Diagnostic testing for syphilis

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INTRODUCTION — Syphilis is a sexually transmitted disease caused by the spirochete Treponema pallidum. The manifestations of disease are notoriously protean, with different stages occurring over time in untreated disease [1-3]. Patients may seek evaluation of symptoms or signs of primary infection (eg, chancre), secondary infection (eg, diffuse rash), or tertiary infection (eg, symptoms of aortic insufficiency). Alternatively, patients may be completely asymptomatic and only identified on routine screening.

The diagnosis of syphilis is most commonly made by serologic testing, a technique first described by Wasserman in 1906 [4]. The appropriate use and interpretation of diagnostic testing is important for optimal patient management.

Diagnostic testing for suspected syphilis will be reviewed here. Laboratory monitoring of patients undergoing therapy is discussed elsewhere. (See "Laboratory monitoring of patients undergoing treatment for syphilis" .)

The pathophysiology, natural history, clinical manifestations, and treatment of this disorder are discussed separately. (See "Pathophysiology, transmission, and natural history of syphilis" and "Pathogenesis, clinical manifestations, and treatment of early syphilis" and "Pathogenesis, clinical manifestations, and treatment of late syphilis" .)

TARGET GROUPS FOR TESTING — Serologic testing for syphilis is performed in the following scenarios:

Suspected disease (eg, patient with a painless genital ulcer consistent with a syphilitic chancre)

Screening of high-risk populations (eg, patients presenting to a STD clinic, inmates, persons with multiple sexual partners, men who have sex with men who engage in high-risk behaviors)

Routine screening (eg, women attending antenatal or family planning clinics)

Serologic testing is also recommended by the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association at least annually for all sexually active HIV-infected patients; more frequent screening (every three to six months) is recommended for those with multiple sex partners, unprotected intercourse, sex in conjunction with illicit drug use, and methamphetamine use [5].

The rationale for screening for syphilis in asymptomatic patients is related to the natural history of the disease and to issues of public health. Although early stage syphilis will often resolve without treatment, untreated syphilis may progress to later stage disease, which can cause severe morbidity and which can be generally more difficult to treat. Furthermore, patients with unsuspected early primary or secondary disease can have lesions (eg, chancres and condyloma lata) that are teeming with spirochetes, making them highly infectious to others. Thus, it is important to screen for syphilis in certain high-risk patient populations. The United States Preventive Services Task Force (USPSTF) recommends screening men who have sex with men (MSM) who engage in high-risk behaviors, commercial sex workers, persons who exchange sex for drugs, and inmates in adult correctional facilities [6]. Screening for syphilis is discussed in detail elsewhere. (See "Screening for sexually transmitted infections" .)

Screening in pregnant women is recommended to prevent in utero transmission of asymptomatic infection, which can lead to congenital syphilis. This issue is discussed in detail elsewhere. (See "Syphilis in pregnancy" .)

DIAGNOSTIC TESTING METHODS — T. pallidum cannot be cultured in the laboratory. Thus, syphilis must be identified by either direct visualization of the organism in clinical specimens, or, more commonly, by serology.

Serologic testing traditionally involves a nonspecific nontreponemal antibody test followed by a more specific treponemal test for diagnostic confirmation [5]. The combination of a compatible clinical presentation plus reactive serologies for syphilis represents a presumptive clinical diagnosis (see 'Serologic tests' below).

Techniques to diagnose syphilis directly from clinical specimens include darkfield microscopy, direct fluorescent antibody (DFA) and investigational polymerase chain reaction (PCR) testing methods. Identification of T. pallidum by either darkfield microscopy or DFA represents a definitive diagnosis of syphilis (see below). These procedures provide definitive rather than presumptive diagnostic information, but are more labor intensive, and are infrequently used currently.

Serologic tests — Serologic testing is the mainstay of diagnosis of syphilis due to the complexities of direct visualization techniques. There are two types of serologic tests for syphilis: nontreponemal tests (that are traditionally used for primary screening) and specific treponemal tests (usually done to confirm infection). The use of only one test is insufficient for diagnosis since each test has diagnostic limitations [7].

Many laboratories have changed the sequence of testing, as discussed below [8]. (See 'Testing algorithms' below.)

Nontreponemal tests — Nontreponemal tests (also known as tests for reagin antibodies) are based upon the reactivity of serum, from patients with syphilis, to a cardiolipin-cholesterol-lecithin antigen. Although these screening tests are non-specific and therefore not definitive, they have traditionally been used for initial syphilis screening due to their relative low cost and ease of performance.

Nontreponemal tests include:

Venereal Disease Research Laboratory (VDRL)

Rapid Plasma Reagin (RPR)

Toludine Red Unheated Serum Test (TRUST)

In general, these assays are semi-quantitative in that the amount of antibody present (both IgM and IgG) generally reflects the activity of the infection. Positive nontreponemal tests are reported as a titer of antibody (eg, 1:32, which represents the detection of antibody in serum diluted 32-fold). Titers tend to wane over time even without treatment, but successful therapy accelerates the pace of antibody decline. Changes in titer are followed after treatment to detect a therapeutic response. (See "Laboratory monitoring of patients undergoing treatment for syphilis", section on 'Changes in titer' .)

Serologic testing is an indirect method of diagnosis since it relies upon a humoral immune response to infection. As such, it has some inherent limitations, particularly in the HIV-infected patient with advanced immunosuppression. (See 'Diagnosis of syphilis in HIV-infected patients' below and "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient" .)

False positive nontreponemal tests have also been associated with pregnancy, intravenous drug use, tuberculosis, rickettsial infection, non-syphilis treponemal infection, and endocarditis, among others [9,10]. Consequently, a reactive nontreponemal test must always be confirmed with a specific treponemal test for proper interpretation. (See 'Interpretation of serologic testing' below.)

Treponemal tests — Treponemal tests have historically been more complex and expensive to perform; they have traditionally been used as confirmatory tests for syphilis when the nontreponemal tests are reactive. Recent versions of these tests have been automated, enhancing simplicity and facilitating ease of use.

Specific treponemal tests include:

Fluorescent treponemal antibody absorption (FTA-ABS)

Microhemagglutination test for antibodies to Treponema pallidum (MHA-TP)

Treponema pallidum particle agglutination assay (TP-PA)

Treponema pallidum enzyme immunoassay (TP-EIA)

As a group, these tests are based upon the detection of antibodies directed against specific treponemal antigens and thus tend to be more specific than non-treponemal tests. Treponemal tests are qualitative only and are reported as "reactive" or "nonreactive" [11]. EIA has become the favored method of confirmatory diagnosis in many laboratories, particularly those with large volumes of testing and increasingly have become the preferred screening test rather than using non-treponemal tests. (See 'Nontraditional screening approaches' below.)

Direct methods — Direct identification of spirochetes can be accomplished either through darkfield microscopy or direct fluorescent antibody testing.

Darkfield microscopy — Traditionally, the quickest and most direct method for diagnosing primary and secondary syphilis has been direct visualization of the spirochete from moist lesions (eg, mucous membranes) [11]. Darkfield microscopy enables demonstration of thin, delicate, corkscrew-shaped organisms with rigid, tightly wound spirals. A positive darkfield slide illustrates the characteristic motility associated with T. pallidum: a forward and backward motion with rotation about the longitudinal axis (picture 1) [11]. Soft side-to-side bending and twisting may also be seen.

Failure to identify the organisms in a specimen does not exclude the diagnosis of primary syphilis. Optimal performance of darkfield microscopy starts with adequate collection of the specimen and its expeditious delivery to the microscopist who should be experienced in the identification of T. pallidum. Moreover, the proper equipment must be readily available so that the specimen can be examined promptly.

In clinical practice, darkfield microscopy is generally limited to clinics that specialize in the diagnosis and treatment of sexually transmitted diseases (STDs). The specifics of specimen collection and the use of a darkfield microscope are described elsewhere [11].

Direct fluorescent antibody testing — An alternative method of identifying T. pallidum from lesions is direct fluorescent antibody testing (DFA-TP) [12]. This technique has the advantage of permitting the identification of the organism when smears cannot be examined immediately. It also avoids the problem of misidentifying other miscellaneous spirochetes since it is specific for T. pallidum antigens.

This test requires a fluorescence microscope and a trained and experienced technologist [13]. DFA-TP is not widely available in most STD clinics, but can be ordered from many state health departments. Air-dried specimens of lymph node aspirates, genital mucosal lesions, and chancres may be sent for evaluation; however, local requirements for specimen collection should be clarified prior to sending any specimens for DFA testing.

The clinical performance of these tests is at least in part related to the population being tested; the greater the pretest probability that syphilis is present, the better the test performance. In general, test performance with fresh specimens results in the best sensitivity (approaching 100 percent for the DFA), but a negative test does not totally exclude the diagnosis of syphilis [9].

Investigational techniques — Molecular and serologic techniques to diagnose syphilis are being explored to improve turnaround times for testing and to enhance sensitivity and specificity [14,15].

Rapid serologic testing — There has been considerable interest in simple, rapid tests for T. pallidum infection; advantages include rapid diagnosis at the point of care (within 5 to 20 minutes) and low cost of testing (ie, $1 to $3 per test) [16]. Most of the assays that have been developed have been treponemal assays; such assays do not distinguish between active and treated syphilis since treponemal antibody tests are non-quantitative and are not used to assess response to treatment [17].

Several tests are available for rapid syphilis testing, but none have been approved by the Food and Drug Administration (FDA) for the diagnosis of syphilis. Immunochromatography-based point-of-care tests to diagnose early syphilis have been evaluated and found to have good sensitivity and specificity [16,18-21]. The advantages of these assays include use of blood from a finger stick and the availability of rapid results (15 to 20 minutes), which can be interpreted by non-laboratory personnel. Since these tests detect T. pallidum recombinant antigens, the results correlate closely with those from more traditional treponemal-specific tests. In a meta-analysis of 33 studies that compared point-of-care diagnostic tests for syphilis with a T. pallidum-specific reference standard, using serum samples, point-of-care tests had sensitivities ranging from 74 to 90 percent and specificities ranging from 94 to 99 percent [22]. When whole blood samples were used, sensitivities ranged from 74 to 86 percent and specificities ranged from 96 to 100 percent.

Polymerase chain reaction testing — Investigational polymerase chain reaction (PCR) assays for T. pallidum, based on the detection of various DNA target sequences, have been evaluated using a variety of methods (eg, classical PCR, nested PCR, reverse-transcription PCR, and quantitative PCR). Compared to clinical diagnostic criteria (history, physical findings, results of serologic testing), the sensitivity of PCR testing in swab specimens of mucosal sites has ranged from approximately 70 to 95 percent with a specificity from 92 to 98 percent [23-25]. In a recent study, the concordance between a nested PCR assay and the physician’s diagnosis was 82.6 percent [25]. Unfortunately, sensitivity tends to be much lower in blood specimens (approximately 24 to 32 percent).

A multiplex polymerase chain reaction (M-PCR) assay has also been developed that can simultaneously detect Treponema pallidum, Hemophilus ducreyi (the etiologic agent of chancroid), and herpes simplex [26-28]. (See "Chancroid" .)

TESTING ALGORITHMS

Standard algorithms — Standard testing algorithms include screening with a nontreponemal test such as the RPR; a reactive specimen is then confirmed as a true positive with a treponemal test, such as the FTA-ABS [7]. Confirmational testing is necessary due to the potential for a false-positive screening test result [29]. However, it is highly unlikely that any one patient will have false positive tests using both reagin and treponemal techniques. (See 'Interpretation of serologic testing' below.)

All persons who are diagnosed with syphilis should be offered HIV testing and counseling.

Nontraditional screening approaches — In 2008, the CDC reported that four New York City laboratories had reversed the traditional order of screening and confirmatory tests for syphilis (ie, specific treponemal testing prior to non-specific treponemal testing) [8]. Since an automated treponemal test can be less expensive than an RPR test in high-volume laboratories, reversal of the traditional syphilis screening sequence was initiated principally for cost reasons. This approach has become increasingly popular in many laboratories, particularly those with relatively high volumes of syphilis testing.

However, this change in diagnostic procedures resulted in test results that would not have been identified by the traditional testing algorithm. A reactive treponemal test result was followed by a nonreactive nontreponemal test result in 3 percent of 116,822 specimens. The significance of these paired testing results is unclear since this order of testing has not been employed clinically; as a result, such nontraditional testing algorithms can lead to confusion regarding patient management [8].

Importantly, the positive predictive value (PPV) and negative predictive value (NPV) of treponemal EIA tests as screens for syphilis depend on the prevalence of syphilis in the population being screened. One study reported the overall seroprevalence of syphilis in the United States to be 0.71 percent, a frequency that indicates the negative predictive value of the treponemal EIA exceeds 98 percent. However, the positive predictive value in such a population may be as low as 12 percent [17,30].

The CDC has published some suggestions for diagnostic management for clinicians who receive these discordant results [7,8]:

If there is a history of previously treated syphilis, the non-reactive nontreponemal test indicates that active infection is unlikely and no further treatment or testing is warranted.

For persons without a history of treatment, the CDC recommends that a second, different treponemal test (preferably the Treponema pallidum-Particle agglutination assay [TP-PA]), should be performed [7]. If the TP-PA test is nonreactive, and the patient has no symptoms or behavioral risk to suggest syphilis, the clinician may decide that no further evaluation or treatment is indicated; this approach is supported by one prospective study of more than 21,000 patients undergoing syphilis screening in a low prevalence setting [31].

If the second treponemal test is reactive, clinicians should discuss the possibility of infection and offer treatment to patients who have not been previously treated. Such patients are unlikely to be infectious (unless history or physical examination suggests otherwise) and should be treated for late latent infection, even though they do not meet standard surveillance criteria [8].

Although the CDC recommends further testing in these unclear scenarios, we prefer a more directed, patient-centered approach. First, a directed history (including symptoms and behavioral risks) and physical examination should be performed with attention to findings associated with syphilis. If a chancre or rash is found, a nontreponemal test should be repeated to assess for seroconversion, and appropriate treatment should be administered at the same patient encounter. The response to treatment should be monitored clinically and serologically.

If no signs or symptoms of syphilis are found, we counsel patients regarding a possible diagnosis of late latent syphilis and offer the opportunity to do further diagnostic testing. If a repeat treponemal test is negative we do not suggest any further evaluation. If the repeat treponemal test is positive, we recommend treatment for late latent syphilis. (See 'Interpretation of serologic testing' below.)

It should be noted that the recommendations from the CDC may not be appropriate outside of the US where the epidemiology of disease may be different. Additional analyses will be required to determine the total cost implications of these alternative screening methods. Given concerns regarding health care costs, the use of nontraditional screening methods may increase in the future.

INTERPRETATION OF SEROLOGIC TESTING — Proper interpretation of syphilis testing is critical for appropriate patient management.

Definitive diagnosis of syphilis — When both nontreponemal and treponemal tests are reactive, persons should be considered to have active syphilis, unless this is ruled out by prior treatment history.

Symptomatic persons can be staged as having primary, secondary, or tertiary syphilis depending on their clinical manifestations. Asymptomatic persons with reactive nontreponemal and treponemal serologies are diagnosed with "latent" syphilis. The diagnosis of neurosyphilis is discussed separately. (See "Pathogenesis, clinical manifestations, and treatment of early syphilis" and "Pathogenesis, clinical manifestations, and treatment of late syphilis" and "Neurosyphilis" .)

Patients with a history of treated syphilis — In persons who were treated in the past, newly acquired syphilis infection is diagnosed if quantitative testing on an RPR test (or another nontreponemal test) reveals a fourfold or greater increase in titer. The prior baseline titer can often be determined by calling the local public health department, which maintains a registry of past positive tests. When possible, all titers should be compared using the same test methodology.

Titers of nontreponemal assays decline following successful therapy and serologic testing usually revert to nonreactive over time; however, some patients may remain "serofast"; these patients may have reactive nontreponemal tests, but at low titer (eg, 1:2), despite successful treatment.

Specific treponemal tests may remain positive for an extended period (eg, years) in many patients, despite adequate treatment and clinical response. Thus, a reactive treponemal test in a person with a history of treated syphilis should not be used alone to diagnose newly acquired syphilis.

Serologic monitoring of the patient with syphilis following treatment is discussed in detail elsewhere. (See "Laboratory monitoring of patients undergoing treatment for syphilis" .)

False positive test results — False positive tests for syphilis (sometimes referred to as "biologic false positive tests") can occur with both nontreponemal and treponemal tests. A false positive test result may be identified by a reactive nontreponemal test followed by a non-reactive treponemal test. It is estimated that 1 to 2 percent of the United States population has false positive nontreponemal test results [11]. False positive tests are particularly common during pregnancy. (See "Syphilis in pregnancy" .)

Some false positive nontreponemal test results are transitory and are related to an acute event, such as an acute febrile illness (eg, endocarditis, rickettsial disease) or recent immunization [9]. Test abnormalities attributed to these conditions typically last for six months or less.

Other etiologies for false positive results of nontreponemal testing include a variety of chronic conditions, such as autoimmune disorders (particularly systemic lupus erythematosus), intravenous drug use, chronic liver disease, and perhaps underlying HIV disease.

These false positive test results tend to be of low titer, but this is not always true, especially in HIV-infected patients; thus, the level of the titer alone does not reliably help the clinician differentiate between a true or false positive result. It is very important that each reactive nontreponemal test be followed with specific treponemal testing to determine if the result may be a false positive test or indicative of active syphilis. (See 'Diagnosis of syphilis in HIV-infected patients' below.)

False negative test results — The sensitivity of nontreponemal testing increases with the duration of infection [32]. A false negative syphilis test result may be identified by a nonreactive nontreponemal test in a patient with clinical signs or symptoms consistent with syphilis (eg, painless chancre). Further testing, based on clinical suspicion, can lead to a reactive specific treponemal test result. This type of testing pattern can be seen with very early infection (before serum antibodies have developed) or in a patient with a "prozone reaction".

Testing prior to antibody formation — Probably the most common cause of a false negative nontreponemal result is performance of the test prior to the development of humoral antibodies (figure 1). For example, 20 to 30 percent of patients presenting with a chancre will not have a reactive serologic test for syphilis [32]. In this setting, testing for treponemal antibodies is usually also nonreactive. If clinical suspicion is high, repeat serologic testing is indicated at a later time point (eg, one to two weeks later). If darkfield microscopy is available, scrapings of the lesion may be diagnostic.

Prozone reaction — A second major cause of a false negative test result is the "prozone reaction". This phenomenon occurs in less than 2 percent of samples from patients with syphilis.

The prozone reaction refers to nonvisualization of agglutination, which normally occurs when antigen and antibody bind together to form a complex. When antibody titers are high (as in secondary syphilis), an overabundance of antibodies interferes with clumping of antigen-antibody complexes.

Experienced laboratory technologists may suspect the prozone phenomenon when an apparent nonreactive test exhibits a rough or granular appearance [6]. When such a specimen is diluted, sufficient agglutination can be seen and the true sample reactivity becomes apparent.

Early treatment — A patient with a history of early treatment intervention may have no laboratory evidence of prior syphilis because of full seroreversion in both nontreponemal and treponemal serologies. However, this is uncommonly seen.

Finally, the natural history of a true positive screening test is usually to become nonreactive over time, even without treatment.

DIAGNOSIS OF SYPHILIS IN HIV-INFECTED PATIENTS — In the HIV-infected patient with syphilis, the approach to diagnosis is generally made in the same way as for HIV-uninfected persons [33]. However, some caveats regarding the HIV-infected patient with advanced AIDS are important to note. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient" .)

Diagnosis in patients with untreated AIDS — Prior to the era of potent antiretroviral therapy (ART), the accuracy of diagnostic testing was less clear in patients with advanced HIV infection. These observations may be applicable to the newly diagnosed patient with HIV infection who presents with symptoms or signs of syphilis, particularly those with low CD4 counts.

In a 1991 study of 341 patients with syphilis, the geometric mean rapid plasma reagin titers were significantly higher in HIV-infected patients, although the clinical stage of syphilis at presentation did not differ [34]. In addition, HIV-infected individuals had a greater incidence of falsely reactive nontreponemal tests than those without HIV infection [35,36]. In two series of HIV-infected patients, for example, the rate of false positive tests was higher than controls for both the VDRL (6.8 versus 0.2 percent) and the RPR test (11 versus 0.8 percent) [35,36]. Overall, however, nontreponemal screening was accurate in the vast majority of patients. (See "Screening laboratory tests in HIV-infected patients" .)

In contrast, in patients with advanced immunosuppression, false negative testing for syphilis can be seen [37,38]. This variability is thought to reflect abnormally active B-cell function during early HIV infection and B-cell failure during late-stage HIV infection.

If serologic tests do not confirm the presence of syphilis in clinically suspected cases, other diagnostic procedures should be considered, including:

Repeat serology after one to two weeks to determine late seroconversion

Biopsy of lesion for evidence of spirochetes [37,38]

Discussion with laboratory personnel about possible prozone phenomena

DIAGNOSTIC TESTING FOR NEUROSYPHILIS — Examination of cerebrospinal fluid is the only way to diagnose asymptomatic neurosyphilis [39]. A positive CSF VDRL is considered highly specific for neurosyphilis, but sensitivity is poor; only about 50 percent of patients with neurosyphilis have a positive CSF VDRL. Elevations of white blood cells and protein are non-specific, especially in HIV-infected patients. Thus, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count and protein, and a reactive CSF-VDRL with or without clinical manifestations [7].

If the CSF-VDRL is nonreactive, and neurosyphilis is suspected, a CSF FTA-ABS (Fluorescent treponemal antibody absorption (FTA-ABS)) can be ordered [7]. Although it is less specific than a CSF-VDRL, the CSF FTA-ABS test is highly sensitive; neurosyphilis is highly unlikely with a negative CSF FTA-ABS test [7].

The diagnostic approach to neurosyphilis is discussed in detail elsewhere. (See "Neurosyphilis" .)

HIV-seronegative patients — T. pallidum disseminates widely after initial infection, and examination of the cerebrospinal fluid (CSF) during primary and secondary syphilis reveals a high incidence of central nervous system involvement. The identification of asymptomatic neurosyphilis is important for the proper management of persons with reactive syphilis serologies. Details of the approach to the diagnosis and management of neurosyphilis are discussed elsewhere. (See "Neurosyphilis" .)

HIV-seropositive patients — In HIV-infected patients, the presence of a serum RPR ≥1:32 or a CD4 count <350 cells/mm3 were both associated with an increased risk of neurosyphilis [40]. The diagnosis of neurosyphilis in the HIV-infected patient is discussed elsewhere. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient" .)

DIAGNOSIS OF REINFECTION — Diagnosis of reinfection versus continued infection due to treatment failure can be difficult if a patient is lost to follow-up without intervening monitoring. One study suggested that reinfection is suggested by the following [41]:

Prior history of an appropriate treatment regimen

Clinical manifestations of either primary or secondary syphilis

History of new risk factor(s)

A fourfold decline in RPR titers after retreatment (for example, a decline in titer from 1:64 to 1:16)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5 th to 6 th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10 th to 12 th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

Basics topic (see "Patient information: Syphilis (The Basics)")

SUMMARY AND RECOMMENDATIONS

Syphilis is a chronic infection caused by the spirochete Treponema pallidum. (See 'Introduction' above.)

Serologic testing is the mainstay of diagnosis of syphilis due to the complexities of direct visualization techniques and lack of culture techniques for T. pallidum. (See 'Diagnostic testing methods' above.)

Persons considered at "high risk" for syphilis include men who have sex with men, inmates, persons with multiple sexual partners, patients with another sexually transmitted disease, and sexually active HIV-infected patients. We recommend screening for syphilis in patients considered at high risk (Grade 1A). (See 'Target groups for testing' above.)

Syphilis testing is also routinely performed during pregnancy to prevent transmission of infection from an asymptomatic mother to her infant. (See "Syphilis in pregnancy" .)

Nontreponemal assays are semi-quantitative and are reported as a titer of antibody. The height of the antibody titer generally reflects the activity of disease; titers decline following appropriate treatment. (See 'Nontreponemal tests' above.)

In contrast, treponemal tests are either reactive or nonreactive; once positive due to syphilitic infection, they tend to remain positive for an extended period in most patients. (See 'Treponemal tests' above.)

Historically, the standard testing algorithm has been to perform initial screening with a nontreponemal test (eg, a VDRL test) and to confirm any reactive non-treponemal test with a treponemal-specific test (eg, a FTA-ABS test). Increasingly, this order has been reversed in clinical laboratories at least in part to achieve cost savings. Syphilis screening is now frequently done with a treponemal-specific ELISA and positive tests are followed by the quantitative non-treponemal test. This can create some degree of diagnostic confusion. (See 'Testing algorithms' above.)

False positive nontreponemal tests can be due to acute illness (eg, endocarditis) or due to chronic diseases (eg, autoimmune disorders). (See 'Interpretation of serologic testing' above.)

The approach to the diagnosis of syphilis in the HIV-infected patient is similar to the HIV-seronegative patient. The limitations of serologic testing must be considered in the patient with clinically suspected

disease, nonreactive testing, and advanced immunosuppression. (See 'Diagnosis of syphilis in HIV-infected patients' above.)

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