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Evidence Report/Technology Assessment

Number 54

Management of Allergic and Nonallergic Rhinitis

Summary

Introduction

Twenty to 40 million Americans are affected by allergic rhinitis, making it the sixth most prevalent chronic illness. The peak prevalence of allergic rhinitis is observed in children and young adults. Prevalence estimates range from 10 to 30 percent of adults and up to 40 percent of children, making allergic rhinitis currently the most common chronic condition found in children. Furthermore, in the past 30 years, there has been a dramatic increase in the prevalence of allergic rhinitis in "Westernized" societies; and studies from England, Sweden, and Australia have reported a doubling of prevalence over this time.

Allergic rhinitis is responsible for at least $1.8 billion annually for the direct cost of physician visits and medication expenses, or nearly 2.5 percent of the $47 billion annual direct cost for respiratory treatment in the United States. Moreover, the estimated value of lost productivity to employers and society resulting from allergic rhinitis approaches nearly $3.8 billion annually. In the mid-1990s the resulting total annual cost for allergic rhinitis amounted to $5.6 billion.

Rhinitis, in which the classification by etiology may be allergic or nonallergic, is a disorder characterized by inflammation of the mucous membranes lining the nasal passages. The symptoms of allergic rhinitis, which can be difficult to accurately distinguish from those of vasomotor rhinitis, typically include sneezing, nasal itch, rhinorrhea, nasal obstruction, post-nasal drip and occasionally nasal pain. Based on timing or periodicity of symptoms, allergic rhinitis may be classified as either seasonal or perennial.

The symptoms of allergic rhinitis result from exposure to allergens in a susceptible (sensitized) individual. Allergens include pollen, grass, weed, and house-dust mite etc., and symptoms are triggered by the interaction of an allergen with immunoglobulin E (IgE) molecules which bind through the high affinity IgE receptor to the surface of mast cells in the nasal mucosa or to circulating basophils. Recognition of the allergen by the IgE antibody leads to activation of the mast cell or basophil, causing the release of a variety of mediators, including histamine and leukotrienes, which in turn attract inflammatory cells from the peripheral circulation. This orchestrated chain of events results in the characteristic clinical features of allergic rhinitis.

Nonallergic rhinitis is characterized by sporadic or persistent perennial nasal symptoms that do not result from IgE-mediated immunopathologic events. The symptoms can be similar to allergic rhinitis, but with a less prominent nasal itch and conjunctival irritation. The distinction between allergic and nonallergic rhinitis can be difficult to distinguish clinically, but the distinction may be important for prognosis and treatment decisions.

Methods

The evidence report on the management of allergic rhinitis from which this summary is taken is based on a systematic review of the literature. The American Academy of Family Physicians served as the science partner on this report. The American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and

Immunology also provided technical experts to work with the staff of the New England Medical Center Evidence-based Practice Center (EPC). Through a series of teleconferences, this panel of experts worked to identify specific issues and refine key questions central to this report, and they nominated peer reviewers who were not involved in the synthesis of evidence or in the writing of this report. The EPC then conducted a comprehensive search of the medical literature to identify studies addressing the key questions specified by the panel on the management of allergic rhinitis and nonallergic rhinitis.

With input from the science partners, the following questions were formulated:

Question 1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor)?

1.1 What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination, and diagnostic testing?

1.2 What is the minimum level of testing necessary to differentiate allergic from nonallergic rhinitis?

Question 2. Is differentiating allergic from nonallergic rhinitis important?

2.1 Are treatments different?

2.2 Are outcomes different?

Question 3. How does one treat nonallergic and allergic rhinitis?

3.1 For nonallergic rhinitis:

a) What is the efficacy of antihistamines (all classes), nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics, or cromoglycate compared with placebo?

b) What are the side effects due to antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics, or cromoglycate?

3.2 For allergic rhinitis:

a) What is the efficacy of antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy (desensitization), nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium).

b) What are the side effects/adverse events due to antihistamines, nasal corticosteroids, sympathomimetics, or leukotriene modifiers?

3.3 Do efficacy and side effects of treatment vary by severity of rhinitis or patient characteristics?

Question 4. How does treatment of allergic rhinitis impact on the development of asthma?

4.1 What is the likelihood of developing asthma with untreated allergic rhinitis (natural history)?

4.2 How does treatment of allergic rhinitis affect the likelihood of developing asthma?

4.3 How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis?

Studies for the literature review were identified primarily through a MEDLINE® search of English language literature published between 1966 and October 2000. The investigators also consulted technical experts and examined references of published meta-analyses and selected review articles to identify additional studies. Articles that met the inclusion criteria were incorporated in the evidence report.

For this evidence report, the EPC compiled evidence tables of study features and results, appraised the study methods, and summarized results. If published meta-analyses were available on specific treatment topics, the effects of treatments evaluated in these reports were assessed.

Inclusion Criteria

The MEDLINE® search yielded 3,354 titles. The titles and abstracts of these citations were screened and 228 full-length articles were retrieved for further examination. Reports published only as abstracts in proceedings were rejected from further consideration. Specific inclusion criteria were developed for each of the key questions. Included for questions 1 and 2 were all cross-sectional and prospective studies evaluating diagnostic methods in allergic and nonallergic rhinitis including, but not limited to, allergen skin testing, serum IgE measurements, nasal provocation challenge, nasal rhinomanometry and nasal biopsy. Included for question 3 were randomized controlled trials of the following interventions in allergic rhinitis: antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy, nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene modifers and sympathomimetics. Included in the treatment of nonallergic rhinitis were randomized controlled trials of antihistamines, nasal corticosteroids, sympathomimetic agents, leukotriene modifers, anticholinergics and cromoglycate. Included for question 4 were prospective studies evaluating the relationship between

allergic rhinitis and subsequent development of asthma or bacterial sinusitis.

Grading and Summarizing of the Evidence

The evidence-grading scheme used assessed four dimensions that are important for the interpretation of the evidence:

- Study size
- Applicability
- Summary of efficacy and safety outcomes
- Methodological quality

Reporting the Evidence

The evidence found for the management of allergic and nonallergic rhinitis is summarized in two complementary forms in the full evidence report: first, the evidence tables provide detailed information on key features of study design and results of all the studies reviewed; second, a narrative and tabular summary of the strength and quality of the evidence of each study is provided for each comparison.

Results

General Observations

In addition to the conclusions described in this summary, the investigators believe that the data support the following observations:

- Most of the clinical trials were supported by pharmaceutical companies.
- There were no studies that addressed the specific question of practical clinical interest: Is differentiating allergic rhinitis from nonallergic rhinitis important? Are treatments or outcomes different? Differentiation of allergic from nonallergic rhinitis is important if treatments are significantly different and if the outcomes of treatment including prevention of complications differ in response to those treatments. However, similar treatments are frequently employed in the two conditions.
- There were few trials in nonallergic rhinitis and their size was generally small. Thirteen trials conducted between 1982 and 1999 enrolled about 450 patients. In several comparisons of interest, there were only 20 to 30 patients in the trials. There were no studies that examined the efficacy of leukotriene modifiers. There were only two randomized controlled trials, with a total of 90 patients, that examined the role of oral decongestants in the relief of symptoms of nasal congestion.
- The trials were heterogeneous with respect to inclusion criteria, dosage regimens, study duration and reporting of results.
- The lack of reporting of data on variability of the outcome estimates made it difficult, if not impossible, to perform meta-analysis.
- Although almost all the studies analyzed were randomized controlled trials, many did not meet high standards for methodological quality.
- There were no specific studies of the pediatric population. Even though some studies may have enrolled patients in pediatric ranges, separate data were not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Specific Results

- No studies were found that specifically sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms, signs on physical examination, or the presence or absence of comorbid conditions.
- The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature. There were no studies addressing the question of minimum level of diagnostic testing necessary to differentiate between allergic and nonallergic rhinitis that met the inclusion criteria.
- No diagnostic test has been specifically developed to diagnose nonallergic rhinitis.
- Given the absence of studies to differentiate nonallergic rhinitis, diagnostic testing rather than symptoms or signs is necessary to differentiate isolated vasomotor or nonallergic rhinitis from allergic rhinitis. Only one small recent study suggests that total serum IgE may be as useful as specific allergy skin prick tests which, in turn, are more useful than radioallergosorbent testing (RAST) in confirming a diagnosis of allergic rhinitis.

Nonallergic Rhinitis: Efficacy of Treatment

- **Antihistamines (all classes) versus placebo:** Only one study which examined the role of antihistamines in the treatment of nonallergic rhinitis met the inclusion criteria. However, because the antihistamine used an ingredient in an antihistamine-decongestant combination product, the outcomes related to the

antihistamine component of this drug cannot be separately identified. The Food and Drug Administration (FDA) recently approved a nasal topical product – azelastine (an H1 antihistamine) – for the treatment of vasomotor rhinitis.

- **Nasal corticosteroids:** Two of three identified studies employed budesonide and the other used beclomethasone. One study indicated that the symptoms of nasal congestion were improved by budesonide without alteration in other symptoms of nonallergic rhinitis. In the other two studies, comparison was made between the nasal corticosteroid and nasal ipratropium bromide. One study favored the nasal corticosteroid but the other failed to differentiate between the two interventions on the basis of symptom relief. Intranasal corticosteroids have been recommended for long-term therapy in nonallergic rhinitis and the two are approved by the FDA.
- **Sympathomimetics versus placebo:** Only two randomized controlled studies were identified which examined the role of oral decongestants (phenylpropolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on relief of symptoms of nasal congestion. However, the FDA has urged companies marketing phenylpropanolamine to voluntarily withdraw the drug from the market while the FDA initiated regulatory actions to mandate such withdrawals. The only currently available orally active decongestant, pseudoephedrine, was not identified in any clinical trial concerning management of nonallergic rhinitis.
- **Leukotriene modifiers versus placebo:** No studies were identified looking at the efficacy of leukotriene modifiers in the treatment of nonallergic rhinitis.
- **Anticholinergics versus placebo:** Each of these five trials studied intranasal ipratropium bromide and each study demonstrated the efficacy of ipratropium in reducing nose blowing frequency and rhinorrhea.
- **Cromoglycate versus placebo:** Two randomized controlled trials identified as looking at the effects of cromoglycate in nonallergic rhinitis recorded improvement in symptoms of rhinitis with active treatment compared to placebo.
- **Side effects/adverse effects:** There were no side effects or adverse events reported in the studies of antihistamines or nasal corticosteroids. There is a report on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. In the two studies comparing cromoglycate, there were no significant adverse effects associated with its use. In only one of the two studies involving sympathomimetics were adverse events such as drowsiness, nausea and headache described. Significant side effects of nasal dryness and nasal irritation were recorded in three of the five studies looking at ipratropium.

Allergic Rhinitis: Efficacy of Treatment

- **Antihistamines vs. nasal corticosteroids:** One published systematic review reported that for six individual nasal symptoms studied, as well as for overall nasal symptoms, nasal corticosteroids produced significantly greater relief than did oral antihistamines. The search identified eight new studies that were not included in this meta-analysis. Seven of the studies favored intranasal corticosteroids over antihistamines both in respect to improvement in global nasal symptoms as well as in most individual nasal symptoms. One study showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies clearly favor the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are true for both seasonal allergic rhinitis and perennial allergic rhinitis.
- **Antihistamines vs. immunotherapy:** No randomized controlled trials were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered as a long-term disease-modifying treatment measure requiring months to years of treatment, whereas antihistamines are most often used for immediate symptom relief. Therefore, direct comparisons with respect to effectiveness/efficacy are not likely to be undertaken.
- **Nasal corticosteroids versus immunotherapy:** No randomized controlled trials were identified which directly compared immunotherapy with intranasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis.
- **Sedating versus nonsedating antihistamines:** With respect to symptom alleviation in seasonal and perennial allergic rhinitis, study results indicate no consistent benefit of sedating antihistamines over nonsedating antihistamines. However, the side-effect profile favors use of nonsedating antihistamines.
- **Other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium):** Studies provide strong support for the beneficial effect of cromoglycate in the management of both seasonal and perennial allergic

rhinitis. Two clinical trials were identified which looked at the effects of decongestant drugs in allergic rhinitis and suggest some benefit in relief of nasal congestion but not other symptoms. The trial of ipratropium showed no significant differences between dosages of ipratropium but there was significant reduction in rhinorrhea and postnasal drip.

- **Side effects/adverse events:** A majority of the studies reported no major adverse events associated with the use of antihistamines. In those studies where major adverse events were reported, somnolence, dry mouth, dizziness and headache were identified most frequently. These symptoms were seen almost exclusively with the sedating antihistamines. Epistaxis, headache and pharyngitis were the most frequently reported side effects of nasal corticosteroids. None of the studies reported systemic side effects from intranasal corticosteroids in the short-term treatment studies. There is a report on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. No major adverse events were reported in studies of cromolyn; among the minor reported side effects were high frequency of nasal irritation, headache and nasal congestion.

Effect of Selected Variables on Efficacy and Side Effects

No data to address this question were found. There were no studies that categorized patients by disease severity or concurrent disease while addressing either efficacy or safety.

Likelihood of Developing Asthma With Untreated Allergic Rhinitis

Studies addressing the temporal relationship between onset of rhinitis symptoms and onset of asthma symptoms have revealed that a significant proportion of patients experience rhinitis symptoms in advance of the development of clinical symptoms of asthma. Two prospective cohort studies have been published which show an increased likelihood of patients with allergic rhinitis developing asthma over time.

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Asthma

No study was identified which addressed the question of whether treatment of allergic rhinitis can actually prevent the development of asthma. The data, however, suggest a mechanistic linkage between these two diseases and the ability of nasal corticosteroids in treating allergic rhinitis to impact certain characteristics of asthma (e.g. seasonal increase in bronchial hyper-responsiveness).

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Bacterial Sinusitis

The link between allergic rhinitis and rhinosinusitis is known. Cross-sectional studies have shown an increased prevalence of acute and chronic bacterial sinusitis among allergic rhinitis patients. Similarly, there is an increased prevalence of atopy and allergic rhinitis among patients with chronic bacterial sinusitis. However, in order to determine the effect of treatment of allergic rhinitis on the development of bacterial sinusitis, data from prospective studies on the outcomes of treated and untreated allergic rhinitis are needed. No such studies meeting these criteria were identified.

Future Research

More research on key clinical questions in allergic and nonallergic rhinitis should be funded by nonproprietorial sources. Almost every trial that reported funding sources was funded by a pharmaceutical company. These trials usually address issues of the drug of one company versus the drug of another company. Thus, important questions about optimal clinical management of patients are often not addressed or relevant clinical information is unavailable.

Better assessment of allergic and nonallergic rhinitis is required. The minimum amount of diagnostic testing required to differentiate between these two conditions remains uncertain. Research should be conducted to determine the type and panel size of inhalant aeroallergen skin testing and on RAST. Research on whether recommendation/implementation of standard measures to minimize exposure to indoor aeroallergens, such as house-dust mites, pet allergens and cockroaches, might be cost effective in the management of chronic rhinitis. Further research should be conducted to determine the effects of minimizing exposure to allergens, even in the absence of differentiation between allergic and nonallergic rhinitis and even without determining a patient's precise allergic sensitivities.

Additional studies are needed to address other specific questions:

- The role of antihistamines for symptom relief in nonallergic rhinitis.
- The role of nasal corticosteroids in nonallergic rhinitis. If it can be rigorously documented that nasal corticosteroids are helpful to treat nonallergic rhinitis, the need to differentiate from nonallergic rhinitis may be lessened.
- The role of antihistamines in nonallergic rhinitis with eosinophilia syndrome (NARES).
- The role of cromoglycate use in nonallergic rhinitis.

- The role of allergen avoidance in patients with allergic rhinitis. Would this approach obviate the need for diagnostic testing in a substantial proportion of patients?
- The efficacy of a myriad of complementary therapies now being employed in the treatment of nonallergic rhinitis.
- Whether interventions for allergic rhinitis have preventive effects on asthma.

Higher quality studies and more studies for multiple but standardized research variables are needed. Standards for clinical trials in allergic and nonallergic rhinitis must adhere to those for clinical trials in general. After the FDA approval of a drug, additional high-quality trials of rhinitis relief are still needed to understand the optimal use of the drug in specific populations and settings. The trials should enroll greater numbers of patients for longer intervals than has generally been true in the past; apply blinding and "active" placebos when appropriate or uniform control treatments otherwise; and employ adequate between-arm washout intervals, and assess side effects.

A major limitation of the data identified in this analysis is the heterogeneity of inclusion and exclusion criteria, diagnostic tests, outcome measures, and circumstances of testing found in the randomized controlled trials. This situation makes synthesizing the research results confusing and difficult. Reducing this heterogeneity by implementing a set of standard research variables would greatly assist when comparing studies. The characteristics of patients enrolled in studies also need to be clearly defined. This is critical to ensure internal validity and to allow for study comparisons, data analyses, and in the application of the results to clinical practice. Standardization of research variables would also aid in identifying the best strategies for identifying patients with allergic or nonallergic rhinitis.

Ordering Information

The full evidence report from which this summary is taken was prepared for AHRQ by the New England Medical Center Evidence-based Practice Center, Boston, MA, under contract No. 290-97-0019. It is expected to be available in late spring 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 54, *Management of Allergic and Nonallergic Rhinitis*. Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.

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AHRQ Pub. No. 02-E023
May 2002

ISSN 1530-440X