Normal Ranges of Streptococcal Antibody Titers Are Similar Whether Streptococci Are Endemic to the Setting or Not

Andrew C. Steer, Suzanna Vidmar, Roselyn Ritika, Joseph Kado, Michael Batzloff, Adam W. J. Jenney, John B. Carlin and Jonathan R. Carapetis

Published Ahead of Print 3 December 2008.

Updated information and services can be found at:
http://cvi.asm.org/content/16/2/172

REFERENCES

These include:
This article cites 22 articles, 4 of which can be accessed free at:
http://cvi.asm.org/content/16/2/172#ref-list-1

CONTENT ALERTS

Receive: RSS Feeds, eTOCs, free email alerts (when new articles cite this article), more»

Information about commercial reprint orders: http://journals.asm.org/site/misc/reprints.xhtml
To subscribe to another ASM Journal go to: http://journals.asm.org/site/subscriptions/
Normal Ranges of Streptococcal Antibody Titers Are Similar Whether Streptococci Are Endemic to the Setting or Not \*\^\*\^\*\*\*

Andrew C. Steer, 1 Suzanna Vidmar, 2 Roselyn Ritika, 3 Joseph Kado, 3 Michael Batzloff, 4 Adam W. J. Jenney, 1 John B. Carlin, 2 and Jonathan R. Carapetis 1, 5

Centre for International Child Health, University of Melbourne, Melbourne, Victoria, Australia 1; Clinical Epidemiology and Biostatistics Unit, Murdoch Children’s Research Institute, and University of Melbourne, Melbourne, Victoria, Australia 2; Fiji Ministry of Health, Suva, Fiji Islands 3; Queensland Institute of Medical Research, Brisbane, Queensland, Australia 4; and Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia 5

Received 6 August 2008/Returned for modification 12 October 2008/Accepted 24 November 2008

Group A streptococcal (GAS) serology is used for the diagnosis of post-streptococcal diseases, such as acute rheumatic fever, and occasionally for the diagnosis of streptococcal pharyngitis. Experts recommend that the upper limits of normal for streptococcal serology be determined for individual populations because of differences in the epidemiology of GAS between populations. Therefore, we performed a study to determine the values of the upper limit of normal for anti-streptolysin O (ASO) and anti-DNase B (ADB) titers in Fiji. Participants with a history of GAS disease, including pharyngitis or impetigo, were excluded. A total of 424 serum samples from people of all ages (with a sample enriched for school-aged children) were tested for their ASO and ADB titers. Reference values, including titers that were 80% of the upper limit of normal, were obtained by regression analysis by use of a curve-fitting method instead of the traditional nonparametric approach. Normal values for both the ASO titer and the ADB titer rose sharply during early childhood and then declined gradually with age. The estimated titers that were 80% of the upper limit or normal at age 10 years were 276 IU/ml for ASO and 499 IU/ml for ADB. Data from our study are similar to those found in countries with temperate climates, suggesting that a uniform upper limit of normal for streptococcal serology may be able to be applied globally.

Streptococcal antibody tests are used for the diagnosis of antecedent infections caused by the group A streptococcus (GAS) and are particularly useful for the diagnosis of acute rheumatic fever and acute post-streptococcal glomerulonephritis. Acute rheumatic fever is an autoimmune disease that follows infection with GAS; however, the isolation of GAS is uncommon (<15%), and so confirmation of the diagnosis often relies on streptococcal antibody tests (13). While a number of tests utilize different antigens of GAS, the most frequently performed tests are those that determine the anti-streptolysin O (ASO) titer and the anti-DNase B (ADB) titer (8, 18). Ideally, it is recommended that the titer be determined in the acute phase and then determined in the convalescent phase 14 to 28 days later, with a positive result defined as a rise in titer of twofold or more (26). However, it is not always practicable to obtain a second sample for titer determination, particularly in developing countries, where acute rheumatic fever is the most common. Therefore, it is generally accepted that if only a single specimen is available, a titer greater than the upper limit of normal at the initial testing can be considered presumptive evidence of a preceding streptococcal infection (10, 12, 26).

The upper limit of normal for streptococcal serology has been defined by separating the upper 20% from the lower 80% of the group distribution in a dichotomous fashion (4, 12, 26). The choice of the 80th centile cutoff rather than more traditional upper-limit-of-normal calculations (e.g., 2 standard deviations from the mean) is based upon studies that found that more than 80 to 90% of patients with acute rheumatic fever or post-streptococcal glomerulonephritis have streptococcal titers that are above the 80th centile for the healthy controls with no clinical evidence of recent streptococcal infection (4, 26). Therefore, it is assumed that in any population a proportion of apparently healthy individuals will have had a recent, subclinical GAS infection (4).

Streptococcal titers vary according to a number of factors, including age and population. In developed countries, where impetigo caused by GAS is uncommon, streptococcal titers in the population primarily reflect the incidence of pharyngeal infection with GAS; therefore, the titers in healthy people are low in early childhood, rise to a peak in children aged 5 to 15 years, decrease in late adolescence and early adulthood, and then flatten off after that (9, 12). In contrast, in populations with high rates of impetigo, background antistreptococcal titers are often very high, especially in children, probably because most children tested have had a recent streptococcal infection (15, 25).

Because of these differences in titers with age, it is recommended that age-stratified upper-limit-of-normal values be determined for populations of interest by testing people who have not had a recent streptococcal infection (12). Age-stratified upper-limit-of-normal reference values have been defined for the U.S. pediatric population, the Australian pediatric population, and the Indian pediatric population, among others (5, 7, 9, 11, 17). However, there has been no investigation of upper-limit-of-normal values for populations in the Pacific re-
region, where some of the highest rates of acute rheumatic fever and acute post-streptococcal glomerulonephritis are known to occur and where impetigo is common in children (6, 21, 24).

For studies that determine streptococcal serology reference ranges, it is important that a representative group of individuals without a known recent streptococcal infection be sampled (12). The immune response to GAS infections should be considered in determining which subjects should be excluded from analysis (18). The ASO titer tends to rise a week following infection, peaks at 3 to 5 weeks, and begins to decline after 8 weeks; and it responds more vigorously to pharyngal infection than skin infection. The ADB titer peaks at 6 to 8 weeks after infection and begins to decline at 12 weeks, and it responds vigorously to both pharyngeal and skin infections. Therefore, subjects with recent pharyngitis or skin infections should not be included in the sample. The exclusion of children with GAS throat carriage is not necessary, as all healthy pediatric populations include carriers of GAS (9).

A variety of statistical techniques for constructing age-specific reference values are available (27). Previous comparable studies investigating reference values for streptococcal serology have used nonparametric calculations by pooling data by age group and calculating an 80th centile cutoff value for each of the age groups (7, 9). However, more robust and efficient statistical methods that take advantage of parametric regression modeling techniques are available for the analysis of age-specific reference values (16).

In this study, we document for the first time the normal ranges of the ASO and ADB titers in all age groups in a Pacific island country and also present an alternative method for analyzing these data.

MATERIALS AND METHODS

Setting. Fiji is a nation of approximately 330 islands located in the western Pacific. It has a population of 827,900 people comprising two major racial groups: indigenous Fijians (57.3%) and Indo-Fijians (37.6%) (3). Fiji is ranked 90 of 177 nations on the United Nations Development Programme’s Human Development Index. It has a per capita gross domestic product of $6,066 and an infant mortality rate of 16.8 per 1,000 population (1, 2). Approximately 49% of the population lives in rural areas (3). The major hospital, the Colonial War Memorial Hospital, is located in the capital, Suva, on the main island of Viti Levu, and predominantly serves the largest region of Fiji, the Central Division. GAS disease is common in Fiji, with high rates of invasive GAS disease, acute rheumatic fever, and rheumatic heart disease (14, 19, 22). In addition, there is a high prevalence (over 55%) of impetigo among schoolchildren (20), and the incidence of GAS culture-positive sore throat is similar to that in developed countries.

Sample. Blood was collected from participant groups enrolled in two different studies. The first group comprised 280 volunteers of all ages identified through the Colonial War Memorial Hospital. The enrollment was designed so that there was an even distribution of participants from birth to age 65 years. All of these 280 participants were prospectively screened for current or recent GAS infection. We excluded any participant from enrollment by direct inquiry of the participant and by checking their medical records for the following: a history of acute rheumatic fever, rheumatic heart disease, or invasive GAS disease and a history of GAS pharyngitis in the preceding 14 days, and 273 children with evidence of impetigo were excluded from the analysis, there were no children with a history of GAS pharyngitis in the preceding 14 days, and 273 children with evidence of impetigo were excluded from the analysis. When the data were log transformed, it was noted that there were three extreme outliers (one participant with an ASO titer of >1,999 and two participants with ADB titers of >2,999), and these values were excluded from the analysis. Therefore, a total of 424 blood samples were included in the study. Table 1 summarizes the demographic features of the study participants.

ASO and ADB titer analysis. There was a peak in the mean titers of both ASO and ADB in the 5- to 14-year-old age group, with a gradual decrease occurring following this peak (Fig. 1). The estimated median and 80% upper-limit-of-normal values for five age groups are presented in Table 2. There are no values presented in Table 2 for children aged less than 1 year because of the small number of values and the steep incline of the curve. Table 3 presents these data in more detail for children aged 5 to 14 years.
DISCUSSION

We found the normal values for streptococcal serology to be similar to those that have been reported from other regions. In comparison to data from the United States and from Australia, we found that the overall values for the ASO titers were only slightly lower in our study and that the values for the ADB titers were only slightly higher (8, 9). The slightly higher ADB titers are probably due to the fact that impetigo is endemic in Fiji, particularly in children (20). Although we excluded children with a recent history of impetigo, the ADB titers remain elevated for many months; hence, we are likely to have included some children whose ADB titers were in the process of returning to their baseline level after a case of impetigo.

Although some have claimed that normal ranges for streptococcal antibody titers are higher in populations with endemic streptococcal infections, this is incorrect. The studies on which these statements were based did not meticulously exclude children with recent streptococcal infections. For example, a study with an aboriginal community in Australia, in which impetigo was very common among the children of the community, found median titers of 256 IU/ml and 3,172 IU/ml for ASO and ADB, respectively, but did not exclude children with current or recent impetigo (15). The very close similarities of the titers between our study in a tropical country and studies in temperate zones provide evidence and impetus for the notion that single upper-limit-of-normal values for ASO and ADB titers may be able to be applied globally. Similar data from India support this notion (11,12).

By applying the simple nonparametric technique that has
been used in previous studies to analyze our data, we found cutoff values similar to those obtained by the parametric method. However, the parametric method of data analysis that we used in this study has some advantages over the nonparametric method. The nonparametric method often produces implausible irregular patterns in the centiles with age, unless a large sample is used and wide age intervals are specified. The results may be artificially affected by the choice of age groups, especially when tertiles have a complex pattern of change with age. In comparison, the curve-fitting method produces smooth centile curves (that is, the reference value varies smoothly with age), and it allows both the level and the spread of the reference distribution to change with time.

We will recommend that Fijian clinicians use a single upper-limit-of-normal cutoff value for children aged 5 to 14 years (that is, the estimated 80% upper-limit values at 10 years, which were 276 IU/ml for the AS0 titer and 499 IU/ml for the ADB titer; Table 2) rather than the cutoff values for subgroups, such as 4 to 5 years, 6 to 9 years, and 10 to 14 years, as recommended in other studies. This is because only minimal variability in the year-by-year values was found for children aged 5 to 14 years (Table 3). The use of a single cutoff value for this age group also makes it far simpler for laboratory staff to report results and for clinicians to interpret them (12).

This study provides upper-limit-of-normal values for streptococcal serology for people of all ages in Fiji determined by using a robust and readily repeatable parametric statistical technique. These upper-limit-of-normal values will guide clinicians in Fiji when they consider the diagnosis of post-streptococcal diseases in their patients and will provide useful baseline data for future studies of interventions against GAS disease in Fiji. Our data could also be applied to surrounding Pacific island countries.

ACKNOWLEDGMENTS

This study was funded by a grant from the National Institute of Allergy and Infectious Diseases (grant U01AI60579).

There is no conflict of interest for any author.

We acknowledge the following people: all people who agreed to participate in the study; the Fiji Group A Streptococcal Project team, including Laisiana Matatolu, Frances Matanatabu, Maureen Ah-Kee, and Loraine Kelpie; the laboratory and clinical staff at the Colonial War Memorial Hospital, particularly Eka Buadromo, Joe Bolqace, and Tagica Taratai; Robert Gibb at the Department of Microbiology, Pathology Queensland; and the staff of the Streptococcal Laboratory of the Queensland Institute of Medical Research, in particular, the director, Michael Good.

REFERENCES