Probability of Asthma Based on Methacholine Challenge*

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Methacholine inhalation challenge has become an accepted test to determine the presence of airway hyperresponsiveness, a hallmark of asthma. To help physicians interpret the results of a methacholine challenge test in a clinical setting, we analyzed the test data of 1,105 subjects, asthmatics and nonasthmatics. Applying Bayes' theorem, a nomogram was constructed incorporating the prechallenge clinical diagnosis with the response to methacholine to give a posttest probability of the diagnosis of asthma. The resulting curves represent different levels of cumulative breath units at which a methacholine challenge can be considered positive. The results of a methacholine challenge test, in association with a physician's clinical assessment, can be a valuable tool in the diagnosis of asthma in those patients with an atypical history and/or physical examination.

(Chest 1992; 101:630-33)

Methacholine inhalation challenge has been well established as a procedure capable of demonstrating bronchial reactivity in research and clinical situations. Due to its safety profile and sensitivity, it is a useful diagnostic test in both children and adults.

In a recent article, Gilbert and AuchenLOSS reported the posttest probability of asthma in a small population of smokers and nonsmokers. To our knowledge, this is the first work to address the use of decision analysis in the diagnosis of asthma.

Using a larger population composed of asthmatics, atopics from asthma families, atopics from normal families, normal individuals from asthma families, and normal individuals from normal families, we undertook a similar approach. This population represents a heterogeneous group of individuals with variable allergic, family, and respiratory histories. The results of our analysis provide a scale by which physicians can use their clinical judgment (pretest probability) of asthma certainty for any individual which would be strengthened or diminished following the results of a methacholine challenge test (posttest probability).

**Methods**

**Subjects**

The subjects included in this study were part of a larger study, the Natural History of Asthma conducted at Creighton University School of Medicine. All subjects were originally enrolled in one of two study populations: (1) 53 asthma families, totaling 658 individuals, were ascertained by the recruitment of an asthma proband, varying in age from 5 to 80 years; and (2) 26 normal families, totaling 447 individuals, were ascertained by recruitment of a normal proband, ages 5 to 80 years. Families in this group had a negative family history of asthma for three generations of immediate family members. Ascertainment criteria have been described previously.

There was no statistical difference in age, race (all caucasian individuals except one asthma family), or sex distribution between the asthma families and normal families.

The Natural History of Asthma study included an extensive respiratory and allergic disease questionnaire that was administered to each study individual. Questions were adapted from the American Thoracic Society, Division of Lung Disease of the National Heart, Lung, and Blood respiratory questionnaire.

The subjects selected for this study belonged to one of five groups: subjects with current asthma, normal individuals from normal families, normal individuals from asthma families, subjects from normal families with laboratory evidence for atopy, and subjects from asthma families with laboratory evidence for atopy.

**Procedure**

The presence or absence of asthma or allergic disease was defined specifically by the response to the detailed respiratory disease questionnaire. A full explanation of the questions used to establish these diagnoses has been published previously.

Nonallergic status was defined by negative responses to our respiratory disease questionnaire criteria for asthma. In addition, nonallergic subjects gave negative responses to all of the following questions: (1) Have you ever had hay fever? (2) Have you ever had nonseasonal nasal allergies? (3) Have you ever had hay fever during any specific time of the year? (4) Have you ever had hay fever symptoms after exposure to any of the following: dust, mold, pollen, food, pets, drugs, or other? (5) Have you ever consulted a physician for hay fever? (6) Have you ever received allergy desensitization shots? (7) Have you ever had eczema or been told by a physician that you had eczema or atopic dermatitis? Individuals were classified as allergic if they responded with a positive answer to any of the above questions.

The methacholine responsiveness for the Natural History of Asthma prospective study was determined by two methods previously described. In brief, these methods were as follows: (1) by determining the dose-response curves to increasing concentrations of methacholine while the number of breaths was kept constant (Table 1), and (2) by determining the dose-response curves by keeping the concentration constant while the number of inhalations

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was increased. The second method of methacholine inhalation was used before 1979. In studies previously reported from our laboratory, the correlation between the two methods was extremely high \((r = 0.96)\).

Spirometry was performed with a spirometer (Pulm/Norm model 560, Cardio-Pulmonary Instruments, Houston, Tex). Measurements included a forced vital capacity, forced expiratory volume in 1 s \((FEV_1)\), forced expiratory flow rate from 25 percent to 75 percent of the total volume \((FEF_25-75)\), and peak expiratory flow rate \((PEFR)\).

The methacholine challenge was stopped and the accumulated dose determined when the subjects sustained a 35 percent or higher fall in \(FEV_1\), as compared with the postsaline solution baseline or if all the steps were completed. The results in this article are expressed as the provocative dose of methacholine causing a fall in FEV\(_1\) of at least 20 percent \((PD_{20})\).

Complete prick (1:20 w/v) and intradermal (1:1000 w/v) skin testing was performed with antigens (supplied by Center Laboratories, Fort Washington, NY) common to the Midwest, including house dust, danders of cat and dog, and mixed antigens of ragweed, grass, molds, trees, and Western weeds. Individual skin test responses were measured and scored. We assigned a 4 + intradermal wheal (mean diameter \(>15\) mm or pseudopen) an arbitrary score of 7.5; a 3 + wheal (12.5 to 15 mm), a score of 5.5; a 2 + wheal (10 to 12 mm), a score of 3.0; a 1 + wheal (7 to 10 mm), a score of 1.5; an equivocal wheal (4.5 to 7 mm), a score of 1; and no response wheal (\(<4\) mm), a score of 0. The total intradermal skin test scores are the sum of the individual antigen scores.

As shown by Gilbert and Auchincloss,\(^1\) the posttest probability of asthma after a positive methacholine challenge test can be calculated using Bayes' theorem as follows:

\[
PP = \frac{P \times SE}{P \times SE + (1 - P) \times (1 - SP)}
\]

Likewise, the posttest probability of asthma after a negative methacholine challenge can be calculated as shown:

\[
PP = 1 - [(1 - P) \times SP] \times [(1 - P) \times SP + P \times (1 - SE)]
\]

In the above theorem, sensitivity (SE) describes the ability of a test to detect affected persons in the population studied;\(^4\) specificity (SP) describes the ability of a test to detect normal persons in the population studied;\(^5\) the pretest probability (P) is the physician's estimate of the likelihood that the patient has the disease before the test results are considered; and the posttest probability (PP) represents the likelihood of asthma considering the pretest probability and the test results.

The subjects were instructed to avoid treatment with all antihistamine medication for 72 h before the visit and to stop treatment with all bronchodilator medication (except oral steroid) for at least 12 h before the visit. The subjects signed a consent form and were examined by a physician. The protocol was approved by the Institutional Review Board of Creighton University School of Medicine.

**RESULTS**

This study reports the results of 1,105 individuals, 5 to 80 years of age, selected from the larger population of our Natural History of Asthma study.\(^6\) One hundred eighty-nine subjects (100 male and 89 female) were identified as being current asthmatics based on questionnaire criteria. Nine hundred sixteen subjects (435 male and 481 female) comprised the group of nonasthmatic subjects. The latter group was further subdivided in atopic individuals from asthma families (143 subjects), atopic individuals from normal families (66 subjects), nonatopic individuals from asthma families (326 subjects), and nonatopic individuals from normal families (381 subjects). The age distribution, skin test scores, and IgE levels for the above groups are presented in Table 2.

The analysis of our data produced the curves shown in Figure 1. The pretest probability is shown on the abscissa, the posttest probability on the ordinate. The curves represent different levels of cumulative breath units (bu) at which the test could become positive, i.e., 25 bu, 50 bu, 100 bu, and 200 bu. Negative results are represented by a single curve at 200 bu. For example, a physician estimated that a patient had a 50 percent likelihood of asthma based on history and results of physical examination. If the patient had a positive methacholine challenge with a \(PD_{20}\) of 50 bu, the posttest probability of asthma is approximately 80 percent.

### Table 1—Dosimeter Technique: Methacholine Challenge Protocol Used Since 1979

<table>
<thead>
<tr>
<th>Dose (mg/ml)</th>
<th>No. of Breaths</th>
<th>bu</th>
<th>Cumulative bu</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>0.2</td>
<td>5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>0.6</td>
<td>5</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>2.0</td>
<td>5</td>
<td>10.0</td>
<td>14.5</td>
</tr>
<tr>
<td>6.0</td>
<td>5</td>
<td>30.0</td>
<td>44.5</td>
</tr>
<tr>
<td>20.0</td>
<td>5</td>
<td>100.0</td>
<td>144.5</td>
</tr>
<tr>
<td>60.0</td>
<td>5</td>
<td>300.0</td>
<td>444.5</td>
</tr>
<tr>
<td>60.0</td>
<td>6</td>
<td>360.0</td>
<td>804.5</td>
</tr>
</tbody>
</table>

### Table 2—Characteristics of Study Population (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic</th>
<th>All</th>
<th>Asthma Family</th>
<th>Nonasthma Family</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>189</td>
<td>916</td>
<td>469</td>
<td>447</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>100</td>
<td>435</td>
<td>214</td>
<td>221</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>481</td>
<td>255</td>
<td>226</td>
</tr>
<tr>
<td><strong>Allergic rhinitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>116</td>
<td>209</td>
<td>143</td>
<td>66</td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>707</td>
<td>326</td>
<td>381</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>19.1 ± 12.4</td>
<td>24.7 ± 18.1</td>
<td>26.8 ± 18.4</td>
<td>22.5 ± 17.5</td>
</tr>
<tr>
<td><strong>IgE</strong></td>
<td>389.9 ± 471.1</td>
<td>119.1 ± 260.0</td>
<td>153.3 ± 320.4</td>
<td>86.5 ± 182.3</td>
</tr>
<tr>
<td><strong>Skin test score</strong></td>
<td>12.4 ± 12.2</td>
<td>3.3 ± 7.2</td>
<td>4.6 ± 8.4</td>
<td>2.0 ± 5.3</td>
</tr>
</tbody>
</table>
of new asthma drugs, in genetic, and epidemiologic studies. In addition, it can be used in a clinical setting as a tool in the diagnosis of asthma and to assess the patient's response to therapy. As with any laboratory test, it is not infallible. Physicians are still confronted with the uncertainties on how to interpret the results of a methacholine challenge study, especially when dealing with a patient with an atypical history. In this study we attempted to address this problem by applying a discrimination analysis to a larger population of asthmatics, atopics, and normal individuals. The result of our analysis is shown in Figure 1. This nomogram is slightly different than that of Gilbert and Auchincloss. Their data were based on a very select population with a 100 percent specificity, which is highly unlikely in the clinical setting. Our study included subjects with allergic rhinitis and family members of asthmatics. We have shown previously that these groups have an increased nonspecific bronchial responsiveness, often in the asthmatic range. Our observations have agreed with those of other studies.

Based on our protocol, as shown in Table 1, a subject could inhale up to 800 bu of methacholine, thereby

Smoking will increase airway responsiveness to methacholine to some extent, as shown in Figure 2, but not significantly.

Table 3 shows the false-positive and the false-negative rates for the different cutoffs. With increased cumulative concentrations of methacholine, sensitivity increases and specificity decreases, which would make the test less reliable when high doses of methacholine are used.

**Discussion**

Methacholine inhalation challenge tests have been widely used in research to evaluate the effectiveness

![Figure 1](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21640/)

**Figure 1.** Curves for the posttest probability of asthma. The numbers along the curves represent the cumulative breath units (bu) at which the test could become positive. A single curve represents a negative test at 200 bu.

**Table 3—False-Positive and False-Negative Rates for the Different Cutoffs**

<table>
<thead>
<tr>
<th>bu</th>
<th>F+</th>
<th>F−</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>8.7</td>
<td>41.8</td>
</tr>
<tr>
<td>50</td>
<td>14.1</td>
<td>31.7</td>
</tr>
<tr>
<td>100</td>
<td>21.4</td>
<td>21.7</td>
</tr>
<tr>
<td>200</td>
<td>29.9</td>
<td>14.8</td>
</tr>
</tbody>
</table>

![Figure 2](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21640/)

**Figure 2.** Effects of smoking on airway responsiveness to methacholine. The solid line represents the positive test for the whole group. The dotted line shows the response of smokers. The dashed line shows the response of nonsmokers.
detecting subjects with minimal bronchial hyperresponsiveness, which increases the rate of false-positive results (Table 3). Furthermore, it has been shown that the majority of patients with current asthma will respond with a 20 percent fall in FEV₁ by 225 bu. In the clinical setting, therefore, a nomogram with curves of up to 200 bu is more relevant.

Methacholine is a safe drug to be used in clinical challenges. A study comparing methacholine and histamine found methacholine to best distinguish asthmatics from normal subjects, to have a lower incidence of side effects, to have good correlation with exercise response, and to correlate well with response to histamine. The reproducibility, specificity, and sensitivity of methacholine are well known. We conclude that methacholine challenge can be a useful tool in the diagnosis of asthma along with an adequate history and physical examination.

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