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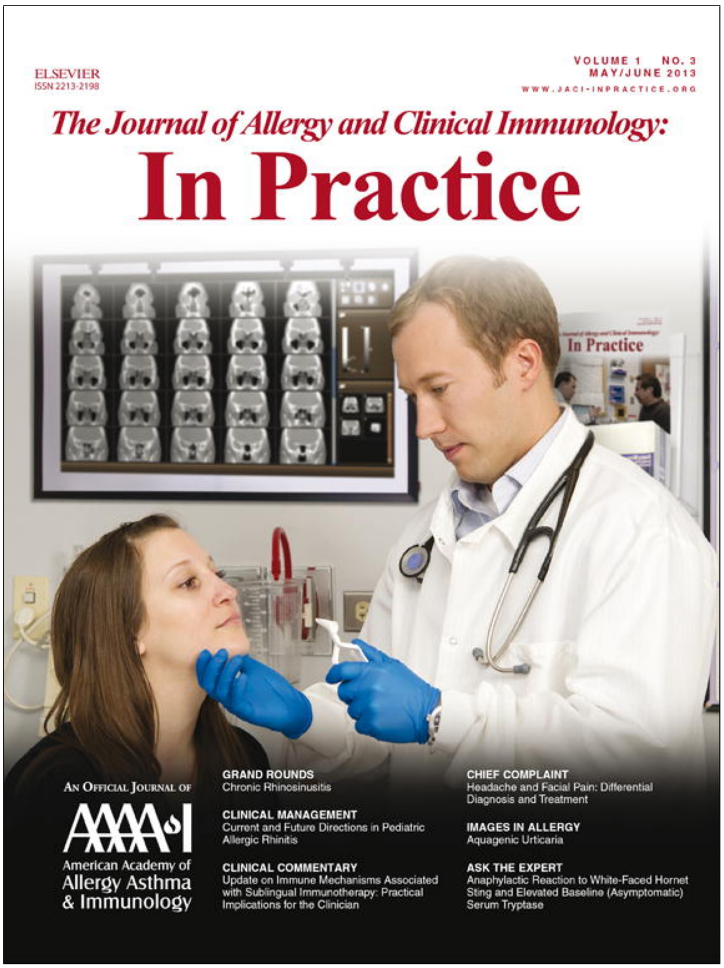

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Clinical Management Review

Current and Future Directions in Pediatric Allergic Rhinitis

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members Deborah Gentile, MD, Ashton Bartholow, BS, Erkka Valovirta, MD, PhD, Glenis Scadding, MD, and David Skoner, MD

Activity Objectives:

1. Recognize that allergic rhinitis (AR) symptoms affect sleep in children with AR.
2. Gain familiarity with guideline-directed therapy of AR.
3. Distinguish the differential effects of intranasal corticosteroids on growth in children with AR.
4. Appreciate that labeling of generic medications may not match that of branded products.
5. Gain familiarity with the concept of bystander immune suppression.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: D. Gentile has received research support from Merck, Teva, GlaxoSmithKline, and Sunovian and has received lecture fees from Merck and Teva. G. Scadding is on the board for GlaxoSmithKline, Uriach, Meda, Stallergenes, and Alk; has received consultancy fees from Merck, Oxford Therapeutics, Ono, and Britannia; and has received lecture fees from GlaxoSmithKline, Meda, and Stallergenes. D. Skoner has received research support from Greer Laboratories, Novartis, Merck, GlaxoSmithKline, and Teva; has received consulting fees from Merck, Sunovion, and Istavision; and has received lecture fees from GlaxoSmithKline, Merck, Novartis, Teva, and Sunovion. A. Bartholow and E. Valovirta declared that they have no relevant conflicts of interest.

BACKGROUND: Allergic rhinitis (AR) is a common pediatric problem that significantly affects sleep, learning, performance, and quality of life. In addition, it is associated with significant comorbidities and complications.

OBJECTIVE: The aim was to provide an update on the epidemiology, comorbidities, pathophysiology, current treatment, and future direction of pediatric AR.

METHODS: Literature reviews in each of these areas were conducted, and the results were incorporated.

RESULTS: The prevalence of AR is increasing in the pediatric population and is associated with significant morbidity, comorbidities, and complications. The mainstay of current treatment strategies includes allergen avoidance, pharmacotherapy, and allergen specific immunotherapy.

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Abbreviations used
ADHD- Attention deficit hyperactivity disorder
AH- Antihistamines
AR- Allergic rhinitis
CRD- Component-resolved diagnostics
DC- Dendritic cell
FDA- Food and Drug Administration
FEIA- Fluorescent enzyme immunoassay
HCP- Health care provider
ICS- Inhaled corticosteroid
INCS- Intranasal corticosteroids
OCS- Oral corticosteroids
OME- Otitis media with effusion
OR- Odds ratio
OSA- Obstructive sleep apnea
OTC- Over-the-counter
PAA- Pediatric Allergies in America
QoL- Quality of life
SCIT- Subcutaneous immunotherapy
SIT- Specific immunotherapy
SLIT- Sublingual immunotherapy
Treg- Regulatory T [cell]

CONCLUSIONS: In the future, diagnosis will be improved by microarrayed recombinant allergen testing and therapy will be expanded to include emerging treatments such as sublingual immunotherapy and combination products. **© 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:214-26)**

Key words: *Allergic rhinitis; Pediatrics; Specific immunotherapy; Intranasal corticosteroids; Antihistamines; Leukotriene modifiers*

Allergic rhinitis (AR) is a chronic inflammatory disease of the upper airways, and its symptoms include nasal congestion, rhinorrhea, sneezing, and itching. Symptoms can also involve the eyes, ears, and throat, including postnasal drainage. The prevalence of AR is increasing, and it is currently estimated to affect approximately 60 million people in the United States. The prevalence of AR in adults is estimated at 10% to 30%, and the prevalence in children is approximately 40%. In addition, 80% of patients develop symptoms of AR before 20 years of age, with 40% of those becoming symptomatic by 6 years of age.[1,2]

AR was previously classified as seasonal and/or perennial. However, a new classification system (Figure 1) was designed to better classify the disorder and includes the categories of intermittent and persistent AR.[3] Patients experiencing symptoms fewer than 4 days per week or for fewer than 4 weeks at a time are classified as having intermittent AR. Patients experiencing symptoms more than 4 days per week or more than 4 weeks at a time are classified as having persistent rhinitis. The severity of rhinitis is classified as mild or moderate to severe. This classification is based on whether the AR symptoms result in any impairment of daily activities, sleep disturbances, and the degree of troublesome of symptoms. Symptoms of AR are triggered by exposure to allergens, including pollens, molds, pets, dust mites, cockroaches, and rodents.

AR is associated with significant morbidity and also affects patients' quality of life (QoL), emotional well-being, productivity, and cognitive functioning.[4-6] Many of these issues are related to poor sleep quality and sleep disturbances caused by AR. AR also places a large economic burden on the US health care system and includes both direct and indirect costs.[7-9] Indeed, one recent estimate places the total annual costs of AR at approximately $11.2 billion, which is double the estimated cost in 2000.

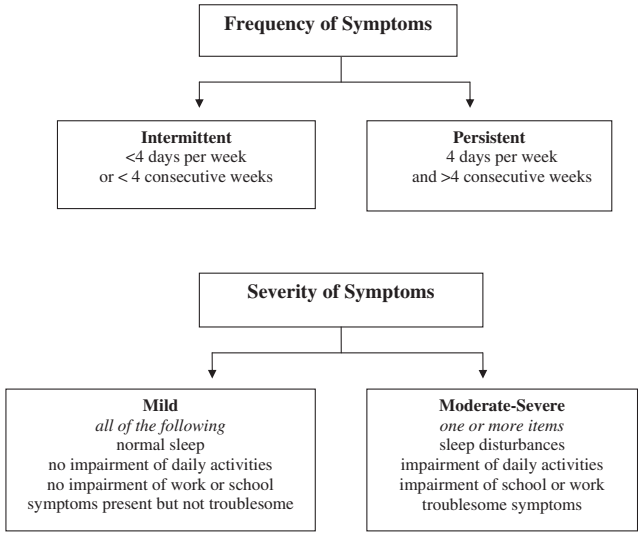

FIGURE 1. Classification of AR.

Treatment of AR begins with environmental controls to reduce allergen exposure. Pharmacologic intervention is often required to control moderate-to-severe symptoms, and the mainstay of treatment consists of intranasal corticosteroids (INCSs), oral and intranasal antihistamines (AHs), oral and topical decongestants, and leukotriene receptor antagonists.[7,10,11] Concerns over potential systemic side effects of INCSs in pediatric patients include growth effects and cortisol suppression.[12,13] Specific immunotherapy (SIT) is an effective treatment for AR, but its use in pediatric patients is limited by inconvenience and safety concerns. The development of sublingual immunotherapy (SLIT) for the treatment of AR may offer a safer and more convenient route of treatment for pediatric patients and has the potential to offer disease-modifying and preventative activity if introduced at an early age.[14-16]

EPIDEMIOLOGY

Most of the available data in the literature has focused on adults with AR, and until very recently little has been available about prevalence, burden, QoL effects, and comorbidities in children. Recently, the Pediatric Allergies in America (PAA) national survey was conducted to gain insights into pediatric AR. PAA survey was a comprehensive national telephone screening of 35,757 US households to identify subjects between 4 and 17 years of age with AR.[5] The PAA survey identified 500 children with AR diagnosed by a health care provider (HCP) and who had symptoms of AR and had taken medication for AR in the past year. A comparison of 504 children without AR was also identified. The PAA survey found 13% of children had a HCP-confirmed diagnosis of AR and were symptomatic within the past year. This estimate falls at the lower end of previous estimates of 10% to 40% prevalence of AR in US children. In the PAA survey, 61% of children were diagnosed with AR by 6 years of age, and most of these children were diagnosed by pediatricians

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who do not routinely use skin or blood tests to confirm a diagnosis of AR. Underuse of confirmatory testing for AR in the PAA survey likely resulted in an overall underreporting of AR prevalence in the survey population.

In the PAA survey, 62% reported that AR was seasonal only and that 37% reported that it was perennial. Among those reporting seasonal AR, 76% and 34% reported worse symptoms during the spring and fall, respectively (multiple answers were permitted). The most common triggers of nasal symptoms included pollen, dust, and pet dander. In addition, nonallergic triggers such as weather, fumes and odors, and exercise were commonly reported. In the PAA survey, 88% reported that AR symptoms were moderately or extremely bothersome, and 80% reported use of AR medication within the past year. Most identified nasal congestion as the most bothersome symptom, followed by headache, runny nose, and postnasal drip. The burden of AR affected the overall health perception of participants with only 43% of participants with AR reporting a rating of excellent health compared with 59% of those without AR ($P < .001$). Finally, physical, mental, emotional, and social problems were more frequently reported in children with AR.[5]

As with other atopic diseases, including asthma, eczema, and food allergies, AR prevalence in children has increased in recent years. von Mutius et al[17] reported a significant increase in seasonal AR in German school children from 2.3% in 1991 to 5.1% in 1996. This rate of increase is comparable with that observed in adults over the same time period. Risk factors for pediatric AR include atopy, high socioeconomic status, and positive family history. The Tucson Children's Study reported a significant association between physician-diagnosed maternal AR and diagnosis of AR at 6 years of age (odds ratio [OR], 2.2; 95% CI, 1.35-3.54).[18] The development and expression of allergic diseases is hypothesized to involve interplay between genetic predisposition and prenatal as well as early-life environmental exposures at a critical time when the immune system is still undergoing development. Numerous studies have shown positive associations between early-life exposures to infections, indoor and outdoor air pollution, and diet on the development of pediatric AR. Many of these studies reported associations between low levels of exposure to microbial components, including endotoxin, and T_H2 allergic diseases.[19] More recent studies in this area have focused on the degree of microbial diversity and the development of allergic disease.[20] Other studies have shown positive associations among early-life exposure to allergens, respiratory viruses, environmental tobacco smoke, and components of outdoor air pollution and the development of T_H2 allergic skewing, elevated IgE levels, and increased prevalence of allergic diseases.[21-23] More recent studies have shown associations between diet and nutrition, including early childhood, prenatal, and maternal, on allergic predisposition.[24] Specifically, diets high in fat, low in fresh fruits and vegetables, and deficiencies of vitamins A and D have been shown to correlate with asthma and atopy.

COMORBIDITIES AND COMPLICATIONS

AR is often accompanied by certain comorbidities and complications. AR often precedes the development of asthma in children, and this sequence is commonly called the atopic march. Indeed, previous studies have shown a strong epidemiologic link between AR and asthma with AR occurring in most patients with asthma, particularly those diagnosed during childhood. For example, Wright et al[18] showed that the presence of physician-diagnosed AR during infancy was associated with a twofold risk of developing asthma by 11 years of age. In addition, they reported that approximately one-third of children with AR develop asthma, whereas only 5% of children with asthma do not have AR. Similarly, the PAA survey found that among children with AR, 39% were diagnosed with asthma. Numerous studies have shown that in children with AR the ratio of concomitant asthma in boys to girls is roughly 2:1.[25,26] The PAA survey reported a concomitant diagnosis of asthma in 45% and 33% of male and female children with AR, respectively.[5] Numerous studies have shown that treatment of AR will improve asthma outcomes. Corren et al[27] found that treatment of AR with INCSs with or without AHs significantly decreased the risk of emergency department visits and hospitalizations for asthma. Other studies have shown that omalizumab and leukotriene modifiers have efficacy in both AR and asthma.[28,29] Recent studies have reported that the use of SIT in children with AR can decrease the risk of subsequent development of asthma. Novembre et al[30] showed that children on SLIT to grass pollen were 3.8 times less likely to develop asthma after 3 years than the control subjects. Similarly, Niggemann et al[31] showed that children treated for 3 years with subcutaneous immunotherapy (SCIT) to grass and/or birch pollen had significantly less asthma after 5 years (OR, 2.68; 95% CI, 1.3-5.7).

Otitis media with effusion (OME) is a significant medical problem in children with at least 80% of all children having one episode and 40% having three or more episodes by 3 years of age.[32] Tomonaga et al[33] reported that in children with AR, 21% had OME, whereas only 6% of the control group had OME. In addition, in children with OME, 50% had AR, whereas only 17% of the control group had AR.[33] Caffarelli et al[34] showed a significant association between AR symptoms and OME in pediatric patients and concluded that AR may play a role in the pathogenesis of OME. Similarly, Chantzi et al[35] found that IgE sensitization and nasal obstruction were independent risk factors in children with OME. With the use of an experimental model, Skoner et al[36,37] have shown that provocative nasal challenge with allergens and allergic mediators results in Eustachian tube dysfunction. The PAA survey indicated that children with AR were five times more likely to experience pressure-related ear pain during their worst month for allergy symptoms and two times as likely to undergo surgery (typanostomy tube placement, adenoidectomy, and/or tonsillectomy) than controls without AR.[5] Nguyen et al[38] provided confirmatory evidence that allergic inflammation can be seen in OME by the presence of T_H2 skewing in middle ear effusions obtained from children with AR. Collectively, these data support a role for AR in the development of OME and provide a rationale for the evaluation of AR as a factor in the development of OME in children with AR symptoms.

Sinusitis is another potential complication of AR. The relationship may involve rhinitis leading to obstruction of the osteomeatal complex or individual manifestations of shared inflammation. In a US population of children with AR, 53% had abnormal sinus imaging.[39] Huang et al[40] found that prevalence of sinusitis was higher in children with perennial AR than among children with seasonal AR and that mold allergy was an important risk factor for the development of sinusitis. The Allergies in America Survey found that 43% of children with AR had sinus

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problems and that significantly more children with AR than children without AR had headaches, facial pain, and pressure.[5] In addition, orbital complications, including preseptal cellulitis, periostitis, and subperiosteal abscess, have been shown to occur in children with AR. Holzmann et al[41] evaluated 102 children who presented with orbital swelling and reported underlying AR in 64.3% with preseptal cellulitis, 25% with periostitis, and 76.5% with subperiostal abscess. AR should be considered a potential factor in the development of sinusitis and its complications in children with AR symptoms.

Nasal congestion and obstruction as a result of AR might contribute to mouth breathing that has been linked to an increased incidence of orthodontic malocclusions and habitual snoring.[42] Chng et al[42] identified AR as the strongest risk factor for habitual snoring, and the PAA survey reported that twice as many children with AR snore every night or most nights compared with children without AR. In children with snoring due to AR, obstructive sleep apnea (OSA) may be present and may lead to additional medical problems.[43] Potential neurobehavioral consequences of OSA include excessive daytime sleepiness, impaired vigilance, mood disturbances, and cognitive dysfunctions. Other potential medical complications of OSA include hypertension, diabetes mellitus, hepatic dysfunction, and increased perioperative risks. McColley et al[44] showed that more than one-third of children referred for polysomnography had AR. It is acknowledged that not all mouth breathing and snoring in children is caused by AR, but it should be included in the differential diagnosis, and an evaluation for AR should be performed if clinically warranted.

Impaired sleep and subsequent daytime drowsiness and fatigue due to nasal congestion and obstruction are a main complication of AR. Among adolescents with AR, Juniper et al[45] found that 78% lacked a good night's sleep, 75% were unable to get to sleep, and 64% wake up in the middle of the night. In the PAA survey, 40% of children with AR reported that AR symptoms interfered with sleep.[5] Poor sleep and symptoms of AR such as sneezing, nasal rubbing, and rhinorrhea can also negatively affect school performance. Although the rate of absenteeism is roughly equal among children with and without AR, presenteeism (or diminished performance while at school) is a significant burden of AR. In the PAA survey, 40% of parents reported that their children's AR interfered with their school performance.[5] The impairing effect of AR on learning was confirmed in a trial conducted by Vuurman et al.[46] In the PAA survey, 40% of children with AR had diminished school performance.[5] The PAA survey generated evidence that children with AR may experience substantially more mental, emotional, and social problems than children without AR. For example, children with AR experience significantly fewer positive feelings such as energetic, calmness, peacefulness, and happiness. Children with AR also reported that their health interfered with normal childhood activities.

Another complication in pediatric AR is irritability, behavior problems, and mood disorders. Borres et al[47] surveyed adolescent patients with AR and found that most were embarrassed by their symptoms of AR. An overlap also exists between AR and attention deficit/hyperactivity disorder (ADHD). Brawley et al[48] found that 75% of children with ADHD report symptoms of AR and that 69% had positive allergy skin tests. These results suggest that nasal obstruction, sleep disturbance, and other symptoms of AR may contribute to symptoms seen in ADHD and, depending on the clinical history, that evaluation and treatment of AR may be beneficial in children diagnosed with ADHD with clinical symptoms of AR. However, it should be noted that to date no association exists between positive allergy skin tests and ADHD.

PATHOPHYSIOLOGY

AR is a chronic respiratory illness defined as inflammation of the nasal epithelium and is characterized by anterior and posterior rhinorrhea, sneezing, and nasal blockage, caused by exposure to an allergen to which the person is sensitized. AR can also manifest with ocular redness and lacrimation, and, additionally, itching of the ears and palate. Other comorbidities of AR were described earlier in this review.

AR is the most common form of noninfectious rhinitis and is associated with an IgE-mediated immune response against allergens.[49] Typical allergens include house dust mites, grass pollen, tree pollen, weed pollens, cat, dog, and molds.[50] In the absence of demonstrable systemic sensitization, AR may be due to local IgE production in the nose.[51]

IgE antibodies are preformed from previous exposure to allergen, sit on the surface of mast cells, and are allergen specific. On re-exposure to allergen, IgE is cross-linked, and this is the signal that leads to mast cell degranulation. This results in the release of a variety of inflammatory mediators, including histamine. The role of histamine in allergic diseases is well defined.[52] Histamine mediates its effects via an established set of histamine receptors (H1, H2, H3, and H4 receptors). The biological effects of histamine in the allergic reaction are related to activity of H1 receptors, including smooth muscle contraction, bronchospasm, increased endothelial permeability, and stimulation of sensory nerves and cough receptors.[53] In the nose, the result is sneezing, itching, and rhinorrhea, stemming from the IgE-mediated mast cell response. For approximately 65% of subjects, this is represented by an infiltration of the nasal mucosa by eosinophils, basophils, and T cells that express factors to facilitate IgE synthesis (IL-4) and to promote eosinophil growth (IL-5). Nasal congestion is largely unaffected by AHs, suggesting that other mediators such as prostaglandin D_2, leukotrienes, and the inflammatory late-phase response with cellular influx to the mucosa, are likely involved.

Recent findings have indicated that other mechanisms may be involved in the pathophysiology of AR, including the identification of H4 receptors that are not inhibited by H1-antagonists and the insufficient suppression of allergic responses by regulatory T (Treg) cells.[54] Treg cells are a type of T lymphocyte, along with T_H2 cells. Patients with AR often have large amounts of T_H2 cells that are found in the nasal mucosa, which contribute to an eosinophilic IgE-mediated inflammatory response. Allergens activate the release of thymic stromal lymphopoietin (TSLP) or can be presented on the surface of cells such as dendritic cells (DCs) and macrophages. TSLP is located predominately in the respiratory tract, gut, and skin, and it promotes hypersensitivity diseases, which include asthma and AR. TSLP also initiates T_H2-associated responses by promoting the maturation of DCs into the type 2 subtype, which in turn attracts T_H2 cells. These T_H2 cells release cytokines such as IL-4, which increase the amount of IgE-producing plasma cells, IL-5, which recruits eosinophils, and IL-13, which can attract DCs. Treg cells, when operating efficiently, can suppress inflammation and cause the apoptosis of these T_H2 cells. They also can communicate with antigen presenting cells (such as DCs) to

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inhibit recruitment and activation of inflammatory T cells.[55] The recent findings that promote AR pathogenesis also include the upregulation of T_H2 cytokines through epithelial-derived pathways.[54]

In addition to environmental factors, there is also a genetic component to AR, as reported previously in monozygotic and dizygotic twin studies, although the individual chromosomes and genes involved have not been definitively pinpointed.[54]

CURRENT TREATMENT STRATEGIES

Current AR treatment is summarized in Table I and includes avoidance of relevant allergens and triggers and use of SIT. An effective partnership between the patient, caregivers, and medical team is also essential to ensuring effective treatment of AR. A summary of each of these strategies follows.

Allergen avoidance

The lack of hay fever outside the pollen season indicates that complete allergen avoidance can be effective. Unfortunately, complete avoidance is rarely possible, especially for outdoor allergens. A few, small, poorly designed studies have reported on house dust mite avoidance in children with AR, and most show little or no benefit of avoidance measures.[56] Nocturnal temperature-controlled laminar airflow is a new device that distributes a filtered cooled laminar airflow, descending from an overhead position, which displaces aeroallergens from the breathing zone. This device has been shown to improve poorly controlled allergic asthma in children,[57] and it also shows some benefit in rhinitis (Boyle, personal communication). Evidence on pet allergen avoidance is lacking. Avoidance of other rhinitis triggers, such as cigarette smoke, outdoor pollutants, fumes, and irritants, is sensible. Administering saline by spray, droplets, or irrigation has been shown to enhance the control of AR symptoms in subjects on INCSs.[58]

Pharmacotherapy

Undertreatment of AR is common and is attributed to underdiagnosis as well as prejudice against some treatments, such as INCSs, which are underused despite their good safety record.[51] Guideline-directed therapy is summarized in Figure 2,[51,59] may involve more than one therapeutic agent, and provides better symptom control and improved QoL than nondirected treatment.[60,61]

Oral or intranasal antihistamines. Second-generation AHs are effective for AR when administered by oral and intranasal routes and are generally well tolerated,[62-66] although they may cause sedation.[67] Orally administered second-generation AHs include cetirizine, fexofenadine, loratadine, desloratadine, and levocetirizine, and all are available as over-the-counter (OTC) products except desloratadine. Intranasally administered second-generation AHs include azelastine and olopatadine and are available by prescription only (Table II).

First-generation AHs should no longer be used, given their unfavorable therapeutic index.[68]

Intranasal corticosteroids. INCSs are the most effective agents in adults as evidenced by meta-analyses,[69-71] and they are superior, or equal, to the combination of an AH and an anti-leukotriene agent.[72] INCSs treat the inflammatory component of

TABLE I. Current treatment strategies for pediatric AR

Avoidance of relevant allergens and triggers
Pharmacotherapy
Oral or AHs
Intranasal corticosteroids (INCSs)
Systemic corticosteroids (short-term acute treatment)
Leukotriene receptor antagonists
Intranasal anticholinergics
Intranasal cromolyn
Anti-IgE
Specific immunotherapy (SIT)
Subcutaneous immunotherapy (SCIT)
Sublingual immunotherapy (SLIT)
Surgery (rarely needed)
Partnership
Patient/caregivers
Medical providers

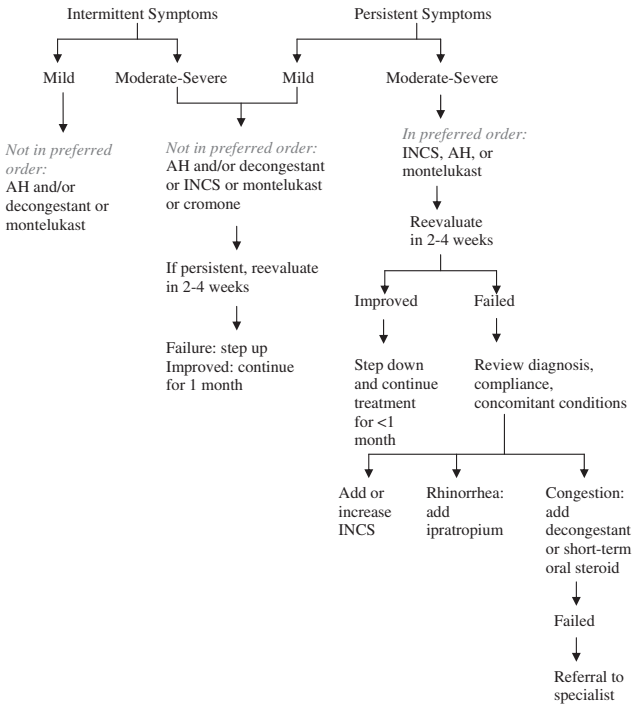

FIGURE 2. Algorithm for the treatment of AR. Consider allergen and irritant avoidance and SIT if appropriate.

AR, and results from a large number of well-designed studies support their use in children and adolescents[73-83] (Tables III and IV). A recent Cochrane review[84] reported limited evidence to support INCS effectiveness but had unfortunately excluded all the recent high-quality randomized controlled clinical trials because their design incorporated the use of rescue medications. Several studies have shown that the effect of INCSs may commence within a day of starting therapy.[85] INCSs may also improve coexisting conjunctivitis,[86-88] asthma and bronchial hyperreactivity.[27,89-92] In general, INCSs are well tolerated. Newer, once-daily products, including fluticasone propionate,[93] mometasone,[94] and fluticasone furoate, are preferred because

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TABLE II. Antihistamines used in pediatric AR

	Formulation	OTC/prescription	Ages/doses
Loratadine	Oral	OTC	2-6 y: 5 mg QD >6 y: 10 mg QD
Desloratadine	Oral	Prescription	6-11 mo: 1 mg QD 1-5 y: 1.25 mg QD 6-11 y: 2.5 mg QD >12 y: 5 mg QD
Cetirizine	Oral	OTC	6 mo-12 mo: 2.5 mg QD 12 mo-2 y: 2.5 mg QD/BID or 5 mg QD 2-5 y: 2.5-5 mg QD >6 y: 5-10 mg QD
Levocetirizine	Oral	Prescription	6 mo-5 y: 1.25 mg QPM 6-11 y: 2.5 mg QPM >12 y: 2.5-5 mg QPM
Fexofenadine	Oral	OTC	2-11 y: 30 mg BID >12 y: 60 mg BID or 180 mg QD
Olopatadine (665 μg/spray)	Inhaled	Prescription	6-11 y: 1 spray each nostril BID >12 y: 2 sprays each nostril BID
Azelastine (137 μg/spray)	Inhaled	Prescription	5-11 y: 1 spray each nostril BID >12 y: 1-2 sprays each nostril BID
Azelastine/fluticasone (137 μg/50 μg/spray)	Inhaled	Prescription	>12 y: 1 spray each nostril BID

BID, Twice daily; *QD*, once daily.

TABLE III. Nasal corticosteroids used in pediatric AR

	Ages/doses
Fluticasone propionate (50 μg/spray)	>4 y: 1-2 sprays each nostril QD
Fluticasone furoate (27.5 μg/spray)	>2 y: 1-2 sprays each nostril QD
Mometasone (50 μg/spray)	2-12 y: 1 spray each nostril QD >12 y: 2 sprays each nostril QD
Beclomethasone (Qnasal) (80 μg/spray)	>12 y: 2 sprays each nostril QD
Beclomethasone (Beconase) (42 μg/spray)	>6 y: 1-2 spray each nostril BID (max 4 sprays each nostril BID)
Ciclesonide (Zetonna) (37 μg/spray)	>12 y: 1 spray each nostril QD
Ciclesonide (Omnaris) (50 μg/spray)	>6 y: 2 sprays each nostril QD (seasonal allergic rhinitis) >12 y: 2 sprays each nostril QD (perennial allergic rhinitis)
Budesonide (32 μg/spray)	6-12 y: 1-2 spray each nostril QD >12 y: 1-4 sprays each nostril QD
Flunisolide (25/29 μg/spray)	6-14 y: 2 spray each nostril BID >14 y: 2 spray each nostril BID/TID (max 8 sprays each nostril QD)
Azelastine/fluticasone (137 μg/50 μg/spray)	>12 y: 1 spray each nostril BID

BID, Twice daily; *QD*, once daily; *TID*, three times daily.

TABLE IV. Future directions in pediatric AR

Use of microarrayed recombinant allergens for diagnosis
Conduct of more clinical trials in young children
Impact of health care reform
New therapies
Dry spray INCSs (beclomethasone and ciclesonide)
Combination products (intranasal AHs/INCSs)
Sublingual SLIT
Generic and OTC switches
Role of allergy/immunology specialist

they have been shown to not reduce growth velocity during 1 year of therapy compared with older products such as beclomethasone and budesonide.[95]

Systemic corticosteroids. Systemic corticosteroids are rarely used in pediatric patients with AR because of the availability of effective alternatives with better safety profiles. Some studies on systemic corticosteroid therapy were performed in adults and showed that a 30-mg dose was effective.[96] Depot corticosteroid injections are not recommended because they are associated with local atrophy of the skin and muscles, reduced bone mineralization, and impaired growth.[97] In the rare event that systemic corticosteroid treatment is necessary in children with AR, a short course with 10 to 15 mg of oral prednisolone a day for 3 to 7 days should be sufficient, and referral to a specialist should be strongly considered.

Leukotriene receptor antagonists. Montelukast was effective in both seasonal and perennial AR in two well-designed, but small, pediatric studies,[98,99] as well as in two meta-analyses dominated by adult studies.[71,100]

Intranasal anticholinergics. Anticholinergics are effective in controlling watery nasal discharge but not for itching, sneezing, or congestion.[49] Their use in children has not been well evaluated.

Intranasal decongestants. Topical decongestants can be used briefly for severe nasal obstruction; however, prolonged use may lead to rhinitis medicamentosa that is characterized by rebound swelling of the nasal mucosa.[101]

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Intranasal cromolyn. This is a weakly effective treatment for AR.[49] It is safe, but its main disadvantage is that it needs to be used three to four times a day.

Anti-IgE. Omalizumab is approved by the US Food and Drug Administration (FDA) for treatment in patients 12 years of age and older with severe allergic asthma and has also been shown to improve AR in these patients.[102] However, it is not currently FDA approved for the treatment of AR, and, if approved, its use would be costly and most likely not be covered by insurances for the treatment of AR without concomitant severe allergic asthma.

Specific immunotherapy

SIT is the specific treatment of IgE-mediated allergic diseases by repeated application of relevant allergen by subcutaneous or sublingual routes.

Subcutaneous immunotherapy. SCIT involves repeated injections with allergen extracts and is reserved for patients with severe AR with insufficient symptom control or side effects with pharmacotherapy. Therapy should be initiated by a physician trained in the diagnosis, treatment, and follow-up of children with AR.[103] There should be a clear history of allergen-driven AR with evidence of relevant specific IgE.[104] A standardized registered or approved allergen extract or preparation should be used. Significant concurrent disease, fixed airway obstruction, and severe asthma are contraindications.[104] Factors associated with severe adverse effects are unstable asthma, elevated allergen exposure during therapy, concomitant diseases such as severe infections, and inexperienced health care staff. Some evidence suggests that AH premedication may reduce the rate of adverse effects. Pretreatment with anti-IgE has been used successfully to minimize adverse reactions during dose escalation but is costly and is unlikely to be covered by insurance.[105]

A Cochrane review reported the efficacy of SCIT[106]; however, it did not include any studies conducted exclusively in children. More recent data indicate the effectiveness of SCIT in children with allergies to pollens and house dust mites. SCIT is generally well tolerated in children, but trained staff must administer SCIT, and full resuscitation facilities must be immediately available because it has been associated with systemic reactions.[104] SCIT may alter the natural history of allergic disease in childhood.[107] A cohort of 205 children aged 6 to 14 years with pollen AR and without persistent asthma were randomly assigned to receive SCIT for 3 years or to be in an open control group. The actively treated group had significantly fewer AR and asthma symptoms after 3 years (OR, 2.52). Ten years after random assignment, 149 subjects aged 16 to 25 years were re-evaluated. At this follow-up, significant improvements in AR persisted, and the likelihood of developing asthma was significantly reduced in those treated with SCIT (OR, 2.5; 95% CI, 1.1-5.9). When adjusted for bronchial hyperresponsiveness and asthma status at baseline and including all observations over the entire 10-year follow-up (children with or without asthma at baseline, n = 189; 511 observations), the OR for absence of asthma was 4.6 (95% CI, 1.5-13.7) in the group treated with SCIT.[107] In a cohort study of US children with AR, those in the SCIT group incurred 33% ($1625) lower health care costs.[108]

Sublingual immunotherapy. SLIT is also effective in adults and children.[109,110] Its main advantage is that only the initial dose requires medical supervision, and subsequent daily doses are taken at home. A recent systematic review in 2011 reported effectiveness of SLIT for AR due to pollen and house dust mites.[111] Both continuous and seasonal dosing protocols show efficacy. Two commercial grass extracts in dissolvable tablet form have received European market authorization for patients at least 5 years of age. Both of these products are nearing submission for consideration for approval by the US FDA.

In controlled clinical trials, SLIT appears to be safer than SCIT, and its side effects are usually restricted to the upper airways and gastrointestinal tract. However, currently not enough data or experience with SLIT is available to be certain that it is entirely safe. This is particularly true in subjects with a history of anaphylaxis and/or moderate-to-severe persistent asthma that are routinely excluded from participation in phase III clinical trials of SLIT. Rare anaphylactic episodes occur with SLIT, but no deaths have been reported.[109] Currently, not enough data and experience with SLIT are available to confirm safety. Recent evidence suggests persistence of clinical and immunologic benefit after 3 years of continuous use,[109] which is similar to that observed with SCIT. In addition, some local oral changes unique to SLIT have been reported.[112] Placebo-controlled trials of long-term effects of SLIT on AR and asthma are currently being conducted, and there is cautious optimism that SLIT will be an effective therapy for AR and possibly prevent the development of asthma.[113]

Surgery

Surgery is rarely needed in children with AR and/or sinusitis with the exception of children with significant underlying problems such as cystic fibrosis or immune deficiencies.[114]

Partnership

As with any long-term treatment, a partnership among the patient, caregivers, and medical providers will help to maximize the response to AR treatment. Reassurance about the need for treatment and its safety are essential. The provider should review the specifics about how, when, and why to take prescribed medications for AR. In particular, for children with persistent AR, the importance of taking regular therapy, even on symptom-free days, should be emphasized.[49,59] This is similar to the approach used for the treatment of persistent asthma, and daily treatment will minimize persistent inflammation in AR and potentially reduce the deleterious effects of upper respiratory tract infections.[115]

FUTURE DIRECTIONS

Diagnosis

Diagnostic methods are of concern, with allergists predominantly conducting skin testing and general practitioners and pediatricians generally testing for allergen-specific IgE in the blood. The blood test was formerly called RAST, but over the past 20 years, many technological advances have made that original test obsolete. Newer, more advanced, accurate, and sensitive tests have replaced the RAST test. This includes the ImmunoCAP Specific IgE blood test, which provides a significant improvement over the original RAST test. It is the most sensitive testing method available today and is a highly accepted method used throughout the world, including the United States. The ImmunoCAP has also been accepted by the FDA as a quantitative measure of allergen-specific IgE, showing accuracy and reliability across the entire clinical range. The test is endorsed by the National Institutes of

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Health and other health organizations such as the America Academy of Allergy, Asthma and Immunology and the America College of Allergy, Asthma and Immunology. However, many general practitioners and pediatricians are unable to adequately interpret the results of such blood tests; therefore, they fail to diagnose allergy and use the results to provide salient, accurate advice on environmental allergy control measures.

The availability of microarrayed recombinant allergens for diagnostic testing in the future is likely to change the diagnostic landscape for AR tremendously. The primary advantage of adopting a multiplexed platform is that specific IgE to potentially thousands of allergens can be assayed in parallel with just a small amount of serum. Strengths and weaknesses of molecularly defined allergy testing and the microarray platform were reviewed,[116] but the potential for greater resolution between clinical reactivity and asymptomatic sensitization with this platform seems promising.

The specificity of the adaptive immune response, including IgE, lies at the submolecular level. Therefore, there are significant limitations to using an IgE response to an antigenically complex whole allergen extract as a disease biomarker, and these limitations have been reviewed elsewhere.[117] This has sparked the development of molecular or component-resolved diagnostics (CRD), also known as molecular allergy diagnosis, in which individual allergen molecules are used to characterize a patient's IgE specificity. CRD is available in Europe as either panels of selected (recombinant and purified native) allergens that can be used in a fluorescent enzyme immunoassay (FEIA; ImmunoCap) or a microarray-based assay (Immuno Solid phase Allergen Chip) of more than 100 molecules.[118] In the United States, CRD is available only as a research tool. The primary advantage of using a microarray for CRD is that specific IgE to large numbers of allergens could be assayed with only a small amount of serum.

Although much work has already been done with food allergens,[119] current aeroallergens that are relevant to AR and being developed for CRD include tree and grass pollen (recombinant Phl p 1, 2, 5, and 6 and Bet v 1 and 2, respectively), and ragweed and mugwort pollen (natural and recombinant Amb a 1, 5, 6, 8, 9 and Art v 1, 3, 4, 5, 6, respectively).

In 2003, Jahn-Schmid et al[120] compared a limited recombinant allergen array with conventional testing with the use of 50 subjects with presumed birch or timothy grass allergy and a group of controls. Proteins, including Phl p 1, 2, 5, and 6 and Bet v 1 and 2, were printed, and specific IgE was detected with a fluorophore-labeled secondary antibody. Similar dynamic ranges, sensitivities, and specificities were detected compared with conventional CAP-FEIA. Concordance rates between the microarray and the CAP-FEIA techniques were 100% and 94%, respectively. All negative controls were negative in both assays. Correlations between the assays exceeded 0.9. However, lack of provocation testing of the subjects severely undermines the conclusions that can be made from this and other larger studies.[121]

CRD diagnostics is in its infancy, and larger studies with better design will be needed to critically evaluate the diagnostic and prognostic power of CRD compared with existing test modalities.

Guidelines

National/international clinical practice guidelines on the management of AR were developed over the past 15 years[3,122,123] and have improved the care of patients with AR.[60] Pertinent to children with AR, guidelines recommend that more studies be conducted in young children, emphasize that AR is often overlooked and underdiagnosed in preschool children, and recognize the importance of management of the child with AR at school.[124]

Potential effect of health care reform

Access to the care of allergists and the management of AR will undoubtedly be affected by the reform of the American health care system. The sources of payment, including government, employer, insurers, and individuals, will be instrumental in determining the direction of AR health care in the United States. Indeed, new research from Truven Health Analytics, Harvard, and the University of Michigan found that as copayments increase, work absenteeism climbs and productivity drops, most likely as a result of employees electing not to seek care.[125]

The medical decision making for this condition is largely in the hands of nonspecialists now, but it could shift even more into the primary care arena or even require no physician involvement at all with the shift from prescription to OTC status for many of the AR medications. The systems used by third-party payers to determine the reimbursement HCPs receive will also be important. In the United States, these include concepts of fee-for-service, managed care, capitation systems, Diagnosis-Related Groups, Resource Based Relative Value Scale, Ambulatory Payment Classifications, and related concepts.

New/future therapies

The older chlorofluorocarbon that propelled dry intranasal steroid sprays was discontinued a number of years ago because of the Montreal Protocol,[126] leaving the United States with an abundance of wet aqueous sprays. Indeed, no dry spray options were available until recently when two formulations received FDA approval, beclomethasone[127] and ciclesonide.[128] These dry sprays have different delivery characteristics and may be preferred by certain patient populations, including children and teenagers, patients with a nose so blocked that the aqueous spray runs back out, and patients who do not like the feeling of runoff in the back of the nose from the aqueous spray.[129] Another newer intranasal steroid spray is the aqueous formulation of fluticasone furoate.[130] A growth study conducted in accordance with FDA guidance[131] recently showed a small effect (−0.27 cm/year) of fluticasone furoate on childhood growth. Indications to treat ocular in addition to nasal symptoms have been received for many of the newer agents.[128]

The role of intranasal AHs in AR management has been a source of disagreement in recent iterations of AR guidelines.[132] The Allergic Rhinitis and its Impact on Asthma update states that intranasal AHs should not be used for perennial AR and promotes the use of second-generation oral AHs over intranasal AHs for adults and children with seasonal AR and over leukotriene receptor antagonists for AR.[123] In response, a prominent group of experts wrote an editorial in support of the US Rhinitis Practice Parameters,[133] which recommends intranasal AHs as first-line therapy.[122]

Although many studies have looked at the combination of an INCS with an AH or LRA, most have concluded that combination therapy is no more effective than monotherapy with INCSs.[134-137] However, a different type of AR combination therapy has emerged and looks promising. Recent trials that combined intranasal AHs and INCSs have provided strong evidence that such dual therapy is more efficacious than therapy

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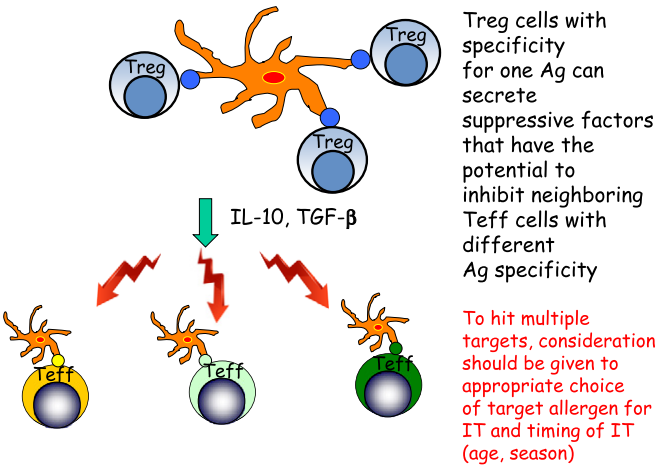

FIGURE 3. Bystander immune suppression. *IM*, Immunotherapy; *Teff*, effector T [cell]. Courtesy of Anuradha Ray, PhD, of University of Pittsburgh School of Medicine.

with either agent alone in patients with moderate-to-severe AR.[138-140]

One of the greatest opportunities for the US allergist in the near future is the imminent availability of SLIT versus the conventional SCIT.[141-143] The best and most comprehensive trials of SIT have now been conducted with SLIT grass tablets in both adults and children and showed highly significant and consistent reductions in nasal and ocular symptoms and medication use. Another trial showed a persistent benefit that is maintained for at least 2 years after a 3-year course of SLIT grass tablet therapy, representing a possible disease-modifying effect.[144,145] It is possible that both grass and ragweed tablets will become available simultaneously in the United States, and tablets for tree pollen, dust mite, cat, and dog could be available in the more distant future. The convenience of home administration, lack of need for painful shots, and improved safety profile should provide the greatest opportunity and benefit for pediatric patients and allergists. Adherence with daily therapy (versus weekly injections) will be an ongoing challenge as with any chronically administered therapy. At the center of a growing debate is the role of single-antigen SLIT in patients with multiple allergen sensitizations.[146,147] Traditionally, SIT has been tailored to include all allergens to which a patient is allergic. However, this practice has not been validated in large, well-designed, randomized, double-blinded clinical trials. Indeed, most SIT safety and efficacy studies have been conducted with single-allergen extracts even though most patients are polysensitized. As summarized in Figure 3, emerging data suggest that induction of immune tolerance to one specific antigen or allergen can result in bystander immune suppression of other effector cells with different antigen or allergen specificity.[148] Recently, results from several studies have implicated a variety of immune cells, including DCs and Treg cells, and cytokines, including IL-10 and TGF-β, in this phenomenon.[149,150] These results have profound implications that may significantly affect and simplify the future treatment of polysensitized patients.

Influence of generics/OTC switches

Significant challenges and opportunities face pediatric allergists and children with AR. One is the switch from prescription to OTC status of many of the medications used to treat pediatric AR.[151] AHs became OTC products a number of years ago. That change improved access to AHs for pediatric patients, provided one less reason to see an allergist, and allowed insurers to shift costs for such treatment to the patient. A similar effort to move INCSs to OTC products was unsuccessful a number of years ago but has recently been reinitiated. Safety concerns associated with appropriate and inappropriate use in children was cited as major deterrents.[95,152] That situation has only worsened, however, because studies recently conducted with the use of the rigorous design recommendations of the FDA guidance[153] have shown growth effects of intranasal fluticasone furoate,[131] and a recent follow-up publication from the Childhood Asthma Management Program study showed adults treated with inhaled corticosteroids (ICSs) for asthma as children were slightly shorter than those not treated with ICSs.[154] Furthermore, we have little or no data on the growth effects of one of our most common therapeutic approaches for children with AR and asthma, that is, combined use of INCSs and ICSs. Moreover, rare neuropsychiatric behavioral effects have rarely been reported after montelukast use.[155]

The bioequivalence and consistency in the safety labeling of generic medications are concerns. Generic products may have greater dosage variability and different insipient ingredients than brand medications. These factors could potentially result in differences in efficacy and safety during generic switchovers. In addition, despite an FDA mandate, nearly 80% of generic manufacturers produce labels differing from brand products.[156] The overall clinical relevance of these discrepancies is unknown but is in conflict with the expectations of patients, providers, and the FDA. Finally, the emerging availability of generic formulations for AHs and INCSs and more recently, montelukast has resulted in insurers often requiring a failure of a trial of a generic product before giving patients access to nongeneric products, which consumes valuable time of office staff in completing required forms (Table II).

The challenges and opportunities facing pediatric allergists and children with AR can be surmounted with thoughtful planning, based on evidence and united efforts of all interested parties.

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