

# A Control Model to Evaluate Pharmacotherapy for Allergic Rhinitis in Children

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**Importance:** Although the question of whether early diagnosis and treatment of pediatric allergic rhinitis (AR) improve disease control is important, a more crucial question is whether we can evaluate the effect of treatment on disease control using an impairment-risk model.

**Objective:** To conduct a systematic review evaluating application of a control model based on domains of impairment and risk (similar to that used for asthma) in pharmacotherapy for children with AR.

**Evidence Acquisition:** We searched the MEDLINE and EMBASE databases (January 1, 1996, through May 31, 2012) for controlled studies lasting 2 weeks or longer in children with confirmed diagnoses of AR, including measures assessing impairment and/or risk of comorbid conditions.

**Results:** Sixteen controlled clinical trials, including more than 3000 children (aged 2-18 years) with AR (seasonal, n=2290; perennial, n=800), met the study criteria. All medication classes improved impairment related to AR, but between-treatment comparisons were limited

because of different assessments. Intranasal steroids improved risk outcomes associated with asthma and obstructive sleep apnea. Small single studies suggested possible effects of oral antihistamines on asthma and sleep-disordered breathing. No risk data were available for nasal antihistamines or montelukast sodium.

**Conclusions:** Treatment of AR, particularly with intranasal steroids, improves disease control in children by reducing disease-associated impairment and risk. All AR medications with proved efficacy probably improve impairment, paralleling symptom reduction. Intranasal steroids may reduce the likelihood of comorbidities that increase health care use. These observations, although limited by different protocols and outcomes measures among studies, support current practice recommendations. Studies that use standardized measures of impairment to permit better comparison and appropriate protocols for risk evaluation are needed.

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**A**STHMA AND ALLERGIC RHINITIS (AR) are systemic inflammatory conditions with commonalities based on pathologic mechanisms and treatments.<sup>1,2</sup> Similar to asthma, the burden of AR can be defined using a control model in which control is defined as the degree to which the manifestations of AR (symptoms, functional impairments, and possible adverse events) are minimized, and the goals of therapy are met.<sup>3,4</sup> Control can then be assessed in terms of impairment and risk (**Table 1**).

In asthma, the control model is used to guide treatment decisions and monitor patient outcomes.<sup>3,4</sup> However, unlike asthma, AR is considered by many patients and clinicians to be “just an annoying condition” despite evidence to the contrary, particularly for children.<sup>5,6</sup> Indeed, AR is more common in children than in adults, affecting up to 40% of children in the United States, 10% more than the highest prevalence estimates for adults.<sup>7-10</sup> These estimates may be low: when asked about AR onset, most adult patients report experiencing symptoms as children, often by the time they entered school.<sup>8</sup> The Pediatric Allergies in America survey reported that of 1068 children with nasal allergies, more than 50% had their conditions diagnosed before age 6 years, with the remainder having their conditions diagnosed during their school-age years.<sup>11</sup>

Like asthma, the early onset of AR symptoms should be a red flag for a potentially serious lifelong effect, and the younger the child, the greater the likelihood of severe and persistent disease and related comorbidities later in life.<sup>12</sup> The negative effect of early symptoms should not be downplayed.

In the Pediatric Allergies in America survey, parents reported that AR symptoms interfered with their children's physical activities, social activities, concentration, school performance, and sleep.<sup>11</sup>

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**Table 1. Definitions and Criteria for Impairment and Risk in Allergic Rhinitis<sup>3,4</sup>**

Term	Definition	Criteria
Impairment	The frequency and intensity of symptoms and functional limitations that the patient is experiencing or has recently experienced	Troublesome symptoms, use of rescue medications; sleep disturbance and associated daytime fatigue; reduced nasal airflow; negative effect on daily activities, including performance and concentration; and diminished overall quality of life
Risk	The likelihood that the patient will experience a progressive increase in symptom severity, comorbid conditions, and/or adverse effects of treatment	Symptom exacerbations, progressive increase in symptom severity over time, comorbid conditions (eg, asthma, rhinosinusitis, otitis media, sleep apnea, adenoidal hypertrophy), and adverse events related to treatment

These findings in a large population survey support observational data<sup>13,14</sup> and data from validated questionnaires,<sup>15-23</sup> all indicating that, as for adults, AR reduces overall quality of life for children.

Of greater concern, perhaps, is that like persistent asthma, AR will over time progress to a chronic mucosal inflammation, increasing symptom severity, nasal obstruction, and the development and severity of other linked airway diseases, such as asthma, rhinosinusitis, and otitis media.<sup>1,2,9,11,24</sup> An increased risk for obstructive sleep apnea (OSA) also has been documented.<sup>1,8,24,25</sup>

The question of interest then is not simply whether early diagnosis and treatment of pediatric AR will improve disease control but whether we can evaluate the effect of treatment on disease control using an impairment-risk model. A systematic review of the literature was undertaken to address the question.

## METHODS

Searches of the MEDLINE and EMBASE databases (January 1, 1996, through May 31, 2012) were conducted using the Medical Subject Headings *allergic rhinitis (seasonal, perennial)* with *antihistamines, comorbidity, impairment, (intra)nasal steroids, and leukotriene antagonists* and limited to children (ages 0-18 years), English language, and humans. Secondary searches used terms for specific medications (eg, beclomethasone dipropionate and cetirizine) and specific comorbid conditions (eg, asthma and otitis media). Additional studies were located by review of the Cochrane Database of Studies and by references in published articles. Studies that met the following inclusion criteria were evaluated: medications approved in the United States for maintenance treatment of AR in children; controlled studies of 2 weeks or longer in children with confirmed diagnoses of AR; effect of treatment on impairment evaluated by quality of life, daily activities, and/or sleep impairment and associated fatigue, daytime drowsiness, decreased concentration, or performance; and/or effect of treatment on the potential risk of comorbid conditions, focusing on asthma, otitis media, sleep apnea, and rhinosinusitis.

## RESULTS

The outcomes of the database search are shown in the **Figure**, and the studies are summarized in eTable 1 (<http://www.jamaped.com>).<sup>14-22,26-32</sup> Most studies were of moderate or high quality.<sup>33</sup> A total of 3090 children were included in the trials that met the inclusion crite-

ria: 3046 with AR and 44 healthy, nonallergic controls. Treatment numbers are given in **Table 2**. Most studies included school-aged children (6-18 years old), 2 studies<sup>16,27</sup> evaluated children 2 to 6 years old (n = 73), and 1 study<sup>28</sup> evaluated children 12 to 17 years old (n = 240).

## IMPAIRMENT

Nine studies<sup>14,16-22,28</sup> reported data about the effect of treatment on measures of impairment: 9 included antihistamines, 5 included intranasal steroids (INs), and 1 included montelukast sodium.<sup>16</sup> All treatment classes showed positive effects on total quality-of-life scores using validated questionnaires<sup>14-22</sup> and on impairment that could be assessed specifically as activity, sleep and learning, and emotions.

### Activity

Improvements in the activity domain of the Pediatric Rhinitis Quality of Life Questionnaire (PRQLQ) were reported on treatment with oral antihistamines (OAHs) in a 4-week study<sup>17</sup> of 177 school-aged children with seasonal AR (SAR) and a 6-week study<sup>20</sup> of 306 school-aged children with perennial AR (PAR) and, separately, on treatment of SAR with olopatadine hydrochloride in school-aged children in two 2-week studies.<sup>21,22</sup> With olopatadine, the improvements in the PRQLQ activity domain were mirrored in improvements in the function domain of the Caregiver Treatment Satisfaction Questionnaire (CGTSQ). Similar, albeit small, improvements in the activity domain were reported for both fluticasone propionate and loratadine compared with placebo after 2 weeks of treatment in 60 children with SAR and using a different survey, the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ).<sup>14</sup> Six weeks of INs in 14 school-aged children with PAR produced significant improvements in the mean "energy level" score of the Rhinitis Quality of Life Questionnaire (RQLQ), a surrogate marker because the RQLQ does not include an activity domain.<sup>15</sup>

### Sleep

For INs, two 6-week studies reported reductions in AR-disturbed sleep in children with PAR: one in 26 preschool-aged children<sup>27</sup> and the other in 14 school-aged children.<sup>15</sup> In the Bender and Milgrom<sup>15</sup> study, significant

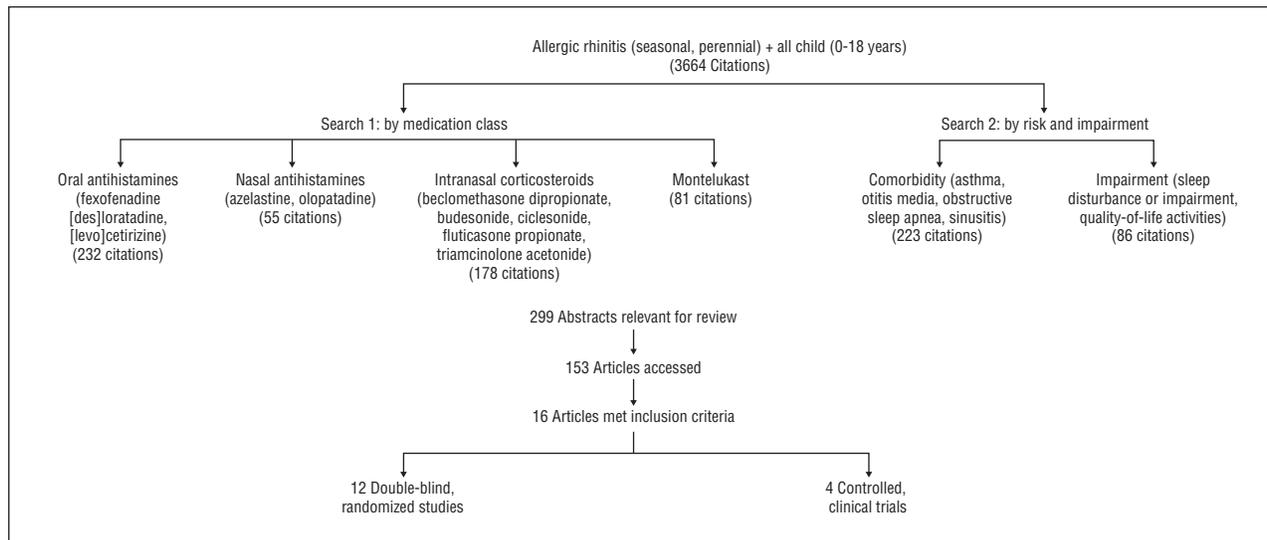


Figure. Search strategy and outcomes.

Table 2. Number of Study Children Treated<sup>a</sup>

Treatment	Children With PAR		Children With SAR		Total		All
	R, DB, PC Studies	Studies With Matched Controls	R, DB, PC Studies	Studies With Matched Controls	R, DB, PC Studies	Studies With Matched Controls	
Intranasal steroids	113	64 <sup>b</sup>	150	48	263	112	375
Oral antihistamines	253	0	239	0	492	0	492
Nasal antihistamines	0	0	1065	0	1065	0	1065
Leukotriene receptor antagonist	20	0	0	0	20	0	20
Placebo	324	0	770	0	1094	0	1094
Healthy, matched control	0	26	0	18	0	44	44
<b>Total</b>	<b>710</b>	<b>90</b>	<b>2224</b>	<b>66</b>	<b>2934</b>	<b>156</b>	<b>3090</b>

Abbreviations: DB, double-blind; PAR, perennial allergic rhinitis; PC, placebo-controlled; R, randomized; SAR, seasonal allergic rhinitis.

<sup>a</sup>Only medications approved in the United States are included.

<sup>b</sup>Includes 50 children who used an oral antihistamine for the first 10 days of a 3-month treatment period.<sup>30</sup>

improvements also were reported for the RQLQ scores for daytime sleepiness, possibly reflecting better nighttime sleep. In addition, significantly better scores were determined for irritability (see “Emotions” subsection in the “Impairment” subsection of the “Results” section) and energy level (see “Activity” subsection in the “Impairment” subsection of the “Results” section), outcomes considered to be indirectly associated with better sleep.<sup>15</sup> Significant improvements in sleep quality ratings were observed for cetirizine and montelukast in a 12-week, placebo-controlled study<sup>16</sup> of 60 children with PAR. Subjectively, parents and caregivers reported that children treated with olopatadine slept more peacefully as symptoms improved during 2 weeks.<sup>22</sup> In contrast, no effect on sleep disruption or daytime fatigue was reported in the 2-week comparison of fluticasone and loratadine.<sup>14</sup>

### Learning

The practical problem domain of the PRQLQ revealed improvements with treatment in the studies evaluating both oral and nasal antihistamines.<sup>17,20-22</sup> In the compari-

son of fluticasone and loratadine, significant improvements in memory and delayed recall vs placebo were determined for the INS but not the OAH using the California Verbal Learning Test.<sup>14</sup>

### Emotions

Both fluticasone and loratadine produced limited improvements compared with placebo in the ARQLQ domain emotional function after 2 weeks of treatment.<sup>14</sup> Other studies used tools that did not include an “emotion domain” per se but revealed significant improvements in measures related to emotions: specifically, in the CGTSQ family disruption score after 2 weeks of treatment with olopatadine in children with SAR<sup>21,22</sup> and in the RQLQ irritability score after 6 weeks of an INS in children with PAR.<sup>15</sup>

### RISK

Five studies (4 INS studies<sup>15,30-32</sup> and 1 OAH study<sup>29</sup>) evaluated the potential effect of treating AR on out-

comes related to comorbid conditions. No data were available for nasal antihistamines or leukotriene receptor antagonists or for the comorbidities otitis media or rhinosinusitis.

### Asthma

Treatment with an INS alone reduced outcomes related to asthma risk as measured by lung function tests and asthma symptom scores.<sup>30-32</sup> A study<sup>30</sup> of schoolchildren with moderate to severe PAR and no history of asthma found that approximately 25% had abnormal lung function as evidenced by a forced expiratory flow between 25% and 75% of vital capacity of less than 80% and reversible airway obstruction. Treatment for 3 months with intranasal budesonide significantly improved all pulmonary function test results ( $P < .04$ ) in conjunction with reductions in AR symptoms. Similar data were reported in an earlier study<sup>32</sup> with triamcinolone acetonide nasal spray. Bronchial hyperresponsiveness measured by methacholine challenge testing was evident in children with symptomatic SAR, regardless of asthma status, although reactivity was greater with concomitant asthma. Triamcinolone acetonide nasal spray decreased bronchial reactivity in both groups, with the greatest response seen in the children with concomitant asthma. In contrast, triamcinolone acetonide nasal spray improved nasal symptoms without affecting the lower airway in a separate study<sup>31</sup> of 60 nonasthmatic children with SAR to grass and/or weed pollens and who also had increased responsiveness to methacholine during their pollen season.

One small placebo-controlled study<sup>29</sup> of 20 children with PAR and mild asthma reported less use of asthma medications after 6 months of cetirizine given for the AR. Other measures of asthma severity were not evaluated.

### Obstructive Sleep Apnea

A potential reduction of risk for OSA was suggested by significant improvements in the quality and pattern of sleep evidenced by polysomnography after 6 weeks of INS treatment in 14 school-aged children with PAR.<sup>15</sup> Treatment also decreased the apnea-hypopnea index, a specific measure of risk ( $P < .004$ ).<sup>15</sup>

### COMMENT

To our knowledge, this is the first application of a control model to evaluate the effect of treating pediatric AR, and, not surprisingly, the body of evidence is limited. Clinical trials were not undertaken in children until recently, and subanalyses of adolescents are usually not performed in studies that include adolescents and adults.

Regarding impairment, it is likely that all treatments found to improve symptoms will have some benefit. Impairment, to a large extent, reflects the specific effect of symptoms on the patient's (and family's) daily activities. All indicated medication classes for pediatric AR improved some measure of impairment (eTable 1), although direct comparisons are difficult because of the use of different assessment measures.

Most of the recent studies used validated surveys, primarily, the PRQLQ and the ARQLQ. Unfortunately, despite the common origin, these use different domains (eTable 2),<sup>34-37</sup> reflected here in the lack of emotional function outcomes for studies using the PRQLQ.<sup>16-22</sup> Data from the ARQLQ for children as young as 8 years suggested positive effects of INSs and OAHs on emotional function,<sup>14</sup> which could not be confirmed in studies using the PRQLQ. More recently, the CGTSQ has been added, providing input from parents and caregivers. Although the CGTSQ does not include emotional function, it includes a score for overall negative effect of the child's AR on family life.<sup>21,22</sup> We considered that score to reflect emotional function, at least in part. In addition, we considered improvements in the irritability score of the RQLQ after treatment with INSs to be an emotional effect and a sleep effect.<sup>15</sup>

Earlier studies rarely used validated questionnaires but often reported symptom-free days or less disruption of sleep, outcomes related to impairment. By way of illustration, the 1996 comparison of fluticasone propionate and loratadine in 240 children with SAR reported better outcomes with fluticasone based on the percentage of symptom-free days (fluticasone, 36%; loratadine, 7.7%;  $P = .0001$ ).<sup>28</sup> We included that as a surrogate marker for impairment, but the question remains whether it is truly a measure of impairment or a measure of efficacy.

Sleep disturbance related to AR symptoms (congestion, sneezing, and rhinorrhea) is one of the most common disease effects and probably accounts for much of the daytime fatigue and associated behavioral changes attributed to AR, including presenteeism, irritability, and poor performance in school.<sup>10,11,14</sup> In adults, relieving symptoms, particularly congestion, with INSs can reduce daytime fatigue.<sup>38</sup> Similar data are reported in children for all medication classes,<sup>15,16,22,27</sup> although one study<sup>14</sup> reported no improvement in sleep disruption or fatigue after 2 weeks of loratadine or fluticasone.

More data for impairment are needed and should reflect use of comparable standard validated assessment tools, such as the ARQLQ (with its emotional function domain) along with the CGTSQ in younger children. Data to assess risk were limited. The potential for reducing the risk and/or severity of asthma and sleep-disordered breathing is suggested for INSs, although the studies were of limited duration (4-24 weeks; eTable 1).

Like adults, children with asthma and concomitant AR require more medical care, use more prescriptions, and have higher medical costs for their asthma.<sup>39-43</sup> Epidemiological studies<sup>44-46</sup> in adults have found that appropriate and early treatment of AR can reduce asthma exacerbations, use of asthma-related urgent care, and need for asthma medications. In these studies, the benefits occurred with both INSs and second-generation antihistamines, but the greatest effects were observed with INSs. In children with PAR and asthma, administration of an aerosol inhaled corticosteroid through the nose (using a face mask or spacer) has been found to improve asthma scores and spirometry to the same degree as administering the molecule by oral inhalation.<sup>47,48</sup> Improvements in lung function and asthma scores were reported in the pediatric studies<sup>30-32</sup> with INSs that met our criteria, and one study<sup>29</sup> with the second-generation antihistamine ce-

tirizine indirectly suggested a positive effect through less use of asthma medications. Whether these outcomes represent true reductions in risk as determined by milder disease severity and altered immunopathologic mechanisms is not known. Longer-term studies are needed. Also of interest, based on the aerosol inhaled corticosteroid data, is whether the newer aerosolized INs alone can treat both AR and asthma.<sup>49</sup>

The effect of AR on sleep spans both control domains: sleep disturbance being a measure of impairment and sleep-disordered breathing an outcome related to risk. Sleep-disordered breathing is a nasopharyngeal effect presenting with nasal congestion and obstruction, habitual snoring, labored breathing, and increasingly severe sleep disruption.<sup>50</sup> It is a topic of increasing concern in children, and untreated or undertreated AR may be one of the factors that can lead to sleep apnea.<sup>51,52</sup> It is unclear whether sleep disruption, sleep-disordered breathing, and AR-associated OSA are separate entities or represent a continuum, from impairment to risk. However, early onset (ie, during toddlerhood) should be a red flag for potential neurobehavioral problems during the school years. This was the conclusion from a recently published survey of 11 000 children: children with sleep-disordered breathing before age 3 years were significantly more likely to demonstrate deficits in emotional regulation, attention, and social interaction at age 7 years.<sup>51</sup>

One study<sup>15</sup> that met the inclusion criteria suggested that treatment with INs decreased the negative sleep patterns associated with development of OSA in 4- to 9-year-old children with PAR. Similar results were subsequently reported for combined OAH and INs treatment using sleep actigraphy in older children with SAR, but doses were not specified, so this study could not be included in the data table.<sup>53</sup> More data are needed to make specific statements regarding treatment effect on sleep-disordered breathing and risk for OSA. Intranasal steroids have been proposed as a first-step alternative to surgery for some children with OSA related to adenotonsillar hypertrophy, and studies to evaluate aerosol INs have been recommended because of their potentially greater reach into the airways.<sup>49,54</sup> A recent Cochrane review<sup>54</sup> reported a potential benefit of INs for children with mild-to-moderate OSA.

Another common comorbidity of childhood AR is otitis media, which may cause hearing loss and associated developmental delay.<sup>55,56</sup> Treatment of AR with antihistamines, decongestants, INs, and combinations has been proposed as a means to lessen otitis media and hearing loss, but these data are unclear. Recent Cochrane reviews of randomized, well-controlled trials reported no benefits from using these agents to treat otitis media in children—either for symptom improvement that might translate into reduced impairment or for resolution of disease or reduced disease severity, measures of risk.<sup>55,56</sup> No studies met all of our inclusion criteria. Of interest, though, is an older long-term evaluation of INs (dose not specified) given for AR in 120 children 3 to 9 years old who also had chronic otitis media with effusion. Treatment decreased AR symptoms and also increased ventilation of the middle ear, improved hearing, and reduced the need for grommet insertion.<sup>57</sup>

The lack of appropriate trials for the systematic review is disappointing. Although a large number of controlled trials were identified, few met the set criteria, largely because of differences in protocols and outcome measurements. The lack of standardization in how studies are reported further limited direct comparisons. Similar challenges to analyzing data were identified in a comprehensive meta-analysis of AR medications in children and adults.<sup>6</sup>

For risk, the short duration of the identified studies (4-24 weeks) is not optimal. Longer-term trials are needed to address how treatment affects the development of comorbid conditions over time. For example, as early as 1968, it was suggested that long-term immunotherapy might reduce the development of asthma in children with hay fever.<sup>58</sup> Since then, studies of schoolchildren with hay fever treated by immunotherapy (subcutaneous<sup>59,60</sup> or sublingual<sup>61</sup>) for 3 to 5 years have found significant reductions in the number of children who develop asthma compared with their peers treated with medications alone. Similarly, the Early Treatment of the Atopic Child study<sup>62</sup> used the onset of asthma as the primary end point for an 18-month evaluation of OAH treatment in infants with atopic dermatitis, assessing the benefits of therapy over time for preventing serious comorbidity. These types of protocol are needed to better assess whether medications, especially INs, would similarly reduce risk.

In addition, we could not evaluate adverse effects of treatment, an important component of risk. Many studies only listed adverse effects, and “weighting” values to compare local adverse effects of different medication classes could not be applied.

Over time, undertreated (or untreated) AR contributes to increasing disease severity, diminished quality of life, and the development of serious comorbid conditions.<sup>1</sup> How long it takes for this to occur is unclear and requires further study. However, it is interesting that surveys of children with AR reveal more seasonality and intermittent symptoms than adults, who report more perennial disease.<sup>11</sup> Is the progression to year-round symptoms illustrative of increased disease severity? We do not know because children with seasonal symptoms have yet to be followed up to adulthood, and the adults surveyed with perennial disease generally were not questioned about their childhood symptoms. Data are needed.

On the basis of the limited data available, all AR medications are likely to improve impairment to some degree. In addition, appropriate use of INs may prevent progression to more severe disease and the risk of comorbidities that increase health care use, specifically asthma and sleep-disordered breathing. The findings support current guidelines and practice parameters that recommend INs as the most effective maintenance therapy for AR, regardless of patient age.<sup>10</sup>

A critical take-away from this systematic review is the lack of appropriate data for comparing medication classes approved to treat pediatric AR in the United States, particularly in relation to evaluating the control model. Impairment and risk are agreed on outcomes for managing a chronic condition such as AR, but current study designs, particularly in children, are not conducive to providing that information or allowing comparisons of treat-

ments. Standards that include appropriate indicators for impairment and duration for risk are needed.

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