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# Clinical Prescribing of Allergic Rhinitis Medication in the Preschool and Young School-Age Child

## What are the Options?

*Stanley P. Galant*[1] and *Robert Wilkinson*[2]

1 Department of Paediatric Allergy/Immunology, University of California, Irvine, California, USA
2 Department of Pharmacy, St Joseph Hospital, Orange, California, USA

## Contents

Abstract . . . . . 453
1. Aetiology, Epidemiology and Impact of Allergic Rhinitis (AR) in Children . . . . . 454
2. Evaluation and Diagnosis . . . . . 454
3. Pathogenesis . . . . . 455
4. Treating AR in the Child . . . . . 455
   4.1 Histamine $H_1$ Receptor Antagonists (Antihistamines) . . . . . 456
   4.2 Decongestants . . . . . 458
   4.3 Intranasal Corticosteroids . . . . . 458
   4.4 Mast Cell Stabilisers . . . . . 461
   4.5 Anticholinergic Agents . . . . . 461
5. Conclusions and Recommendations . . . . . 461

## Abstract

Allergic rhinitis (AR) is the most common chronic condition in children and is estimated to affect up to 40% of all children. It is usually diagnosed by the age of 6 years. The major impact in children is due to co-morbidity of sinusitis, otitis media with effusion, and bronchial asthma. AR also has profound effects on school absenteeism, performance and quality of life.

Pharmacotherapy for AR should be based on the severity and duration of signs and symptoms. For mild, intermittent symptoms lasting a few hours to a few days, an oral second-generation antihistamine should be used on an as-needed basis. This is preferable to a less expensive first-generation antihistamine because of the effect of the latter on sedation and cognition. Four second-generation antihistamines are currently available for children under 12 years of age: cetirizine, loratadine, fexofenadine and azelastine nasal spray; each has been found to be well tolerated and effective. There are no clearcut advantages to distinguish these antihistamines, although for children under 5 years of age, only cetirizine and loratadine are approved. Other agents include pseudoephedrine, an oral vasoconstrictor, for nasal congestion, and the anticholinergic nasal spray ipratropium bromide for rhinorrhoea. Sodium cromoglycate, a mast cell stabiliser nasal spray, may also be useful in this population.

For patients with more persistent, severe symptoms, intranasal corticosteroids

are indicated, although one might consider azelastine nasal spray, which has anti-inflammatory activity in addition to its antihistamine effect. With the exception of fluticasone propionate for children aged 4 years and older, and mometasone furoate for those aged 3 years and older, the other intranasal corticosteroids including beclomethasone dipropionate, triamcinolone, flunisolide and budesonide are approved for children aged 6 years and older. All are effective, so a major consideration would be cost and safety. For short term therapy of 1 to 2 months, the first-generation intranasal corticosteroids (beclomethasone dipropionate, triamcinolone, budesonide and flunisolide) could be used, and mometasone furoate and fluticasone propionate could be considered for longer-term treatment. Although somewhat more costly, these second-generation drugs have lower bioavailability and thus would have a better safety profile.

In patients not responding to the above programme or who require continuous medication, identification of specific triggers by an allergist can allow for specific avoidance measures and/or immunotherapy to decrease the allergic component and increase the effectiveness of the pharmacological regimen.

## 1. Aetiology, Epidemiology and Impact of Allergic Rhinitis (AR) in Children

Allergic rhinitis (AR) is currently the most common of all chronic conditions in children. The disease can be classified as seasonal or perennial, depending on when the child appears to have symptoms most predominantly. Those children with seasonal allergic rhinitis (SAR) have symptoms predominantly in the spring and fall generally due to tree, grass and weed pollen, and occasionally mold spores, whereas those with perennial allergic rhinitis (PAR) have symptoms all year long secondary to year-round indoor allergens, such as the housedust mite, animal danders, mould spores and cockroach allergens (the latter particularly in the inner city). PAR generally occurs in younger children and is frequently associated with otitis media with effusion and sinusitis, while the SAR pattern is usually seen in older children and adults. The 2 conditions can occur together and are not different diseases; therefore treatment is the same.

A 1988 US survey found AR to be present in 59.7 cases per 1000 children up to the age of 18 years.[1] This probably is an underestimate, since it included only those with SAR or hayfever. A prospective study of 747 children in Tucson, Arizona, found that 42% of families interviewed had a physician diagnosis of AR by the age of 6 years, and half of these children developed this condition in the first year of life.[2] The prevalence of AR worldwide appears to be similar to that of the United States.[3] The estimated direct expenditure for AR and allergic conjunctivitis in children 12 years of age or less was estimated to be $2.3 billion in the US in 1996.[4] Risk factors for developing AR include a family history of atopy, serum immunoglobulin (Ig) E levels ≥100 IU/ml before the age of 6 years, higher socioeconomic class, exposure to indoor allergens, and a positive skin test indicating specific IgE antibodies.[5]

AR can have a profound effect on a child's quality of life. Children with AR more likely to demonstrate shyness, depression, anxiety, fearfulness and fatigue compared with nonallergic peers.[6] Furthermore, these children miss 2 million days of school each year in the US, and even when they attend school their ability to learn and process cognitive input is significantly impaired.[7] If left untreated, AR can exacerbate and contribute to symptoms of asthma, sinusitis and otitis media with effusion.[8]

## 2. Evaluation and Diagnosis

The diagnosis of AR is highly dependent on obtaining a comprehensive history from an older child or from the parent of a younger child. Signs and symptoms in older children with SAR include a history of paroxysmal sneezing, nasal itching, clear rhinorrhoea and red, itchy, watery eyes, par-

ticularly during the pollen season. With PAR, these symptoms are much less dramatic and are often characterised by chronic nasal obstruction with snoring and mouth breathing, chronic postnasal drip frequently associated with chronic cough and throat clearing, and sinus headaches. In addition to these more localised manifestations, many children with AR experience systemic symptoms including weakness, malaise, fatigue, irritability, poor appetite and sleep disturbances.[8]

On physical examination, the classic signs include allergic shiners, allergic nasal crease often accompanied by high arched palate, and open mouth characteristic of chronic nasal obstruction due to enlarged, pale nasal turbinates.

To establish a diagnosis of AR, however, one must identify the presence of specific IgE antibodies by skin or blood tests (i.e. radioallergosorbent test) and correlate this with the history. As in adults, inhalant allergens are the most frequent triggers in childhood AR. However, allergy testing for pollens is typically done after the age of 2 to 3 years.[6] Food allergy may be relevant, particularly in younger children aged less than 2 years.[9]

## 3. Pathogenesis

Atopic individuals inherit the tendency to develop AR. Prolonged exposure to indoor allergens results in production of IgE antibodies that bind to mucosal mast cells and circulating basophils. Thus sensitised, the patient develops acute nasal and ocular symptoms following further exposure.[10] This response, which can occur within minutes of exposure and is termed the early-phase allergic response, is caused primarily by the release of mast cell mediators. These include histamine, tryptase, prostaglandin D2 and the cysteinyl leukotrienes (LT) C4, D4 and E4.[10] A late-phase response that occurs 4 to 8 hours after allergen exposure in 50% of patients is thought to be due to cytokine release by mast cells and thymic-derived helper T cells called $T_H2$ cells. The late-phase response is characterised by profound infiltration and activation of migrating and resident cells.[10] This inflammatory response is thought to be responsible for the persistent, chronic signs and symptoms of AR, particularly nasal obstruction and increased sensitivity of the nasal mucosa to allergens and irritants.

## 4. Treating AR in the Child

The principles of managing chronic AR in children are similar to those in adults, and include environmental avoidance measures, pharmacotherapy and, in those not responding to the latter 2, immunotherapy. In all cases, the goal of therapy includes controlled symptoms without altering the child's ability to function and, in addition, prevention of the potential sequelae of AR mentioned above. Since the main purpose of this paper is to describe current concepts in pharmacotherapy, readers are referred to an excellent recent review by Dykewicz et al.[5] for a discussion of the other therapeutic modalities.

The various classes of medication that are useful in AR and their effects on specific symptoms are presented in table I and are discussed in detail

**Table I.** Efficacy of various drug classes for symptoms of allergic rhinitis[a,b]

| | Pruritus | Rhinorrhoea | Nasal blockage | Eye symptoms |
|---|---|---|---|---|
| Oral antihistamines | +++ | ++ | ± | +++ |
| Topical antihistamines (e.g. azelastine) | +++ | ++ | ++ | ± |
| Oral decongestants | -- | ± | +++ | -- |
| Antihistamine/decongestant combinations | +++ | ++ | +++ | +++ |
| Topical decongestants[c] | -- | ± | +++ | -- |
| Intranasal corticosteroids | +++ | +++ | ++(+) | + |
| Intranasal sodium cromoglycate | + | + | ± | -- |
| Intranasal ipratropium bromide | -- | +++ | -- | -- |
| Oral corticosteroids[d] | +++ | +++ | +++ | ++ |

a Reproduced from Galant & Wilkinson,[11] with permission.
b Range from no efficacy (--) to profound efficacy (+++).
c Restrict use to never more than 3 consecutive days.
d Limit use to temporary therapy in urgent or severe cases.

**Table II.** Comparison of selected antihistamines[a]

| Drug name | Onset of action (h) | Sedation | Dosage schedule | Age (y) |
|---|---|---|---|---|
| **First-generation antihistamines** | | | | |
| Brompheniramine | 1 | Yes | tid-qid | <6[b] |
| Chlorphenamine | 1 | Yes | tid-qid | >2 |
| Clemastine | 1 | Yes | bid | >6 |
| Cyproheptadine | 1 | Yes | bid-tid | >2 |
| Diphenhydramine | 1 | Yes | tid-qid | >2 |
| Hydroxyzine | 1 | Yes | tid-qid | <6[b] |
| Triprolidine | 1 | Yes | tid-qid | <6[b] |
| **Second-generation antihistamines** | | | | |
| Azelastine[c] | 1 | Slight | bid | >5 |
| Cetirizine | <1 | Slight | od | >2 |
| Fexofenadine | 1-2 | No | bid | >6 |
| Loratadine | 1-3 | No | od | >2 |

a Reproduced from Lasley and Shapiro,[16] with permission, and Galant and Wilkinson.[11]

b Consult a physician.

c Intranasal application.

**bid** = twice daily; **od** = once daily; **qid** = 4 times daily; **tid** = 3 times daily.

below. These discussions will be followed by general therapeutic recommendations for patients with mild, moderate and severe AR based on the relative merits of the drug classes and pharmacoeconomic consideration where appropriate.

### 4.1 Histamine $H_1$ Receptor Antagonists (Antihistamines)

First- and second-generation antihistamines are very effective in the treatment of AR because they alleviate both nasal and ocular symptoms. Antihistamines antagonise histamine directly, but reversibly, at the $H_1$ receptor, thereby blocking the physiological effects of histamine on blood vessels, mucous-secreting glands, and sensory nerve endings in the nose.[11] In addition, several antihistamines, including the second-generation agents fexofenadine hydrochloride and loratadine, also appear to block release of histamine and other inflammatory mediators from mast cells and basophils *in vivo*.[12] The second-generation antihistamine cetirizine inhibits LTC4 and D4 production in nasal secretions and inhibits recruitment of eosinophils in the cutaneous late-phase model.[13,14] Another second-generation agent, azelastine hydrochloride, in addition to high affinity for the $H_1$ receptor administered as a nasal spray, is inhibitory to several cells and chemical mediators of the inflammatory response.[15]

In children, as in adults, oral antihistamines continue to be the mainstay of treatment for AR. Two generations of antihistamines are currently available, the first-generation sedating antihistamines, some of which are available without prescription (e.g. diphenhydramine and chlorphenamine), and the second-generation nonsedating antihistamines, which require a prescription (table II). The first- and second-generation antihistamines are equally effective. However, the problems of nonspecificity, sedation and frequent drug administration limit the usefulness of the first-generation antihistamines. In addition, these agents have been associated with paradoxical stimulation (particularly in the young child), blurred vision, urinary retention, dry mouth, tachycardia, constipation and weight gain, particularly with cyproheptadine.[17,18] Thus, second-generation antihistamines have advantages over the first-generation antihistamines, including greater specificity, with binding predominantly at the $H_1$ receptor and minimal binding to serotonin, cholinergic or $\alpha$-adrenergic receptors. This specificity of binding results in a decreased drying effect at the mucosal surface, and less gastrointestinal upset.

The second-generation antihistamines are also more lipophobic, with minimal penetration into the central nervous system (CNS), and thus have minimal sedation.[17,19] The absence of sedation and cognitive effect is a critical advantage in children as in adults. Vuurman et al.[7] found that children with AR scored substantially better in learning measures when treated with second-generation antihistamines compared with those treated with first-generation antihistamines, suggesting that the former should be used in children whenever possible.

Four second-generation antihistamines are currently available for children under 12 years of age. Cetirizine is approved for children aged 2 years and above for both SAR and PAR, loratadine for those 2 years and above with SAR, azelastine for those aged 5 years and above for SAR, and fexofenadine is approved for children 6 years of age and older with SAR. Pharmacological characteristics in adults of these 4 drugs are shown in table III. Pharmacokinetic studies have shown that the terminal elimination half-life for antihistamines undergoing extensive first-pass metabolism in the liver cytochrome P450 system is often shorter in infants and young children.[20] These differences are not found for histamine $H_1$ receptor antagonists that are eliminated largely unchanged.[20] Pharmacokinetic data for cetirizine show that children aged less than 12 years have a greater clearance and elimination half-life compared with adults,[21] while the clearance for loratadine and fexofenadine is not significantly different in children and adults.[22,23] Pharmacokinetic data for intranasal azelastine is not available in children under 12 years.

Dosages and costs in the US of the second-generation antihistamines are shown and compared with an example of the first-generation product dephenhydramine HCL in table IV. Cetirizine (5mg, 10mg), loratadine (10mg), and fexofenadine (30mg) are available as tablets; cetirizine (5mg/5ml) and loratadine (5mg/5ml) are available as a syrup; and loratadine has a rapidly dissolving tablet (10mg) [table III]. Cetirizine has been evaluated in doses ranging from 2.5mg to 10mg in double-blind, controlled studies in children as young as 2 years of age with SAR and PAR, and found to be effective and well tolerated.[25,26] In children aged 6 to 11 years, the major adverse effects were abdominal pain in 4.4% receiving 5mg and 5.6% in those receiving 10mg compared with 1.9% in the placebo group. Somnolence was found in 1.9% and 4.2% receiving 5mg and 10mg, respectively, compared with 1.3% in those receiving placebo.[25,26] In addition, the efficacy and tolerability of loratadine has been reported in children as young as 2 years taking 5mg or 10mg.[27] No significant adverse effects, particularly somnolence, were found.[27] The effectiveness of fexofenadine 30mg tablets was demonstrated in 1 study in children aged 6 to 11 years with SAR compared with placebo controls, along with extrapolation of efficacy in patients over 12 years of age and pharmacokinetic comparisons in adults and children.[28] The tolerability of this product was demonstrated in 2 placebo-controlled 2-week studies.[29] Again no significant adverse events, particularly somnolence, were reported.

Azelastine nasal spray (0.14 mg/metered dose per nostril twice daily) was reported to be effective

**Table III.** Pharmacokinetics of second-generation antihistamines[a,b]

| | Cetirizine | Loratadine | Fexofenadine | Azelastine |
|---|---|---|---|---|
| Time to peak concentration (h) | 1 | 1.3 | 2.6 | 4-6 |
| Onset of action (h) | <1 | 1-3 | 1 | 0.5-2[c] |
| Time to peak effect (h) | 4-8 | 8-12 | 2-3 | 4 |
| Half-life (h) | 7-10 | 8.4-15 | 14.4 | 22-36 |
| Duration – single dose (h) | 24 | 24-48 | 12-24 | 10-12 |
| Elimination pathway | Renal | Hepatic | Renal/faeces | Hepatic |
| Active metabolites | No | Yes | No | Yes |
| Drowsiness/somnolence (drug/placebo) | 13.7%/6.3% | 8%/6% | 1.3%/0.9% | 11.5/5% |

a Reproduced from Galant & Wilkinson,[11] with permission.

b In adults.

c 0.5 to 2h for intranasal azelastine.

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