

ORIGINAL ARTICLE

Serum IgE and eosinophil count in allergic rhinitis—Analysis using a modified Bayes' theorem

M. Demirjian^{a,*}, J.S. Rumbyrt^b, V.C. Gowda^a, W.B. Klaustermeyer^a

^a Division of Allergy & Immunology, Department of Medicine, Veterans Affairs Greater Los Angeles Healthcare System, The David Geffen School of Medicine at UCLA, United States

^b Denver Allergy & Asthma Associates, P.C., Golden, CO 80401, United States

Received 30 April 2011; accepted 27 May 2011

Available online 5 October 2011

KEYWORDS

Rhinitis;
IgE level;
Eosinophil count;
Bayes' theorem;
Atopy

Abstract

Background: To use probability theory to establish threshold values for total serum IgE and eosinophil counts that support a diagnosis of allergic rhinitis and to compare our results with previously published data.

Methods: Prospective study of rhinitis patients using a modified version of Bayes' theorem. Study included 125 patients at the West Los Angeles VA Medical Center diagnosed with rhinitis who completed allergy consultation and immediate hypersensitivity skin testing.

Results: Eighty-nine of 125 patients were atopic by prick and/or intradermal skin testing. Using a modified version of Bayes' theorem and positive and negative probability weights, calculations for different thresholds of serum IgE and eosinophil counts were summated and a posttest probability for atopy was calculated. Calculated posttest probabilities varied according to the threshold used to determine a positive or negative test; however, IgE thresholds greater than 140 IU/ml and eosinophil counts greater than 80 cells/ml were found to have a high probability of predicting atopy in patients with rhinitis. Moreover, IgE had a greater influence than eosinophil count in determining posttest probability of allergy in this population. Considerable differences were noted in the IgE levels of atopic and non-atopic patients, including those with asthma or a history of smoking. However, these differences were not observed with eosinophil levels.

Conclusions: Using a modified version of Bayes' theorem to determine posttest probability, IgE threshold levels greater than 140 IU/ml and eosinophil counts greater than 80 cells/ml in an individual with clinical signs and symptoms of rhinitis are likely to correlate with an atopic aetiology. This model of probability may be helpful in evaluating individuals for diagnostic skin testing and certain types of allergy-modifying treatment.

© 2011 SEICAP. Published by Elsevier España, S.L. All rights reserved.

* Corresponding author.

E-mail addresses: mdemirjian@mednet.ucla.edu (M. Demirjian), william.klaustermeyer@va.gov (W.B. Klaustermeyer).

Introduction

Many investigators have used total serum immunoglobulin E (IgE) and eosinophil count for evaluating allergic disease.¹⁻⁴ While attempts have been made to define normal/abnormal thresholds for each,^{5,6} there is no consensus in the literature for a given threshold value of IgE or eosinophil count that confirms atopic disease. Currently, there is great interest in the measurement of total IgE levels given the advent of omalizumab, a recombinant DNA-derived humanised IgG_{1κ} monoclonal antibody against human IgE. Clinical studies with omalizumab required patients to have a baseline IgE between 30 and 700 IU/ml.⁷⁻¹⁰ Total IgE levels can be affected by race,¹¹ smoking history,¹²⁻¹⁵ age,¹⁶⁻¹⁸ season,¹⁹ and non-atopic disease.²⁰⁻²² To confirm the presence of atopy, physicians have relied on serum antigen specific IgE testing, prick or intradermal skin testing.^{23,24} In this study we have used probability theory to evaluate total serum IgE and eosinophil count as factors for predicting the likelihood of atopy in rhinitis.

Bayes' theorem calculates the probability of disease after performing a test, given the test's sensitivity, specificity, and estimated probability of disease before the test.²⁵ A modified version of Bayes' theorem introduced by Rembold and Watson combines a test's sensitivity and specificity into a single value known as a "weight".²⁶ Positive tests (i.e. tests whose values exceed a given threshold) will have positive weights and negative tests (i.e. tests whose values are less than a given threshold) will have negative weights. Since positive weights indicate an increase in the likelihood of disease and negative weights suggest a decreased likelihood of disease, the greater the weight (positive or negative), the greater the influence in predicting the likelihood of disease.

The present study uses this modification of Bayes' theorem to establish practical thresholds (upper limits of normal) for serum IgE and eosinophil counts for atopy in allergic rhinitis. By altering threshold values using computer-assisted analysis, positive and negative weights were calculated from an array of thresholds and graphed as threshold versus weight. The main advantage of this process is that the sum of the weight factors can be converted to a posttest probability using a simple conversion table (Fig. 1). Thus, for allergic rhinitis, two factors (IgE and eosinophil count) can be taken into consideration to screen or determine whether atopy is likely to be present.

Methods

Three hundred and fifty-eight consecutive patients were referred to the Allergy/Immunology clinic at the West Los Angeles VA Medical Center over a 24-month period. One hundred and eighty-four of 358 patients (51%) were diagnosed with rhinitis based on a history of seasonal or perennial

Probability	Weight
1.00	+ ∞
0.99	+4.6
0.98	+3.9
0.95	+2.9
0.90	+2.2
0.85	+1.7
0.80	+1.4
0.75	+1.1
0.70	+0.8
0.65	+0.6
0.60	+0.4
0.55	+0.2
0.50	0
0.45	-0.2
0.40	-0.4
0.35	-0.6
0.30	-0.8
0.25	-1.1
0.20	-1.4
0.15	-1.7
0.10	-2.2
0.05	-2.9
0.02	-3.9
0.01	-4.9
0	- ∞

Figure 1 A statistical calculation of probability and weight. This figure is used to convert positive and negative weights into posttest probabilities (expressed in percentage probability). Note that the scale is non-linear (taken from Rembold and Watson²⁶).

symptoms with exposure to common allergens. One hundred and twenty-five of 184 (67%) completed immediate hypersensitivity skin testing using a prick and/or graded intradermal technique to determine the presence of atopy. The criteria for atopy were as follows: (1) a positive prick test with any routine or screening antigen; (2) positive intradermal test at 1:10,000 dilution (or greater) with two or more routine antigens; and (3) a positive intradermal test at 1:10,000 dilution (or greater) with any screening antigen. A positive reaction was defined according to previously described criteria.²⁷ Atopy was defined as a positive skin test reaction and a correlating clinical history. Rhinitis patients with skin test results ($n=125$, 89 atopic, 36 non-atopic) and either serum IgE ($n=117$), eosinophil count ($n=110$), or both were included in the data analysis. Geometric mean values were calculated for serum IgE and eosinophil counts.

Data analysis

A test's sensitivity and specificity are defined as follows²⁸:

$$\begin{aligned}
 \text{Sensitivity} &= \text{true positive rate} \\
 &= \frac{\text{\#of diseased patients with a (+) test}}{\text{total \# of diseased patients}} \\
 &= \frac{\text{\#of atopic patients with rhinitis and a (+) test}}{\text{total \# of atopic patients with rhinitis}}
 \end{aligned}$$

$$\begin{aligned} \text{Specificity} &= \text{true negative rate} \\ &= \frac{\# \text{ of disease free patients with a } (-) \text{ test}}{\text{total } \# \text{ of disease free patients}} \\ &= \frac{\# \text{ of non-atopic patients with rhinitis and a } (-) \text{ test}}{\text{total } \# \text{ of non-atopic patients with rhinitis}} \end{aligned}$$

Moreover, according to the modified version of Bayes' theorem,²⁶ the positive and negative weight of a test is determined from the sensitivity and specificity as follows:

$$(+)\text{weight} = \ln \frac{\text{true positive rate}}{\text{false positive rate}} = \ln \frac{\text{sensitivity}}{1 - \text{specificity}}$$

$$(-)\text{weight} = \ln \frac{\text{false negative rate}}{\text{true negative rate}} = \ln \frac{1 - \text{sensitivity}}{\text{specificity}}$$

Using these definitions, the more positive the weight, the greater the likelihood that the disease is present; the greater the negative weight, the greater the likelihood that the disease is not present.

However, because sensitivity and specificity vary according to the threshold (upper limit of normal) of a test, the weight of a test will also vary with the threshold. A computer-assisted analysis was used to calculate positive and negative weights from an array of thresholds and the results were graphed as threshold vs. weight.

Results

One hundred and eighty-four of 358 (51%) patients diagnosed with rhinitis after initial evaluation were scheduled for skin testing and 125 of 184 (67%) patients completed skin testing to determine the presence of atopy. Eighty-nine of 125 (71%) patients were atopic, of whom 83 were male and 6 female (Table 1). Sixty-eight of 89 (76%) atopic patients

had a history of smoking (past or current) and 34 of 89 (38%) had asthma. For the non-atopic patient group, 27 of 36 (75%) had a history of smoking and 10 of 36 (27%) had asthma. The mean age of patients who had skin testing was 57 years with a range of 21 to 87. There were no significant differences noted between atopic and non-atopic patients, nor between the subgroups of patients with a history of smoking or asthma, with regard to distribution of age.

Total serum IgE was measured in 83 atopic patients and 36 non-atopic patients. The mean IgE level in atopic patients was 115 IU/ml and the mean IgE level in the non-atopic patients was 27 IU/ml. Atopic patients with asthma had the highest mean IgE (175 IU/ml) and female non-atopic patients had the lowest mean IgE (4 IU/ml). Atopic male patients had a mean IgE of 130 IU/ml compared to atopic female patients with a mean IgE of 16 IU/ml; non-atopic males had a mean of 32 IU/ml whereas non-atopic females had a mean of 4 IU/ml. Differences were also noted in the mean IgE of atopic and non-atopic current smokers, 113 IU/ml and 24 IU/ml, respectively.

Eosinophils were measured in 78 of 89 atopic patients and 32 of 36 non-atopic patients. The mean eosinophil count in the atopic patients was 219 cells/ml and in the non-atopic patients 135 cells/ml. The highest and lowest mean values of 276 and 105 cells/ml were seen in the atopic and non-atopic female patients respectively. Unlike the case with the IgE level, no significant differences in the eosinophil count were noted in the atopic/non-atopic subgroups with regard to gender or smoking. However, non-atopic patients with asthma did tend to have higher counts than non-atopic patients without asthma (172 cells/ml vs. 125 cells/ml).

Table 1 Geometric means of IgE and eosinophils for atopic and non-atopic patients with rhinitis.

Patient population	n-total	IgE	(n)	Eosinophils	(n)
A					
Atopic patients	89	115	(83)	219	(78)
Atopic males	83	130	(78)	215	(73)
Atopic females	6	16	(5)	276	(5)
Atopic smokers	68	113	(64)	208	(61)
Atopic non-smokers	21	118	(19)	261	(17)
Atopic asthma	34	175	(33)	216	(27)
Atopic non-asthma	55	87	(50)	220	(51)
B					
Non-atopic patients	36	27	(34)	135	(32)
Non-atopic males	33	32	(31)	139	(24)
Non-atopic females	3	4	(3)	105	(3)
Non-atopic smokers	23	24	(23)	133	(20)
Non-atopic non-smokers	9	34	(8)	106	(8)
Non-atopic former smokers	4	35	(3)	233	(4)
Non-atopic asthma	10	40	(10)	172	(8)
Non-atopic non-asthma	26	23	(24)	125	(24)

The units for IgE are in IU/ml and for eosinophils are in cells/ml. The (n) refers to the number of patients for whom data were available.

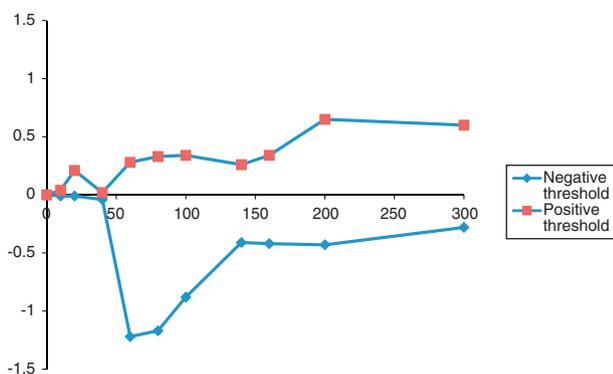


Figure 2 Weight vs. threshold for eosinophils.

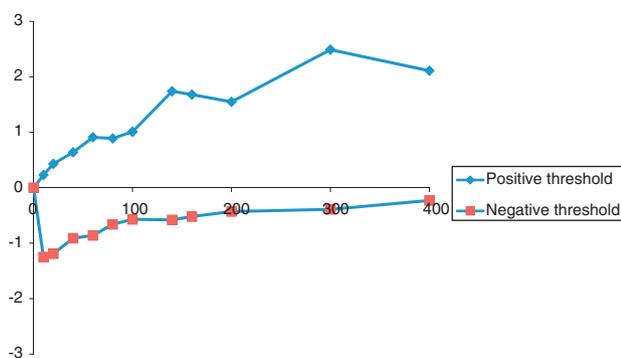


Figure 3 Weight vs. threshold for serum IgE.

Figs. 2 and 3 graphically depict the calculated positive and negative weights for a range of selected thresholds of eosinophils and IgE levels. For both curves, as the thresholds increase the positive weight becomes more positive and the negative weight becomes less negative. Thus, as the eosinophil and IgE thresholds increase, so does the likelihood of atopic disease. Moreover, beyond an eosinophil count of 300 cells/ml and an IgE of 400 IU/ml, the positive weight becomes infinitely large, indicating that the probability of atopic disease beyond these thresholds is virtually 100%.

For eosinophils (Fig. 2), there is not much difference in the positive or negative weights until the threshold reaches 60 cells/ml. The largest difference between positive and negative weights was found at thresholds of 60 cells/ml (positive weight = 0.28, negative weight = -1.22, difference = 1.50) and 80 cells/ml (positive weight = +0.33, negative weight = -1.17, difference = 1.50) (Table 2).

Fig. 3 shows a similar but more pronounced trend for increasing thresholds of IgE when compared to the curve in Fig. 2. The largest differences between the positive and

negative weights were found at IgE thresholds of 140 IU/ml (positive weight = +1.74, negative weight = -0.58, difference = 2.32) and 300 IU/ml (positive weight = +2.49, negative weight = -0.39, difference = 2.88) (Table 2).

Discussion

The distribution of male and female patients was consistent with that expected for a VA population. As such, the number of female patients was significantly reduced (six atopic and three non-atopic). The average age of our patients (57 years) must also be taken into account as serum IgE has been reported to be higher in younger aged groups.^{29,30}

Nonetheless, IgE levels obtained from our general and subset patient populations were not different from what has been previously published. For example, non-atopic patients' serum IgE level of 27 IU/ml was quite similar to that obtained by Burrows et al. for patients without asthma (26 IU/ml) and Droste et al.'s value of 25 IU/ml in patients without allergic rhinitis.^{31,32} Similarly, Klink et al. reported a value of 20 IU/ml in normal males, age 15–74 and Simoni et al. reported a value of 19 IU/ml in females, and 29 IU/ml in males ages 8–78.^{33,34} Moreover, our average value of 115 IU/ml obtained for atopic patients was in agreement with that published by Haahtela et al. for skin test positive patients (116 IU/ml),³⁵ but somewhat lower than the values of 142 IU/ml reported by Hetman et al.,³⁶ 204 IU/ml by Campos et al.,³⁷ 225 IU/ml reported by Mullarkey et al.,³⁸ and 326 IU/ml reported by Bousquet et al.³⁹ Interestingly, however, when Hetman's data was separated by age, mean values of 103 IU/ml and 74 IU/ml were obtained for the 41–50-year age group and 51–60-year age group, respectively,³⁶ and atopic rhinitis patients over the age of 40 had a mean IgE of 94 IU/ml in Wittig's collection of data.³¹ It is therefore most likely that the differences in our reported mean values are due to age. With regard to patients with asthma, our atopic asthma patients had a mean IgE of 175 IU/ml and our non-atopic asthmatics had an IgE of 40 IU/ml. Burrows et al. reported that asthma subjects in the age range of 35–54 had an average IgE of 117 IU/ml with 72% having positive skin tests and in the 55 and older group, the mean IgE was 56 IU/ml with 39% having positive skin tests.³¹ Finally, in Wittig's study of IgE levels in asthmatic patients, the mean IgE for patients over the age of 40 was noted to be 172 IU/ml, the majority of whom were known to have previous evidence of atopy.⁴⁰

The influence of cigarette smoking on IgE levels was also evaluated in our study. In the non-atopic non-smoking, smoking and ex-smoking populations, the mean IgE levels in our patients were 34 IU/ml, 24 IU/ml and 35 IU/ml,

Table 2 Positive and negative weights for randomly selected values of IgE (IU/ml) and eosinophils (cells/ml).

Eosinophils	±Weight	-Weight	IgE	±Weight	-Weight
40	+0.02	-0.04	20	+0.43	-1.19
60	+0.28	-1.22	80	+0.89	-0.66
80	+0.33	-1.17	100	+1.01	-0.57
140	+0.26	-0.41	140	+1.74	-0.58
300	+0.60	-0.28	300	+2.49	-0.39

respectively. In the atopic population, patients who smoked had a mean IgE of 113 IU/ml and non-smokers 118 IU/ml. This is in agreement with other studies in which smokers tended to have higher IgE levels than non-smokers.⁴¹ It has been theorised that smokers may have a higher than average antigenic load due to tobacco smoke or have an increased colonisation of the airways with microorganisms that could stimulate an IgE response.⁴²

Our data also show that eosinophil counts are consistently higher in the atopic population and this trend was not influenced by gender, the presence of asthma, or whether or not the individual smoked. Although the significance of blood eosinophilia is disputed, this trend has been reported by others.^{43–45} In normal patients with no skin reactivity and in asymptomatic patients with positive skin reactivity, Felarca and Lowell found mean eosinophil counts of 100 cells/ml and 202 cells/ml respectively.⁴⁶ These figures are in agreement with our non-atopic (eosinophils = 135 cells/ml) and atopic (eosinophils = 219 cells/ml) populations.

The thresholds of 140 IU/ml for serum IgE level and 80 cells/ml for eosinophil count were chosen because it was at these points on the graphs that the curves made their largest initial divergence and where the largest difference between the positive and negative weights occurred (Figs. 2 and 3). In the ideal situation, as the threshold value is approached, the positive weight becomes more positive and the negative weight less negative. Furthermore, beyond the threshold point, the positive weight should become infinitely positive (i.e., the probability of the disease being present approaches 100%). This trend is certainly seen for the IgE data presented in Fig. 3. Beyond the threshold of 140 IU/ml, the positive weights tend to become infinitely positive and the negative weights approach zero. The threshold value of 140 IU/ml for atopy is not radically different from what has been previously published. For example, Grater et al. performed 5500 IgE measurements in 7000 referred patients and determined that IgE levels greater than 80 IU/ml should be the minimum level required to confirm atopy.⁴⁷ In addition, in two independent studies, Mullarkey and Zetterstrom et al. reported strong evidence for the presence of atopic disease when IgE values were greater than 100 IU/ml.^{48,49} Hetman et al. found a preponderance of atopic individuals with IgE levels greater than 120 IU/ml,³⁶ and Haahetela et al. concluded that IgE values greater than 160 IU/ml suggest atopy.³⁵ This trend is not seen as clearly with the data obtained for eosinophils. There is not the large divergence as seen with the IgE data in Fig. 3. The largest difference between the positive and negative weights is 1.50 and is seen at both the 60 and 80 cells/ml threshold. This finding is somewhat surprising since the mean eosinophil count in our atopic and non-atopic populations was considerably higher than either of these values (Table 1). Nonetheless, the 80 cells/ml threshold was chosen since the positive weight was greater (0.33 vs. 0.28) and the negative weight less (−1.17 vs. −1.22) (Table 2). Unlike mean IgE, there are few reports in the literature that estimate a threshold for eosinophils to suggest atopy. Using the data from Table 2, we randomly summated eosinophil counts and IgE levels and calculated the posttest probability for atopy. The posttest probability for atopy was greatest when both IgE and eosinophil counts exceeded the threshold and lowest when neither exceeded the threshold value.

We also determined that IgE levels had a greater influence than eosinophil counts in determining posttest probability for atopy in this veteran population.

Recent novel therapies using monoclonal anti-IgE antibody such as omalizumab in effect utilise threshold values for allergic disease based on total serum IgE level. Using probability theory in our VA population, a total IgE level of 140 IU/ml may be a useful threshold as a preliminary screen for allergic disease. We are not aware of any other studies that have used a modified Bayes' theorem to determine the presence of atopy and suggest that additional trials be conducted in allergic populations with a different prevalence of disease.

This study demonstrates that IgE levels greater than 140 IU/ml and eosinophil counts greater than 80 cells/ml are suggestive of an atopic aetiology for patients with signs and symptoms of rhinitis. Our data were collected from a referred population where the pretest probability of the disease (i.e., prevalence of atopy) was quite high (70%). Since this has a great influence in determining posttest probability, it is suggested that IgE and eosinophil counts may have an even greater influence in a population with a lower pretest probability of disease. Furthermore, although this study was conducted in a veteran population where the number of younger patients and female patients was quite small, our data were in general agreement with previous reports. However, caution should be used when applying them to the population as a whole since others have reported that both age and sex may influence IgE levels and eosinophil counts. Nevertheless, these data do suggest that IgE levels and eosinophil counts are important factors in the evaluation of the atopic patient, with IgE having the greater impact in determining posttest probability of atopy.

Conflict of interest

Dr. Rumbyrt is currently on the speaker's bureau for Glaxo-SmithKline, Merck, Astra Zeneca and has received research support from GlaxoSmithKline and Schering AG. Dr. Gowda is on the speaker's bureau for GlaxoSmithKline and Meda Pharmaceuticals and has received clinical research support from Novartis.

Appendix A. Determination of posttest probability

A posttest probability is determined from a posttest weight using Fig. 1. A posttest weight is calculated by sequentially adding the weights of any/all tests to the pretest weight. The pretest weight is determined from the pretest probability of the disease in question (i.e., the prevalence of disease in the population being studied). In this series, the pretest probability (prevalence of disease in the population being studied) was 70% (89 atopic patients/125 patients skin tested for atopy). The test weight for given thresholds of IgE and eosinophils were added to the pretest weight, and the sum (posttest weight) converted to a posttest probability for atopy using Fig. 1. The weight of a test (positive or negative) was chosen based on whether or not the observed test value exceeded a selected threshold. In other words, if a threshold value 'x' is chosen, and the observed test value

exceeds "x" the positive weight is used in the determination of posttest probability. If the observed value is less than "x", the negative weight is used. This five-step process is summarised as follows.

A.1. Calculation of posttest probability

1. Estimation of pretest probability (=prevalence of disease in population).
2. Conversion of pretest probability to a pretest weight (Fig. 1).
3. Selection of positive and negative test weight depending on test threshold.
4. Calculation of posttest weight:

$$\text{Posttest weight} = \text{pretest weight} + \text{test 1 weight} + \text{test 2 weight} + \dots$$
5. Conversion of posttest weight to a posttest probability (Fig. 1).

References

1. Holford-Strevens V, Warren P, Wong C, Manfreda J. Serum total immunoglobulin E levels in Canadian adults. *The Journal of Allergy and Clinical Immunology*. 1984;73:516–22.
2. Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Speizer FE, van der Lende R. The relationship of eosinophilia and positive skin test reactivity to respiratory symptom prevalence in a community-based population study. *The Journal of Allergy and Clinical Immunology*. 1990;86:99–107.
3. Sorensen H, Ashoor AA, Maglad S. Perennial rhinitis in Saudi Arabia. A prospective study. *Annals of Allergy*. 1986;56:76–80.
4. Stenius B, Wide L, Seymour WM. Clinical significance of total IgE and of specific IgE to *Dermatophagoides* spp., grass pollen and other common allergens. II. Relationship to clinical manifestations. *Clinical Allergy*. 1972;2:303–6.
5. Brown WG, Halonen MJ, Kaltenborn WT, Barbee RA. The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. *The Journal of Allergy and Clinical Immunology*. 1979;63:328–35.
6. Hamburger R. The genetic implications of positive RAST in low IgE individuals. *Immunology and Allergy Practice*. 1980;2:8–12.
7. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest*. 2004;125:1378–86.
8. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *The Journal of Allergy and Clinical Immunology*. 2001;108:184–90.
9. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and fcepsilonRI on basophils. *The Journal of Allergy and Clinical Immunology*. 2004;113:297–302.
10. Casale TB, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. 2001;286:2956–67.
11. Grundbacher FJ. Causes of variation in serum IgE levels in normal populations. *The Journal of Allergy and Clinical Immunology*. 1975;56:104–11.
12. Gerrard JW, Heiner DC, Ko CG, Mink J, Meyers A, Dosman JA. Immunoglobulin levels in smokers and non-smokers. *Annals of Allergy*. 1980;44:261–2.
13. Sapigni T, Biavati P, Simoni M, et al. The Po River Delta Respiratory Epidemiological Survey: an analysis of factors related to level of total serum IgE. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology*. 1998;11:278–83.
14. Oryszczyn MP, Annesi-Maesano I, Charpin D, Paty E, Maccario J, Kauffmann F. Relationships of active and passive smoking to total IgE in adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). *American Journal of Respiratory and Critical Care Medicine*. 2000;161 4 Pt 1:1241–6.
15. Miyake Y, Miyamoto S, Ohya Y, et al. Relationship between active and passive smoking and total serum IgE levels in Japanese women: baseline data from the Osaka Maternal and Child Health Study. *International Archives of Allergy and Immunology*. 2004;135:221–8.
16. Nye L, Merrett TG, Landon J, White RJ. A detailed investigation of circulating IgE levels in a normal population. *Clinical Allergy*. 1975;5:13–24.
17. Mediaty A, Neuber K. Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. *Immunity & Ageing*. 2005;2:9.
18. Crawford WW, Gowda VC, Klaustermeyer WB. Age effects on objective measures of atopy in adult asthma and rhinitis. *Allergy and Asthma Proceedings*. 2004;25:175–9.
19. Duc J, Peitrequin R, Pecoud A. Value of a new screening test for respiratory allergy. *Allergy*. 1988;43:332–7.
20. Kalliel JN, Goldstein BM, Braman SS, Settupane GA. High frequency of atopic asthma in a pulmonary clinic population. *Chest*. 1989;96:1336–40.
21. Klaustermeyer WB, Krouse HA. The laboratory assessment of allergic disease in a veteran population. *Military Medicine*. 1989;154:81–3.
22. Sue MA, Krouse HA, Klaustermeyer WB. IgE in allergic disease in a veteran population. *Military Medicine*. 1986;151:420–1.
23. Merrett TG, Pantin CF, Dimond AH, Merrett J. Screening for IgE-mediated allergy. *Allergy*. 1980;35:491–501.
24. Reddy PM, Nagaya H, Pascual HC, et al. Reappraisal of intracutaneous tests in the diagnosis of reaginic allergy. *The Journal of Allergy and Clinical Immunology*. 1978;61:36–41.
25. Griner PF, Mayewski RJ, Mushlin AI, Greenland P. Selection and interpretation of diagnostic tests and procedures. Principles and applications. *Annals of Internal Medicine*. 1981;94 4 Pt 2:557–92.
26. Rembold CM, Watson D. Posttest probability calculation by weights. A simple form of Bayes' theorem. *Annals of Internal Medicine*. 1988;108:115–20.
27. Krouse HA, Klaustermeyer WB. Immediate hypersensitivity skin testing: a comparison of scratch, prick, and intradermal techniques. *Immunology and Allergy Practice*. 1980;2:13–20.
28. Sox Jr HC. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. *Annals of Internal Medicine*. 1986;104:60–6.
29. Delespesse G, De Maubeuge J, Kennes B, Nicaise R, Govaerts A. IgE mediated hypersensitivity in ageing. *Clinical Allergy*. 1977;7:155–60.
30. Geha RS, Human IgE. *Human IgE*. *Journal of Allergy and Clinical Immunology*. 1984;74:109–20.
31. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *The New England Journal of Medicine*. 1989;320:271–7.
32. Droste JH, Kerhof M, de Monchy JG, Schouten JP, Rijcken B. Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study. The Dutch ECRHS Group. *The Journal of Allergy and Clinical Immunology*. 1996;97:922–32.
33. Klink M, Cline MG, Halonen M, Burrows B. Problems in defining normal limits for serum IgE. *The Journal of Allergy and Clinical Immunology*. 1990;85:440–4.

34. Simoni M, Biavati P, Baldacci S, et al. The Po River Delta epidemiological survey: reference values of total serum IgE levels in a normal population sample of North Italy (8–78 yrs). *European Journal of Epidemiology*. 2001;17:231–9.
35. Haahtela T, Suoniemi I, Jaakonmaki I, Bjorksten F. Relationship between serum IgE concentration and occurrence of immediate skin test reactions and allergic disorders in young people. *Allergy*. 1982;37:597–602.
36. Hetman S, Kivity S, Greif J, Fireman EM, Topilsky M. IgE values in the allergic and healthy Israeli population. *Annals of Allergy*. 1988;61:123–8.
37. Campos A, Reyes J, Blanquer A, Linares T, Torres M. Total serum IgE: adult reference values in Valencia (1981–2004). Usefulness in the diagnosis of allergic asthma and rhinitis. *Allergologia et Immunopathologia*. 2005;33:303–6.
38. Mullarkey MF, Hill JS, Webb DR. Allergic and nonallergic rhinitis: their characterization with attention to the meaning of nasal eosinophilia. *The Journal of Allergy and Clinical Immunology*. 1980;65:122–6.
39. Bousquet J, Coulomb Y, Arrendal H, Robinet-Levy M, Michel FB. Total serum IgE concentrations in adolescents and adults using the phadebas IgE PRIST technique. *Allergy*. 1982;37:397–406.
40. Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. *The Journal of Allergy and Clinical Immunology*. 1980;66:305–13.
41. Warren CP, Holford-Strevens V, Wong C, Manfreda J. The relationship between smoking and total immunoglobulin E levels. *The Journal of Allergy and Clinical Immunology*. 1982;69:370–5.
42. Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *The American Review of Respiratory Disease*. 1981;124:523–5.
43. Bhandari CM, Baldwa VS. Relative value of peripheral blood, secretion and tissue eosinophilia in the diagnosis of different patterns of allergic rhinitis. *Annals of Allergy*. 1976;37:280–4.
44. Stevens WJ, de Clerck L, Vermeire PA. Total blood eosinophilia in allergic (type I allergy) and non-allergic asthma, rhinitis and cough. *Allergologia et Immunopathologia*. 1984;12:53–9.
45. Urmil G, Bazaz-Malik G, Mohindra SK. Significance and comparison of blood, nasal secretion and mucosal eosinophilis in nasal allergy. *Indian Journal of Pathology & Microbiology*. 1984;27:27–32.
46. Felarca AB, Lowell FC. The total eosinophil count in a nonatopic population. *The Journal of Allergy*. 1967;40:16–20.
47. Grater WC, Pavuk J, Budd C. Value of immunoglobulin E (IgE) in the private practice of allergy. Eight years experience: 1973–1981. *Annals of Allergy*. 1983;50:317–9.
48. Mullarkey MF. Eosinophilic nonallergic rhinitis. *The Journal of Allergy and Clinical Immunology*. 1988;82 5 Pt 2:941–9.
49. Zetterstrom O, Johansson SG. IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy. A diagnostic approach. *Allergy*. 1981;36:537–47.