recommended for children under 4 years of age. For children aged 4-5 years, the recommended dosage is 15 mg to be administered every 6-8 hours. For children aged 6-11 years, the recommended dosage is 30 mg to be administered every 6-8 hours. For children aged 12 years and older, the recommended dosage is 60 mg to be administered every 6-8 hours.	[131]
Oxymetazoline (nasal spray)	This medication is not recommended for children under 6 years of age. For children aged 6-11 years, the recommended dosage is 1 spray (0.05%) to be administered in each nostril every 10-12 hours.	[134]

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	For children aged 12 years and older, the recommended dosage is 1-2 sprays (0.05%) to be administered in each nostril every 10-12 hours.	

9.5 MAST Cell Stabilizers

Cromolyn sodium and other mast cell stabilizers are routinely used for allergy treatment. Allergy symptoms are alleviated by stopping mast cells from releasing inflammatory compounds like histamine. Nasal symptoms such as itching, runny nose, sneezing and blocked nose can be alleviated by mast cell stabilizers like cromolyn sodium [135]. An effective mast cell stabilizer, cromolyn sodium, has been found to reduce nasal allergy symptoms. Inhibiting mast cell degranulation is how this drug works [136]. Ratner et al. [137] and Chang and Shiung, [138] found that cromolyn sodium helped lower rhinorrhea, sneezing and nasal obstruction, contributing to better overall management of nasal symptoms. If therapy is started before an allergic reaction occurs, it can reduce the severity of symptoms by blocking the release of inflammatory mediators from mast cells. To retain its preventative benefits, cromolyn sodium requires daily usage and does not relieve acute symptoms immediately [139].

9.6 Leukotriene receptor antagonists (LTRA)

Inflammatory mediators belonging to the leukotriene family include LTA4, LTB4, LTC4, LTD4 and LTE4. Allergic rhinitis and asthma symptoms are alleviated by LTRAs because they inhibit cysteinyl LT1 (CysLT1) receptor activity [140]. Although LTRAs (such as Montelukast) appear to be more effective in AR than placebo, they offer no improvement over topical steroid therapy. It appears that antihistamines work better together, although LTRAs are less effective when used alone [141]. In a pollen chamber for Japanese Cedar, Hashiguchi et al. [142] tested its effectiveness and found no significant difference between it and a placebo. Its benefit when used in conjunction with other medications is a high level of safety [143]. Confusion, slurred speech, vertigo or dizziness, delusions or hallucinations and other neuropsychiatric symptoms are uncommon in children and adolescents, although they occasionally occur [143]. Patients with AR with coexisting asthma (particularly exercise-induced) are advised to use LTRAs rather than oral antihistamines, per the ARIA guidelines [144].

Table 6: Overview of all treatments of allergic rhinitis with benefits and limitations

Treatment	Description	Benefits	Limitations
Allergen Avoidance	Measures to reduce exposure to specific allergens	Reduces allergen exposure, alleviates symptoms	Complete avoidance may be challenging, not always feasible
Antihistamines	Medications that block histamine receptors	Provides relief from itching, sneezing, nasal congestion and other allergic symptoms	May cause drowsiness (sedating antihistamines), dry mouth and other side effects

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Intranasal Corticosteroids	Steroid medications applied directly to the nasal passages	Reduces inflammation, alleviates nasal congestion, sneezing, itching and improves overall symptom control	Potential for local side effects such as nasal irritation, nosebleeds and throat irritation
Decongestants	Medications that relieve nasal congestion	Provides temporary relief of nasal stuffiness and congestion	May cause rebound congestion if used for an extended period, have systemic side effects such as increased heart rate, elevated blood pressure and potential for drug interactions
MAST Cell Stabilizers	Medications that prevent the release of allergic mediators	Helps prevent allergic reactions, reduces nasal itching, sneezing and other symptoms	Requires regular and frequent use, may take several weeks to achieve optimal effect
Leukotriene Receptor Antagonists (LTRA)	Medications that block the action of leukotrienes	Reduces inflammation, helps control nasal and respiratory symptoms	May have limited efficacy in some individuals, possible side effects such as headache, gastrointestinal disturbances and behavioural changes
SLIT (Sublingual Immunotherapy)	Allergen immunotherapy administered under the tongue	Convenient home administration, potential for improved adherence, can be effective in reducing allergy symptoms	May take several months to years to achieve optimal effect, potential for local side effects such as oral itching, swelling and throat discomfort
SCIT (Subcutaneous Immunotherapy)	Allergen immunotherapy administered via injections	Effective in reducing allergy symptoms and medication use, potential to modify the course of the disease	Requires visits to healthcare provider for injections, potential for allergic reactions at the injection site (systemic reactions are rare but possible), may not be suitable for individuals with needle phobia or those unable to tolerate injections

9.7 Allergen Immunotherapy

Allergen immunotherapy is the only treatment available for people with IgE-mediated allergy disorders that modifies the immune system. When treating allergic rhinitis in children, it is best to do it early in the disease progression. This may affect how quickly

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the disease develops [145]. Systemic responses are uncommon (1.53%) and the technique is safe for children [146]. The subcutaneous (SCIT) and sublingual (SLIT) administration routes have been effective, especially in pollen-sensitive children. Avoiding injections and the convenience of home administration are two significant benefits of SLIT in the pediatric population [147], [148]. Epicutaneous IT is a potential alternative, especially for food allergies. Still, it is not yet feasible for routine use and requires extensive research on a broad scale to verify its viability [149], [150], [151].

9.7.1 SLIT

With a high adherence rate (70%) even after 3 years of therapy [152] and an excellent profile of safety, usually mainly moderate application-site responses (oral pruritus, throat irritation, oral paresthesia), SLIT appears to be particularly useful in children [153]. There seems to be equal effectiveness in SLIT and SCIT; however, further head-to-head trials would be needed [154]. Several trials have shown substantial improvement in symptom ratings after adding symptomatic treatments or SCIT for birch [155], grass (mono- and poly-allergic) [156] and house dust mite (HDM) [157-159]. At the end of sublingual treatment for HDM, the total nasal symptoms score (TNSS) decreased significantly from 11.27 (9.81±12.73) for monosensitized patients to 3.48 (1.98±4.98) and from 11.54 (10.04±13.04) to 3.56 (2.00±5.16) for polysensitized patients [159]. After treatment, IL-2 and TGF-1 levels rose, whereas IL-4 and IL-17 levels fell dramatically [158].

9.7.2 SCIT

SCIT is highly successful and safe in children, although it may be less agreeable for this population to come for follow-up appointments and injections [148]. It's possible that once-monthly injections might be more tolerated than constant sublingual dosing [160]. SCIT also makes it simpler to track progress and stay on schedule. Systemic responses (moderate to severe) may be less common in SCIT compared to SLIT, with reports ranging from 0.1% to 0.2%, although in other cases reaching as high as 0.4% [161]. Skin responses at the injection site are more common than systemic reactions (9.3% vs 4.7%), but can be prevented in the same way as local (oral) reactions [148].

Table 7: Allergen Immunotherapy for treating allergic rhinitis in Children

Allergen Immunotherapy for treating allergic rhinitis in Children	
Treatment Approach	Allergen Immunotherapy is the primary treatment for modifying the immune system in people with IgE-mediated allergy disorders.
Early Intervention	Early treatment in the disease progression of allergic rhinitis is recommended for better outcomes in children.
Safety and Systemic Responses	Allergen Immunotherapy, including subcutaneous (SCIT) and sublingual (SLIT) routes, has been shown to be safe for children with uncommon systemic responses (1.53%).
Benefits of Sublingual (SLIT)	SLIT has high adherence (70%) even after three years of therapy, with convenience of home administration and minimal side effects such as throat irritation or oral pruritus.
Efficacy of SLIT	SLIT has shown comparable effectiveness to SCIT in improving symptoms ratings in birch, grass and house dust mite allergies.

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Improvement in Symptom Ratings	After sublingual treatment for house dust mite allergy, total nasal symptoms score (TNSS) reduction has been observed.
Changes in Cytokine Levels	Following treatment, IL-2 and TGF-1 (immune system regulators) levels increase, while IL-4 and IL-17 (associated with allergic responses) decrease.
Success and Convenience of SCIT	SCIT is highly successful and safe in children, with the advantage of easier progress tracking and adherence to treatment schedules.
Local and Systemic Reactions	Systemic responses in SCIT are less common (0.1% to 0.4%), with skin responses at the injection site being more frequent but manageable.

10. EMERGING THERAPIES FOR PEDIATRIC AR

There are two main areas of progress in the pharmacotherapy of AR in children: enhancement of allergen immunotherapy (AIT) and the development of biologicals. The latter has gained prominence, prompting studies of local biomarkers such as filaggrin, ORMDL and IL-33, as well as new molecules that influence up and downstream inflammatory pathways in allergic disorders [162], [163].

10.1 Novel Aspects in Allergen Immunotherapy

Peptide immunotherapy, intra-lymphatic immunotherapy [164], immune-modulating adjuvants, recombinant allergens and nanoparticles are some novel therapeutic approaches now being studied and developed [162]. E-health resources are developing rapidly, particularly for SCIT and SLIT long-term monitoring. One benefit is that real-world data may be generated on a massive, even population-wide scale [165], with appreciation to the 'toy factor' and, therefore, frequent usage, especially for mobile phone Apps [166], [167].

10.2 Biologicals

As biologicals or biologics, human monoclonal antibodies that target IgE, Interleukin 4 and Interleukin 5 are currently being used or are undergoing Phase III studies. IgE-specific omalizumab has been the longest [168]. Benralizumab specifically acts on the IL-5 receptor, whereas Mepolizumab and Reslizumab target IL-5. Dupilumab, the latest drug in this class, targets both IL-4 and IL-13, which in turn affects eosinophils and the production of IgE antibodies. Monoclonal antibodies against IL-33, TSLP (Tezepelumab) and IL-25 are being developed or tested to target upstream pathways regulating epithelial cytokine production [162]. Studies are being conducted on both omalizumab and dupilumab for AR, while dupilumab is not yet licensed for use in all countries. Children benefit from both. Response to omalizumab is highly correlated with IgE levels [168]. Dupilumab has been shown to have beneficial effects in patients with coexisting asthma (decreased rates of severe asthma exacerbations, increased forced expiratory volume in 1 second, enhanced health-related quality of life in patients with rhinoconjunctivitis and decreased levels of type 2 inflammatory biomarkers) [169]. Expenses and failure to follow or maximize the benefits of conventional therapy remain the primary obstacles. If eight or more hospitalizations are expected even with the biologic therapy, the cost-benefit ratio improves with omalizumab [168]. This will be primarily influenced by the health care

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systems of individual countries and the future costs of long-term biologic therapy, in addition to ethical issues.

11. COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAM)

Given the widespread use of CAM, it is appropriate for doctors to inquire about patients' experiences with CAM without passing judgment. Clinicians have difficulty evaluating CAM treatments and providing advice since few well-designed clinical studies investigate their efficacy in treating allergic rhinitis. It is desirable to offer some information regarding CAM treatments, including a discussion of the lack of high-quality studies assessing some of these therapies, for the sake of the patients who choose to explore them for managing allergic rhinitis. Alternative and complementary medicine (CAM), such as traditional Chinese medicine, homeopathy, acupuncture and herbal treatments, have all been utilized to treat allergic rhinitis [170]. Several studies [170], [171] have demonstrated that acupuncture can help people with allergic rhinitis.

12. ADHERENCE ISSUES IN CHILDREN

When treating children, nonadherence can pose serious challenges. Children typically have a negative attitude toward taking medications and this can reduce the therapeutic benefit they provide. The clinician can help reduce this issue by prescribing medicines that may influence adherence, such as consistency, taste, dosing frequency and capsule/tablet size [172]. Additionally, it is beneficial to explain to children the rationale behind each medication they are expected to take, noting both the potential effects of the medication and the effects that are desired. Considering the drug's physical properties and having an open and honest conversation with children and their parents can improve adhesion [173]. If practitioners take into consideration the requirements of their young patients, medication adherence can be improved and allergic rhinitis in children can be managed more effectively [174].

13. CONCLUSION

Despite its prevalence, pediatric allergic rhinitis has a profound effect on a child's health, academic performance and overall happiness. Otitis media, asthma and sinusitis are all co-morbidities that are more likely to occur in people with this condition. It is assured that there are many treatments available and they work just as well for children as they do for adults. However, when dealing with young children, it is crucial to think about pediatric dose standards and medication adherence. The burden is on clinicians to know about the options and choose the best therapy for each child. The goal is to lessen the possibility of problems, improve overall health and relieve symptoms. Adherence to prescribed therapies is crucial for achieving desired outcomes. Healthcare providers may improve children's health and well-being by treating allergic rhinitis more effectively after they have a thorough understanding of the challenges and factors involved in managing the condition.

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14. RECOMMENDATIONS

1) The distinct physical signs and symptoms of allergic rhinitis in children, such as allergic shiners and creases, must be recognized. A quick diagnosis can lead to better long-term outcomes and rapid treatment. 2) A systematic evaluation must be carried out, which should include a detailed medical history, a physical examination and considering any potential exposures to allergens. With the help of this evaluation, specific triggers can be identified and treatment plans can be tailored accordingly. 3) Environmental control measures play a significant role in the treatment of allergic rhinitis. Regular cleaning, avoiding pet dander and using dust-mite-proof bedding can all reduce allergen exposure and symptoms. 4) The child age, severity of symptoms and medication safety profiles should guide the selection of pharmacological agents. Decongestants can be used for short-term relief, while intranasal corticosteroids and non-sedating second-generation antihistamines are frequently the backbone of treatment. Clear instructions and close monitoring should accompany the use of medications. 5) Allergen immunotherapy, which can be given through a route that is either sublingual or subcutaneous, may be beneficial for children who have severe and persistent allergic rhinitis. This treatment approach is to diminish critically susceptible reactions and desensitize the insusceptible framework. Nevertheless, careful patient selection and monitoring are required due to the possibility of adverse reactions. 6) It is essential to provide children with education and support. Explain the nature of allergic rhinitis, the significance of following treatment plans and methods for coping with symptoms. Collaborating with allergists and pulmonologists may be beneficial in cases of complex or refractory allergic rhinitis. This multidisciplinary approach may be used to treat underlying comorbidities as well as provide comprehensive care.

15. FUTURE PROSPECT

1) Immunotherapy research holds potential for more specific and individualized treatment options. Looking into novel allergen extracts, changing the protocols for immunotherapy and using adjuvants to make the treatment work better. 2) The formation of monoclonal antibodies that target specific allergic pathways like IL-4, IL-13 and IgE could be a breakthrough in the treatment of allergic rhinitis. These targeted therapies may improve symptom control and disease modification with fewer systemic side effects. 3) Further understanding of epigenetics and the microbiome in unfavorably prompt remedial procedures. Targeting epigenetic modifications and the microbiome could open new treatment and prevention options. 4) With the development of genomic and proteomic technologies, individual genetic and molecular profiles that contribute to allergic rhinitis can now be identified. This may open the door to individualized treatment plans that are tailored to each child's unique underlying mechanisms. Children with allergic rhinitis can gain access to specialized care, remote monitoring and self-management tools by integrating telemedicine and digital health solutions. Patients may find that they are better able to follow to their treatments, receive assistance more easily and receive useful educational resources as a result of this technology.

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Conflict of interests

The Authors Declare No Conflicts Of Interest.

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