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RPR and the Serologic Diagnosis of Syphilis

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A 45-year-old man presents in clinic for follow-up after a recent emergency department evaluation for dysuria. He was diagnosed with gonococcal urethritis and treated with intramuscular ceftriaxone and oral azithromycin. His dysuria resolved and he now feels well. He was divorced 10 years previously and has since had multiple sexual partners. He reports sex only with women. His examination is normal, including the genitalia and skin. He has no neurologic deficits. Screening for other sexually transmitted infections reveals hepatitis B virus serologies consistent with previous immunization, a negative human immunodeficiency virus (HIV) enzyme immunoassay (EIA), and reactive syphilis test results (**Table 1**).

The patient does not recall prior syphilis diagnosis or treatment. The local health department has no record of syphilis testing for him.

Table 1. Patient Test Results

Laboratory Test	Value	Reference Range
RPR	1:8	Nonreactive
TP-EIA	Reactive	Nonreactive

Abbreviations: RPR, rapid plasma reagin; TP-EIA, *Treponema pallidum* enzyme immunoassay.

HOW DO YOU INTERPRET THESE RESULTS?

A. The patient has latent syphilis and requires 2.4 million U intramuscularly of benzathine penicillin G weekly for 3 doses (total 7.2 million U penicillin).

B. The patient has low titers representing the serofast state and does not require treatment.

C. The patient has falsely elevated titers and should undergo repeat testing.

D. The patient needs a lumbar puncture to assess for asymptomatic neurosyphilis.

Answer

A. The patient has latent syphilis and requires 2.4 million U intramuscularly of benzathine penicillin G weekly for 3 doses (total 7.2 million U penicillin).

Test Characteristics

A clear understanding of the diagnosis of syphilis is of particular public health importance because the incidence of syphilis in the United States is increasing. Currently, an estimated 55 000 new cases are diagnosed each year.[1] *Treponema pallidum*, the spirochete that causes syphilis, cannot be cultured. Thus, diagnosis requires indirect techniques such as serologic testing, relying on the detection of both treponemal and nontreponemal antibodies. Treponemal tests detect antibodies to specific antigenic components of *T pallidum*, while nontreponemal tests detect antibodies to a nonspecific cardiolipin-cholesterol-lecithin reagin antigen produced by the host in response to syphilis infection.[2]

The rapid plasma reagin (RPR), a nontreponemal test, has traditionally been used as an initial screening test for syphilis because it is widely available, relatively easy to perform, and inexpensive (Medicare midpoint reimbursement, RPR with reflex titer, $8.11).[3] Additionally, RPR is a quantitative test and antibody titers can be monitored to assess treatment response.[4] However, the RPR requires a visual assessment for the presence of flocculation (aggregation of particles), a process that requires laboratory technologist time and is not suitable for automation. Furthermore, false-positive results may occur in the setting of autoimmune disease, pregnancy, tuberculosis, or other inflammatory conditions; thus, RPR testing requires confirmation with treponemal serologic tests such as the *T pallidum* enzyme immunoassay (TP-EIA).[5] Although false-positive results also occur with TP-EIA, it is unlikely that a patient will have both false-positive reagin and false-positive treponemal serologies. Therefore, the presence of a reactive nontreponemal test and a reactive treponemal test is diagnostic of syphilis (**Table 2**).[4,6,7]

Application to This Patient

This patient has late latent syphilis and should receive 3 weekly injections of benzathine penicillin G.

Because the patient is asymptomatic with reactive serologies, he has latent syphilis. Latent syphilis can be divided into early-latent syphilis, diagnosed within 1 year of infection, and late-latent syphilis, diagnosed 1 year or more after infection. When the date of original infection is unknown, the patient is considered to have late-latent syphilis.[8,9]

Early-latent syphilis is treated with a single intramuscular dose of benzathine penicillin G, while late-latent syphilis requires 3 weekly doses of benzathine penicillin G.[6] Following successful treatment, the RPR declines over time and may become nonreactive. However, the RPR may remain reactive at a low titer (generally <1:8), a condition referred to as the serofast state. The serofast state does not apply to this patient because he has no previous syphilis history. He does not have falsely elevated titers; his treponemal and nontreponemal tests were both reactive, making the diagnosis of syphilis and obviating the need for repeat testing. Because *T pallidum* can invade the central ner-

Table 2. Sensitivity and Specificity of Serologic Tests[a]

	Sensitivity at Given Stage, %				
	Early Stage				
	Primary	Secondary	Latent	Tertiary	Specificity, %
Nontreponemal					
RPR, % (range)	86 (77-100)	100	98 (95-100)	73	98 (93-99)
Treponemal					
IgM-EIA	93	85	64	NA	NA
IgG-ELISA	100	100	100	NA	100

Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; NA, not available; RPR, rapid plasma reagin.

[a] Data are adapted.[4,7]

vous system early, neurosyphilis should be considered in any patient with reactive syphilis serologies. Lumbar puncture is usually suggested following treatment failure or in patients with neurologic symptoms. The likelihood of neurosyphilis is greater in patients with higher RPR titers (>1:32) and in HIV-infected patients with lower CD4 cell counts.[10]

What Are Alternative Diagnostic Testing Approaches?

Traditionally a nontreponemal test, such as the RPR, has been used for screening, followed by confirmatory treponemal testing (eg, TP-EIA). Recently, many laboratories have reversed the order, screening with the automated TP-EIA and using the more labor-intensive nontreponemal (eg, RPR) test for confirmation. This reverse sequence screening may engender diagnostic dilemmas, particularly when the screening treponemal test is reactive and the nontreponemal test is nonreactive. In patients without previously treated syphilis, an alternative treponemal test such as the *T pallidum* particle agglutination (TPPA) assay should be performed to confirm the positive TP-EIA. In the case of this patient, both treponemal and nontreponemal tests were reactive, a finding diagnostic of syphilis.

Patient Outcomes

Syphilis diagnosed at any stage is deemed a notifiable disease[6]; accordingly, this patient's positive titers were reported to the health departments for his respective state and county. At follow-up testing, his RPR was nonreactive, indicating effective treatment. In general, declining RPR titers are expected after successful treatment; the US Centers for Disease Control and Prevention recommends repeating the RPR at 6, 12, and 24 months posttreatment for late-latent syphilis.[6] The expected rate of RPR decline after treatment is not well defined, particularly for latent syphilis with a relatively low pretreatment titer (as in this case). A confirmed 4-fold or greater RPR increase indicates reinfection or treatment failure and the need for repeat HIV testing, cerebrospinal fluid examination for neurosyphilis, and additional treatment based on the stage of syphilis diagnosed.

Clinical Bottom Line:

- The inability to culture T pallidum clinically necessitates the use of serologic testing to diagnose patients with syphilis.
- Nontreponemal and treponemal tests are used in combination to identify patients with syphilis and nontreponemal tests are used to monitor the response to treatment.
- Proper classification of the stage of syphilis at diagnosis and initiation of treatment provides the basis for defining adequate serologic response over time.

ARTICLE INFORMATION

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