REVIEW ARTICLE

Management of Allergic Rhinitis

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Allergic rhinitis is the most common chronic childhood disease. Reduced quality of life is frequently caused by this IgE-mediated disease, including sleep disturbance with subsequent decreased school performance. Asthma and exercise-induced bronchospasm are commonly seen concurrently with allergic rhinitis, and poorly controlled allergic rhinitis negatively affects asthma outcomes. Nonsedating antihistamines or intranasal azelastine are effective agents to manage allergic rhinitis, often in combination with oral decongestants. For moderate to severe persistent disease, intranasal corticosteroids are the most effective agents. Some patients require concomitant intranasal corticosteroids and nonsedating antihistamines for optimal management. Other available agents include leukotriene receptor antagonists, intranasal cromolyn, intranasal ipratropium, specific immunotherapy, and anti-IgE therapy.

KEYWORDS: allergic rhinitis, drug therapy, management, pediatrics

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INTRODUCTION

Allergic rhinitis is the most common chronic pediatric disease, affecting up to 40% of children.[1,2] The incidence of allergic rhinitis in pediatric patients may be underestimated due to the difficulty for young children to identify and articulate the clinical manifestations. Beyond its bothersome symptoms such as runny nose, sneezing, and nasal stuffiness, it is increasingly recognized that poorly managed allergic rhinitis reduces quality of sleep, school performance, and social functioning.[3-5] As such, allergic rhinitis is associated with fatigue, irritability, and school absences.[3-5]

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Pathophysiology, Classification, Diagnosis, and Costs of Allergic Rhinitis

Allergic rhinitis is an inflammatory disease of the nasal mucosa characterized by the symptoms of pruritis, sneezing, nasal discharge, and stuffiness induced by an IgE-mediated response.[6-10] The complex cascade of events resulting from exposure to aeroallergens is beyond the scope of this review. Table 1 lists some of the most important mediators and cells involved in the pathophysiology of allergic rhinitis.[6,10]

ABBREVIATIONS: EIB, exercise-induced bronchospasm; IL4, interleukin 4; IL5, interleukin 5; MFNS, mometasone furoate nasal spray; RANTES, regulated upon activation normal T-cell expressed and secreted; QOL, quality of life

Classification of allergic rhinitis, commonly referred to as "hay fever," was formerly termed either seasonal or perennial. Seasonal allergic rhinitis occurs in the springtime due to tree or grass pollen, or in late summer and autumn,

Table 1. Examples of Cells and Mediators Central to Pathophysiology of Allergic Rhinitis

Cells	Examples of Function Related to IgE-Mediated Rhinitis
Mast cells	Upon exposure to allergens, release inflammatory mediators such as histamine and leukotrienes
Eosinophils	Recruited to nasal mucosa, release major basic protein, eosinophil cationic protein, and other inflammatory biochemicals
Th2 type Lymphocytes	Release cytokines that recruit eosinophils and basophils to the nasal mucosa
Basophils	Release histamine and leukotrienes
Mediators	**Function Related to IgE-Mediated Rhinitis**
Histamine	Vasodilation and increased vascular permeability
Leukotrienes	Nasal blockage and increased vascular permeability
Cytokines (e.g., IL4, IL5)	Eosinophil recruitment, activation
Chemokines (e.g., eotaxin, RANTES)	Eosinophil, basophil recruitment

IL4, interleukin 4; IL5, interleukin 5; RANTES, regulated upon activation normal T-cell expressed and secreted

most commonly due to ragweed. Perennial allergic rhinitis occurs all year due to triggers such as mold, dust mites, cockroaches, and pets. Many patients with perennial allergic rhinitis have worsening symptoms at peak pollen season.

More recent classification of allergic rhinitis is "intermittent" or "persistent" disease. *Intermittent AR* is defined as symptoms present for less than 4 days per week and for less than 4 weeks. *Persistent AR* is defined as symptoms that have lasted longer than 4 weeks or symptoms that occur greater than 4 days per week.[11] Severity of the disease is further classified as either mild or moderate-severe. Patients with mild disease should not experience sleep disturbances, bothersome symptoms, or impairment of daily activities, including school, work, and leisure activities. Patients with moderate-severe disease do experience one or more of the above mentioned symptoms.[11]

Diagnosis of allergic rhinitis is primarily based on a detailed history from parents or other caregivers. Table 2 summarizes key components of the diagnosis.[6,12] Other forms of rhinitis such as viral rhinitis or non-allergic rhinitis with eosinophilic syndrome must be ruled out. Definitive diagnosis requires identification of specific IgE that corresponds to the history. For example, a positive skin test to ragweed in association with rhinitis symptoms in late summer and early fall where ragweed is present confirms the diagnosis.

The costs associated with allergic rhinitis are estimated to be approximately 2.7 billion dollars in direct costs yearly, and significant indirect costs are due to lost school days-approaching 2 million lost days in the US annually.[13] While independent of allergic rhinitis, asthma and sinusitis serve to enhance allergic rhinitis-related productivity-loss rates.[13]

EFFECT OF ALLERGIC RHINITIS ON QUALITY OF LIFE

Because allergic rhinitis is not a life-threatening illness, it may not receive the attention that it deserves in terms of its effects on diminishing quality of life (QOL). The impact of allergic rhinitis on a child's QOL can be quite negative. Juniper et al.[8,9] developed QOL measurements for adolescents and children ages 6-16 years with rhinoconjunctivitis. Among QOL concerns, perhaps the best studied factor is the effect of allergic rhinitis on quality of sleep.[3] Because allergic rhinitis causes sleep disturbance, the resulting daytime somnolence and fatigue can impair learning and result in decreased performance at school and during sports.[4,5] Allergic rhinitis also leads to school absenteeism and may be associated with depression, anxiety, and family dysfunction.[7,14]

QOL is further reduced by headaches, altered or decreased sense of taste and smell, and embarrassing sneezing episodes at school or social functions.

LINK BETWEEN ASTHMA AND ALLERGIC RHINITIS

There is a definite link between asthma and allergic rhinitis; many asthmatic patients also suffer from allergic rhinitis, or the triad of asthma, allergic rhinitis, and atopic dermatitis. Jani and Hamilos[15] reviewed the relationship between asthma and allergic rhinitis. The respiratory tract is increasingly viewed as continuous and interactive, and diseases of the upper and lower airways as reflections of a *systemic* inflammatory response to airway challenge.[15]

Asthma and allergic rhinitis have several common characteristics, including a strong genetic predisposition, many of the same inflammatory cells and mediators (Table 2) and numerous identical immunologic triggers, such as tree and grass pollen, ragweed, housedust mites, and molds. Optimal control of asthma requires excellent control of allergic rhinitis. Intranasal corticosteroids reduce bronchial hyperreactivity and the risk of emergency department visits and hospitalizations.[16,17]

INCIDENCE OF EXERCISE-INDUCED BRONCHOSPASM IN PATIENTS WITH ALLERGIC RHINITIS

Up to 40% of patients with allergic rhinitis have exercise-induced bronchospasm (EIB), which is a large population, considering that several million children suffer from allergic rhinitis.[18] Exercise may be the only trigger of bronchospasm in these patients who do not have a diagnosis of asthma. In young children and adolescents, EIB is highly significant with regard to participation in team sports, playing outside with friends and family, and effects on overall health. EIB continues to be underdiagnosed in the US.[19]

If there is any evidence of shortness of breath, chest tightness, or coughing after roughly 6 to 8 minutes of exercise, especially in cold, dry air, patients with allergic rhinitis should be assessed for EIB by spirometry or peak expiratory flow (PEF). A 15% decrease in FEV_1 or PEF after a short period of vigorous exercise is indicative of EIB, which can be easily prevented by short-acting inhaled $beta_2$-agonists before exercise or by other drug therapy.[20]

Table 2. Key Elements of the Diagnosis of Allergic Rhinitis

History
Positive family history of allergic rhinitis or asthma
Typical symptoms associated with springtime or late summer/fall
Symptoms associated with other triggers such as pets, molds, perfumes
Typical Signs and Symptoms (a few examples)
Thin, clear rhinorrhea
Nasal congestion
Sneezing episodes
Itchy nose, eyes, palate
Mouth breathing
Coughing
Skin Testing
Aeroallergens
Food allergens in infants and early childhood

MANAGEMENT PLAN

Environmental Control

Environmental control is essential to optimal management of allergic rhinitis. Whenever possible, completely avoiding allergens and nonallergenic triggers is desirable. For many common aeroallergens, including tree and grass pollen, minimizing exposure is the only practical approach. Reducing exposure to molds, dust mites, and cockroaches is important, as well as avoiding secondhand smoke, perfumes, and household cleaning products.

When educating patients about environmental control, it is necessary to be practical and sensitive to the patient. For example, pets are of special importance to many children and adults, and it can be unproductive to tell a parent and child to "get rid of the dog." On the other hand, if the child is allergic to the dog or cat, the pet should not be in the bedroom at night, and should be kept outside as often as possible. Additionally, while avoiding outdoor sports and play is not practical in children, attempts to limit time outdoors during peak pollen season are desirable. An appropriate balance must be found to maximize the QOL of

the child and family while minimizing exposure to AR and asthma triggers.

Drug Therapy

Current optimal drug therapy is effective and safe for most children with AR; two expert panels have provided recommendations.[11,21] For management of intermittent or mild persistent allergic rhinitis, current guidelines recommend oral nonsedating antihistamines or intranasal antihistamines.[11,21] Intranasal cromolyn may also be used. For moderate to severe allergic rhinitis, intranasal corticosteroids are recommended.[11,21] If intranasal corticosteroids do not provide optimal relief, the combination of these agents with nonsedating antihistamines and oral decongestants should be considered. Other agents, including leukotriene receptor antagonists, intranasal ipratropium, and specific immunotherapy are further therapeutic options (Table 3).

Table 3. Drug Therapy Options in Allergic Rhinitis

Intermittent
Oral antihistamines or intranasal antihistamines (if congestion, combination antihistamine/ decongestant)
OR
Intranasal cromolyn
OR
Leukotriene receptor antagonist
Persistent
Mild Persistent
Oral antihistamines or intranasal antihistamines (if congestion, combination antihistamine/ decongestant)
OR
Intranasal cromolyn
OR
Leukotriene receptor antagonist
Moderate to Severe Persistent
Intranasal corticosteroids

If intranasal corticosteroids do not provide optimal relief, add antihistamine or antihistamine/decongestant
Depending on response, can add intranasal ipratropium or leukotriene receptor antagonist

THERAPEUTIC AGENTS FOR ALLERGIC RHINITIS

Antihistamines

Histamine was first discovered over 80 years ago as a major pathogenic mediator of allergic complications including rhinitis and urticaria. Since the discovery of the histamine receptor antagonist in 1937 by Staub and Bovet, in excess of 40 compounds considered first generation antihistamines have been developed and marketed to the public.[22-24] A primary constituent of specific immunity, histamine is a protein found in all body tissues, but is particularly evident in the lungs, mast cells, and basophils. H_1 receptors are found on nerve endings, and distributed in the brain, smooth muscle and glandular cells, endothelial cells, the adrenal medulla and heart.[25]

Since their inception, first generation antihistamines remain one of the most widely used classes of drugs in the world. Diphenhydramine, chlorpheniramine, hydroxyzine, brompheniramine, and doxylamine are included in this class. These H_1 receptor blockers exert their effects by competitively antagonizing histamine at the H_1 receptor sites, resulting in decreased vascular permeability, decreased pruritus, and respiratory smooth muscle relaxation. Relative efficacy and safety of antihistamines such as hydroxyzine, diphenhydramine, and chlorpheniramine have been shown in several comparative trials.[26-30]

While antihistamines have helped control allergic rhinitis and other allergic disorders successfully, their lack of specificity is responsible for many of their adverse effects. They act primarily on the peripheral H_1 receptors and are able to cross the blood brain barrier. Adverse effects attributed to this include marked sedation, central nervous system dysfunction and anticholinergic adverse effects resulting in cognitive function impairment.[31]

Of these symptoms, sedation remains the most frequently reported and troublesome adverse effect of the first generation H_1 antagonists. These antihistamines cause psychomotor impairment, degraded attention and memory, all of which affect occupational and academic performance as well as social functioning.[31,32] Cognitive impairment and sleepiness while driving are particularly problematic.[32] Since numerous first generation products are available in relatively inexpensive nonprescription allergy and cold products, parents of small children and adolescent patients need counseling regarding the risks of sedation with these older antihistamines. In certain individuals, the H_1

antagonist can paradoxically increase euphoria, nervousness, diplopia and tremors.[33]

Simons[34] has discussed the usefulness of first generation antihistamines in children with concomitant urticaria or atopic dermatitis with severe pruritus where the benefit outweighs the risk. Additionally, children with anaphylaxis who require IV diphenhydramine are also candidates for H_1 antagonists. Aside from these exceptions the first generation antihistamines are not considered the drugs of choice in treating allergic rhinitis in children. Simons also states that H_1 receptor antagonists are not particularly useful in children suffering from otitis media and other upper respiratory ailments. In contrast, however, the H_1 receptor antagonists may be beneficial in some children who have mild asthma.

Second Generation Antihistamines

In the early 1980's the newer, second generation H_1 receptor antagonist antihistamines (e.g., loratadine, terfenadine, aztemizole) were developed and marketed for use in both pediatric and adult populations. In post marketing surveillance, terfenadine and aztemizole were discovered to prolong the QTc interval in some patients, leading rarely to fatal ventricular arrhythmias.[31] After withdrawal of these 2 drugs from the market in the late 1990s, loratadine, fexofenadine, and desloratadine continue to be available as safe and effective nonsedating antihistamines. Cetirizine is classified a "low-sedating" antihistamine.

Referred to as the 'non-sedating' antihistamines, these drugs made important advances for children suffering from allergic rhinitis. Nonsedating antihistamines are less susceptible to crossing the blood brain barrier, in part because they consist of larger molecules than those of the first generation antihistamines as well as being less lipophilic. Other mechanisms that differ from the first generation antihistamines are thought to include inhibition of calcium ion influx across the mast cells thus preventing mediator release.[25] In terms of tolerability, the nonsedating antihistamines have been shown to have similar side effect profiles as placebo and are less impairing with respect to sleep, EEG, cognitive performance and anticholinergic side effects.[33] Furthermore, since newer agents are efficacious, cetirizine, fexofenadine, and loratadine are logical choices for treating allergic rhinitis in pediatric patients < 12 years of age. Desloratadine offers similar efficacy and safety as loratadine, but is more expensive.[34]

Sedation caused by second generation antihistamines is seen most notably with cetirizine, which is a metabolite of hydroxyzine. Its mechanism of action involves selective inhibition of the peripheral H_1 receptors. Studies have documented negligible anticholinergic properties and penetration into the CNS thereby reducing the sedating properties commonly found with the first generation antihistamines. Cetirizine has anti-inflammatory properties that play a role in diminishing symptoms of AR as well as asthma.[35]

Ng et al.[36] studied the sedating effects of chlorpheniramine and cetirizine, a first and second generation antihistamine respectively, on school children with allergic rhinitis. The children were given 4 mg chlorpheniramine and 10 mg cetirizine. Using the P300 event related potential as an objective measure of sedation relative to placebo, both cetirizine and chlorpheniramine were found to cause sedation in children. Consequently, cetirizine is the only second generation antihistamine with an FDA label in the package insert warning against sedation.

Another clinical study involving cetirizine documented its effectiveness in treating AR in the pediatric population. Ciprandi et al. studied cetirizine in 20 children with a mean age of 13.7 years. Inflammatory cells and cytokines, specifically IL4 and IL8, were significantly decreased after 2 weeks of cetirizine therapy.[37]

Fexofenadine, the active metabolite of terfenadine, is an oral second generation formulation used to treat symptoms of allergic rhinitis in children 6 years of age and older. Few studies are available to support its use in children under 6 years of age. Meltzer et al.[38] studied the safety and efficacy of fexofenadine, 30 mg BID and 15 mg, in children 6-11 years of age in two week trials. The findings in each group show a low incidence of both adverse events and medication discontinuation. The placebo group reported having similar adverse events as the 30 mg BID group (24.4% vs. 24.1%) vs. 28.4% for all fexofenadine treated subjects.[38]

A study conducted by Wahn and colleagues[39] evaluated fexofenadine in children ages 6-11

years and showed relief of AR symptoms including nasal congestion and ocular symptoms not typically realized with other antihistamines. The broad relief of symptoms implies fexofenadine's mechanism of action involves more than just antagonism at the H_1 receptor. Incidence and severity of adverse effects were similar to those of placebo. As with other clinical trials, the proven efficacy and safety of fexofenadine in children demonstrate a 60 mg dose 2 times per day in children ages 6-11 years is effective in diminishing symptoms of allergic rhinitis.[39]

Another clinical study[40] evaluated patients with moderate to severe allergic rhinitis using 180 mg of fexofenadine daily and a 10 mg standard dose of cetirizine in a 2-week, multicenter, double-blind, randomized study. The primary objective was to evaluate the level of drowsiness and motivation in individual patients. Fexofenadine caused significantly less somnolence than did cetirizine. In addition, overall motivation in the patient sample taking fexofenadine was higher than for cetirizine.[40]

Simons et al.[41] studied the clinical pharmacology of fexofenadine in 14 healthy children with a mean age of 9.8 ± 1.8 years. All children were given either a 30 mg or 60 mg capsule of fexofenadine with 150 mL water. The side effect profile of fexofenadine in children was minimal with only one child experiencing somnolence after a 30 mg dose. Unlike fexofenadine's parent compound, terfenadine, the EKG was normal, with no reports of prolonged QTc interval.

Intranasal antihistamines such as azelastine are safe and effective in children with allergic rhinitis.[42] Azelastine is indicated for pediatric patients ages 5-12 years. Unfortunately, some patients complain of a bitter taste. In addition, intranasal azelastine has a higher incidence of somnolence versus placebo.[32]

Other Considerations Regarding First vs Second Generation Antihistamines

There is a significant cost differential between first and second generation antihistamines. While nonsedating antihistamines are generally recommended for treatment of allergic rhinitis in children, available studies have yielded mixed results and there is still some debate among clinicians. It is imperative to balance both cost issues and QOL for the patient.

Bender et al.[43] conducted a meta-analysis evaluating the sedation effects and performance impairment of diphenydramine compared to placebo and second generation antihistamines. Although diphenhydramine produced more somnolence and performance impairment than placebo or second generation antihistamines, the results were highly variable among the different trials. Sedation was also noted in the second generation groups when compared with placebo. From this meta-analysis, the authors conclude that a clear difference cannot be found between the first and second generation antihistamines.[43]

A review by Blaiss[44] discusses the available second generation antihistamines and their place in the treatment of seasonal allergic rhinitis in children. Based on the studies presented, treating children with these newer agents may be more efficacious and cost-effective in the long term by halting development of other conditions, including asthma. In the short term, children can be treated for their symptoms, and ideally with less sedation. It is important to consider each agent individually, as some of the second generation agents have a higher propensity for psychomotor performance impairment than others.[44]

As pharmacists, it is also important that we make our patients aware of active ingredients in different brand name products. Due to the nature of advertising, it might not be obvious to some parents that Alavert® and Claritin® both contain the same active ingredient. If parents are treating their children with over the counter (OTC) antihistamines, they should be aware of this in order to avoid giving larger than recommended doses of loratadine and increasing the probability of experiencing somnolence and other adverse effects.[45]

Decongestants

Since antihistamines do not affect nasal stuffiness, many patients are improved clinically by combining an oral decongestant with the antihistamine.[12] Indeed, numerous nonprescription and prescription products are combinations of antihistamines and oral decongestants such as pseudoephedrine. For adolescents participating in team sports, these agents may be banned, as they are banned in International competi-

Table 4. Examples of Commonly Prescribed Drugs for the Treatment of Allergic Rhinitis in Pediatric Populations

Medications	Usual Pediatric Doses
Oral Antihistamines	
First generation	
Chlorpheniramine	2-5 yrs: 1 mg q 4–6 hrs (maximum 4 mg daily) 6-12 yrs: 2 mg q 4–6 hrs or 8 mg SR daily < 6 yrs: extended release not recommended
Diphenhydramine	2-5 yrs: 6.25–12.5 mg q 4–6 hrs 6-12 yrs: 12.5–25 mg q 4–6 hrs
Hydroxyzine	2 mg/kg/day in 3 divided doses or at HS
Second Generation	
Cetirizine (Zyrtec) tablet and syrup	12-23 mo: 2.5 mg daily initially; maximum 2.5 mg BID 2-5 yrs: 2.5 mg initial dose, may be increased to 2.5 mg q 12 hrs or 5 mg/day 6-11 yrs: 5–10 mg daily
Fexofenadine (Allegra)	6-11 yrs: 30 mg BID* 30 mg QD with impaired renal function
Leukotriene Antagonists	
Montelukast (Singulair)	2-5 yrs: 4 mg chewable tablet/day, taken in the PM 6-14 yrs: 5 mg chewable tablet/day, taken in the PM
Decongestants	< 2 yrs: 4 mg/kg/day in divided doses every 6 hrs
Pseudoephedrine (Sudafed)	2-5 yrs: 15 mg every 6 hrs (maximum 60 mg/24 hrs) 6-12 yrs: 30 mg every 6 hrs (maximum 120 mg/24 hrs)
Decongestant Nasal spray/drops	< 6 yrs: to be determined by physician 2-6 yrs: 2-3 drops of 0.126% or 0.16% solution in the nose every 4 hrs as needed†
Phenylephrine	6-12 yrs: 2-3 sprays of a 0.25% solution every 4 hrs as needed
Intranasal Antihistamines	< 5 yrs: As determined by the physician
Azelastine (Astelin)	5-11 yrs: 1 spray per nostril BID

**Safety not established in children < 6 years of age*
†Intranasal decongestant to be used only on a short-term basis (3 days maximum)

tion (i.e., Olympics). Pseudoephedrine is not recommended for use in pediatric patients less than 12 months of age.[31] Oral phenylephrine is rapidly degraded by monoamine oxidase, and has not been demonstrated to be effective. Until clinical trials are conducted that demonstrate efficacy, oral phenylephrine should not be recommended. Because of increasing restrictions on pseudoephedrine due to its use in the illegal production of methamphetamine, some pharmacies have oral phenylephrine available as a nasal decongestant.

Short term use of topical decongestants is acceptable for severe stuffiness, especially for patients with moderate to severe persistent disease who need intranasal corticosteroids. Use of topical decongestants for more than 3 or 4 days may be associated with rebound congestion ("rhinitis medicamentosa"), and limited use must be strictly followed.[6] Pediatric doses for decongestants as well as other AR pharmacotherapies are listed in Tables 4 and 5.

Intranasal Corticosteroids

As mentioned previously, intranasal corticosteroids are the agents of choice for children with moderate to severe persistent allergic rhinitis.[11] These highly efficacious antiinflammatory medications are frequently used in combination with nonsedating antihistamines plus decongestants in children to achieve optimal outcomes.

Intranasal corticosteroids are well documented to be generally safe in children.[11,31] However, nasal bleeding (blood tinged mucus) and local irritation manifested as burning or stinging can occur with regular use. If improperly used, long term nasal corticosteroids may rarely result in septal perforation.[31] Patients need to be informed of the proper administra-

Table 5. Commonly Prescribed Intranasal Corticosteroids Used in the Treatment of Pediatric Allergic Rhinitis

Intranasal Corticosteroids	Usual Pediatric Dosage
Beclomethasone (Beconase)	6-12 yrs: starting dose1 inhalation in each nostril BID (maximum 2 sprays each nostril BID)
Fluticasone (Flonase) 100 µg	≥ 4 yrs: 1 spray per nostril QD. Dose may be increased to 2 sprays in each nostril QD then decreased to 1 spray QD for maintenance therapy
Mometasone (Nasonex) 50 µg	2-11 yrs: 1 spray per nostril QD
Budesonide (Rhinocort) 32 µg*	≥ 6 yrs: 64 mcg/day as 1 spray per nostril (maximum 128 mcg QD as 2 sprays/nostril)
Triamcinolone (Nasacort) 55 µg	6-11 yrs: starting dose 1 spray in each nostril daily: Max dose 2 sprays per nostril QD†

**Rhinocort Aqua has no preservative or perfumy odor (annoying to some patients)*
†Safety not established in children less than 6 years of age

tion when using longer extension applicators, aqueous sprays and lower velocity sprays. In addition, directing the spray away from the nasal septum will help minimize local trauma. It is prudent to regularly re-evaluate the septum in children to assess for damage to any part of the nasal passages.

Concerns regarding growth suppression with low- to moderate-dose topical corticosteroid use in children have been reduced to a great degree with long term studies of oral inhalation corticosteroids for treatment of asthma.[46,47] However, in order to further allay safety concerns for children receiving intranasal corticosteroids, studies in pediatric patients using the intranasal route of administration were essential. Pediatric studies have assessed growth suppression as well as adrenocortical suppression and bone metabolism.[48-63] Intranasal corticosteroids in current use have minimal systemic effects due to low bioavailability.[64]

Recent Safety Trials Assessing Systemic Effects

Skoner et al.[48] studied the potential for growth suppression in 100 children 6-9 years of age for 1 year using intranasal beclomethasone. Fifty-one children were treated with 168 mcg beclomethasone twice daily and 49 children received placebo. Stadiometric measurements of stature were taken at 1, 2, 4, 6, 8, 10, and 12 months. Of the 90 children who completed the yearlong study, the beclomethasone treatment group experienced an overall growth rate of 5 cm compared to 5.9 cm in the placebo group. These differences in growth rate were limited to the initial part of the study period, suggesting that this was a short-term steroid-related suppression, and not a chronic effect of the inhaled corticosteroid.

Schenkel et al.[49] studied the effects of mometasone furoate nasal spray (MFNS) in a randomized, placebo-controlled, double blind, multicenter study in children between the ages of 3 and 9 years with perennial allergic rhinitis. A total of 98 subjects were randomized to 100 mcg MFNS daily or placebo for 1 year. Height was measured at approximately 1, 2, 3, 6 and 9 months and at 1 year. The results demonstrated no difference in mean height between those children receiving MFNS and those receiving placebo.

A clinical study using 64 mcg/day budesonide aqueous nasal spray in 78 children aged 2-5 with allergic rhinitis for 6 weeks demonstrated no HPA suppression.[50] Administration was well tolerated by children resulting in no differences between the treatment and placebo group. A randomized, double-blind, parallel-group, placebo-controlled, multi-center study using 65 children aged 2-3 studied the effect of fluticasone propionate aqueous nasal spray on the HPA axis.[51] This study demonstrated no effect on HPA axis function with a dose of 200-mcg fluticasone daily. The results were conclusive as measured by a 12 hour urinary free cortisol test in these young patients with documented allergic rhinitis. The patients also tolerated the fluticasone at the given dose. Other studies have also demonstrated no detectable suppression of HPA after administration of fluticasone or triamcinolone nasal sprays.[52,53]

In spite of clinical trials studying nasal corticosteroids in children that demonstrate safety and tolerability, the FDA still recommends

children's height be regularly monitored. In addition, children should receive the lowest possible effective therapeutic dose, preferably in the morning, when treating allergic rhinitis with intranasal corticosteroids.[31,65,66] Safety concerns with pediatric use of intranasal corticosteroids are logically somewhat increased in patients who require concomitant oral inhalation corticosteroids for asthma, especially in patients who require high doses.

A precautionary note regarding systemically acting steroids in children is appropriate here. Use of short courses of oral corticosteroids in children is discouraged except in cases involving nasal polyps or an intractable symptom profile. Most importantly, short courses of systemically acting steroids should be considered for allergic rhinitis *only* when topical corticosteroids and other standard management, including environmental control, are ineffective. The foregoing FDA recommendation regarding stadiometric assessment is particularly important in pediatric cases involving systemic corticosteroid therapy.

Leukotriene Receptor Antagonists in Pediatric Patients

Current literature suggests that the use of leukotriene receptor antagonists, including montelukast, pranlukast and zafirlukast in pediatric patients, either alone or in combination with antihistamines, for treatment of allergic rhinitis is safe.[67] Pediatric studies have demonstrated the use of 5 mg daily doses of montelukast to be a safe and effective medication in the treatment of allergic rhinitis.[68] Recently, montelukast 4 mg daily was FDA approved for children ages 2 to 5 years.

A recent study compared the efficacy of fluticasone propionate nasal spray monotherapy versus fluticasone plus cetirizine, fluticasone plus montelukast, and cetirizine plus montelukast. The results document fluticasone to be more effective as monotherapy in treating allergic rhinitis. In addition, there was no clear advantage to using combination therapy with cetirizine or montelukast in these patients.[69] When used alone, however, montelukast is shown to be more effective than placebo in treating and controlling symptoms of rhinitis.[70,71] Based on a review of studies to date, leukotriene receptor antagonists are not highly effective in the management of allergic rhinitis, but are more efficacious than placebo as monotherapy.[71]

Intranasal Cromolyn

Cromolyn Sodium is an anti-allergic medication often used as adjunctive therapy or in the prophylactic treatment of rhinitis. This drug exerts its therapeutic effect by inhibiting degranulation of sensitized mast cells, hence blocking the release of histamine and other allergic mediators. Cromolyn exhibits poor systemic absorption. Consequently, cromolyn has a favorable side effect profile, is devoid of drug interactions and is well tolerated making it one of the safest preparations for use in pediatric patients.[72]

Minor irritation such as sneezing, nasal stinging or burning, and epistaxis occur less than 10% of the time and there has been no evidence of septal perforation. Patient compliance may be an issue with cromolyn, however, since successful treatment usually requires QID dosing, but may require up to 6 administrations daily. Consequently, cromolyn is not the preferred treatment for rhinitis.[73]

Intranasal Anticholinergics

Ipratropium bromide nasal spray is a synthetic quaternary amine used in the treatment of rhinitis. The anhydrous solution comes as a 0.03% or 0.06% metered dose manual pump spray in an isotonic aqueous solution with a pH adjusted to 4.7 making it compatible with the nasal mucosa. It works by antagonizing the action of acetylcholine, resulting in reduced production, and a more viscous mucus production. As a quaternary amine, it is not readily lipophilic. Consequently it does not readily cross the gastrointestinal and nasal membranes, nor does it readily cross the blood brain barrier, thus greatly limiting systemic anticholingeric effects which would otherwise limit the clinical safety profile of this drug. Less than 20% of an 84 mcg per nostril dose is absorbed from the nasal mucosa after administration in normal healthy volunteers and those with perennial rhinitis.[74]

The safety and efficacy of ipratropium bromide 0.06% nasal spray was studied in 230 children aged 2 to 5 years with rhinorrhea due to the common cold or allergies.[75] Of the 230

children studied, 187 suffered from allergies and 43 had colds. Those children with colds received 84 mcg per nostril 3 times daily for 4 days and those with allergies received 42 mcg per nostril. The results of the open-label, multicenter study demonstrated that most parents (> 90% in both groups) felt ipratropium nasal spray was "very useful" or "somewhat useful" and 67% of parents in the common cold group and 91% of parents in the allergy group found administration of the nasal spray easy. There were no reported serious or systemic anticholinergic adverse events and the nasal spray was well tolerated by the children.[75]

The side effect profile of nasal ipratropium is benign with epistaxis and nasal dryness being the most frequently reported events. Although this medication has a safe and effective profile, and is useful in controlling rhinorhea, it is recommended ipratropium be used in conjunction with a decongestant or nasal steroid for treatment of rhinitis at diminished doses.[76]

Specific Immunotherapy

Almost one century after its discovery, more than 60 million people worldwide are treated with specific immunotherapy, commonly referred to as "allergy shots." For many patients, specific immunotherapy has been very effective in controlling symptoms of allergic rhinitis.[77-79]

The immunotherapy process is one in which the patient is systematically and increasingly desensitized to the offending allergens. Allergic desensitization is accomplished through exposure to the allergen in incrementing doses over the course of several months, typically as subcutaneous injections. Initially, the injections are given on a weekly or bi-weekly basis. The dosing schedule converts to a once-monthly regimen upon attainment of a tolerated therapeutic level. The goal is to desensitize or hyposensitize the patient to a level of reduced symptoms normally triggered by allergen exposure.[77]

The dosing and schedule can vary with each case. The potential complexity of immunotherapy regimens requires that the physician be well versed with the technique through required training and experience to make such a determination. The practitioner should also have available resuscitation equipment including: adrenaline 1:1000 for intramuscular use, oxygen, an inflatable bag and mask ventilator, a nebuliser and bronchodilator nebuliser solution, needles and tubing for intravenous access, intravenous fluids for volume replacement, parenteral antihistamine, and parenteral corticosteroid. Although immunotherapy is generally a very safe procedure, the potential exists for life-threatening reactions in some individuals. Consequently, patients should remain in the physician's office for at least 20–30 minutes following specific immunotherapy. Evidence from U.S. studies indicate that fewer than 1% of immunotherapy patients experience severe systemic reactions.[80] One study documented that examined immunotherapy-related mortality between 1985–1993 observed a total of 35 deaths out of 52.3 million administrations associated with this technique.[81]

Currently, this therapeutic approach is called for in three situations: cases manifested by severe, intractable symptoms unresponsive to other treatments; cases where the patient or physician is unwilling to accept or prescribe, respectively, currently available chronic pharmacotherapeutic regimens; and cases with comorbid conditions such as upper airway disease, heart disease, or hypertension. The absolute contraindication to immunotherapy pertains to individuals who previously had a life-threatening response to this form of therapy. In addition to this absolute prohibition, several relative contraindications exist which permit immunotherapy only in the presence of a favorable risk-benefit profile. Immunotherapy is typically not indicated in patients with an FEV_1 < 70% of predicted values; unstable asthma manifested by nocturnal asthma; eczema; and in patients using beta-blocker ophthalamic solutions such as timoptic. In addition, this therapeutic format is typically not recommended for use in the very young, elderly, or those who are sensitive to only a single seasonal allergen.[82]

Anti-IgE Therapy—Omalizumab

Since AR is an IgE-mediated disease, it is logical that anti-IgE therapy would be efficacious in treating this common problem. Indeed, clinical trials have demonstrated the efficacy and safety of the humanized monoclonal antibody omalizumab (Xolair) in pediatric patients

with allergic rhinitis.[83,84] Unfortunately, the drug is extremely expensive and is given subcutaneously every 2 to 4 weeks. Thus, it is neither cost effective nor convenient for most patients with allergic rhinitis. On the other hand, omalizumab is cost effective in patients with severe persistent asthma who have frequent emergency department visits and hospitalizations despite optimal conventional management.[85] Thus, these patients who also have allergic rhinitis will have benefit for their nasal allergies as well as their severe asthma.

SUMMARY

Allergic rhinitis remains one of the most often treated problems in medicine. This is reflected by the plethora of available prescription and non-prescription medications used to treat this condition. The first generation antihistamines cause significant sedation resulting in increased somnolence and degraded cognitive ability. Second-generation antihistamines and intranasal corticosteroids have proven safe and effective in treating pediatric patients. Whether used in combination or individually, these medications are considered first line therapy in children.

Several studies have documented acceptable safety and efficacy profiles of the second-generation antihistamines used in children. Within this class, cetirizine is the only medication that has documented increased sedation, however, due to its proven efficacy and safety, cetirizine, along with loratadine and fexofenadine are considered excellent choices in treatment of allergic rhinitis in pediatric patients. Neither loratadine nor fexofenadine show much sedation, and both have been proven very safe for use in pediatric populations. Antihistamines frequently require concomitant oral decongestant therapy for optimal response.

Intranasal corticosteroids have been studied extensively in children, particularly in light of concerns of reduced bone growth as well as HPA suppression. While long-term use at established higher doses showed some systemic adverse effects, the FDA recommends administering intranasal corticosteroids to children at the lowest possible dose. Aside from a few minor side effects such as a bleeding nose, blood tinged mucus, and local irritation, intranasal corticosteroids are generally well tolerated by pediatric patients and most effective in relieving associated symptoms of allergic rhinitis. These agents have the highest efficacy in moderate to severe persistent allergic rhinitis.

It is important to consider treating pediatric patients on an individual basis according to symptom severity. Alternative treatment options including specific immunotherapy, intranasal azelastine, leukotriene receptor antagonists, intranasal cromolyn, and ipratropium bromide nasal spray are all viable options and have proven safe in treating allergic rhinitis in children. However, these alternatives are not without limitations, and their use should be considered carefully prior to administration to children. Anti-IgE therapy is very expensive, but for patients with severe persistent asthma, including frequent emergency department visits and hospitalizations, this novel therapy will be of benefit for patients with concurrent rhinitis.

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