EDUCATIONAL COMMENTARY – UPDATE ON SYPHILIS TESTING

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- discuss the cause, signs, and symptoms of syphilis infection.
- discuss the laboratory tests performed in the diagnosis of syphilis.
- compare and contrast the advantages and disadvantages of the algorithms used in syphilis testing.

History of Syphilis

Some anthropologists believe that syphilis was originally a disease of the Americas introduced into Europe by Spanish sailors returning from Columbus's voyages. The first recorded epidemic of syphilis occurred in Europe in 1494, in French troops who are thought to have contracted it from Spanish mercenaries serving the king of France. The disease spread easily among a European population lacking immunity. Other historians, though, believe that syphilis in Europe predated the discovery of America and was in fact described by Hippocrates in classical Greece. These historians suggest that many illnesses that medieval physicians ascribed to leprosy were actually cases of syphilis.¹

Description of the Disease

Syphilis is a sexually transmitted bacterial disease caused by a spirochete, Treponema pallidum. Symptoms include sores in the external areas of the genitalia, anus, or rectum, or on the lips and inside the mouth. Some infected individuals display no symptoms and are unaware of their infections. In such cases, patients may remain undiagnosed for many years. Lack of symptoms does not eliminate the possibility of complications later in the disease process.

Syphilis progresses in 3 stages. In the primary stage, the patient usually develops a chancre, a small, round, painless sore. Between 10 and 90 days after exposure, the chancre appears at the site where the bacterium entered the body. The chancre persists for 3 to 6 weeks and heals without treatment. Because the chancre spontaneously resolves, the patient may not seek medical care. The onset of secondary syphilis occurs from 3 weeks to 6 months after the appearance of the primary lesion. Symptoms may include a cutaneous rash, fever, sore throat, headache, malaise, and mucous patches in the mouth. The primary and secondary stages of syphilis are highly infectious. The latent period follows
the secondary stage and is a noninfectious phase that may last from 6 months to 25 years. No signs or symptoms are present during the latent period. At any time in this phase, the patient’s status may revert to the secondary stage. Tertiary syphilis is the final stage of syphilis and occurs from 1½ to 25 years after infection. In this stage, neurosyphilis or cardiovascular disease may develop. Approximately one-third of patients who are not treated develop tertiary syphilis.

Even with an early or a latent infection, syphilis may be transmitted to a fetus by an infected mother. In congenital syphilis, the newborn may present with the signs and symptoms that are exhibited by adults in the secondary stage of the disease. The child may be born blind, deaf, or with scarring, deformities, or neurological deficits. Nearly half of those infected with syphilis in the womb die shortly before or after birth. Testing and treatment for syphilis in pregnant women is critically important to prevent transmission to the fetus.

Because syphilis may be asymptomatic, the Centers for Disease Control and Prevention (CDC) recommends testing for

1) persons at high risk, to detect latent infections;
2) pregnant women, to prevent congenital syphilis; and
3) blood donors, to prevent transmission through blood donation.

Early diagnosis is crucial because effective treatments are readily available. In the early stages of syphilis, a single injection of penicillin can cure the patient. If the patient has been infected for more than a year, multiple treatments with penicillin may be necessary. Other antibiotics may be used in persons allergic to penicillin. Tissue damage sustained before therapy is not corrected by treatment.

**Laboratory Testing**

The spirochete may be visualized in lesion scrapings by using darkfield microscopy. A special condenser on the microscope allows the organism to appear bright against a dark background. The organism has a spiral, corkscrew appearance, and the typical motility of the spirochete may be observed. Specimen collection is crucial to the reliable performance of the procedure. Darkfield microscopy is time-consuming and requires special expertise. As a result, this method is expensive and only performed in clinics that handle large numbers of syphilis cases.

Since *T. pallidum* cannot be cultured, syphilis is most often diagnosed by evaluating the patient’s clinical symptoms in conjunction with two types of serologic tests, nontreponemal and treponemal assays. Nontreponemal assays measure reagin, a nonspecific antibody produced by the immune system of individuals infected with *T. pallidum*. Rather than antibodies to proteins of the spirochete itself, the immune system produces antibodies to cardiolipin, a phospholipid released by cells damaged by the bacterium. Assays that detect reagin include the rapid plasma reagin test and the VDRL test. The other type of assay is the treponemal assay, which detects antibodies produced against the organism. The
most commonly performed of the treponemal assays include the fluorescent treponemal antibody absorption test, the microhemagglutination assay for *T. pallidum*, the *T. pallidum* particle agglutination assay, the enzyme immunoassay, and the chemiluminescence immunoassay. Nontreponemal tests may be nonreactive very early after the onset of the infection and in late stages of the disease. Results of these assays revert to nonreactive after treatment. Treponemal tests are reactive earlier in the disease and remain reactive throughout the lifetime of the patient, even after treatment in most cases. A reactive treponemal assay, therefore, cannot differentiate between an active infection and a past infection that has been treated.

Traditionally, the algorithm used in testing for syphilis includes a nontreponemal assay for screening followed by a treponemal assay on reactive specimens for confirmation. The sensitivity of an assay is a very important aspect of a screening test. A good screening test should be positive for all patients with the disease and produce very few false-negative results. The rapid plasma reagin test and the VDRL test are very sensitive assays and therefore appropriate for use as screening tests. A confirmatory test should have high specificity; that is, it should produce negative results for all specimens from patients who do not have the target disease and should produce very few false-positive results. Assays that measure antibodies to the organism, such as the treponemal assays, are highly specific and function well as confirmatory tests. In addition, screening procedures should be cost-effective. The reagents and supplies for the rapid plasma reagin test or the VDRL test are much less expensive than those required to perform treponemal assays. These procedures can be performed easily, requiring little expertise and minimal instrumentation. This algorithm has been used for many years.

In the past few years, laboratories that perform large volumes of syphilis testing have introduced a new algorithm. Because the treponemal tests performed by enzyme immunoassay or chemiluminescence immunoassay are automated and can be performed cost-effectively in a high-volume setting, these laboratories have reversed the traditional algorithm and perform treponemal tests for screening and follow reactive results with a nontreponemal assay. This algorithm reduces the time and labor involved in the screening process. In some cases, however, problems can occur in interpreting the results of reverse-sequence syphilis testing. Sometimes the treponemal test is reactive, but the nontreponemal test is nonreactive. This discrepancy may occur in patients who had a previous syphilis infection with the persistence of treponemal antibodies. In these patients, reagin dissipates and the patient seroreverts; that is, the patient’s nontreponemal tests become negative. The same discordant results may also occur in patients who have an early infection and have not yet produced reagin. For clinicians using reverse-sequence syphilis screening, the Centers for Disease Control and Prevention (CDC) recommends the use of an additional treponemal test when the first treponemal test is reactive and the follow-up nontreponemal test is nonreactive.4

In February 2011, the CDC analyzed data from five studies that evaluated reverse-algorithm syphilis testing. Of specimens with reactive enzyme immunoassay or chemiluminescence immunoassay
screening tests, 56.7% were nonreactive when tested with a nontreponemal test. Because of the high number of false-positive results likely with the new algorithm, CDC recommended that the traditional algorithm of a nontreponemal test for screening followed by a treponemal test for confirmation be used to screen for and confirm a diagnosis of syphilis.4

Conclusion

Syphilis is a disease that has persisted for centuries. Left untreated, it may cause serious health consequences. Treatment is readily available and very effective. To prevent the spread of syphilis to uninfected individuals and to fetuses, reliable laboratory testing is very important. Traditionally, testing has been performed by screening with a nontreponemal assay followed by testing of reactive samples with a treponemal assay. Recently, some large laboratories have reversed the traditional testing algorithm by screening with an automated treponemal assay and then performing nontreponemal testing on all reactive samples. After reviewing several studies, the CDC recommends that laboratories use the traditional screening and confirmation assays to avoid problems with the interpretation of discordant results.

References


