EDUCATIONAL COMMENTARY – LABORATORY TESTING FOR SYPHILIS

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

• Name and describe the organism that causes syphilis.
• Discuss the signs, symptoms, and transmission of the disease.
• Describe the stages of syphilis.
• List common serologic tests used in the diagnosis of the disease.
• Discuss the uses of quantitative titers in the treatment and monitoring of the disease.

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*, a spiral-shaped bacterium called a spirochete. Prior to the introduction of penicillin, this organism was responsible for devastating epidemics throughout the world. The disease may occur in 4 stages: primary, secondary, latent, and tertiary (late) syphilis. In primary syphilis, an ulcer or chancre develops at the site entrance of the infective agent. This first symptom is painless and appears on skin or mucous membranes of the genital area, mouth, or anus about 2-6 weeks after exposure. It disappears within a few weeks regardless of treatment. Chancres make the individual more vulnerable to co-infection with human immunodeficiency virus (HIV). Because both diseases are sexually transmitted, they may be contracted at the same time.

In secondary syphilis, about 3-6 weeks after the disappearance of a chancre, a brown skin rash can appear on any area of the skin or mucous membranes. In about half of patients, the rash may be seen on the palms of the hands and soles of the feet. The rash may also occur in other locations on the body. Mild fever, fatigue, and swollen lymph nodes may also occur. Healing of the rash occurs within several weeks to a few months even if the patient remains untreated. Symptoms of secondary syphilis may recur periodically for a period of 1-2 years. Latent syphilis may occur between any of the stages of the disease. In latent syphilis, the infected individual displays no symptoms. Only about 1/3 of untreated patients progress to tertiary or neurosyphilis. While both primary and secondary syphilis are infectious, untreated latent or tertiary syphilis is not usually contagious. It may, however, cause heart damage, liver disease, neurological disorders, bone damage, blindness, or death. Tertiary syphilis may occur from 1-30 years after the primary infection. Syphilis may also be passed from an infected mother to her child. Usually proper treatment of the mother during pregnancy prevents congenital syphilis.

Diagnosis of syphilis is dependent upon clinical symptoms and laboratory testing. A darkfield microscope may be used to view the spirochetes in scrapings collected from the chancre. This microscope has a special condenser which makes the organisms appear white against a dark background. After successful treatment with penicillin, motile spirochetes are no longer present.
The most common tests performed to diagnose and monitor syphilis are serologic tests. Two types of serologic tests are available, nontreponemal assays and treponemal assays. The nontreponemal assays are performed as screening tests while the treponemal tests are usually used for confirmation. Commonly used nontreponemal tests include rapid plasma reagin test (RPR) and venereal disease research laboratories assay (VDRL). Treponemal tests include fluorescent treponemal antibody absorption test (FTA-Abs), passive hemagglutination assay for Treponema pallidum (TPHA), enzyme-linked immunosorbent assay (ELISA), and others.

Nontreponemal tests, RPR and VDRL, are positive in 70%-80% of primary syphilis cases, 100% positive at high titers in the secondary stage, and about 70% in cases of untreated late stage syphilis. These assays do not detect antibodies to the treponemal organism itself, but detect reagin which is a nonspecific antibody-like substance produced in patients with syphilis. In a positive or reactive test, clumps form when reagin in the patient’s serum reacts with a reagent antigen comprised of cardiolipin, lecithin, and cholesterol. Positive patient specimens are diluted and retested to determine a quantitative titer. These quantitative titers are used to monitor treatment. Effective treatment produces lower RPR and VDRL titers over time. Serial testing should be performed using the same procedure by the same laboratory. Rising titers reflect active disease and indicate the need for retreatment. Patients with primary syphilis or congenital syphilis are tested using nontreponemal tests approximately 3, 6, and 12 months after treatment. In treated cases of primary syphilis, nontreponemal assay results should be nonreactive within 1 year and for secondary syphilis should be nonreactive within 2 years. Patients with late latent syphilis (> 1 year after infection) should be retested 24 months after therapy. In cases of treated late stage syphilis, results may be nonreactive or positive in low titers. Nontreponemal tests may also be used to detect re-infection with syphilis. Cerebrospinal fluid (CSF) may be tested using the VDRL to detect cases of neurosyphilis. RPR is not appropriate for analyzing CSF specimens.

Since false positive nontreponemal test results often occur in a variety of conditions, including infectious mononucleosis, pregnancy, malaria, leprosy, systemic lupus erythematosus and other autoimmune diseases, positive screening tests must be confirmed using a treponemal assay. These assays detect specific antibodies produced by the patient in response to components of the Treponema pallidum organism itself. The most commonly performed confirmation assay is the FTA-Abs test. It is an indirect immunofluorescence assay which requires a high degree of technical proficiency to perform. Another common treponemal test is the TPHA. It has the advantage of being easier to perform and interpret. Quantitative titers are performed in both of these tests and are useful in diagnosis. However, treponemal assays remain positive after treatment and, therefore, are not useful in monitoring the effectiveness of treatment or the detection of re-infection.
Since the advent of penicillin during World War II, syphilis has become easy to treat. Early administration of the antibiotic provides a cure in 95% of patients. Treatment of late syphilis requires the administration of penicillin for a longer duration. For patients who are allergic to penicillin, other antibiotics may be used, but the duration of the therapy is considerably longer.