Chapter 2. Methods

This evidence report on the management of allergic rhinitis is based on a systematic review of the literature. Meetings and teleconferences of the EPC staff with technical experts were held to identify specific issues central to this report. A comprehensive search of the medical literature was conducted to identify studies addressing several key questions on the management of allergic rhinitis and nonallergic rhinitis. We compiled evidence tables of study features and results, appraised the methodological quality of the studies, and summarized their results. We identified published meta-analyses on specific treatment topics and evaluated and reported the findings of these reports.

The American Academy of Family Physicians originally proposed this topic and served as the primary science partner of 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 EPC staff to refine key questions, identify important issues, and nominate peer reviewers. The science partners were not involved in the synthesis of evidence or in the writing of this report.

Key Questions Addressed in the Evidence Report

The purpose of an evidence report is to summarize information from relevant studies addressing specific key questions. It is beyond the scope of an evidence report to cover all possible related issues for a topic. The aim of this evidence report is to determine how one diagnoses allergic and nonallergic rhinitis and to determine the minimum level of testing that is needed to differentiate allergic from nonallergic rhinitis; whether differentiating allergic from nonallergic rhinitis is important; the effectiveness of treatments in nonallergic and allergic rhinitis; and how treatment of allergic rhinitis impacts the development of asthma. With input from the science partners of this report, the following key questions (and sub-questions) were formulated. Patient population for this evidence report will include male and female children and adults, minorities, low-income, and elderly patients.

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

What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination and diagnostic testing?
What is the minimum level of testing necessary to differentiate allergic from nonallergic rhinitis?

Question 2. Is differentiating allergic from nonallergic rhinitis important?

Are treatments different?
Are outcomes different?

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

For nonallergic rhinitis:

a) What is the efficacy of antihistamines (all classes), nasal corticosteroids,

sympathomimetics, or leukotriene modifiers compared with placebo?

b) What are the side effects due to antihistamines, nasal corticosteroids, immunotherapy, sympathomimetics, cromolyn, and leukotriene modifiers?

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, leukotriene modifiers?

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?

What is the likelihood of developing asthma with untreated allergic rhinitis (natural history)?
How does treatment of allergic rhinitis affect the likelihood of developing asthma?
How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis?

Literature Search

Studies for the review of the primary literature were identified primarily through a Medline search of English language literature conducted between 1966 and October 2000. We 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 our evidence report.

Search Terms and Strategies

The literature search was conducted to identify clinical studies that reported primary data and published between 1966 through October 2000. The Medline search strategy is listed in Table 1. Separate searches were conducted to identify meta-analyses of nasal corticosteroids, immunotherapy and sedating and nonsedating antihistamines. The text words or medical subject headings for all treatments included ‘rhinitis, perennial and allergic,’ ‘histamine antagonists,’ ‘nasal decongestants,’ ‘ipratropium,’ ‘cromolyn sodium,’ ‘leukotriene antagonists,’ and ‘anti-inflammatory agents.’ The search was limited to human studies and published in English.

Medline search results were screened and potential studies were identified for retrieval based on setting, study question, population, and disease. Articles involving minority populations and gender issues were especially searched for (although none were found). Studies with no specific reference to allergic or nonallergic rhinitis were excluded. After retrieval, each paper was screened to verify that the condition and treatments under investigation were appropriate to each study question.

Study Selection

The Medline search yielded 3,381 citations. We screened the titles and abstracts of these

citations and retrieved 228 full-length articles 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 and these are discussed below.

Question 1: Diagnosis of Allergic and Nonallergic Rhinitis

We included 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.

Question 2: Differentiation of Allergic from Nonallergic Rhinitis

We included cross-sectional and prospective studies addressing diagnostic methods of differentiation of allergic from nonallergic rhinitis.

Question 3: Treatment of Allergic and Nonallergic Rhinitis

We included randomized controlled trials (RCTs) 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 inhibitors, and sympthomimetics. In the treatment of nonallergic rhinitis we included randomized controlled trials of antihistamines, nasal corticosteroids, anticholinergics, and sympathomimetic agents. We excluded uncontrolled trials, case reports, and case series.

Question 4: Impact of Treated and Untreated Allergic Rhinitis on Development of Asthma and Bacterial Sinusitis

We included prospective studies evaluating the relationship between allergic rhinitis and later development of asthma or bacterial sinusitis. Cross-sectional studies, case reports, and case series were excluded.

We placed no restrictions on the patients' gender or ethnicity. Specifically, AAFP was interested in studies about minorities, low-income, and elderly patients. However, we found no study that addressed these populations in its entirety or as subgroups.

Data Abstraction

After categorizing all retrieved studies according to the above criteria a total of 88 studies qualified for data abstraction. Data for evidence tables were abstracted using the forms shown in the appendix. Information abstracted included the study population characteristics, inclusion and exclusion criteria, the descriptions and the diagnostic criteria, potential verification bias as well as the main results and the conclusions of the study. In addition, data for quality assessment of individual studies were systematically abstracted. Data were abstracted by one member and then verified by a second member. If two abstractors disagreed, a third party methodological expert resolved the dispute.

Reporting the Results

The evidence we found is summarized in three complementary forms. The evidence tables provide detailed information about key features of study design and results of all the studies reviewed. A narrative and tabular summary of the strength and quality of the evidence of each study are provided for each drug class.

Evidence Tables

For each of the study questions, separate evidence tables were constructed for the allergic and nonallergic populations. These tables are presented under the Evidence Tables section of this evidence report. The evidence tables list the clinical studies found for each of the drug class comparisons and that met the inclusion criteria. The specific information included in the evidence tables is described above.

Summarizing the Evidence of Individual Studies

Grading of the evidence can be useful by indicating the overall "quality." A simple evidence grading system using a single scale may be desirable, however, the "quality" of evidence is multi-dimensional, and a single metric cannot fully capture information needed to interpret a clinical study (Lowell and Franklin, 1965; Settipane, 1986; Silberg, Lundberg, and Musacchio, 1997; Varley, 1964). We believe that information on individual components of a study contribute more to the evaluation of evidence by deliberating bodies than a single summary score. The evidence-grading scheme we used here assesses four dimensions that are important for the proper interpretation of the evidence:

- study size
- applicability
- summary of efficacy and safety outcomes
- methodological quality

Study Size

The study (sample) size is used as a measure of the weight of the evidence. A large study provides a more precise estimation of the treatment effect but does not automatically confer broad applicability unless the study included a broad spectrum of patients. Very small studies, taken individually, cannot achieve broad applicability. But several small studies that enrolled diverse populations, taken together, may have broad applicability. The study size is included as a separate dimension used to assist the assessment of applicability. For summarizing all studies, this would be the number of studies and the total number of patients in these studies.

Applicability

Applicability, also known as generalizability or external validity, addresses the issue of whether the study population is sufficiently broad to be generalizable to the population at large. Individual studies are often unable to achieve broad applicability due to restricted study population characteristics and a small number of study subjects (Lau, Ioannidis, and Schmid, 1997). We define the applicability grade as below:

I. Patients enrolled in the trial represent a broad spectrum of the population (high degree of

applicability). Typically this would be a large study, although a large study in itself does not guarantee a high degree of generalizability.

II. The study included only a narrow/restricted study population, but the result is relevant to similar types of patient population (restricted applicability). Typically this would be a small study, but may also be a large study of a very homogeneous population.

III. Narrow sample, not well generalizable to other groups, or studied outlier population that is not immediately relevant to the study question (very limited direct applicability or not applicable), or where the study reported only limited information.

N.D. No data or insufficient information reported to assess the applicability.

Methodological Quality

Methodological quality or internal validity addresses the design, conduct, and reporting of the clinical trial. Some of the items belonging to this entity are widely used in various "quality" scales and usually include items such as concealment of random allocation, treatment blinding, and handling of dropouts. Most of the studies included in this evidence report are randomized controlled trials, we define a three categories scale to report the methodological quality: A (least bias), B (susceptible to some bias), or C (likely to have large bias).

A. Double-blinded, well-concealed randomization, few drop outs, and no (or only minor) reporting problem of the trial that is likely to cause significant bias.

B. Single-blinded only, unclear concealment of randomization, or has some inconsistency in the reporting of the trial but is unlikely to result in major bias.

C. Unblinded study, inadequate concealment of random allocation, high drop-out rate, or has substantial inconsistencies in the reporting of the trial such that it may result in large bias.

Summary of Efficacy and Side-effect Outcomes

Outcomes studied included the effect of nasal corticosteroids vs. antihistamines, sedating vs. nonsedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene inhibitors, and sympathomimetics in both allergic and nonallergic rhinitis. In addition, we examined the evidence for a causal link between allergic rhinitis and development of asthma or bacterial sinusitis.

The efficacy outcomes reported by most studies addressing the same question in this evidence report were often heterogeneous and not readily amenable to meta-analysis. Different studies often used different combinations of outcomes such as watery eyes, itchy eyes, rhinorrhea, sneezing, itchy nose, and nasal congestion. Outcomes were typically assessed using categorical scales but the range of scales varied across studies.

Summarizing side effects is also problematic due to non-standard reporting of these outcomes by individual studies. Studies frequently do not define side effects, do not report the same side effects or do not use the same metric to report the same side effect, and many studies do not report side effects.

The evidence tables report detailed information about the outcomes. The summary tables in the result section report primarily the nasal symptoms. Consistency of effect across most studies addressing the same question is used as an indication of efficacy for the treatment being evaluated.

Table 1. MEDLINE Search Strategy

1. rhin$.tw.
2. exp rhinitis, allergic, perennial/
3. exp rhinitis/
4. 1 or 2 or 3
5. limit 4 to human
6. limit 5 to english language
7. exp histamine antagonists/ or exp histamine h1 antagonists/
8. exp nasal decongestants/
9. exp ephedrine/ or exp phenylpropanolamine/
10. exp phenylephrine/
11. exp cromolyn sodium/
12. (ipratropium bromide or oxitropium bromide).mp.
13. exp ipratropium/
14. exp scopolamine derivatives/
15. exp anti-inflammatory agents/
16. exp leukotriene antagonists/ or exp leukotrienes/
17. exp drugs, chinese, herbal/
18. 6 and (6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17)
19. exp clinical trials/
20. exp randomized controlled trials/
21. (random$ or rct).tw.
22. 6 and (19 or 20 or 21)
23. 6 and (19 or 20 or 21)
24. limit 6 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
25. 23 or 24
26. prevalen$.af.
27. prevalen$.af.
28. inciden$.af.
29. inciden$.af.
30. exp rhinitis, allergic, perennial/ep
31. 6 and (27 or 28 or 30)
32. exp "sensitivity and specificity"/
33. exp diagnosis/
34. exp reproducibility of results/
35. exp false negative reactions/ or false positive reactions/
36. exp logistic models/
37. exp regression analysis/
38. predictive value.tw.
39. diagnos$.tw.
40. diagnos$.tw.
41. (sensitivity and specificity).tw.
42. accuracy.tw.
43. logistic regression.tw.
44. screening.tw.

45. roc.tw.
46. reproducibility.tw.
47. (false positive or false negative).tw.
48. likelihood ratio.tw.
49. 32 or 33 or 34 or 35 or 36 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 6 and 49
51. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or48.mp. [mp=title, abstract, registry number word, mesh subject heading]
52. 6 and 51
53. limit 52 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical
trial, phase iv or controlled clinical trial or randomized controlled trial)
54. exp rhinitis, allergic, perennial/di
55. limit 54 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
56. 53 or 55
57. 25 or 31 or 56
58. limit 57 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschchrift or interview or legal cases or letter or periodical index or review of reported cases) [Limit not valid in: MEDLINE; records were retained]
59. 57 not 58