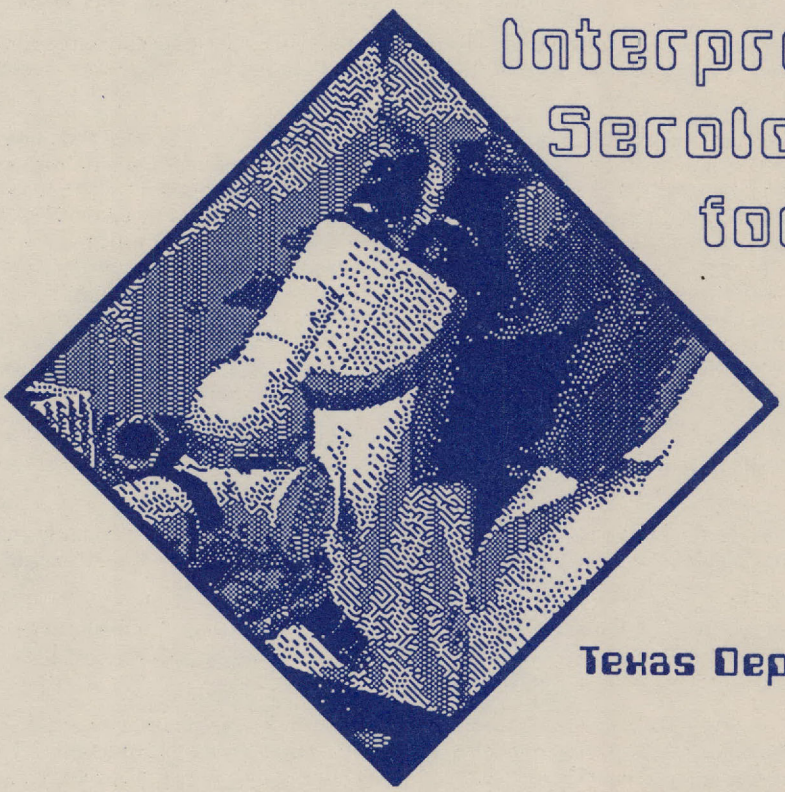
Interpretation of Serologic Tests for Syphilis



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INTERPRETATION OF SEROLOGICAL TESTS FOR SYPHILIS

Proper evaluation of serological test results in syphilis is often a confusing matter. Many physicians are confronted only rarely with problems in this regard. The following comments are provided as a matter of review. More extensive discussion may be found in the references listed at the end of this article. Several tests are in use. Most common of these are the RAPID PLASMA REAGIN CARD (RPRC) TEST, the VENEREAL DISEASE RESEARCH LABORATORY (VDRL) TEST, the MICRO-HEMAGGLUTINATION for TREPONEMA PALLIDUM (MHA-TP) TEST and the FLUORESCENT TREPONEMAL ANTIBODY ABSORPTION (FTA-ABS) TEST.

Nontreponemal Antigen Tests

Nontreponemal antigen tests, including the RPRC and VDRL Tests, are designed to test serum for reagin, a heterogeneous group of antibodies which combine with a cardiolipin-lecithin antigen. This antigen, usually derived from beef heart, is a normal component of human tissue. The RPRC and VDRL Tests are sometimes described as standard tests for syphilis (STS).

The RPRC Test is quick, inexpensive, and easy to use; it is exceptionally useful in screening. Like its older nontreponemal counterpart, the VDRL, it may be quantitated. These tests are very sensitive; i.e. there are few false negatives, except as discussed below.

RPRC quantitative tests are reported as "nonreactive" or "reactive" at dilutions of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, etc. While considerable confidence may be placed in the RPRC or VDRL Tests, it must be remembered that **patients with active infectious primary syphilis frequently have nonreactive VDRL and RPRC Tests.** This is a result of the patient's immune system lagging behind the disease process. At the time of the appearance of the primary lesion, the chancre, only about 25% of the cases will have a reactive VDRL or RPRC Test. After the chancre has been present for one week, some 50% will have a reactive test; after two weeks, the ratio rises to 75%. Almost all will have reactive serologies 3-4 weeks after appearance of the primary lesion; and virtually 100% of the cases will have a reactive serology by the time secondary syphilis develops. Although the development of secondary syphilis may take as long as six months, the rash or other signs may appear even before the primary lesion has "healed." Treatment with penicillin and other antibiotics will interrupt the development of subsequent stages of the disease if the dosage is adequate. If the dosage is NOT adequate, the development of clinical signs may be disrupted to some extent or delayed temporarily; the development of seroreactivity to the RPRC or VDRL Tests may also be masked or delayed by inadequate treatment.

Prior to treatment of any patient for syphilis, a quantitative VDRL or RPRC Test should be performed. The test should be repeated one month after therapy and on several occasions over the next two years — see Table.

Individuals who are recent (within 90 days) contacts of patients with infectious syphilis (primary and secondary stages) and who have negative RPRC or VDRL findings still must receive prophylactic treatment for syphilis as an epidemiologic control measure.

In untreated primary syphilis the seroreactivity usually reaches a titer of at least 1:4. Following treatment of primary syphilis, the reactivity may be expected to continue to rise for a few weeks but should revert to nonreactivity within 6-12 months following treatment. Ninety-seven percent will be nonreactive within two years.

In SECONDARY or EARLY LATENT syphilis, the VDRL and/or RPRC Tests are invariably reactive, usually with a titer of 1:32 or higher. While the titer may continue to rise immediately after successful treatment, the reactivity should gradually revert to nonreactivity within 18 months following the completion of successful treatment. After 2 years, over 75% will be nonreactive. If the patient with secondary syphilis develops a VERY strong reactivity, the VDRL or RPRC Test could be read spuriously as nonreactive, due to the prozone phenomenon. The laboratory should, therefore, be asked to dilute the "nonreactive" serum and continue the titration in all cases wherein suspicious lesions or clinical findings are present.

LATE syphilis (syphilis of more than one year's duration) may be symptomatic or asymptomatic. A patient may have late syphilis, either acquired or congenital, and have a nonreactive VDRL or RPRC Test. Further evaluation by means of a test such as the MHA-TP is necessary in such persons suspected of having late stage manifestations of syphilis. Cerebrospinal fluid (CSF) studies are recommended to rule out neurosyphilis in these cases. Late syphilis must be adequately treated.

Treatment of late syphilis may have no effect on the titer of reactive RPRC or VDRL Tests, but after successful treatment, the titer usually decreases "four-fold" (by two "tubes"; e.g., from 1:32 to 1:8). A stable or rising titer during the two years of observation after treatment suggests a treatment failure, reinfection, or a diagnostic error.

In any treatment situation, failure of the highest titer achieved (the highest titer may be reached a week or two after treatment is instituted) to decrease four-fold within one year suggests a treatment failure and warrants reevaluation of the case.

In cases wherein the epidemiological and clinical information fails to support serological findings, the diagnosis of syphilis should be questioned. A "biologic false positive" basis for seropositivity should be sought.

Biologic false positivity, meaning a nonsyphilitic basis for reactive RPRC or VDRL Tests, must be established by the use of a treponemal antigen test such as the MHA-TP. The RPRC and the VDRL are two among many nontreponemal antigen tests. Among the nontreponemal tests, "false positivity" or "false reactivity" occurs in at least 1% of persons tested. Barring laboratory error, the treponemal antigen tests are seldom falsely positive. They are more complicated and expensive to perform, and there are relatively more false negative test results. **Treponemal antigen tests, such as the MHA-TP and FTA-ABS, are inappropriate for use as screening tests.** They also are not quantitative tests, and cannot be used for following titers in response to therapy or progression of disease.

Treponemal Antigen Tests

Treponemal tests detect an antibody that is directed toward pathogenic members of the genus *Treponema*.

The Bureau of Laboratories, Texas Department of Health, uses the MICRO-HEMAGGLUTINATION FOR TREPONEMA PALLIDUM (MHA-TP) Test for routine confirmatory testing for syphilis. The specificity of the MHA-TP Test is as good as or better than the FTA-ABS Test. Usually, a nonreactive result on an MHA-TP Test will establish the "biologic false positive" diagnosis of a "positive" nontreponemal antigen test (RPRC or VDRL). Transient (acute) false reactivity of the RPRC or VDRL Tests occurs in some patients due to intercurrent viral and bacterial infections, when the serum titer of heterophile antibodies is high. Serum controls used in the laboratory identify this heterophile activity when it occurs in the MHA-TP, permitting further evaluation with the FTA-ABS Test. Infectious mononucleosis (Epstein-Barr viral infections) and viral hepatitis, as well as herpes simplex infections, chancroid, and lymphogranuloma venereum, may be accompanied by biologic false positive serological tests for syphilis. Long term (chronic) biologic false positivity may be present in leprosy and collagen diseases, such as systemic lupus erythematosus and rheumatoid arthritis, as well as in narcotics addiction and in some forms of neoplasms. A determination that a patient has a biologic false positive RPRC or VDRL mandates a search for the etiology of the positivity.

The Bureau of Laboratories will perform the FTA-ABS Test, but only under the following circumstances:

1. In suspected cases of primary syphilis in which two nontreponemal tests performed five days apart have shown a static reactive titer and in which the MHA-TP Test performed on the second specimen was nonreactive. This must be documented when the specimen is sent for FTA-ABS testing.
2. In diagnostic problems arising from conflicts between the overall clinical impression and results from both treponemal and nontreponemal tests. Such conflicts sometimes occur in cases of late syphilis. A brief written description of the diagnostic problem must accompany specimens sent for FTA-ABS testing.

The FTA-ABS Test is performed weekly on Fridays. The RPRC Test is performed on Tuesdays and Thursdays. The MHA-TP Test is also performed on Tuesdays and Thursdays, but only on specimens that are reactive by our RPRC test, or in cases where the results of nontreponemal tests are equivocal and in which information describing this situation accompanies the specimen.

Unlike the nontreponemal antigen tests, the MHA-TP and the FTA-ABS **do not** revert to nonreactivity after successful treatment of syphilis. Once reactive, they almost always stay reactive. Therefore, ordering repeated MHA-TP tests to check on a patient's progress is not warranted. In these situations, the desired information would be obtainable through repetition of the RPRC quantitative test.

Patients treated for OTHER venereal diseases should receive a serological test for syphilis because such persons are at relatively high risk for exposure to syphilis. Adequate penicillin treatment for gonorrhea is probably also effective against incubating syphilis. In such situations, further serological study is generally not needed unless another exposure occurs or new clinical findings warrant additional evaluation. Following recommended treatment of gonorrhea with any drug other than one of the penicillins, a follow-up RPRC quantitative test should be obtained at 3-6 months.

A reactive STS determined on serum raises the question as to whether testing of cerebrospinal fluid (CSF) is indicated. A lumbar puncture is generally **not** indicated during the primary and secondary stages of this infection, unless syphilitic meningitis is suspected or unexplained neurological findings occur. Following proper penicillin therapy for syphilis, a favorable blood serologic response (four-fold titer drop) generally indicates that NO testing of the CSF is required. Final judgment must be based on careful evaluation of the serologic response to treatment while following the serum titer for no less than 12 months, or to reversion to nonreactivity. (See Table.)

Tests of the CSF (VDRL quantitative) SHOULD be performed in:

. . .all cases of congenital syphilis,

. . .any syphilis patient with neurologic signs or symptoms,

. . .patients with syphilis of greater than one year's duration (late syphilis),

. . .patients who continue to have an RPRC titer of 1:8 or more twelve months after treatment, and

. . .patients with primary or secondary syphilis treated with ANY DRUG OTHER THAN PENICILLIN should have a CSF test for syphilis one year after treatment.

A reactive VDRL performed on a sample of spinal fluid should be considered neurosyphilis until proven otherwise. A diagnosis of central nervous system syphilis is supported by CSF findings of lymphocytic pleocytosis (often mild < 100 wbc/mm^3) and normal to elevated protein. In general, interpretation of CSF results may be difficult; consultation with experts is often necessary.

If an RPRC performed on the cord blood of a newborn is reactive, it may represent the passive transfer of maternal antibodies or congenital infection of the newborn. Such infants should be treated at birth if maternal treatment was inadequate or unknown or did not include penicillin, or if adequate follow-up of the infant cannot be ensured.

If the mother received adequate penicillin treatment during pregnancy, the risk to the infant is small. However, in all cases the infant should be tested at birth, 1 month, and every 3 months for the first 15 months, and then every 6 months until nontreponemal serologic tests are negative or stable at low titer. If a serologic test is positive at 3 months, the infant should be treated for congenital syphilis without waiting for subsequent titer results.

Infants with congenital syphilis should have a CSF examination before treatment to provide a baseline for follow-up. Regardless of CSF results, infants should be treated with a regimen effective for neurosyphilis.

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TABLE — Summary of Recommended Follow-Up

Stage	Treatment	Follow-up Posttreatment	
		Serology	Discharge[1]
Primary and Secondary	Yes	1st, 3rd, 6th, 12th months.	End of 1 year.
Contact of Primary or Secondary (even with negative RPRC or VDRL)	Yes		
Latent, both Early and Late	Yes	As above, then every 6 months for second year.	End of 2 years.
Syphilis in Pregnancy[2]	Yes	Monthly until delivery, then as for appropriate stage.	End of 1-2 years, depending on stage
Subsequent pregnancies. No change in titer[2]	No	Initial visit and monthly until delivery.	
Congenital[3]	Yes	1st, 3rd, 6th, 12th, 15th months; then every 6 months for 2 years	End of 2 years.
Neurosyphilis Cardiovascular Syphilis Late Benign Syphilis	Yes	Every 3 months for 1st year. Every 6 months for 2nd year	End of 2 years.

1. A spinal fluid examination is suggested at the time of discharge for all patients with other than primary or secondary syphilis as discharge patients should have either negative serologic tests for syphilis or fixed low titers. Neurosyphilis patients should have a spinal fluid examination at each follow-up visit.

2. Retreatment is indicated if there is any doubt concerning adequacy of previous treatment.

3. An appropriate medical specialist should be consulted regarding treatment of the complications of congenital syphilis.