Chapter 4. Conclusions

Overview

This report summarizes the scientific evidence on four specific questions and associated subquestions in the diagnosis and treatment of allergic and nonallergic rhinitis. The results presented in Chapter 3 are based on the screening of 3,354 MEDLINE titles and 228 full articles, 86 of which were the RCTs and the two prospective cohort studies analyzed in this report. The analysis also describes the limitations of the existing evidence base related to the questions of interest.

General Observations on the Studies Analyzed

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

- Most of the clinical trials were supported by pharmaceutical companies.
- There are 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.
- The number and size of trials in nonallergic rhinitis were small overall. There were 13 trials, from the period 1982 through 1999, which enrolled some 450 patients. In several comparisons of interest, trials were very small - 20 to 30 patients. There were no studies examining the efficacy of leukotriene modifiers. There were only two randomized controlled studies, with 90 enrolled patients, which examined the role of and oral decongestants for the relief of symptoms of nasal congestion. The FDA has urged companies marketing that decongestant, phenylpropolamine, to voluntarily withdraw the drug from the marketplace, while it initiated regulatory actions to mandate such withdrawals.
- Almost all the studies analyzed were RCTs, though most of the evidence for efficacy is based on studies that were given a 'B' or 'C' methodological quality rating, indicating the failure to 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 was not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Conclusions about Specific Questions

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

In this analysis, there were no studies identified hat specifically sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms, or signs on physical

examination, or the presence or absence of comorbid conditions. More importantly, no studies addressing the question of what minimum level of diagnostic testing is necessary to differentiate between allergic and nonallergic rhinitis met the criteria described in the methods section of this report. No diagnostic test has been specifically developed to diagnose nonallergic rhinitis.

Given the absence of studies addressing this question, we can only report that, based on current clinical practices and the analysis of the inclusion criteria employed in studies of nonallergic rhinitis, diagnostic testing rather than symptoms or signs is generally recommended to differentiate isolated vasomotor rhinitis from allergic rhinitis. Diagnostic tests employed fall into two categories: allergy skin testing and RAST.

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

The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature. The study by Ng, Warlow, Chrishanthan, et al. (2000) suggests that total serum IgE may be as useful as specific allergy skin prick tests, which, in turn, are more useful than RAST-type testing in confirming a diagnosis of allergic rhinitis.

2. Is differentiating allergic from nonallergic rhinitis important? Are treatments different? Are outcomes different?

While the importance of distinguishing between allergic and nonallergic rhinitis has not been addressed directly and specifically by the published literature, the results suggest that this distinction is important. Different modalities of pharmacologic therapy for each diagnosis are supported by the literature and, perhaps more importantly, complications or comorbid conditions such as asthma and sinusitis can be impacted by the choice of pharmacotherapy for the underlying rhinitis. One of the potential benefits of differentiating allergic from nonallergic rhinitis would be that only allergic rhinitis can benefit from environmental control measures and immunotherapy.

Certain treatment modalities are well-established in the management of allergic rhinitis (for example, intranasal corticosteroids and oral antihistamines). A small number of studies (3, with a total of 97 patients) have looked at the benefit of nasal steroids in the treatment of nonallergic rhinitis, one with conficting results. However, intranasal corticosteroids are recommended for long-term therapy in nonallergic rhinitis. The FDA has approved two nasal corticosteroids for treatment of nonallergic rhinitis and has also approved one nasal topical product – azelastine (an H1 anithistamine) for treatment of vasomotor rhinitis.

There is some evidence for linkage between allergic rhinitis and asthma and there is also a small body of evidence indicating that appropriate treatment of allergic rhinitis by intranasal corticosteroids may have salutary effects on the features of asthma. Sinusitis is also a well-described secondary complication of allergic rhinitis. Therefore, it is possible that inappropriate diagnosis and treatment of allergic rhinitis may increase the pharmacoeconomic and socioeconomic burden of sinusitis.

3. How does one treat nonallergic and allergic rhinitis?

Nonallergic Rhinitis - Efficacy of Treatments

Antihistamines (all classes) versus placebo. Only one published study meeting the criteria for inclusion examined the role of antihistamines in the treatment of nonallergic rhinitis. Because the antihistamine was used as part of an antihistamine-decongestant combination product, outcomes related to the antihistamine component of this drug cannot be separately identified. Two additional

studies published after the completion of the literature search (Banov and Lieberman, 2001, Gehanno, Deschamps, Garay et al., 2001) demonstrated the efficacy of azelastine nasal spray for the treatment of vasomotor rhintis.

Effect of nasal corticosteroids. Though it is commonly assumed that many physicians recommend a therapeutic trial with nasal corticosteroids in the management of nonallergic rhinitis, there were only three studies identified which examined the efficacy of nasal corticosteroids in the treatment of nonallergic rhinitis. Two of the three studies employed budesonide and the other used beclomethasone. One study indicated that the symptoms of nasal congestion could be 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 and the other study failed to differentiate between the two on the basis of symptom relief. Intranasal corticosteroids have been recommended for long term therapy for nonallergic rhinitis (Settipane and Lieberman, 2001) and two nasal corticosteriods have FDA approval.

Sympathomimetics versus placebo. Only two randomized controlled studies were identified which looked at the role of oral decongestants (phenylpropanolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on relief of symptoms of nasal congestion. Phenylpropanolamine was demonstrated in both trials to be helpful in the management of nasal congestion when used at sufficient dosages (e.g. 100 mg per day dosage). No major impact on the other associated symptoms experienced by patients with nonallergic rhinitis was observed in these studies.

While small in number, these studies do suggest a role for decongestants in treatment of nonallergic rhinitis with specific emphasis on the 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 of the clinical trials concerning management of nonallergic rhinitis.

Leukotriene modifiers. No studies were identified looking at the efficacy of leukotriene modifiers in the treatment of nonallergic rhinitis.

Anticholinergics. Each of five studies identified in the analysis indicated a significant benefit from use of nasal ipratropium bromide (a topically applied anticholinergic agent) in the treatment of the symptom of rhinorrhea (increased nasal secretions) associated with nonallergic or vasomotor rhinitis. Relief of the symptom is dose-dependent - dosing often up to four times a day was required to achieve a significant clinical benefit. Other symptoms such as nasal congestion, nasal itching and sneezing do not appear to be benefited by ipratropium bromide.

Cromoglycate. Both of the two RCTs that examined the effects of cromoglycate in nonallergic rhinitis recorded improvement in symptoms of rhinitis with active treatment compared to placebo. Not all symptoms were improved by cromoglycate in either study and the specific symptoms which benefited most differed between these two studies. However, although small in quantity, the data appear to indicate that sodium cromoglycate may have a role in the management of nonallergic rhinitis.

Side-effects/adverse events. There were no side-effects or adverse events reported in the studies of antihistamines or nasal corticosteroids. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported 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. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

In the two studies examining cromoglycate, no significant adverse events were associated with use. In only one of the two studies involving sympathomimetics were adverse events such as drowsiness, nausea and headache described. This study (Broms and Malm, 1982), involving a combination product (antihistamine plus decongestants) also had patients who described micturition difficulties, which were presumed to be related to the anticholinergic activity of the antihistamine component. Significant side-effects of nasal dryness and nasal irritation were recorded in three of the five studies looking at ipratropium in the treatment of nonallergic rhinitis. Overall, these treatment modalities are very well tolerated and devoid of major side-effects.

In conclusion, the literature concerning treatment of nonallergic rhinitis is scant and no single agent is identified as being uniformly effective in controlling all the symptoms associated with this condition. All treatments appear relatively free of major side-effects. Oral decongestants are effective in controlling the symptom of nasal congestion and ipratropium bromide is beneficial in the management of rhinorrhea. With the exception of azelastine for treatment of vasomotor rhinitis, there is little published evidence for use of antihistamines or nasal corticosteroids for the management of nonallergic rhinitis.

Allergic Rhinitis - Efficacy of treatments

Antihistamines versus nasal corticosteroids. There is strong evidence for the beneficial effects of nasal corticosteroids in the management of allergic rhinitis, and these agents are significantly superior to antihistamines.

The recent meta-analysis by Weiner (Weiner, Abramson, and Puy, 1998) of 17 RCTs published up to 1997 compared intranasal corticosteroids with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. The analysis included several different nasal corticosteroid preparations and several different antihistamines including both nonsedating and sedating antihistamines. For the six nasal symptoms studied as well as for overall nasal symptoms score, nasal corticosteroids produced significantly greater relief than did oral antihistamines. The specific symptoms that were improved included nasal blockage, nasal discharge, sneezing, nasal itching, and postnasal drainage. There were no significant differences identified between treatments for nasal discomfort, nasal resistance, or eye symptoms.

Our search identified eight additional studies that were not included in the Weiner meta-analysis. Seven of the studies favored intranasal corticosteroids over antihistamines both with respect to improvement in global nasal symptoms as well as most individual nasal symptoms. One study showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies show very clear benefits for the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are similar for seasonal allergic rhinitis and perennial allergic rhinitis.

Antihistamines versus immunotherapy. No RCTs were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered a long-term disease modifying treatment measure requiring months to years of treatment whereas antihistamines are often used for immediate symptom relief. Therefore direct comparisons with respect to effectiveness/efficacy are not likely to be undertaken.

Nasal corticosteroids versus immunotherapy. For reasons similar to those above, no RCTs 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 allergic (seasonal) rhinitis, study results indicate no consistent benefit of sedating antihistamines over

nonsedating antihistamines. In the eight randomized controlled clinical trials comparing sedating and nonsedating antihistamines in the treatment of seasonal allergic rhinitis, approximately equivalent numbers of patients seemed to benefit in terms of symptom relief from nonsedating antihistamines as from sedating antihistamines, though the side effect profile favors nonsedating antihistamines. Similar observations were seen with perennial allergic rhinitis except perhaps for a tendency to favor sedating antihistamines. The benefits were seen across a range of symptoms with no specific symptom appearing to be better improved by one class of treatment or the other.

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. Eighteen studies (14/18 studies of seasonal allergic rhinitis and 4/11 studies of perennial allergic rhinitis) included documentation of patient preference or patient willingness to use the drug in the future. In 17 studies there was a clear-cut preference for the active ingredient (cromoglycate). Cromoglycate seems to have higher efficacy in seasonal allergic rhinitis than it does in perennial allergic rhinitis. In those studies that looked at different dosing regimens, higher doses (including higher frequency of dosing) were more effective.

Two clinical trials were identified looking 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 documented no significant differences between dosages of ipratropium but 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 analyzed. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported 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. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

No major adverse events were reported in studies of cromolyn; minor reported side-effects included a high frequency of nasal irritation, headache, and nasal congestion.

Effect of Selected Variables on Effectiveness/efficacy and Side-effects

We found no data to address this question. None of the studies categorized patients by disease severity or concurrent disease when addressing either efficacy or safety.

Review of Relevant Published Meta-analyses

Two relevant meta-analyses were identified in the published literature. The meta-analysis of randomized controlled clinical trials comparing the use of nasal corticosteroids and antihistamines in the management of allergic rhinitis has been described above (Weiner, Abramson, and Puy, 1998). It shows a strong tendency to significantly greater improvement in all symptoms of allergic rhinitis by use of nasal corticosteroids when compared to either sedating or nonsedating antihistamines.

In a recent meta-analysis of specific allergen immunotherapy in the management of allergic rhinitis, Ross, Nelson, and Finegold (2000) document significant benefit for this therapy in the

management of allergic rhinitis. Benefit is seen both with respect to symptom control and symptom medication usage. No other meta-analysis of interest was identified in this analysis.

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

Likelihood of Developing Asthma with Untreated Allergic Rhinitis

As our understanding of allergic rhinitis and asthma is increasing, it is becoming clear that the pathophysiology of the two diseases is very similar. The inflammation seen in the tissues is of similar type in both conditions and many of the inflammatory mediators appear to be similar. Furthermore, in addition to the high frequency of concurrence of these diseases in individual patients, there is now evidence of measurable abnormalities in the airways of patients without clinical manifestations of asthma who suffer with allergic rhinitis. Thus, subclinical asthma appears to be identifiable in patients with 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. A small number of prospective cohort studies (Anderson, Pottier, and Strachan, 1992; Settipane, Hagy, and Settipane, 1994) have been performed and demonstrate an increased likelihood of developing asthma over time in patients with allergic rhinitis.

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 link between these two diseases and an ability to impact certain characteristics of asthma by use of nasal corticosteroids in treatment of allergic rhinitis. Conventional doses of cetirizine, loratadine and oral decongestants have been reported to improve asthma symptoms and pulmonary function in patients with allergic rhinitis.

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 amongst allergic rhinitis patients. Similarly, there is an increased prevalence of atopy and allergic rhinitis amongst 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 is required. We identified no studies meeting these criteria in our literature search.