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Reference Distributions for Immunoglobulins A, G, and M: A Practical, Simple, and Clinically Relevant Approach in a Large Cohort

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Serum immunoglobulins are measured millions of times each year, yet clinical interpretations remain hampered by inadequate age- and gender-specific reference limits. In order to provide more reliable and comprehensive reference distributions for IgA, IgG, and IgM measurements, we analyzed automated immunoassay values from 115,017 serum samples from northern New England patients (99% Caucasian) who were tested in our laboratory between 1986 and 1995. Measurements were standardized to reference material, CRM 470 (RPPHS). A simple, practical, and clinically relevant approach was used to determine reference distributions for the immunoglobulins over a wide range of ages for males and females. Levels of IgA and IgM varied considerably by age, and by gender for IgM. For each of the analytes, the observed 5th and 95th centiles were symmetric about the median and approximately constant over the entire age range. When immunoglobulin reference values are expressed as multiples of the age- and gender-specific regressed medians, the resulting distributions fit a log-Gaussian distribution well. This finding enables interpretation of serum immunoglobulin measurements using a common unit (multiples of the median) that is independent of age or gender. Insights gained from this study can help improve and simplify the interpretation of immunoglobulin measurements. J. Clin. Lab. Anal. 12:363–370, 1998.

Key words: serum proteins; reference ranges; Caucasians; CRM 470/RPPHS; multiple of the median

INTRODUCTION

Since the introduction of serum protein quantification to clinical medicine, numerous publications have presented reference ranges for the major immunoglobulins IgA, IgG, and IgM. Analysis of these proteins can play an integral role in the diagnostic evaluation of patients in virtually every aspect of medicine, but availability of authoritative reference materials and adequate reference ranges is required before clinical interpretation can be provided that affords maximum advantage. Many studies contained in the literature are not suitable sources for reference data. Some are so old that the analytical methods are no longer widely used. Precision and accuracy of the analytical method are addressed rarely. Many studies include only a small number of observations, account inadequately for variables such as age, gender, and race, or poorly document the reference materials used. Often, the statistical analyses do not address outlying values adequately.

The current study provides comprehensive age- and gender-specific reference values for the three major immunoglobulins using a large, well-characterized reference population. All had sought medical attention for some perceived problem that, in the judgment of their physicians, warranted serum protein studies. A companion paper (1) contains an extensive review of the world's literature from 1962 to 1995 and shows these new reference data in the perspective of past publications. The data are presented in some detail to assist laboratories in transferring and validating their own immunoglobulin reference ranges.

MATERIALS AND METHODS

Definitions and Overview

The current study adopted the terminology approved by the International Federation of Clinical Chemists and published by the National Committee for Clinical Laboratory Standards (2). A referent individual is defined as "a person selected on the basis of well-defined criteria." The 115,017 referent individuals were selected *a posteriori* and partitioned

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into 93 groups based on the diagnosis provided on the laboratory requisition slip. Of these, 25,636 were removed from analysis for various reasons. Using reference median values specific for age and gender that were derived in 1983, the immunoglobulin measurements for the remaining 89,381 individuals were converted to multiples of the median. The reference population was selected based on statistical parameters and clinical characteristics of these groups. Medians (and selected centiles) expressed in g/L were then calculated and smooth curves were fitted to the median values. Reference values were converted to multiples of the median, this time using the current age- and gender-specific smoothed medians. The reference distributions were then tested to determine whether they fit a log-Gaussian distribution or other more complex distributions. The resulting parameters were then used to calculate selected age- and gender-specific reference limits and the resulting reference ranges.

Patient Samples

Tests were performed on fresh samples referred to the Foundation for Blood Research for serum protein studies between 1986 and 1995. Sera were separated by centrifugation at the phlebotomy site and promptly shipped to the laboratory where they were refrigerated and run within three working days. Although fasting samples were requested, it is likely that many were not in compliance. The study population is predominately Caucasian, with African-American, Asian, and Native Americans representing one percent or less of the population. The ethnic origins of the population were mainly Anglo-European or French-Canadian.

Serum Protein Reagents and Instrumentation

Antisera were obtained from several sources (Atlantic Antibodies, Scarborough, ME; INCSTAR, Stillwater, MN; and Midland Bioproducts, Scarborough, ME), after assurance that the materials were sufficiently specific, potent, and stable. Each batch of antiserum was compared to previous batches for value recovery and proportionality in actual assays (3). The buffer system used phosphate-buffered saline containing polyethylene glycol (nominal molecular mass 6,000 kDa), to a final concentration of 4.4 percent. Samples were tested using the previously described immunoturbidimetry method for the COBAS FARA system (Roche Diagnostic Systems, Nutley, NJ) (3).

Reference Materials

A clarified and delipidated commercially available serum calibrant was used during the study (INCSTAR, Stillwater, MN). Values for this pool were obtained from the World Health Organization reference materials (4), the College of American Pathologists Reference Material for Serum Proteins (RPSP) (5), and the International Reference Preparation for Proteins in Human Serum (RPPHS) (Certified Reference Material 470) (6). This last standard is obtainable from either the Bureau of Community Reference in Brussels or the College of American Pathologists (Chicago, IL). Measurements were made using several instruments of the same type and several different reference materials. Each change to a subsequent reference material was made only after extensive method verification and value comparison. All results from the current study have been normalized to RPPHS by assaying the previous reference materials against fresh vials of RPPHS. Multilevel comparisons were preformed each time standards were changed (2×). The resulting multiplicative factors were used to convert old values. Factors ranged from 0.87 to 1.00 with the majority being about 0.90.

Removal of Duplicate Records

Demographic data were entered into a database at the time of sample receipt. As part of routine practice, each new patient record was automatically linked with any previously existing records for that individual. A sample was considered to be a duplicate if the patient name was identical and the date of birth and/or reported ages were consistent. When duplicates were identified, the measurements from the first record were matched with the lowest diagnosis code number for the series (i.e., the one with the greatest likelihood of affecting serum protein levels). The earliest record was assumed to have the highest chance of representing the untreated disease state, while the lowest diagnosis code was most likely to be correct. A total of 21,724 duplicate records were removed.

Removal of Records Because of the Presence of Monoclonal Immunoglobulins or Other Reasons

Many patients were referred for serum protein studies with a clinical diagnosis (or a strong clinical suspicion) of a monogammopathy. These cases were placed into the appropriate diagnostic categories (101 to 103). However, an additional 3,912 cases had monoclonal immunoglobulins as an incidental finding and had been classified into other diagnostic groups, based on the suspected diagnosis. These samples were excluded from all analyses as were samples identified with cryoglobulins. A total of 43 individuals were contained in four diagnostic code groups with less than 20 observations. These were also removed from further analyses along with 2,342 with missing age and/or gender. No other sample was removed because of an abnormal immunoglobulin measurement.

Preliminary Normalization of Measurements for Age and Gender

A previously unpublished study of 4,000 individuals without apparent clinical disease was performed in 1983. These medians were consistent with the literature and, being labo-

ratory-specific, were considered sufficient to provide preliminary correction for possible differences in analyte levels. Each mass unit measurement was converted to a unitless multiple of its age and gender-specific median (MoM) using these preliminary reference values. It was necessary to perform this normalization prior to comparing immunoglobulin measurement between diagnostic groups in order to ensure that differences in the statistical parameters were not due to age and/or gender differences. For each analyte, the 93 diagnostic groups was summarized individually by two parameters: the median MoM (expected to be about 1.00), and the log variance (calculated as the difference between the logarithm of the 5th and 95th centile divided by 3.29, squared).

Coding of Diagnosis/Symptom Strings

Overall, 92 percent of samples had an associated diagnosis or symptom provided by the referring physician. Since these alphanumeric strings varied greatly (over 20,000 unique alphabetic strings), they were classified into 93 groups by a clinician experienced in the interpretation of immunoglobulin measurements (RFR). (A list of the codes and related information are available upon request.) Diagnostic groups with codes between 101 and 165 contained individuals with findings that were expected to have a large impact on serum protein levels (e.g., multiple myeloma, cirrhosis, hepatitis, infection, lung disease, leukemia, renal failure, immunodeficiency, or thyroid disease), while diagnostic groups 166 through 195 contained individuals with conditions expected to have minimal or no effect on serum protein levels (e.g., allergies, hypertension, headache, neck pain, neuropathy, syncope, seizures, fatigue, or depression). Code 100 indicated that no diagnosis was provided. If more than one diagnosis code was present, the lowest (most severe) was used. The diagnostic groups 166 and above were designated as the preliminary reference population.

Refinement of the Reference Population

In order to determine which of the diagnostic groups would contribute to the final reference population, published methodology relying on symmetric trimming of values prior to calculating means and standard deviations (7) was used to identify outliers among the diagnostic group parameters associated with codes of 166 and higher. A logarithmic transformation of the variance was necessary because of the nonrandom right skewness of the observed data. The resulting trimmed mean value $\pm$ 1.96 standard deviations (for both the MoM and the log variance) defined limits of acceptability. Immunoglobulin measurements from any diagnostic group falling within the limits were considered reference values, those falling outside were not. This approach was applied separately for IgA, IgG, and IgM, resulting in different numbers of reference values for each.

Fitting the Medians to a Smooth Curve

The logarithm of the age was regressed versus the logarithm of the median analyte value (expressed in mass units), separately for males and females. The log age was used because analyte levels vary more rapidly early in life. Polynomial regression was performed for two groups of patients, younger and older using an age cut-off of between 8 and 36 years of age depending on the analyte. Higher level regression was used only if a significant improvement in r^2 could be obtained. The methodology is similar to that suggested by Royston et al (8). The two curves were then constrained so that a continuous curve was produced. Results from patients younger than one month or older than 85 years of age were not included in the regression analysis.

Statistical analysis was performed using BMDP Statistical Software, Inc. (Los Angeles, CA). Graphics were produced using PICSURE (Precision Visuals, Boulder, CO).

Conversion of Analyte Results to Multiples of the Median (MoM)

As a last step, all analyte values were converted to MoM levels by dividing the measurement (in mass units) by the regressed age- and gender-specific medians. For example, an IgA value of 2.00 g/L in a 37-year-old male would correspond to a MoM of 1.00, indicating that the value is equal to the expected level (median) for a person of that age and gender. However, if that same result was obtained for a 9-year-old male, the MoM would be 1.55, indicating that the level is 55% higher than expected for a person of that age and gender. The MoM has the advantage of removing from interpretation the effects of age and gender.

Distribution of MoM Values

The reference values for males and females between the ages of 1 month and 85 years, expressed as MoM, were then examined to determine whether they fit a log-Gaussian distribution. This was examined graphically by plotting the reference values versus the observed rank of the values (probability plot). If the data fitted a straight line, the distribution is log-Gaussian. Because of the large sample size, statistical tests are able to detect even minor, clinically unimportant deviations from normality. For that reason, we have chosen to rely on visual inspection as the primary indicator of fit (8).

Verification of Measurement Over Time

The median age, the male to female ratio, and the median reference value (after conversion to multiples of the median) by quarter were examined to assess any long-term systematic assay or population changes during the 8½ year study period.

RESULTS

Selection of Diagnostic Groups to Form the Reference Population

The median IgA levels (expressed as MoM) along with the variance of the log MoM levels are shown in Figure 1 for each of the 89 diagnostic groups with at least 20 observations. The circles indicate the preliminary reference population (diagnostic codes 166 and above). The rectangle is drawn at the trimmed mean ± 1.96 standard deviations for both the median (horizontal axis) and log variances (vertical axis) based on the preliminary reference groups. The squares represent the remaining 61 diagnostic groups. Overall, 64 of the 89 groups lie within the rectangle. Results from individuals within these 64 groups compose the reference values for IgA. Individuals from the 25 diagnostic groups represented by filled circles or squares were not included as part of the IgA reference population. This analysis was repeated for IgG and IgM measurements (figures available upon request). A total of 49 and 62 diagnostic groups were found to lie within the rectangles computed for IgG and IgM, respectively.

Computation of Age- and Gender-Specific Medians Values

Overall, 75,092, 66,972, and 72,195 reference values were available for IgA, IgG, and IgM, respectively. Figure 2A displays selected IgA centiles for males. The average age for each interval is plotted on the horizontal axis on a logarithmic scale versus the median analyte level (closed circles) and the 5th and 95th centile (lower and upper open circles, respectively) on the vertical logarithmic axis. The observed centiles are based on about 50 observations each for those under age 10, about 500 for those between 10 and 30, and over 1,000 for the remaining ages. The solid line indicates the regressed medians for IgA. Figure 2B displays a similar analysis of IgA measurements in females with a dashed line indicating the regressed medians. Similarly Figures 3A, 3B, 4A, and 4B display data for IgG and IgM respectively. For all of the analytes, the increase in medians is fit by a straight line in both younger males and females. The pattern becomes more complicated in older individuals. There is little difference in the IgA and IgG median levels for males and females over the entire age range. Males have lower levels of IgM over the entire age range except, perhaps, when very young. For each analyte, the distance from the median to the 95th centile and from the median to the 5th centile is approximately equal across the entire age range. This indicates that each of the distribution

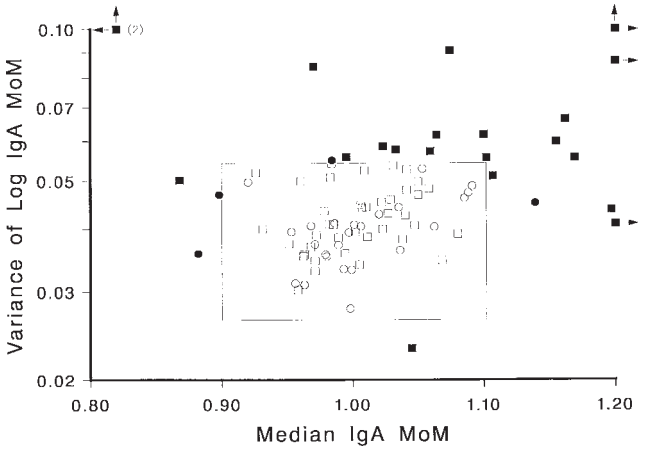

Fig. 1. Scatterplot of IgA median levels versus variance for the diagnostic categories. Diagnostic codes 100 through 165 are displayed as squares (□ ■), while codes 166 and above are circles (○ ●). The rectangle represents the 95% confidence intervals (after trimming) of the median (horizontal axis) and variance (vertical axis) for the diagnostic categories 166 and above. Open symbols (○ □) represent those categories whose values comprise the reference population.

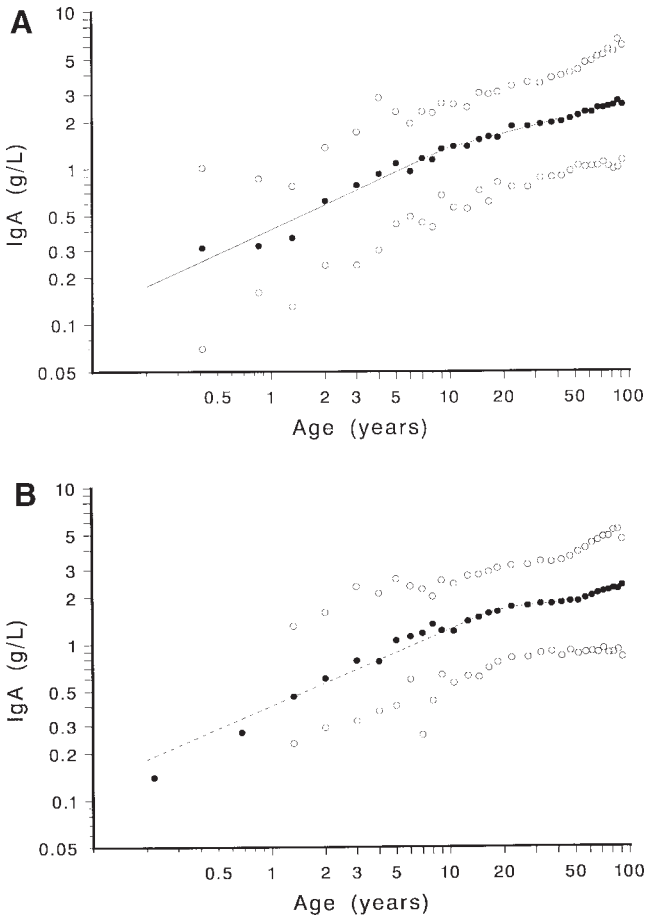

Fig. 2. IgA centiles and medians versus age. The individual's age is displayed on the horizontal logarithmic axis versus the immunoglobulin level on the vertical logarithmic axis. The closed circles (●) represent the observed median level; the lower and upper open circles (○) represent the observed 5th and 95th centiles, respectively. The lines represent the predicted median values. Figures 2**A** and 2**B** show the IgA results for males and females, respectively.

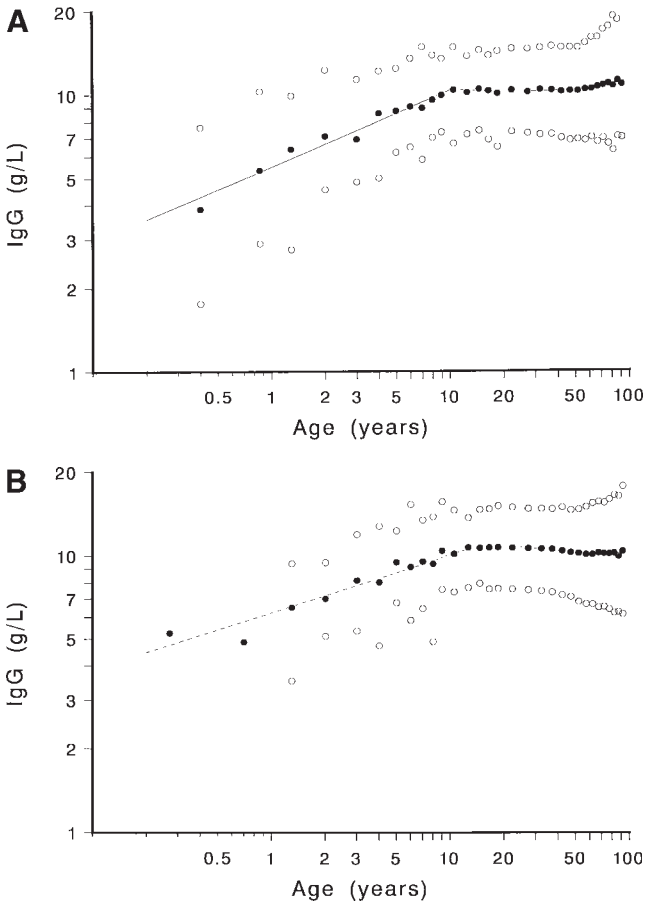

Fig. 3. IgG centiles and medians versus age. The data are presented in the same format as Figure 2. **A** and **B** show the IgG results for males and females, respectively.

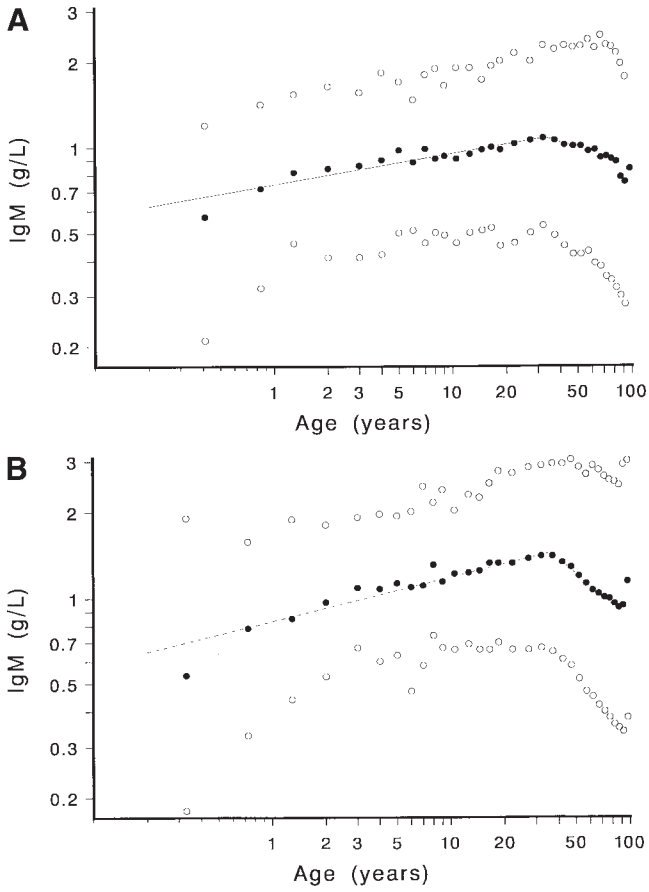

Fig. 4. IgM centiles and medians versus age. The data are presented in the same format as Figure 2. **A** and **B** show the IgM results for males and females, respectively.

is symmetric after a logarithmic transformation, and the variances of the distributions do not change appreciably by age. Table 1 contains the regression equations, along with the age range over which each is valid, for the IgA, IgG, and IgM median values in both males and females.

Fitting MoM Levels to a Population Distribution

Figure 5 shows probability plots of approximately 2,000 IgA, IgG, and IgM measurements (expressed as MoM). The samples were selected to equally represent each year of age. The IgA measurements (Fig. 5A) fit the distribution well be-

TABLE 1. Regression Models and Coefficients for Median IgA, IgG, and IgM Measurements by Age and Gender

		Age range (yrs)			Coefficients		
Analyte	Sex	From	To	Constant	Log age	(Log age)^2	(Log age)^3
IgA	Males	0.5	9.9	–0.39049226	0.52584145	0	0
		10	85	–0.16670145	0.29787467	0	0
	Females	0.5	12.9	–0.39826509	0.48900812	0	0
		13	85	–3.481	7.20874158	–4.70552526	1.03865718
IgG	Males	0.5	10.9	0.73940439	0.27378095	0	0
		11	85	1.15967286	–0.22239426	0.081733446	0
	Females	0.5	8.9	0.79482247	0.20675031	0	0
		9	85	–0.020339	2.13025242	–1.40337307	0.29895903
IgM	Males	0.5	32.9	–0.1312916	0.10880327	0	0
		33	85	0.33762714	–0.19972576	0	0
	Females	0.5	35.9	–0.08036072	0.15436369	0	0
		36	85	0.9472872	–0.5066652	0	0

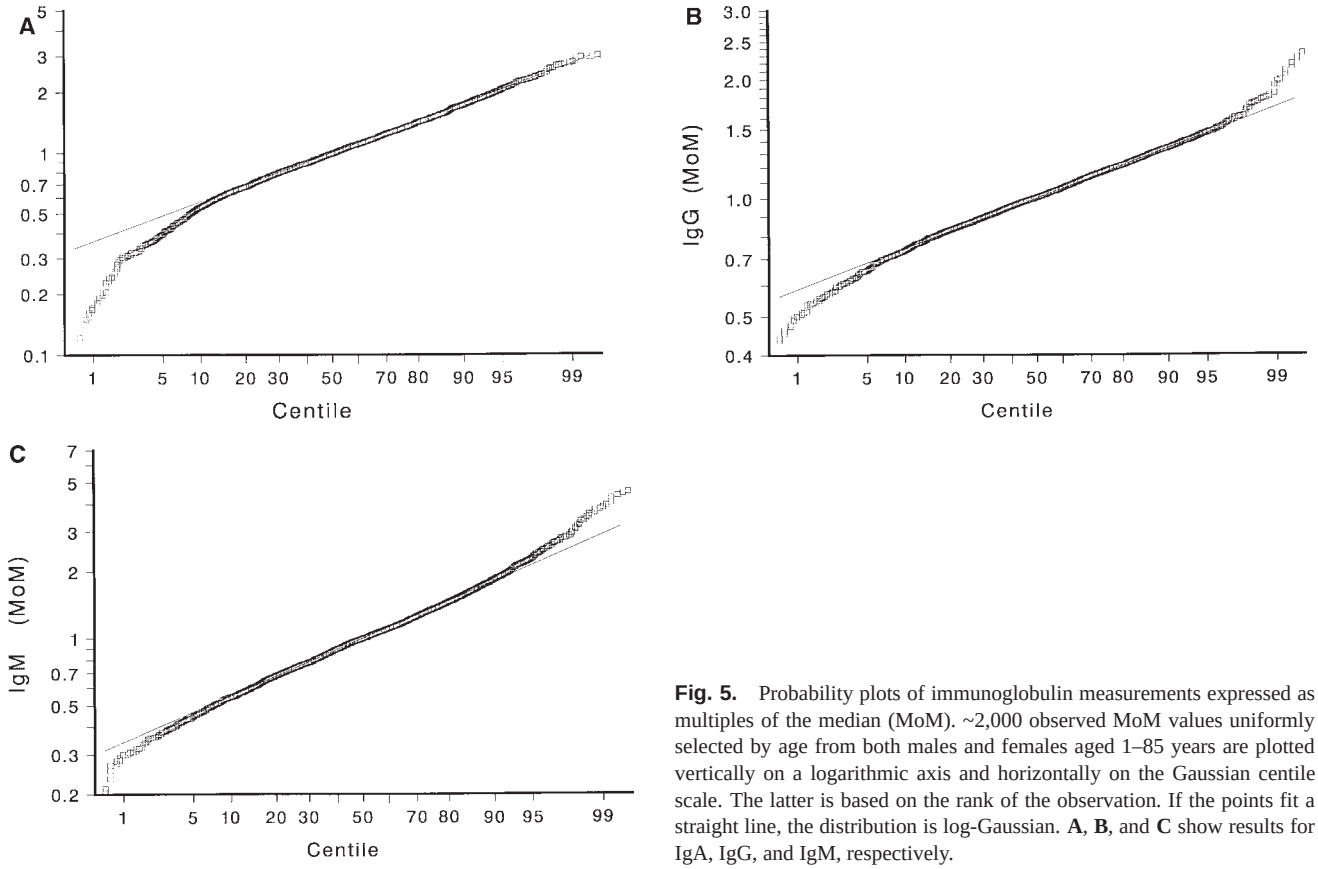

Fig. 5. Probability plots of immunoglobulin measurements expressed as multiples of the median (MoM). ~2,000 observed MoM values uniformly selected by age from both males and females aged 1–85 years are plotted vertically on a logarithmic axis and horizontally on the Gaussian centile scale. The latter is based on the rank of the observation. If the points fit a straight line, the distribution is log-Gaussian. **A**, **B**, and **C** show results for IgA, IgG, and IgM, respectively.

tween the 10th and 99th centiles (log-Gaussian mean and standard deviation of 0.0000 and 0.1896, respectively). The IgG (Fig. 5B) and IgM (Fig. 5C) measurements both fit well between the 5th and 95th centile (corresponding log-Gaussian parameters are 0.0000 and 0.1000, and 0.0000 and 0.2010, respectively). The distribution parameters were similar (log means within ± 0.05 and log SDs within ± 10%) when the analysis was restricted to individuals less than 10 years of age or between 70 and 85 years of age.

Predicting Age- and Gender-Specific Centiles

Because the parameters summarize the distributions well, at least between the 5th and 95th centiles, any centile within this range can be predicted for any age and gender. For example, the 5th (or 95th) centile of the MoM distribution can be found by subtracting (or adding) 1.645 standard deviations from the mean, and then antilogging the result (e.g., estimating the 5th centile for IgA, $10^{(0.0-1.645 * 0.1896)}$ or $10^{-0.312}$ or 0.49 MoM). This MoM level is then converted to mass units by multiplying it by the age- and gender-specific median (e.g., the 5th centile IgA value for a 40.0-year-old male is 0.49 * 2.04 g/L = 1.00 g/L). This methodology can be used to predict any given centile. A reverse procedure can be used to assign a centile to a patient's value; given the expected median for that patient's age and gender. Table 2 contains the predicted 2.5th, 50th, and 97.5th centiles for selected age and gender categories using the Gaussian parameters.

Verification of Results Over the Course of the Study

The median multiple of the median of all three analytes was 1.00 (within statistical limits), except for a two-year period when the IgG median multiple of the median was about 4% high. The average age of patients rose only slightly during the study from 49 to 51 years of age. The percentage of males decreased slightly from 34 to 31 percent of the population studied**.** There was no systematic change in patient referral pattern during the course of the study and the assay results did not show any clinically important differences over time.

DISCUSSION

Introduction of widely available measurement of serum proteins requires reliable reference ranges for clinical interpretation. Many studies attempting to define those ranges have been published but few, if any, have satisfied all the necessary criteria of 1) using adequate reference materials and modern methodology, 2) documenting the health status of the

TABLE 2. Predicted IgA, IgG, and IgM Medians and Selected Centiles Stratified by Age and Gender

Decimal age (years)	IgA (g/L)			IgG (g/L)			IgM (g/L)		
	2.5th	50th	97.5th	2.5th	50th	97.5th	2.5th	50th	97.5th
				Males					
1.0	0.17	0.41	0.96	3.5	5.5	8.6	0.30	0.74	1.83
4.0	0.36	0.84	1.98	5.1	8.0	12.6	0.35	0.86	2.13
7.0	0.48	1.13	2.66	6.0	9.4	14.7	0.37	0.91	2.26
10.0	0.57	1.35	3.18	6.6	10.3	16.2	0.38	0.95	2.35
14.0	0.64	1.50	3.52	6.6	10.3	16.2	0.40	0.98	2.44
18.0	0.68	1.61	3.79	6.5	10.2	16.0	0.41	1.01	2.51
20.0	0.71	1.66	3.91	6.5	10.2	16.0	0.41	1.02	2.54
30.0	0.80	1.88	4.41	6.5	10.2	16.0	0.43	1.07	2.65
40.0	0.87	2.04	4.81	6.6	10.3	16.2	0.42	1.04	2.58
50.0	0.93	2.18	5.14	6.6	10.4	16.4	0.40	1.00	2.47
60.0	0.98	2.31	5.43	6.7	10.5	16.5	0.39	0.96	2.38
70.0	1.03	2.41	5.68	6.8	10.7	16.7	0.38	0.93	2.31
80.0	1.07	2.51	5.91	6.9	10.8	16.9	0.37	0.91	2.25
				Females					
1.0	0.17	0.40	0.94	4.0	6.2	9.8	0.34	0.83	2.06
4.0	0.33	0.79	1.85	5.3	8.3	13.0	0.42	1.03	2.55
7.0	0.44	1.04	2.44	5.9	9.3	14.6	0.45	1.12	2.78
10.0	0.52	1.23	2.90	6.4	10.1	15.9	0.48	1.19	2.94
14.0	0.62	1.46	3.43	6.8	10.7	16.7	0.50	1.25	3.09
18.0	0.69	1.61	3.80	6.9	10.8	17.0	0.52	1.30	3.22
20.0	0.71	1.66	3.91	6.9	10.8	17.0	0.53	1.32	3.27
30.0	0.75	1.77	4.16	6.8	10.7	16.7	0.57	1.40	3.48
40.0	0.78	1.83	4.30	6.7	10.5	16.4	0.55	1.37	3.38
50.0	0.81	1.90	4.46	6.6	10.3	16.2	0.49	1.22	3.02
60.0	0.85	1.99	4.68	6.5	10.3	16.1	0.45	1.11	2.76
70.0	0.90	2.11	4.97	6.5	10.2	16.1	0.42	1.03	2.55
80.0	0.96	2.26	5.32	6.5	10.3	16.1	0.39	0.96	2.38

reference individuals, and 3) studying large numbers of individuals to reliably document possible effects of age, gender, and race. Perhaps the most confounding feature of previous studies has been the lack of attention to precision and accuracy of the laboratory measurements and to variability in reference materials. The latter was corrected worldwide by the release of a large batch of material traceable to existing authoritative reference materials (6).

The current study population is a large cohort of North American Caucasians, in whom stable, precise, and accurate immunoglobulin measurements were obtained within a single laboratory. The group is large enough to reliably estimate the effects of age and gender on the reference distributions for IgA, IgG, and IgM. However, our study has limitations. Since the population was largely drawn from northern New England where the population is relatively homogeneous, it is not possible to extend our conclusions, with assurance, to other ethnic or racial groups. Some relatively small studies have concluded that racial or ethnic differences exist but the findings are not consistent (1). Pre-analytical variables such as fasting status (9), phlebotomy technique (10), time of day (11), season (12), and ambulatory status (13–15), were not standardized as recommended by the NCCLS (16) and the IFCC (17). The health status of reference individuals was not verified because detailed questioning was not feasible for such a large study. Consequently, we were unable to identify individuals who had subclinical or an unidentified illness. However, our less formal approach addresses this issue effectively and efficiently. As shown in the companion paper (1), our data compares favorably with previously reported smaller studies which studied subjects according to such formal guidelines (1). Thus, the main advantage of the current study lies in its large numbers which allow detailed examinations of the effect of age and gender on the reference data for the major immunoglobulins.

Nearly all previous studies define the reference range in terms of analytical units (e.g., the predicted 95% reference range for IgA in the current study is from 0.87 to 4.80 g/L for 40-year-old males). A few studies provide parameters (means and standard deviations) from which reference ranges can be calculated for the specific population being studied. The current study has shown, that the 5th and 95th centiles are symmetric about the medians on a logarithmic scale over the age range studied for both males and females. This suggests that a single set of population parameters reasonably summarizes each analyte's distribution after an appropriate normalization (such as conversion to standard deviation units or multiples of a fractile) (18). We have chosen to represent reference

ranges as multiples (or fractions) of the age- and gender-specific median (MoM). For example, the predicted 95th centile for IgA is 2.05 MoM, regardless of age or gender even though the observed IgA 95th centile for 9-year-old females is 2.53 g/L and for 62-year-old males it is 4.88 g/L. It was suggested that a more complex methodology (19) be used to determine reference values. This alternative method generated results very similar to those reported in this paper. Differences in medians ranged from 2 to 6% over small segments and no appreciable difference everywhere else (data not shown). In light of the reference data available in the literature, such minor differences are not clinically important. The method of normalization used in this study greatly simplifies the interpretation of immunoglobulin values by having only one reference range per immunoglobulin, not the numerous ones that would be required for each age- and gender-specific group. It is for this reason that we chose to use a single estimate of the standard deviation for each immunoglobulin. This choice not only has the advantage of simplifying the calculation of reference ranges, but also allows for easy conversion from analyte measurement in mass units to age- and gender-specific centiles (see above).

The deviations from normality found in the tails of the distributions (Fig. 5) might represent the true distribution of reference values, and other transformations might fit the observed data more closely. Towards this end, other transformations were performed (such as log (x+C) (19)) but little improvement was found (data not shown). Alternatively, the tails of the distributions might contain data from individuals with diagnoses not reflecting their true overall health status. The fitted line may be a more realistic estimate of the true distribution. To verify that these individuals actually represent the extremes of "normality" would require a protracted, arduous, and expensive undertaking.

CONCLUSION

The current study is by far, the largest cohort used to determine reference ranges for IgA, IgG, and IgM. The median levels and widths of our reference ranges are consistent with a review of the world's literature from 1962 to the present (1). It is evident that for these analytes, sufficient variation occurs between males and females and through life that separate reference ranges need to be used for immunoglobulins IgA, IgG, and IgM. The methodology of normalizing assay results to multiples of the median presented in the current study has the potential to simplify the reporting while increasing the clinical utility of immunoglobulin measurements. Although these methods and findings have not been validated for all racial and ethnic groups, they could be considered for use by laboratories making such measurements, especially if the population is mainly Caucasian.

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