

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

What are the Options?

Stanley P. Galant¹ and Robert Wilkinson²

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 bio-availability 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 expo-

sure 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 H₁ 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 H₁ 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 H₁

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 H₁ receptor and minimal binding to serotonin, cholinergic or α -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 H₁ 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.

Table IV. Dosages and costs of second-generation antihistamine products^a

Drug name	Formulation	Children aged 6-11y	Cost/month ^b
Loratadine	10mg tablets	Not approved	\$67.20
	10mg rapid-dissolve tabs	1 tablet od	\$76.81
	Syrup (5 mg/tsp)	1-2 tsp od	\$39.78-\$79.56
Cetirizine		1 tsp od for children 2-5y	
	10mg tablets	NA	\$57.30
	5mg tablets	1-2 tablets od	\$57.30
	Syrup (5 mg/tsp)	1-2 tsp od	\$70.00 ^c
Azelastine nasal spray		0.5-1 tsp od for children 2-5y	\$35.00 ^d
	1.37 µg/spray	1 spray/nostril bid	\$47.00
		(100 actuations/bottle)	
Fexofenadine	30mg tablets	30mg bid	\$31.08
Diphenhydramine ^e	Syrup (12.5 mg/tsp)	0.5-1 tsp tid	\$8.00 generic

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

b Based on US average wholesale price according to 2000 Drug Topics Red Book.^[24]

c 2 teaspoon (tsp) dose.

d 1 tsp dose.

e First-generation antihistamine for comparative cost.

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

and well tolerated in children aged 5 to 12 years with PAR by Herman et al.^[30] using a placebo-controlled, double-blind protocol. In addition to relief of the usual symptoms of AR, nasal obstruction was also reduced. Safety and tolerability have also been established in this age group with SAR, and this is the indication for this product in the US. Efficacy was based on extrapolation of efficacy in adults and supportive data from European trials in children aged 5 to 12 years. Tolerability data were established in 3 well controlled European studies in children 5 to 12 years of age.^[31] The major adverse events noted in adults included a bitter taste, 19.7% compared with 0.6% with placebo, and somnolence, 11.5% compared with 5.4%, respectively; these effects were also seen in children.

4.2 Decongestants

Decongestants such as pseudoephedrine and phenylpropanolamine produce vasoconstriction within the nasal mucosa through stimulation of the α -adrenergic receptor. They may be useful as adjunctive therapy for AR since antihistamines alone generally do not reduce nasal obstruction. However, these agents have no effect on rhinorrhoea,

pruritus or sneezing. Therefore, they may be most effective when used in combination with antihistamines.^[32] However, currently there are no combinations that employ a decongestant with a non-sedating antihistamine for children under 12 years of age, although several are in clinical trials. Decongestants can also be applied topically, in which case agents such as phenylephrine or oxymetazoline should not be taken for more than 4 consecutive days to avoid rebound congestion, termed rhinitis medicamentosa.^[17]

The most commonly used oral decongestant in children is pseudoephedrine, which is given every 6 hours as needed either as a 30mg per teaspoon syrup or a 30mg tablet. The dose is 15mg for children aged 2 to 5 years, and 30mg for children 6 to 11 years. Although most children tolerate these agents well, they can produce adverse effects such as CNS stimulation, increased blood pressure, dysuria, palpitations and tachycardia.^[17]

4.3 Intranasal Corticosteroids

Intranasal corticosteroids are highly effective and have been approved for use in children with both SAR and PAR. They relieve a range of signs

and symptoms that include nasal congestion, rhinorrhoea, itching and sneezing, but are less effective for ocular symptoms.^[33,34] Since AR can be viewed as a chronic inflammatory allergic disease, intranasal corticosteroids would appear well suited to reverse this process. Although the exact mechanism of action is not known, the major pathway involves binding of the steroid molecule to a cytoplasmic receptor that is then transported to the nucleus where it binds to the DNA at the glucocorticoid response element.^[33] This results in inhibition of a variety of pro-inflammatory cytokines that decrease the inflammatory response.

With the current exception of fluticasone propionate (for children 4 years of age and up) and mometasone furoate (for children 3 years of age and up), intranasal corticosteroids sprays are generally approved for use in children as young as 6 years (table V). Pharmacokinetic and pharmacodynamic data shown in table VI have been derived in adults since data are lacking in children.^[35,37] Both local and systemic adverse effects have been reported. Local effects due to irritation include pain, epistaxis and, rarely, perforation of the septum reported in adults. However, no atrophic changes have been reported after up to 10 years of usage in adults.^[38] These effects can usually be overcome by aiming the nozzle away from the septum and/or

using an aqueous preparation instead of a pressurised propellant, if available. In addition, benzalkonium chloride, an antimicrobial preservative, has been proposed to cause burning, irritation and dryness by inhibition of mucociliary transport.^[39] In some patients, selection of a benzalkonium chloride-free preservative may be helpful.

Although asthmatic children appear to eliminate inhaled corticosteroids (e.g. budesonide) twice as quickly as adults,^[40] systemic adverse effects, particularly hypothalamic-pituitary-adrenal (HPA) axis and growth suppression, continue to be areas of concern in this population. The amount of corticosteroid that reaches the systemic circulation is a product of both nasal and oral bioavailability. Most of the intranasal corticosteroid is swallowed, and thus the majority of systemic bioavailability is determined by the absorption from the gastrointestinal tract and degree of first-pass hepatic degradation.^[35] This explains the rather high bioavailability of 20 to 50% for beclomethasone dipropionate, flunisolide and budesonide, compared with less than 1% for fluticasone propionate and mometasone furoate.^[35] Furthermore, it is important to differentiate between systemic effects, which are usually short term, and systemic adverse effects, seen with chronic intranasal corticosteroid usage.^[35,41] Thus, short term effects of these agents on the HPA axis,

Table V. Dosages and costs of intranasal corticosteroids^a

Drug	Dose per spray (µg)	No. doses per container	Sprays per day ^b (children aged 6-11y)	Cost/month ^c (\$)
Beclomethasone dipropionate (MDI)	42	200	1 tid	43.94-44.74
Beclomethasone dipropionate	84	200	1-2 od	53.12
	42	200	1-2 bid	45.05
Budesonide (MDI)	32	200	2 bid or 4 od	37.98
Budesonide (aqueous)	32	60	1 od	48.00
Flunisolide (aqueous)	25	200	1 tid or 2 bid	40.67
Fluticasone propionate (MDI)	50	120	1-2 od ^d	53.36
Mometasone furoate (MDI)	55	120	1 od ^e	51.17
Triamcinolone acetonide (MDI)	55	100	2 od	41.89
Triamcinolone acetonide (aqueous)	55	120	Not approved	38.71

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

b In each nostril.

c For adult dosage; based on average wholesale price according to 2000 Drug Topics Red Book.^[24]

d Children aged 4 years or older.

e Children aged 3 years and older.

bid = twice daily; MDI = metered-dose inhaler; od = once daily; tid = 3 times daily.

Table VI. Selected pharmacokinetic and pharmacodynamic characteristics of intranasal corticosteroids^a

	Systemic bioavailability (%)	Systemic clearance (L/h)	Onset of action
Beclomethasone dipropionate	44	230	3d
Budesonide ^b	34	84	24h
Flunisolide	40-50	48	4-7d
Fluticasone propionate	<1	69	12h
Mometasone furoate	<1	NA	12h
Triamcinolone acetonide	NA	37	24h

a Reproduced from Galant & Wilkinson,^[11] with permission, and product package inserts and Allen.^[35]

b Bioavailability shown for budesonide is for the aqueous pump spray; estimated values for pressurised MDI is 21% and Turbuhaler (not available in the US) is 41%.^[36]

NA = data not available.

as measured by basal area under the curve, plasma cortisol levels or 24-hour urinary free cortisol, reflect the effects of intranasal corticosteroids on hypothalamic-pituitary feedback inhibition, whereas assessment of adrenal function by adrenocorticotrophic hormone stimulation measures the effect of intranasal corticosteroids on HPA axis function. In this respect, there are no studies that show intranasal corticosteroids induced HPA axis suppression regardless of the basal cortisol effect.^[35,41]

Growth inhibition has been found to be a more sensitive indication of intranasal corticosteroids-induced systemic adverse effects than HPA axis suppression.^[42] Short term (<6 months) evaluation of growth inhibition by knemometry assesses the systemic effect of intranasal corticosteroids, compared with intermediate (≥12 months) and long term (>3 years) evaluation, which measures systemic adverse effects.^[35] For the short term effect, budesonide 200µg bid showed significant growth inhibition,^[43] while budesonide 200 and 400µg in the morning^[44] and mometasone furoate 100 and 200µg in the morning did not.^[45] A single dose of methylprednisolone acetate, 60mg intramuscularly, caused suppression for 4 weeks, while budesonide 200µg twice daily caused suppression throughout the 6-week trial.^[43]

Since the reliability of knemometry to reflect risk of long term growth suppression is tenuous at best,^[46] long term studies utilising stadiometry have been evaluated. Growth suppression (average 0.9cm) has been reported with beclomethasone dipropionate (168µg twice daily),^[42] but not mometasone furoate 100µg once daily after contin-

uous daily use for 1 year.^[47] In the former study, HPA axis was not affected.^[42] Although there are no data with fluticasone propionate, long term studies in asthma using 100µg bid showed no significant growth suppression.^[48] One would therefore predict that intranasal fluticasone propionate, with a much lower bioavailability (26.4% vs less than 1%), would have a negligible effect on growth.^[35,37] Two recent long term studies (<3 years) suggest that budesonide 200µg^[49] and 400µg^[50] daily for asthma had little long term effect after transient slowing of growth at 1 year, and patients even obtained normal predicted height.^[51] Children participating in growth studies were mostly between 5 and 11 years of age, although prepubescent children up to 16 years were included in some studies.

These studies suggest that intranasal corticosteroids with high bioavailability can cause short term growth inhibition when used for less than 6 months (e.g. budesonide 200µg twice daily),^[47] or when used on a long term basis (e.g. beclomethasone dipropionate twice daily for ≥12 months).^[42] Therefore, systemic adverse effects may be minimised by using the lowest effective dose, and administration in the morning, particularly with intranasal corticosteroids having the lowest bioavailability.

Finally, it should be emphasised that combining intranasal corticosteroids for AR with inhaled corticosteroids for bronchial asthma can increase the bioavailability of the corticosteroid and, therefore, the risk of systemic adverse effects.

4.4 Mast Cell Stabilisers

Mast cell stabilisers such sodium cromoglycate are less potent than intranasal corticosteroids, but can be useful in relieving nasal itching, rhinorrhoea and sneezing in patients with primarily SAR.^[51] They are approved for children 6 years of age and older, but are well tolerated in even younger children.^[52] Because of the short duration of action of these agents, however, they need to be administered 4 times a day to be effective, thus reducing compliance in most families. The effect of mast cell stabilisers can generally be seen within 4 to 7 days, but may take 2 weeks for more refractory cases. These agents are currently available over the counter. No clinically significant adverse effects are associated with these agents, which could make them more attractive in children.

4.5 Anticholinergic Agents

Cholinergic stimulation of the nose can lead to diffuse rhinorrhoea. This can be prevented or reduced with the use of the topical anticholinergic agent ipratropium bromide, which has been shown to be effective in children with rhinorrhoea secondary to SAR.^[53] The recommended dosage of 0.03% solution is 2 sprays in each nostril twice to 3 times daily for children 6 years of age and older. Ipratropium bromide works quickly and can be used as needed. Adverse effects include dryness of the mouth, which can occur in up to 25% of patients, and a bitter taste.

5. Conclusions and Recommendations

Pharmacotherapy for AR in children should be based on the severity and persistence of symptoms. In a fashion similar to that in bronchial asthma, one can use a step-up programme in cases ranging from mild to severe AR.

For patients with mild, intermittent symptoms that last from hours to a few days, an oral second-generation antihistamine on an as-needed basis might be tried. If nasal congestion is a major factor, pseudoephedrine can be added to the nonsedating antihistamine since there are no nonsedating antihistamine decongestant combinations currently available for use in children. Although first-generation

antihistamines are relatively inexpensive and effective, sedation and reduced cognitive effects preclude their use in most children because these effects in school children outweigh their initial cost advantage. There are no significant advantages in efficacy among the 4 second-generation antihistamines approved for children 11 years of age or younger. This, in addition to only slight differences in onset, duration of action and adverse effects (i.e. slight sedation), makes selection between these agents a difficult task with no clearcut winners. All can be used for SAR and PAR, although cetirizine is the only one approved for both types in the age group discussed.

For patients with moderate to severe symptoms that last more than 1 to 2 weeks despite the use of an antihistamine or antihistamine plus decongestant, intranasal corticosteroids are indicated. However, in children, one might try intranasal cromolyn because of tolerability considerations, although efficacy is modest and compliance might be an issue. To increase efficacy, nasal wash with saline^[54] and 3 or 4 days of topical decongestant may permit better access of the steroid or other topical maintenance medication to the nasal mucosa. Whether there is an advantage in selecting any specific intranasal corticosteroid is far from clear. However, considering the benefit-to-risk ratio, particularly growth suppression in children, the intranasal corticosteroid with the lowest bioavailability, such as fluticasone propionate or mometasone furoate, preferably given in the morning, appear to be a good choice in younger children. Mometasone furoate has specifically been shown not to cause growth suppression.^[47] However, these second-generation intranasal corticosteroids are currently more expensive than the others. Thus, in children with moderate disease who need treatment for less than 1 month, treatment can be started with one of the first-generation intranasal corticosteroids. If symptoms persist, the patient can then be switched to mometasone furoate or fluticasone propionate.

Children receiving intranasal corticosteroids should have their height measured quarterly using a stadiometer, and the lowest dose that controls symptoms should always be used. If AR symptoms are not completely controlled or eye symptoms are

prominent, a second-generation antihistamine may be added to the regimen. Systemic corticosteroids such as prednisone can be used for severe cases of AR for up to 7 days without significant adverse effects or the need for tapering. They can be used in conjunction with intranasal corticosteroids, which are then continued when the prednisone is discontinued. The usual dosage of prednisone is 1 to 2 mg/kg up to 40 mg/day. Fortunately, this is seldom necessary in children with AR.

In patients whose AR is not responding to maintenance therapy with the treatment programme described above, one should strongly consider referral to an allergist in order to identify specific triggers. Attention to avoidance of causative allergens and irritants in the child's environment and, in appropriate cases, immunotherapy can result in increased efficacy of pharmacotherapy and ultimately lessen the need for its chronic use.

Finally, one issue that can affect the outcome of any therapeutic programme is drug adherence. This can be a major problem particularly in children with long term therapy, as children are reluctant to take medication, particularly by the intranasal route. The clinician can improve adherence by selecting oral medications that taste good, require once a day administration, and have an obvious beneficial effect with minimal adverse effects. Nasal sprays can be frightening and painful, particularly to the young child. Education of the patient and family and patience by the medical staff are critical if one is to succeed in treating this chronic condition.

Acknowledgements

The authors would like to thank Marla Nathan and Rhonda Robles for preparation of the manuscript.

References

1. Newacheck PW, Stoddard JJ. Prevalence and impact of multiple childhood chronic illnesses. *J Pediatr* 1994; 124: 40-8
2. Wright AC, Holberg CJ, Martinez FD, et al. Epidemiology of physician diagnosed allergic rhinitis in childhood. *Pediatrics* 1994; 94: 895-901
3. Strachen DP, Sibbald B, Weiland SK, et al. Worldwide variation in the prevalence of symptoms of allergic rhinoconjunctivitis in children: the international study of asthma and allergy in childhood (ISAAC). *Pediatr Allergy Immunol* 1997; 8: 161-76
4. Ray NF, Baranuik JN, Thamer M, et al. Direct expenditure for treatment of allergic rhinitis in 1996, including contributions of related airway illnesses. *J Allergy Clin Immunol* 1999; 103: 401-7
5. Dykewicz MS, Fireman S, Skoner DP, et al. Complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998; 81: 478-518
6. Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. *Ann Allergy Asthma Immunol* 1999; 82: 296-305
7. Vuurman EF, Van Veggel LM, Uiterwijk MM, et al. Season allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993; 71: 121-6
8. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. *J Allergy Clin Immunol* 2000; 105: S616-21
9. Smith L. Special considerations for the child with airway disease. *J Allergy Clin Immunol* 1998; 101: S370-2
10. White M. Mediators of inflammation and the inflammatory process. *J Allergy Clin Immunol* 1999; 103: S378-81
11. Galant SP, Wilkinson R. Allergic rhinitis: assessing current therapeutic options. *Formulary* 1999; 34: 1016-32
12. Simons FER, Simons KJ. The pharmacology and use of H1 receptor antagonist drugs. *N Engl J Med* 1994; 330: 1663-70
13. Naclerio RM, Proud D, Kagey-Sobotoka A, et al. The effect of cetirizine in the early allergic response. *Laryngoscope* 1989; 1999: 596-9
14. Charlesworth EW, Kagey-Sobotoka A, Norman PS, et al. Effect of cetirizine in mast cell mediator release in cellular traffic during the cutaneous late phase reaction. *J Allergy Clin Immunol* 1989; 83: 905-12
15. McNeely W, Wiseman LR. Intranasal azelastine. Review of its efficacy and the management of AR. *Drugs* 1998; 56: 91-114
16. Lasley MV, Shapiro GG. Rhinitis and sinusitis in children. *Pediatr Allergy Immunol* 1999; 19: 437-52
17. Milgrom H, Bender B. Adverse effects of medications for rhinitis. *Ann Allergy Asthma Immunol* 1997; 78: 439-46
18. Bergen Jr SS. Appetite stimulating properties of cypheptadine. *Am Dis Child* 1964; 108: 270-3
19. Meltzer EO. Comparative safety of H1 antihistamines. *Ann Allergy* 1991; 67: 625-33
20. Simons FER. H1 receptor antagonists in children. In: histamine and H1 receptor antagonists and allergic disease. Simons FER, editor. New York: Marcel Dekker, 1996: 329-56
21. Simons FER. H1 receptor antagonists in children. In: Simons FER, editor. Histamine and H1 receptor antagonists and allergic disease. New York: Marcel Dekker, 1996: 175-213
22. Salmun LM, Herron JM, Banfield C, et al. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clin Ther* 2000; 22: 613-21
23. Simons FER, Bergman JN, Watson WTA. The clinical pharmacology of fexofenadine in children. *J Allergy Clin Immunol* 1996; 98: 1062-4
24. 2000 Drug Topics Red Book. Medical Economics Company Inc., Mount Vail, NJ
25. Tinkelman DJ, Kemp J, Mitchell DQ, et al. Treatment of seasonal allergic rhinitis in children with cetirizine and chlorpheniramine. A multi-center study. *Pediatr Asthma Allergy Immunol* 1996; 10: 9-17
26. Baelde Y, Dupont P. Cetirizine in children with chronic allergic rhinitis. *Drug Invest* 1992; 4: 466-72
27. Lutsky BN, Klose P, Melon M, et al. A comparative study of the efficacy and safety of loratadine and terfenadine suspension in the treatment of 3 to 6 year old children with SAR. *Clin Ther* 1993; 15: 855-65
28. Fexofenadine package insert. Feb 2000; Aventis, Kansas City, MO
29. Long J, Meltzer EO, Scott Dawdy K, et al. Safety of fexofenadine HCL in children treated for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; 103: S254

30. Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. *Int J Pediatr Otorhinolaryngol* 1997; 39: 1-8
31. Astelin® Nasal Spray package insert. Cranbury, NJ: Wallace Laboratories, 2000
32. Storms WW, Bodeman SF, Nathan RA, et al. SCH 434: A new antihistamine-decongestant for season allergic rhinitis. *J Allergy Clin Immunol* 1989; 83: 1083-90
33. Laforce C. Use of nasal steroids in managing allergic rhinitis. *J Allergy Clin Immunol* 1999; 103: S388-94
34. Meltzer EO. Treatment options for the child with allergic rhinitis. *Clin Pediatr* 1998; 37: 1-10
35. Allen DB. Systemic effect of intranasal steroids: an endocrinologist's perspective. *J Allergy Clin Immunol* 2000; 106: S179-90
36. Thorsson L, Borgia O, Edsbacker S. Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous spray pump, and powder. *Br J Pharmacol* 1999; 47: 619-24
37. Darrendorf H, Hochhaus G, Meibohm B, et al. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 101: S440-6
38. Kaliner M, Eagleston PA, Matthews KP. Rhinitis and bronchial asthma. *JAMA* 1987; 258: 2851-73
39. Bernstein IL. Is the use of benzalkonium chloride as a preservative for nasal formulation a safety concern? A cautioning note based on compromised mucociliary transport. *J Allergy Clin Immunol* 2000; 105: 39-46
40. Pedersen S, Steffensen G, Ekman S, et al. Pharmacokinetics of budesonide in children with asthma. *Eur J Clin Pharmacol* 1987; 31: 579-82
41. Wolthers OD. Systemic activity vs. systemic adverse effects of nasal glucocorticoids in treatment of allergic rhinitis. *Acta Paediatr* 2000; 89: 1158-66
42. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics* 2000; 105 (2): E23
43. Wolthers OD, Pedersen S. Short term growth in children with allergic rhinitis treated with oral antihistamines, depot and intranasal glucocorticoids. *Acta Paediatr* 1993; 82: 635-40
44. Wolthers OD, Pedersen S. Knemometric assessment of systemic activity of once daily intranasal dry powder of budesonide in children. *Allergy* 1994; 49: 96-9
45. Agertoft L, Pedersen S. Short term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. *J Allergy Clin Immunol* 1999; 104: 948-52
46. Hermanussen M, Burmeister J. Standards for the predictive accuracy of short term body height and lower leg length measures in half annual growth rates. *Arch Dis Child* 1989; 64: 259-63
47. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 2000; 105 (2): E22
48. Allen DB, Bronsky EA, La Force CF, et al. Growth in asthmatic children treated with fluticasone propionate. *J Pediatrics* 1998; 132: 472-7
49. The Childhood Asthma Management Program Research Group. Long term effects of budesonide or nedocromil in children with bronchial asthma. *N Engl J Med* 2000; 343: 1054-63
50. Agertoft L, Pedersen S. Effects of long term treatment with inhaled budesonide on adult height in children with bronchial asthma. *N Engl J Med* 2000; 343: 1064-9
51. Nasalcrom package insert. Rochester, NY: Fisons Corp., 1994
52. Welsh PW, Yuninger JW, Kern AB, et al. Pre-school IgE ragweed antibody levels as a predictor of response to therapy of ragweed hay fever with intranasal cromolyn sodium. *J Allergy Clin Immunol* 1977; 60: 104-9
53. Meltzer EO, Orgel HA, Biondi R, et al. Ipratropium nasal spray in children with perennial rhinitis. *Ann Allergy Asthma Immunol* 1997; 78: 485-91
54. Druce HM, Bonner RF, Patow C, et al. Responsive nasal blood flow to neuro hormones as mentioned by laser doppler velocimetry. *J Appl Physiol* 1983; 57: 1276-80

Correspondence and offprints: Dr *Stanley P. Galant*, 1201 W. La Veta Ave, Suite 501, Orange, CA 92868, USA.