Insurance Testing

THE INDETERMINATE WESTERN BLOT

BY
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Introduction

According to surveys conducted by A. M. Best Company, the AIDS claims incurred by 462 insurers increased by 56% between 1987 and 1988, (AIDS Insurance Reports, Vol 10, No. 2, Feb. 7, 1990). Best estimated that the insurance industry paid a total of 802.2 million in 1988 for AIDS-related life and health claims. California accounted for more than 20% of AIDS-associated insurance pay outs during 1987–1988, and in fact, half of the benefits paid by the entire industry were claims in four states: California, Texas, New York, and Florida. The Fuxman Dynamic Model projects that annual AIDS mortality in the U. S. will pass 55,000 by 1992 and 100,000 by 1994 or 1995 (AIDS Insurance Reports, Vol. 9, No. 11, Nov., 1989.)

With these facts understood, it is not surprising that there is considerable interest by insurance medical directors and underwriters in how to handle an indeterminate Western blot test result. This is particularly true in a presumed low risk population applicant. When presented with an applicant with an indeterminate Western blot, many companies have elected to wait six months and retest. Some individuals will continue to remain HIV positive by EIA and indeterminate by Western blot. Often times the companies are under significant pressure to issue a policy to a low risk individual.

Western blot indeterminate results have been reported from a study at the NIH transfusion service, in EIA-negative blood donors (Gednesca, J. et al., What do western blot indeterminate patterns for human immunodeficiency virus mean in EIA negative blood donors?, The Lancet, Oct. 28, 1989).

The University of Minnesota studied 99 blood donors from a low-risk area of the country who had repeatedly reactive EIA assays for HIV and indeterminate Western blot determinations. These were evaluated for a median of 14 months. The authors concluded “that persons at low risk for HIV infection are rarely if ever infected with HIV-1 or HIV-2.” (N Engl J Med 1990;322:217–22).

Sixty cases with repeatedly reactive EIA for HIV and an indeterminate Western blot, and 60 controls (EIA negative) recruited from HIV testing sites in Washington state were studied for six months. Supplemental HIV tests (HIV culture, polymerase chain reaction or PCR RIA assay, HIVAGEN and ENV 9 recombinant peptide assays) were performed to access their specificity compared to Western blot results after 6 months. Three of sixty cases developed a positive Western blot in 6–10 months, for a seroconversion risk of 5.0%. The authors concluded that “HIV-1 culture, PCR, and ENV 9 may be useful in confirming the lack of HIV-1 infection in low risk cases with indeterminate HIV-1 Western blots. High risk cases and any case with a positive supplemental HIV test need to be followed by Western blot at least six months.” (Celum, C. et al, Indeterminate HIV-1 western blots: risk of seroconversion and specificity of supplemental tests, unpublished data to be published.)

I am very pleased to have Dr. Noce, with his extensive background in this field, as this column’s author. Peter Noce, MD, PhD is diplomate of the American Board of Pathology in Anatomic and Clinical Pathology and is the Medical Director of SmithKline Beecham Clinical Laboratories in Van Nuys, California. This laboratory performs a wide spectrum of clinical laboratory testing and each year conducts thousands of tests for specific antibodies against human immunodeficiency type 1 virus. He has published a number of articles in the areas of biochemistry and anatomic pathology, and is active in local and national professional societies.

The Indeterminate Western Blot

Individuals with acquired immunodeficiency syndrome (AIDS), generate large healthcare expenses. AIDS results from infection by human immunodeficiency virus type 1 (HIV-1), and following infection, specific antibodies are produced against specific viral proteins. Therefore applicants for insurance policies, who are infected with HIV-1, can be identified by detecting these specific antibodies in their sera.

To report the presence of antibodies in sera, there must be at least two reactive screening tests plus a reactive confirmatory test. Screening tests are enzyme immunoassay (EIA) procedures in which viral antigens are bound to microtiter plates. Specimens are incubated in the microtiter wells with the antigens. Antibodies that bind to the HIV-1 antigens are detected colorimetrically using a conjugated antibody to human gamma globulin. When the screening tests are repeatedly reactive the specimen is retested for HIV-1 antibodies by a confirmatory test. The western blot is a widely used confirmatory test that promotes binding of HIV-1 antibodies in a specimen to individual HIV-1 proteins. The HIV-1 proteins are
isolated with a specimen. If HIV-1 antibodies are present in the speci men, they are bound to the membrane-fixed antigens, and visualized colorimetrically through use of conjugated antibodies to human gamma globulin.1

A new generation of confirmatory tests2,3 that uses pure HIV-1 proteins has been produced by recombinant DNA technology. The pure gag/core, polymerase, and coat proteins are fixed to separate microtiter wells, to form a panel of tests. Aliquots of specimens are placed in each well of the microtiter panel. Specific binding of HIV-1 antibodies from the specimen to the pure protein antigens is detected colorimetrically through use of conjugated antibodies to human gamma globulin.

When the sequence of repeated screening and subsequent confirmation is performed with the highest care and quality, three classes of results are generated; negative, positive, and indeterminate. Negative specimens are either nonreactive in the screening test, or if reactive have no detectable antibodies in the confirmatory tests.1 Positive specimens are those repeatedly reactive by screening tests, and have diagnostic patterns of specific antibodies in the confirmatory tests.1 Indeterminate specimens are repeatedly reactive by screening, but have antibody patterns that do not meet the criteria for a positive confirmation.1

The decisions on risks of infection among applicants for insurance who have either negative or positive HIV-1 serology results are straightforward. For individuals from a low risk population who have an indeterminate result, there is a small risk of from two to five percent that they are true positives,1,4,5,6 and will eventually convert to positive serology. The risk of seroconversion is even present at a very low level for seronegative specimens, .001% to .009%. The basis for these seroconversions is the window period following infection by HIV-17 during which the infected individual gradually develops antibodies. Although the average time required to seroconvert from negative to positive is about six weeks, cases have been reported in which up to six or twelve months is required for seroconversion.8,9

However, the vast majority of indeterminate serologies are biological phenomena that are unrelated to HIV-1 infection. A majority of indeterminate serologies in a low risk population have been shown to persist10,11 without clinical signs of disease. Most indeterminate results are caused by seroreactivity against the core proteins of HIV-1. Although cross reactivity of antibodies against other retroviruses has been proposed as the mechanism for indeterminate serologies in healthy patients, this has not been established.5

It has been established that the risk of infection for people with indeterminate serologies who have been selected from low risk populations is small. The chance that an indeterminate test result indicates true infection decreases as the prevalence of HIV-1 infection decreases in a population. Therefore, it is not recommended that a decision to insure be based only on laboratory data. In those cases where the results of serologic testing for antibodies against HIV-1 appear to be inconsistent with other factors about the applicant, then testing for certain markers of Hepatitis B virus infection12 may help in assigning risk.

REFERENCES