

Problems in defining normal limits for serum IgE

24221

Mary Klink, MD, Martha G. Cline, MS, Marilyn Halonen, PhD, and Benjamin Burrows, MD, Tucson, Ariz.

Recommended "normal limits" for serum IgE generally assume that a single upper limit of normal can be applied to all adults. The present article describes the distribution of IgE levels in 2657 subjects in a general population sample in Tucson, Ariz. Limits of IgE defining the lower 5%, 10%, 25%, 50%, 75%, 90%, and 95% in 1569 subjects with negative allergy skin tests and without current asthma, considered a reference group, are provided by age and sex. These cutoffs are then used to compare groups with asthma and with positive allergy skin tests with the reference population. Distributions of IgE levels in these groups are vastly different, but defining an upper "limit of normal" for serum IgE is of doubtful clinical value because there is no single level of IgE that distinguishes different groups with any precision. The spread of IgE values is extremely wide in subjects with and without known allergic diseases. (J ALLERGY CLIN IMMUNOL 1990;85:440-4.)

Measurement of serum IgE has become a routine procedure in many clinical laboratories, and the level of this immunoglobulin is sometimes used in an attempt to distinguish allergic from nonallergic individuals.¹ Although recommended "normal limits" usually vary with age for children,² it is generally assumed that a single limit can be applied to adults, regardless of age or sex.³⁻⁵

In our population studies, however, serum IgE levels appear to decline throughout adult life and tend to be higher in men than in women. Furthermore, there does not appear to be a single cutoff level for serum IgE that reliably delineates subjects with and without allergic disorders. A recent publication from our laboratory suggests that the frequency of asthma increases steadily from the age and sex standardized IgE level and that this is true both in subjects with and without allergy STpos reactions.⁶ Thus, it may be more realistic to consider how an individual's IgE level relates to levels of apparently nonallergic indi-

Abbreviations used

STpos: Skin test positive
STneg: Skin test negative

viduals of the same age and sex rather than to attempt to define a single "normal limit" for this measurement.

In the present article, we describe the distribution of IgE levels in subjects aged 6 years or older who were enrolled in a general population study, and we derive percentile limits to indicate how a given IgE level would relate to levels found in subjects with negative allergy skin tests and without known asthma (our "reference population"). The percent of subjects with asthma, allergic rhinitis, and positive skin tests without allergic disease falling below the various percentile cutoffs for the reference population are then described.

METHODS

The methods of selection and study of the population have been reported in detail.⁷ Subjects in this study are taken from a random stratified sample of white non-Mexican American households residing in Tucson, Ariz., in 1971. Square blocks of households were stratified on the basis of ethnicity, age of the head of household, and socioeconomic status. One of every six households in each of these blocks was asked to participate. Blood samples were obtained and assessed for serum IgE levels from subjects 6 years of age or older. The present analysis is limited to the 2657 subjects who had both serum for IgE level and allergy skin testing

From the Division of Respiratory Sciences, University of Arizona College of Medicine, Tucson, Ariz.

Supported by a National Heart, Lung, and Blood Institute Specialized Center of Research Grant HL14136.

Received for publication June 12, 1989.

Revised Sept. 25, 1989.

Accepted for publication Oct. 4, 1989.

Reprint requests: Benjamin Burrows, MD, Division of Respiratory Sciences, University of Arizona College of Medicine, Tucson, AZ 85724.

1/1/17172

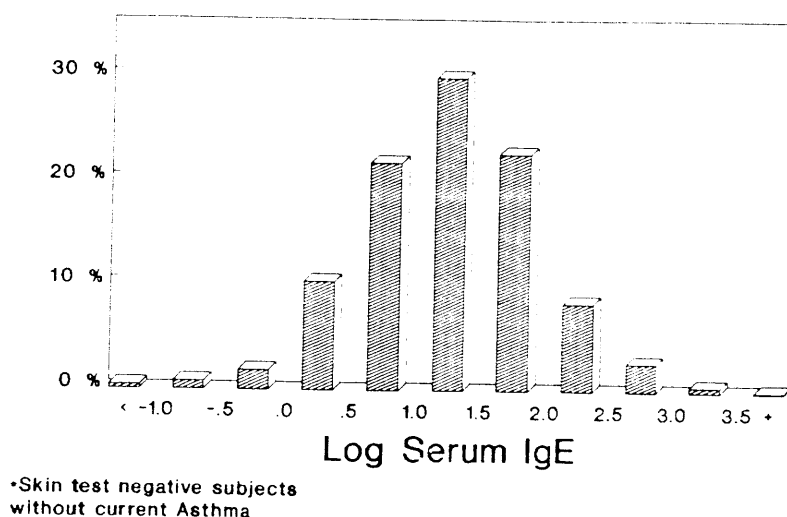


FIG. 1. Distribution of log serum IgE values in the 1569 STneg subjects without current asthma in the Tucson epidemiologic study of airway obstructive diseases. This group of subjects comprises the IgE reference population. The percent of subjects in each IgE range is illustrated on the ordinate.

at the time of enrollment into the study, the same group as the group reported in regard to the relationship of asthma to those same evidences of allergy.⁶ The age range was from 6 to 94 years.

Allergy skin testing was performed by the prick test technique. Five tests were used that included a variety of allergens common to the Tucson area plus a control. Commercially available skin test materials from Hollister-Stier Laboratories (Spokane, Wash.) were used. Test material consisted of (1) house dust, 1:10; (2) Bermuda grass, 1:20; (3) tree mix, 1:20 (olive, mulberry, mesquite, and cottonwood); (4) weed mix, 1:20 (rabbit bush, salt bush, careless weed, Russian thistle, desert ragweed, and slender ragweed); and (5) Dematiaceae mold mix, 1:100 (*Alternaria*, *Helminthosporium*, *Cladosporium*, *Curvularia*, *Spondylocladium*, and *Stemphylium* species). A reaction to any skin test greater than a reaction to the control classified the subject as STpos.

Serum IgE levels were performed with the PRIST method. Duplicate tests were done, and the mean value was expressed as international units per milliliter. As noted in previous articles,^{8,9} the overall distribution of serum IgE levels in our population is log normal. For this reason, log serum IgE was used in all statistical analyses, and central tendencies are reported either as logarithms or as geometric means.

The presence of rhinitis, asthma, and smoking status were based on responses to a self-administered questionnaire. Subjects were considered to have rhinitis if they replied, "Yes, I still have it," to the question, "Have you ever had hay fever or any other allergy that makes your nose runny or stuffy, apart from colds?" Exrhinitis was diagnosed if the response to this question was, "Yes, but I no longer have it." Subjects were considered to have asthma if they gave

an affirmative response to, "Have you ever had asthma?" Asthma was considered current if they replied, "Yes, I still have it," admitted to wheezing or whistling in the chest that occurs apart from colds, or had more than rare "attacks of shortness of breath with wheezing." The presence of eczema was not used in this analysis, since our questionnaire was not designed to identify subjects with this disorder.

Preliminary analyses revealed highly significant differences between IgE levels of STpos versus STneg subjects, regardless of the presence or absence of asthma or rhinitis. Among STneg subjects, those with current asthma demonstrated much higher IgE levels than other STneg subjects, but there were no significant differences in STneg subjects without current asthma related to the presence or absence of exasthma, exrhinitis, or even current rhinitis. In fact, other than current asthma, no reported symptom or disease identified a subset of STneg subjects with a significant elevation of serum IgE. Therefore, we defined our "reference population" as the 1569 subjects with completely negative skin tests who did not have current asthma. There were statistically significant but relatively small differences between smokers and nonsmokers in this group. As will be demonstrated, the degree of misclassification resulting from combining the different smoking groups proved to be very slight and did not appear to justify limiting the reference population to nonsmokers. This would have created quite small groups in certain age ranges of male subjects.

The overall distribution of log IgE values in the reference population (Fig. 1) is remarkably gaussian. The mean log IgE values and their standard deviations in various age groups are presented for each sex in Table I. To age and sex standardize the values for the reference population, "Z scores" were calculated for subjects in each of the age and sex groups presented in Table I. A subject's age and sex

TABLE I. Mean log $\pm$ standard deviation and geometric mean of serum IgE (international units) in reference population*

Age (yr)	Male		Female	
	n	Mean log $\pm$ SD (geometric mean)	n	Mean log $\pm$ SD (geometric mean)
6-14	69	1.612 $\pm$ 0.652 (40.9)	71	1.610 $\pm$ 0.523 (40.7)
15-34	213	1.367 $\pm$ 0.718 (23.3)	201	1.217 $\pm$ 0.663 (16.5)
35-54	145	1.309 $\pm$ 0.669 (20.4)	154	1.163 $\pm$ 0.647 (14.6)
55-74	224	1.297 $\pm$ 0.694 (19.8)	348	1.030 $\pm$ 0.634 (10.7)
75+	61	1.250 $\pm$ 0.669 (17.8)	83	0.948 $\pm$ 0.686 (8.9)

*STneg subjects without current asthma.

TABLE II. Reference values for serum IgE*

Limits of IgE (international units) defining lower							
Age (yr)	5%	10%	25%	50%	75%	90%	95%
6-14							
M	3.9	6.4	15.2	42.2	109.2	256.7	423.6
F	6.2	9.1	18.4	41.7	89.4	177.4	265.1
15-34							
M	1.7	3.0	7.8	24.1	68.7	176.1	305.9
F	1.5	2.5	6.0	17.0	44.8	106.7	177.8
35-54							
M	1.8	3.0	7.4	21.0	55.8	133.9	224.0
F	1.4	2.3	5.5	15.0	38.6	90.1	148.2
55-74							
M	1.6	2.7	6.9	20.4	56.4	140.0	238.8
F	1.1	1.8	4.1	11.0	27.9	64.0	104.2
75+							
M	1.6	2.6	6.5	18.3	48.7	116.8	195.4
F	0.7	1.2	3.1	9.2	25.0	61.4	104.0

*Values in STneg subjects without current asthma.

standardized "Z score" is simply the number of standard deviations by which he or she differs from the mean of their age and sex group. Z score cutoffs below which 5%, 10%, 25%, 50%, 75%, 90%, and 95% of the reference population would fall were then determined. From these scores the actual level of serum IgE required in each age- and sex-specific group could be calculated to place a subject within these percentile limits.

Those subjects not in the reference population were classified into four different subgroups based on skin test status and questionnaire responses: (1) STneg with current asthma (with or without rhinitis), (2) STpos with current asthma, (3) STpos with rhinitis (subsequently called "allergic rhinitis")

but without current asthma, and (4) STpos with no current rhinitis or asthma.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, Ill.). Statistical methods included analysis of variance and chi-square.

RESULTS

The limits for serum IgE levels derived from Z score cutoffs that would place an individual in the lower 5%, 10%, 25%, 50%, 75%, 90%, and 95% of the reference population are presented in Table II. With

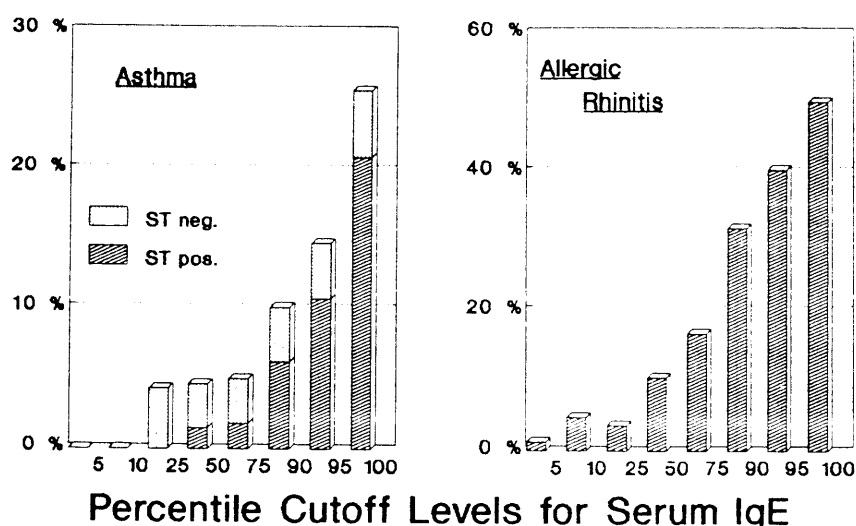


FIG. 2. The prevalence of asthma (with or without rhinitis) by skin test reactivity and of allergic rhinitis (with or without asthma) in the Tucson epidemiologic study according to various percentile levels of the IgE reference population. Only STpos rhinitis cases were considered to have "allergic rhinitis."

TABLE III. Comparison of smokers versus nonsmokers in the reference population

	Cumulative % of reference subjects in lower						
	5%	10%	25%	50%	75%	90%	95%
Current smokers	4.2	8.0	19.0	43.4	68.0	86.4	91.8
Ex- or never smokers	5.3	10.9	27.9	53.1	78.3	91.6	96.5
Total	5.0	10.0	25.0	50.0	75.0	89.9	95.0

TABLE IV. Distribution of serum IgE Z scores in subpopulations as compared to percentile distribution of IgE Z score values in the reference population*

Population	n	Cumulative % of subjects in lower						
		5%	10%	25%	50%	75%	90%	95%
Reference group	1569	5.0	10.0	25.0	50.0	75.0	89.9	95.0
STneg								
Current asthma	93	0	0	12.9	30.1	51.6	73.1	82.8
STpos								
No current disease	376	1.9	2.7	8.5	23.9	49.7	73.7	85.4
Current rhinitis	475	0.2	1.1	3.2	12.8	33.1	62.3	76.4
Current asthma	144	0	0	0	5.6	13.2	35.4	52.1

All other groups have a significantly different distribution than the reference group, $p < .0001$.

*Reference group is STpos subjects without current asthma.

these cutoff levels, we then determined the percent of any other group whose serum IgE level would fall below these reference levels. The differences between current and exsmokers and never smokers in the reference population are presented in Table III. As al-

ready noted, the degree of misclassification based on smoking status, although it is statistically significant, is relatively small and probably of no practical clinical importance.

The percent of subjects with IgE serum levels falling

below the limits for the reference population (Table II) are demonstrated for groups not included in the reference population in Table IV. All percents are highly significantly different from the reference percentiles. However, STpos subjects with previous asthma and without allergic rhinitis were not significantly different from STpos subjects without disease and are not presented separately.

The group that differs most strikingly from the reference population is the group containing STpos subjects with current asthma; >86% of subjects fall in a range that included only the highest 25% of the reference population, and none fall in the range of the lowest 25% of the reference population. Even in this group, however, there is no obvious single point that would allow a clear distinction between a normal and an abnormal serum level of IgE. This is evident if the percent prevalence of diseases in the various IgE categories is considered, as illustrated in Fig. 2. A progressive increase in age and sex standardized IgE level is illustrated in Fig. 2.

DISCUSSION

The major purpose of this study was to describe the distributions of serum IgE levels in that segment of the population least likely to have an allergic problem. These findings should provide reference values with which IgE levels in subjects suspected of having an allergic disease might be compared. Obviously, these data are specific for the population in which they were obtained, white, non-Mexican Americans residing in Tucson, Ariz.

There are obvious limitations in an epidemiologic study of this type. Our allergy skin test battery was limited in regard to the allergens applied. Some of our seemingly STneg subjects might well have reacted to the more complete skin testing used in a clinical evaluation. There are also serious limitations in the determination of the presence or absence of disease based on self-reporting by the subjects. Unfortunately, firm criteria for diagnosing asthma or allergic rhinitis in a population survey do not exist, and we could not verify these reported diagnoses or the lack of disease by performing a full clinical evaluation of all subjects in the study. Thus, our "reference population" undoubtedly includes some subjects with subclinical allergic problems and may even include a few with eczema. For this reason, it is considered only as a reference group rather than as a pure "nonallergic" population. It also includes subjects who, despite reporting allergic rhinitis, have negative allergy skin

tests. Such subjects do not demonstrate any significant elevation of their serum IgE. As noted in a previous article,⁶ we can only presume that such subjects have nonspecific nasal reactions, possibly related to the dry, dusty environment of Tucson.

Although the distributions of IgE levels are vastly different in STpos than in STneg subjects, and even more different in subjects with apparent allergic disease, the spread of IgE values is extremely wide in all groups, and there is no single level of IgE that clearly distinguishes different groups at a level of precision that is clinically meaningful. We are doubtful that defining an upper "limit of normal" for serum IgE is clinically useful, even if the marked effects of age and lesser effects of sex are taken into account. Furthermore, with a continuous variable, such as IgE in which there is a steady increase in the probability of disease with higher age and sex standardized levels, calculation of such indices as sensitivity and specificity are not very meaningful. Even the ranges of IgE levels found in our reference population probably have very limited clinical application. We present them primarily because they appear to be more reasonable than the single value often used as the limit of normal for adults.

REFERENCES

1. VanArsdel PP Jr, Larson EB. Diagnostic tests for patients with suspected allergic disease: utility and limitations. *Ann Intern Med* 1989;110(4):304-12.
2. Kjellman NM, Johansson SGO, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy* 1976;6:51-9.
3. Pharmacia. Phadebas IgE PRIST radioimmunoassay directions for use. Uppsala, Sweden: Pharmacia Diagnostics AB, 1977.
4. Sears MR, Chow CM, Morseth DJ. Serum total IgE in normal subjects and the influence of a family history of allergy. *Clin Allergy* 1980;10:423-31.
5. Braunwald E, Isselbacher KJH, Petersdorf RG, et al. eds. *Harrison's principles of internal medicine*. New York: McGraw-Hill, 1987.
6. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
7. Lebowitz MD, Knudson RJ, Burrows B. Tucson epidemiologic study of obstructive lung diseases. I. Methodology and prevalence of disease. *Am J Epidemiol* 1975;102:137-52.
8. Barbee RA, Halonen M, Lebowitz MD, Burrows B. Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity. *J ALLERGY CLIN IMMUNOL* 1981;68:106-11.
9. Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981;124:523-5.