Treatment of Allergic Rhinitis in Children

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Abstract: Allergic rhinitis is an inflammatory disease of nasal mucosa mediated by IgE-associated response to indoor and outdoor environmental allergens. The treatment of allergic rhinitis involves three main categories: avoidance of allergen, pharmacologic management and immunotherapy. The first therapeutic approach in allergic rhinitis is prevention, which is done by avoidance of causal allergens. This helps reduce the symptoms and the need for medications for allergic rhinitis. But allergen-avoidance measures should be considered before or in association with pharmacologic treatment. The intranasal steroids produce significant relief of all nasal symptoms of allergic rhinitis, including nasal congestion, sneezing, rhinorrhea, and itching. They are the first choice drugs in allergic rhinitis except mild intermittent rhinitis. In mild intermittent allergic rhinitis suggested initial treatment consists of an oral antihistaminic, an intranasal antihistaminic, and/or an oral or intranasal decongestant. Montelukast can be used in children as young as 6 months and it is approved by FDA for treatment of allergic rhinitis, in which it has shown clinical efficacy in both seasonal and perennial AR. Multiple randomized, double-blind, placebo controlled studies have shown efficacy of omalizumab (anti-IgE) in seasonal and perennial allergic rhinitis. However, the application of omalizumab in the treatment of allergic rhinitis in the absence of other atopic diseases will likely be restricted to a narrowly defined set of circumstances due to its cost. Specific immunotherapy should be considered when patients fail to respond to avoidance of allergens and pharmacotherapy or experience side effects, or when it is not cost effective.

Keywords: Allergic rhinitis, children, treatment, allergen avoidance, pharmacotherapy, immunotherapy.

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of nasal mucosa mediated by IgE-associated response to indoor and outdoor environmental allergens. It has traditionally been classified as being seasonal and perennial. Tree, grass, and weed pollens and outdoor molds are common seasonal allergens. Dust mites, cockroaches, indoor molds, and cat, dog, and other danders are perennial allergens. But in recent global guidelines allergic rhinitis is defined as being intermittent or persistent and mild or moderate severe. Intermittent allergic rhinitis is defined on the basis of symptoms that are present for less than 4 days per week or less than 4 weeks in duration. If symptoms are present for more than 4 days per week and are present for more than 4 weeks, allergic rhinitis is defined as being persistent. In mild disease, symptoms do not affect school or work, or impair daily activities, sports, and leisure. Conversely, moderate-severe symptoms can result in impairment of any or all of these activities or aspects of life [1].

The treatment of allergic rhinitis involves three main categories: avoidance of allergen, pharmacologic management and immunotherapy.

ALLERGEN AVOIDANCE

The first therapeutic approach in AR is prevention, which is done by avoidance of causal allergens. This helps reduce the symptoms and the need for medications for AR [2,3].

The beneficial effect of environmental control may take weeks and months. Nevertheless, allergen-avoidance measures should be considered before or in association with pharmacologic treatment.

Dust Mites

Washing bed linens in hot (60 C) water every 1-2 weeks, removal of carpets and stuffed toys in the bedroom, replacing mattress and pillow encasements, reducing the indoor humidity, and damp-cleaning of furniture in bedroom have been recommended to reduce the dust mite exposure [3, 4].

Acaricides (benzyl benzoate, tannic acid) can be effective in reducing the dust mites if used regularly [5, 6] ; but their clinical effect is not proven. The use of allergen-impermeable covers seems to be more effective [7, 8].

Animal Dander

The most appropriate recommendation is to remove the animal from the home and to vacuum-clean all carpets, mattresses and upholstered furniture [3]. Frequent washing the cat (3 times weekly) may also help to reduce the animal danger [9].

Molds

The control of mold allergens requires a concerted approach combining fungicides, measures to reduce humidity, and removal of mold-infested items whenever possible [10].
Outdoor Allergens

There is far less ability to control exposure to outdoor allergens than indoor allergens. An air filter may help to reduce exposure, especially if windows are being left open. After being outside, allergic individuals should wash their hands and faces immediately. When outside, masks and goggles are very effective [11].

PHARMACOLOGICAL MANAGEMENT

In mild intermittent allergic rhinitis suggested initial treatment consists of an oral antihistaminic, an intranasal antihistaminic, and/or an oral or intranasal decongestant. A leukotriene receptor antagonist (LTA) is also a consideration. If intermittent AR is moderate or severe, initial treatment with an intranasal steroid (INS) is usually preferred. Persistent allergic rhinitis is treated in the same manner as moderate or severe intermittent disease. In persistent moderate or severe AR, INSs should be the first choice. With all grades of severity, appropriate follow up should take place in a reasonable amount of time, and therapy should be stepped up and down, as indicated. A pharmacologic treatment algorithm for AR is presented in (Fig. 1) [12].

Intranasal Corticosteroids

The steroids produce significant relief of all nasal symptoms of AR, including nasal congestion, sneezing, rhinorhea, and itching [1]. Corticosteroids act by suppressing the transcription of cytokines and they lead to a reduction of the nasal mucosa inflammatory cells [13]. Due to their mechanism of action, INSs have a slow onset of action. They appear to demonstrate efficacy after 7 hours of treatment but their maximum efficacy may require up to 2 weeks. A once-daily administration is possible with most drugs [14].

A number of INSs are available in both aerosol and aqueous solutions (Table 1) [11]. INSs are superior to antihistamines [15, 16] and leukotriene antagonists [17, 18] and, probably equivalent [19] or even superior [20, 21] to combinations of antihistamines and LTAs. Intranasal fluticasone propionate also improves ocular symptoms in patients with allergic rhinitis [22]. In seasonal AR, INSs should be given regularly and may be used before the beginning of pollen season in severe cases for maximal effect [3].

Under 4 years of age, the treatment of perennial AR safely is difficult. It is found that fluticasone propionate reduces all symptoms of AR without serious adverse effects in this age group [23]. INSs may have occasional adverse effects such as nasal burning, dryness and bleeding from the nasal mucosa. These can occur in 5% to 10% of patients [24].

Flunisolide appears to cause a higher incidence of nasal discomfort [25]. They can be used on a long-term basis without atrophy of the mucosa [26, 27].

After topical application, there is only minimal absorption of INSs and, thus, the risk for systemic side effects is minimal. Studies have shown that at recommended doses, there is minimal to no hypothalamic-pituitary-adrenal axis or on the growth rate [28, 29].

Intranasal beclamethasone caused a small but significant reduction in linear growth in one study with twice-daily dosing [30]. No growth delay was observed in children treated over the course of one year with mometasone [31], fluticasone [32], or budesonide [33, 34].

Oral Antihistamines

Two generations of antihistamines are available; first generation (sedating) antihistamines, such as diphenhydramine, clemastine, tripelennamine, pyrilamine, brompheniramine, chlorpheniramine and triprolidine, which are available without prescription; the second generation (hyposedating or non-sedating) agents, such as cetirizine, fexofenadine, desloratadine, levocetirizine, ebastine, mizolastine, all of which require a prescription except loratadine (Table 2) [11, 35, 36].

H1 antihistamines antagonize the H1 receptor on smooth muscle cells, nerve endings, and glandular cells, leading to a reduction of symptoms, such as sneezing, rhinorrhea and itching. However, they only have a mild effect on nasal congestion [37]. Some studies have found that some drugs, such as desloratadine and fexofenadine reduce nasal congestion, but this effect is inferior to INSs [38,39]. Also in a trial, levocetirizine was given for over 6 months to 551 patients with moderate to severe AR. It was found that levocetirizine improves nasal symptoms including nasal congestion and quality of life [40]. Some of nonsedating antihistamines exert anti-inflammatory properties, such as inhibition of TNF-α induced release of chemokines IL-8 (fexofenadine) [41] and RANTES (desloratadine) [42] as well as reduction of intercellular adhesion molecule 1 expression on cultured keratinocytes (cetirizine) [43]. In infants 6-11 months of age the safety of cetirizine was demonstrated by a double-blind, placebo controlled study [44]. Levocetirizine (a stereoisomer of cetirizine) is effective for relief of nasal congestion in adults and adolescents with perennial AR sensitized to dust mites [45]. Loratadine is effective in AR of children 3-12 years without any side effect [46]. Desloratadine (metabolite of loratadine) reduces nasal congestion and reduces symptoms of perennial AR [38].

Second generation oral antihistamines have better H1-receptor selectivity and less anticholinergic and antiserotonergic side effects. Cetirizine is the only one to cause increased sedation at its recommended dose in person older than 12 years. Antihistamines like terfenadine and astemizole are prone to long QT syndrome when used in combination with drugs that are metabolized by the cytochrome p450 enzyme system and, hence, are no longer available in the market. Other second generating antihistamines do not have cardiac side effects [35].

Intranasal Antihistamines

Intranasal antihistamines reduce itching, sneezing, rhinorrhea and nasal congestion. They can be effective within 20 minutes of administration and their effect lasts about 12 hours. However topical antihistamines and oral antihistamines are significantly less effective than INSs for the treatment of AR, particularly for nasal congestion [35].
Azelastine was found to be effective in the treatment of patients with seasonal AR who do not respond to loratadine and is an alternative to switching to another oral antihistamine or to using multiple antihistamines [47]. Intranasal antihistamines require twice a day dosing. Their use therefore may be recommended for organ limited mild disease and as an “on demand” treatment in addition to a continuous medication [3].

**Decongestants**

Decongestants are used to relieve nasal congestion. Both oral and intranasal preparations exist. Topically applied decongestants belong to the alpha1 adrenergic agonists (phenylephrine) or alpha2 agonists such as imidazoline family (oxymetazoline, xylometazoline, naphazoline), whereas oral vasoconstrictors are primarily noradrenaline releasers (ephedrine, pseudoephedrine, phenylpropanolamine, and phenylephrine) [48].

Their effects begin in 5 to 10 minutes when applied topically and in 30 minutes when administered orally. Decongestants cannot ameliorate symptoms of AR other than nasal congestion [49]. However, when oral decongestants are combined with an antihistamine, all symptoms of AR can be reduced. They also may be helpful when used prior to the administration of INSs in patients with severe nasal congestion [12].

Topical decongestants are not recommended in the treatment of AR, as tolerance and rebound congestion can develop when they are used for longer than 1 week [48]. Oral decongestants have a weaker effect on nasal congestion than...
Table 1. Intranasal Steroids Used in the Treatment of Allergic Rhinitis [11]

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Dose per Actuation (μg)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>42</td>
<td>≥ 6 yr: 168-336 μg/day qd</td>
</tr>
<tr>
<td>Budesonide</td>
<td>32</td>
<td>≥ 12 yr: 64-256 μg/day qd 6-11 yr: 64-128 μg/day qd</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>25</td>
<td>≥ 14 yr: 200-400 μg/day bid 6-11 yr: 150-200 μg/day bid</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50</td>
<td>≥ 4 yr: 100-200 μg/day qd or bid</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>50</td>
<td>≥ 12 yr: 200 μg/day qd 3-11 yr: 100 μg/day qd</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>55</td>
<td>≥ 12 yr: 220-440 μg/day qd or bid 6-11 yr: 220 μg/day qd</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetics and Recommended Doses of Second generation Antihistamines [36]

<table>
<thead>
<tr>
<th>Second generation antihistamines</th>
<th>Onset of action (hrs)</th>
<th>Duration of action (hrs)</th>
<th>Elimination half life (hrs)</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine</td>
<td>3-4</td>
<td>24</td>
<td>4.5-12</td>
<td>≥12 yr: 10 mg qd 6-11 yr: 5-10 mg qd 2-5 yr: 5 mg qd</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>3</td>
<td>≥ 24</td>
<td>21-24</td>
<td>≥12 yr: 5 mg qd 6-11 yr: 2.5 mg qd 2-5 yr: 1.25 mg qd</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>0.7</td>
<td>≥ 24</td>
<td>7-11</td>
<td>≥12 yr: 10 mg qd 6-11 yr: 5-10 mg qd 2-5 yr: 5 mg qd</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.5</td>
<td>&gt; 24</td>
<td>5.5-8.5</td>
<td>≥6 yr: 10 mg qd 6-11 yr: 5-10 mg qd 2-5 yr: 5 mg qd</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>1-2</td>
<td>24</td>
<td>14.4</td>
<td>≥12 yr: 60 mg bid or 180 mg qd 6-11 yr: 30 mg bid</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>1</td>
<td>24</td>
<td>13</td>
<td>≥12 yr: 10 mg qd</td>
</tr>
<tr>
<td>Ebastine</td>
<td>1-3</td>
<td>≥ 24</td>
<td>10-14</td>
<td>≥12 yr: 10-20 mg qd</td>
</tr>
</tbody>
</table>

topical decongestants, but they do not cause rebound vasodilatation [3]. Decongestants should be used with care in children under 1 year of age due to systemic side effects such as tremor, agitation, tachycardia and hypertension [3].

Mast Cell Stabilizers

Cromolyn and nedocromil decrease allergic inflammation by inhibiting the degranulation of sensitized mast cells [50]. Cromolyn sodium has proved effective in reducing both the early- and late phase allergic reaction [51]. It is indicated for both seasonal and perennial AR [52,53]. It’s associated with few mild side effects, such as nasal itching, unpleasant taste and sneezing, has no serious systemic side effects. The 4% intranasal solution is recommended for children 2 years and older. One to 2 sprays in each side of nose 4 times a day are required for the treatment. Efficacy of cromolyn is inferior to antihistamines and INSs in the treatment of AR. Mast cell stabilizers cannot be considered a major therapeutic option in the treatment of AR, but they have role in prophylactic treatment of conjunctivitis [54].

Leukotriene Antagonists

Cysteinyl leukotrienes also play a role in the inflammation of upper airways. High concentrations of leukotriene C4 was found in nasal secretions of atopic individuals after allergen challenge [55]. Montelukast can be used in children as young as 6 months and it is approved by FDA for treatment of AR, in which it has shown clinical efficacy in both seasonal [56, 57] and perennial AR [58, 59]. There was only a marginal benefit in adding montelukast to loratadine, and neither montelukast nor loratadine were effective as INSs [60,61]. In a systematic review and meta analysis combina-
tion of LTA and antihistamines was found to be more effective for nasal symptoms than either alone, but this combination was not statistically significant using a score measuring quality of life [62]. Even if the combination of LTA plus antihistamines was clinically equivalent to INSs, the cost of the two drugs would exceed the cost of INSs alone [63]. Combined montelukast and cetirizine treatment, when started 6 weeks before the pollen season, is effective in preventing AR symptoms and reduces allergic inflammation in nasal mucosa during natural allergen exposure [64].

**Iptaropium Bromide**

When applied topically ipratropium bromide, an antimuscarinic agent, reduces rhinorrhea. Though it does not reduce nasal congestion and pruritus, it is more effective in the treatment of non-AR, such as allergic rhinitis, vasomotor rhinitis, with predominant rhinorrhea [65, 66]. Ipratropium has shown efficacy in perennial rhinitis [67, 68], but no data are available for seasonal AR [3]. It has an onset of action within 15-30 minutes, but due to its pharmacokinetic profile ipratropium is administered 3 to 6 times a day [65]. Side effects are local irritation, dryness, headache, and epistaxis [65, 69].

**Omalizumab (Anti-IgE)**

Omalizumab is a humanized monoclonal antibody (mAb) that forms complexes with free IgE, thereby effectively hindering IgE’s interaction with the high-affinity IgE receptor present on mast cells and basophils. Omalizumab rapidly decreases nasal allergic response and Fc(RI on basophils and dendritic cells [70]. Multiple randomized, double-blind, placebo controlled studies have shown efficacy of omalizumab in seasonal [71, 72] and perennial AR [73, 74]. Omalizumab also improved nasal and bronchial symptoms and reduced visits to physicians for asthma [74]. However, the application of omalizumab in the treatment of AR in the absence of other atopic diseases will likely be restricted to a narrowly defined set of circumstances due to its cost. Omalizumab can be used children age 12 years and older [12].

**Nasal Irrigation**

Nasal saline irrigation has been used for many years in various forms of rhinitis to remove mucus, enhance ciliary clearance, and to remove polen and other allergic or irritant material from nasal mucosa. There is limited data that hypertonic saline is more irritating, but it can stimulate ciliary transport to a greater degree than isotonic saline [75]. In children with seasonal AR nasal hypertonic saline used 3 times daily during the 7-week pollen season reduced need for oral antihistamines during 5 of the 7 weeks [76]. In an adult study of 32 patients, those rinsing with Ringer-Lactate solution after nasal surgery had a significantly better mucociliary transport time than the patients rinsing with isotonic saline solution [77]. More research is required to better define the role of ringer solution for nasal irrigation in allergic rhinitis.

**ALLERGEN IMMUNOTHERAPY**

Specific immunotherapy (SIT) is the only treatment capable of modifying the natural history of allergic diseases and of preventing new sensitizations [78, 79]. SIT has been shown to increase allergen specific IgE antibodies that inhibit the binding of allergen-IgE complexes to B cells, the blocking of IgE facilitated allergen presentation and activation of allergen specific T lymphocytes, and the prevention of allergen-IgE-dependent activation of peripheral basophils [78, 80]. Specifc immunotherapy cause the blunting of allergen driven Th2 responses and reduce IL-4, IL-13, IL-5, and IL-9 in the periphery and/or within target organs.

The efficacy of subcutaneous immunotherapy (SCIT) in children with allergic rhinitis is without doubt [81]. Due to risk of severe and fatal adverse events, an age less than 5 years is a relative contraindication to SCIT [78]. The sublingual immunotherapy (SLIT) is an alternative to SCIT because of its very satisfactory profile. It is safe and the rate of adverse reactions is not greater in children below 5 years of age [81]. In a meta analysis the efficacy of SLIT in children with allergic rhinitis was clearly demonstrated [82]. Also one randomized, controlled open trial demonstrates that SLIT in children with allergic rhinitis may reduce the risk of progression from AR to asthma [83]. Immunotherapy should be considered when patients fail to respond to avoidance of allergens and pharmacotherapy or experience side effects, or when it is not cost effective. Patients may not show improvement for 6-12 months, and if helpful, therapy should be continued for 3-5 years [84]. Due to risk of anaphylactic reaction after injection SCIT should always be administered in supervised clinical settings [85].

**REFERENCES**


