Syphilis Serologies

A Practical Approach for the Primary Care Clinician

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KEYWORDS

• Syphilis • Serology • Sexually transmitted infection • Treponemal testing

KEY POINTS

- Diagnosis of syphilis relies on reactive treponemal-specific and non-treponemal antibody testing and clinical assessment. Local health departments can often provide a syphilis testing and treatment history.
- Serologic antibody testing may be nonreactive early in infection, leading to false-negative results.
- Ensure adequate time has passed (12 months for primary and secondary syphilis, 24 months for latent syphilis) before making a decision about serologic treatment success.
- Lumbar puncture is only indicated in specific scenarios, such as when a patient has neurologic symptoms or non-treponemal test titers increase ≥4-fold in the absence of reexposure.
- Remember to test for HIV and offer HIV pre-exposure prophylaxis to patients with syphilis.

INTRODUCTION

Syphilis is a sexually transmitted infection (STI) caused by *Treponema pallidum* (TP). In 2021, the Centers for Disease Control and Prevention (CDC) reported 176,213 cases of syphilis, a 74% increase since 2017.[1] Although men who have sex with men accounted for almost half (46%) of all primary and secondary syphilis cases, a sustained epidemic among the heterosexual population has also been observed. Paralleling increases in cases among reproductive-aged women, congenital syphilis (CS) cases have

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increased. In 2021, the national CS rate was 77.9 cases per 100,000 live births; a 219.3% increase relative to 2017. Syphilis stages, serologic profiles, and treatment recommendations are reviewed in **Table 1**.

The direct identification of TP (eg, polymerase chain reaction [PCR], dark-field microscopy) is possible but not widely available. Serology is the most common, indirect, diagnostic test for syphilis. Syphilis serology is classified into treponemal tests (TTs; eg, TP passive particle agglutination assay [TP-PA], FTA-ABS [fluorescent treponemal antibody absorption]) and non-treponemal tests (NTTs; eg, RPR [rapid plasma reagin] and VDRL [veneral disease research laboratory]). **Fig. 1** displays a full list of assays. TTs and NTTs differ by their antigen target. TTs detect antibody to TP proteins, whereas NTTs detect nonspecific antibodies directed against lipoidal antigens, damaged host cells, and treponemes.[4]

Two-stage serologic testing with a TT and NTT, along with clinical staging, is required to make a syphilis diagnosis. It is crucial that a provider know the testing algorithm used by their institution or practice. The traditional (or standard) algorithm uses an NTT and reflexes to a TT if reactive, whereas the reverse algorithm begins with a TT and reflexes to an NTT if reactive (see **Fig. 1**). In the case of discordant TT and NTT in the reverse algorithm a second, different, TT is used as a "tiebreaker." There are key principles of syphilis serologies which can be useful to the clinician in navigating their nuances.

The first principle is that TTs generally remain reactive for life (in at least 75% of individuals after initial infection), regardless of treatment.[5] TTs provide no insight as to when a patient was infected, if treatment was completed, or if reinfection has occurred. A reactive TT alone should not necessarily prompt treatment for syphilis, but rather further investigation.

The second key principle is that NTTs offer dilutional antibody titers (eg, 1:64). NTTs are clinically useful in monitoring response to treatment and in distinguishing reinfection from old previously treated infection. NTTs may become nonreactive in persons who are treated for syphilis but also can decline over time in the absence of treatment. The reverse algorithm is more sensitive in detecting prior syphilis infection. In primary syphilis, TTs have sensitivities between 82% and 100%,[4] exceeding those of NTTs with sensitivities between 62% and 76%.[6]

Syphilis serology testing has specific pitfalls that are important for the clinician to be aware of. The goal of this review is to describe a series of clinical scenarios that demonstrate the challenges of syphilis serologic interpretation and provide a rationale for management.

Vignette 1: Primary Syphilis

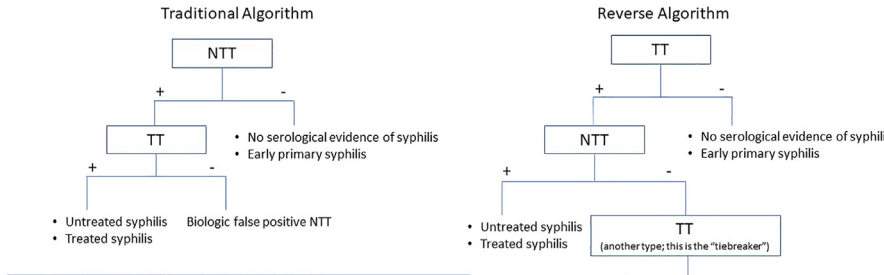
A 43-year-old man contacts his primary care provider requesting testing for STIs and citing the appearance of a painless lesion on his penis 2 days earlier. Six weeks before the lesion appearing, he had condomless oral and anal-receptive intercourse with two new male partners. He was previously in a monogamous relationship and has never had an STI. He is offered empirical treatment for primary syphilis with a single intramuscular injection of 2.4 million international units (MIU) of benzathine penicillin G [BPG] but declines. Specimens sent for testing on the day of initial presentation for *Chlamydia trachomatis*, *Neisseria gonorrhea*, HIV, and herpes simplex virus were all unrevealing, including nonreactive TP enzyme immunoassay (TP-EIA) and RPR. The patient is informed and again offered empirical treatment for primary syphilis, but prefers to return for repeat testing 2 weeks later. His lesion has resolved, and he has no penile discharge, fever, sore throat, rash, or lymphadenopathy. Repeat testing is obtained and notable for a reactive TP-EIA with an RPR antibody titer of 1:32.

Table 1
Stages of syphilis, typical clinical features, expected serologic status, and recommended treatment regimens per 2021 CDC Sexually Transmitted Infection Treatment Guidelines

Stage	Typical Clinical Features	Serology[2]	Treatment[3]
Primary	Painless ulcer (chancre)	TT and NTT may be nonreactive in up to 30%	Recommended: BPG 2.4 MIU once IM Alternative: Doxycycline 100 mg BID for 14 d[a]
Secondary	Any part of the body can be affected. Typical rash is truncal, with palms and soles involved	TT and NTT tests are reactive	Recommended: BPG 2.4 MIU once IM Alternative: Doxycycline 100 mg BID for 14 d[a]
Early latent (<1 y)	No signs or symptoms	TT reactive NTT may be reactive or nonreactive	Recommended: BPG 2.4 MIU once IM Alternative: Doxycycline 100 mg BID for 14 d[a]
Late latent (≥1 y) or Unknown duration			Recommended: BPG 2.4 MIU IM on days 0, 7, 14, for a total of 7.2 MIU Alternative: Doxycycline 100 mg BID for 28 d[a]
Tertiary • Cardiac • Gummatous	Depends on location of lesion(s)	TT reactive NTT may be reactive or nonreactive	Depends on CSF result. If positive, treat for neurologic syphilis. If negative CSF, BPG 2.4 MIU IM on days 0, 7, 14, for a total of 7.2 MIU
Neurologic • Early	Headache, stroke, cranial nerve palsies	TT reactive NTT typically reactive	Recommended: Parenteral aqueous penicillin G 18–24 MIU per day, administered as 3–4 MIU IV every 4 h or continuous infusion for 10–14 d Alternative: Procaine penicillin 2.4 MIU IM once daily, PLUS Probenecid 500 mg orally 4 times/day, both for 10–14 d
Neurologic • Late	Meningovascular: strokes Parenchymatous: (tabes and general paresis) Tabes: shooting pain in the back; gait abnormalities General paresis: cognitive declines (dementia); personality changes; hallucinations	TT reactive NTT typically reactive (NTT uncommonly nonreactive)	
Neurologic • Ocular • Otic	Ocular: Uveitis, neuroretinitis, optic neuritis Otic: Hearing loss, tinnitus	TT reactive NTT typically reactive (NTT uncommonly nonreactive)	Ceftriaxone 1–2 g daily either IM or IV for 10–14 d (limited data)[a]

TT, treponemal test; NTT, non-treponemal test; BPG, benzathine penicillin G; MIU, million international units; BID, twice daily; CSF, cerebrospinal fluid; IV, intravenous; IM, intramuscular.

[a] Thorough clinical and serologic follow-up of persons receiving any alternative therapy is essential.



Nonspecific treponemal tests (NTT)	Treponemal-specific tests (TT)
• Rapid Plasma Reagin (RPR) • Venereal Disease Research Laboratory (VDRL)	*Manual Assays* • *T. pallidum* passive particle agglutination (TP-PA) assay • Fluorescent treponemal antibody absorption (FTA-ABS) • Microhemagglutination assay for *T. pallidum* (MHA-TP) *Immunoassays* • Enzyme Immunoassay (EIA) • Chemiluminescence immunoassay (CIA) • Microbead Immunoassay (MBIA)

Fig. 1. Description of the traditional and reverse testing algorithms and their interpretations.

Discussion

Primary syphilis is heralded by a genital papule which quickly blossoms to a localized and indurated, usually painless ulcer (chancre) with raised margins at the point of inoculation. The median incubation period for a chancre is approximately 21 days and can develop as late as 3 months after exposure.[7] Alternatively, chancres may be multiple, painful, and found at any site of sexual contact including oropharynx, rectum, and cervix.[8] Chancres, when painless, may go unnoticed by the patient. Providers should consider primary syphilis in the differential diagnosis of genital ulcer disease including herpetic lesions, mpox, hemorrhoids, malignancies, inflammatory bowel disease, and other infections. Even in the absence of treatment, chancres resolve within 3 to 6 weeks.[7]

This case provides a key lesson: all serologic assays (TTs and NTTs) can be falsely negative in early disease.[6] This is usually because the test was obtained before TP antibody formation has occurred but can also reflect a rare phenomenon termed the prozone effect. The prozone effect occurs when an excess of antibodies interferes with the visualization of agglutination of an antibody-antigen complex and is more common in primary and secondary syphilis.[6] If there is high clinical suspicion for syphilis, the clinician can notify the laboratory of a suspected prozone effect and request additional dilutions and repeat testing of the sample. For patients in whom there is a high clinical suspicion for primary syphilis, empirical therapy should also be considered.

This patient initially had seronegative primary syphilis, with nonreactive syphilis serologies at the time of their chancre. Seronegative primary syphilis is a well-characterized phenomenon that occurs in up to 30% of patients.[6] It is more prone to occur via the traditional algorithm because TT tends to become reactive before NTTs but can occur with either algorithm.[9] Providers may opt to treat chancres presumptively, pending the result of serologic tests; this will depend on sexual history and epidemiologic risk factors. In individuals with evidence of primary syphilis and who have nonreactive syphilis serologies, testing should be repeated in 2 weeks.[10]

Vignette 2: Secondary Syphilis

A 19-year-old man presents to the emergency department with a 5-day history of worsening fever, myalgias, and rash. He has no significant medical history, is up to date with immunizations, and is not taking any medications. On examination, his temperature is 37.6°C, he has no evidence of meningismus or nuchal rigidity, and neurologic examination is normal. He has sub-centimeter lymphadenopathy in the inguinal, axillary, and epitrochlear regions. A widespread, papular rash is evident on the chest, torso, and back; his palms and soles are not involved. He identifies as bisexual, has condomless sex with male and female partners and is not taking HIV pre-exposure prophylaxis (PrEP). His last sexual exposure was 6 weeks ago, during which he had receptive anal sex with a male he met online. Acute HIV, Epstein Barr Virus (EBV), and syphilis are considered in the differential diagnosis. HIV antigen/antibody test, HIV ribonucleic acid (RNA) assay, and EBV serology were nonreactive or undetectable. However, TP-EIA is positive and a reflex RPR is reactive with a titer of 1:128.

He is diagnosed with secondary syphilis, treated with a single dose of BPG 2.4 MIU intramuscularly and discharged with follow-up for initiation of PrEP given this recent diagnosis of syphilis. At 1 month follow-up, he begins daily PrEP with tenofovir disoproxil fumarate/emtricitabine, and at a 3 month follow-up visit, the RPR titer has declined to 1:64 (a twofold/one-dilution decrease). He subsequently misses his 6 month follow-up visit, but at 12 months, his HIV tests remain negative and the RPR titer is now 1:4 (**Fig. 2**), representing a 32-fold decrease from its peak.

Discussion

Successful treatment of primary or secondary syphilis is defined by resolution of signs and symptoms and by at least a fourfold decline in RPR titer, for example, from an initial titer of 1:128 to 1:32 (**Fig. 3**). CDC guidelines recommend repeat RPR titers at 6 and 12 months but waiting a full 12 months after treatment of primary and secondary syphilis (24 months in those with HIV) before adjudication of treatment success (see **Fig. 2**). In the absence of evidence of reexposure, providers should allow the full recommended time to elapse before considering treatment failure. A $\geq$ 4-fold increase in RPR titer at any time following treatment that is sustained when repeated after a minimum of 2 weeks should prompt an evaluation for reinfection or treatment failure.

Patients often find it difficult to recall their RPR titers. This can pose a challenge when they change providers and particularly if they move between states or countries.

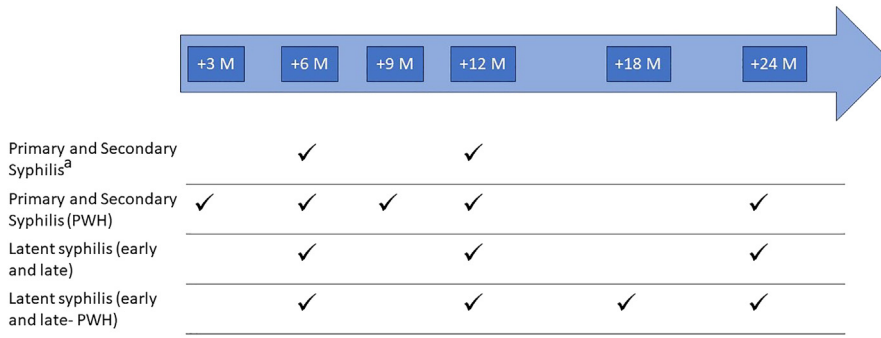


Fig. 2. CDC recommended stage-specific posttreatment intervals for follow-up. NTT, nontreponemal test; PWH, persons with HIV; M, months. [a] Consider more frequent testing.

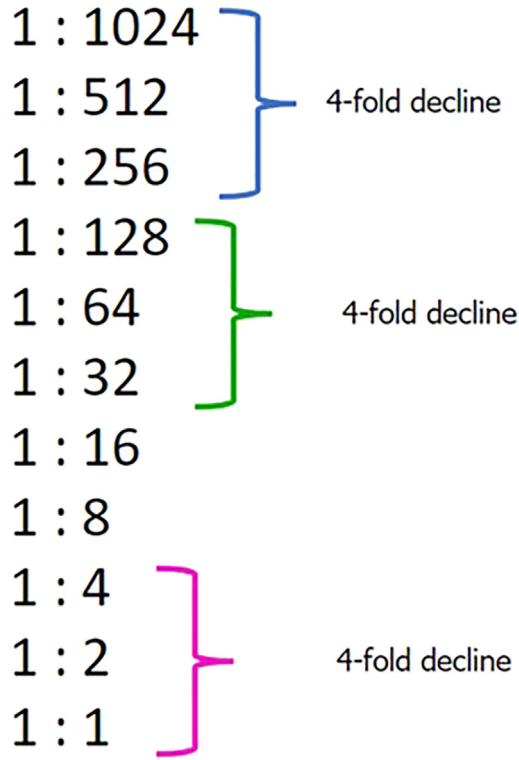


Fig. 3. RPR titer dilutions and examples of fourfold (two dilutions) decreases in titer values.

Providing patients with documentation (such as in **Table 2**) of their syphilis stage, serologic results, and treatment history can empower patients and reduce the likelihood of unnecessary treatment when they undergo future testing.

Vignette 3: Late Latent Syphilis

A 27-year-old man presents to his primary care provider for follow-up STI screening. The patient has a history of syphilis of unknown duration, diagnosed 24 months ago, which was his first visit for STI screening in 3 years. Twenty-four months ago, he reported no genital ulcers, rashes, or other characteristic syphilis symptoms. His physical examination was unremarkable, with no urogenital or mucosal ulcers, rash, or

Table 2
Sample documentation to provide to a patient with their staging, testing, and treatment history

Date	Syphilis Stage	Serologic Results	Treatment Given	Comments
01/01/2022	Secondary	TP-EIA + RPR 1:128	BPG 2.4 MIU × 1	Diagnosed/treated in Baltimore, MD
04/01/2022	-	RPR 1:64	-	-
01/01/2023	-	RPR 1:4	-	Fully treated with adequate serologic response

neurologic abnormalities. TP-EIA was reactive, an RPR was 1:4, and an HIV antigen/antibody test was nonreactive. He was treated with BPG 7.2 MIU administered as three doses of 2.4 MIU intramuscularly each at 1-week intervals. His two partners were diagnosed with late latent syphilis and treated appropriately, and all abstained from sex for 1 week following treatment. The patient's RPR testing was repeated 6, 12, and 18 months ago and all resulted with a titer of 1:2. Today, he reports no new partners, no genital, dermatologic, neurologic, ocular, or otic symptoms, and the physical examination (including neurologic examination) is unremarkable. An RPR is repeated and is 1:2, and repeat HIV antigen/antibody testing is nonreactive.

Discussion

This patient was treated for syphilis of unknown duration 24 months ago but his follow-up NTT has not undergone a fourfold decline. An appropriate serologic response may not occur after treatment, even in the absence of reinfection.[3] This is termed "inadequate serologic response" and best describes the scenario for the patient above. It is estimated that inadequate serologic response is observed at 12 months in approximately 9.4% of cases of primary and secondary syphilis and in 21% of cases of late latent syphilis.[11] Serologic response has been associated with earlier syphilis stage, whereas lower baseline non-treponemal titers,[12,13] older age,[14] female sex,[15] HIV infection,[16] and previous syphilis infection are associated with longer time to achieve a serologic response.

Inadequate serologic response may be distressing for patients and perplexing for their clinicians. For patients identified with inadequate serologic response, the 2021 CDC treatment guidelines recommend careful clinical assessments (including neurologic examinations) and serologic follow-up annually. CSF examination may be considered where follow-up is uncertain or initial high titers (>1:32) do not decrease after 24 months, to determine if asymptomatic neurosyphilis may be the reason for serologic nonresponse. There is currently no evidence for improved clinical outcomes to support additional treatment for patients with inadequate serologic response in the absence of neurosyphilis.[10] However, if ongoing follow-up cannot be assured or if the initial titer was high (>1:32) and does not decrease at least fourfold, it is recommended to retreat with 3 weekly injections of 2.4 MIU of BPG.[3]

It is important to differentiate "inadequate serologic response" from "treatment failure." Concern for treatment failure occurs when there is at least a fourfold *sustained* increase in NTT titer persisting for greater than 2 weeks without signs or symptoms attributable to primary or secondary syphilis, when reinfection is considered unlikely. Along with reevaluation for HIV infection, for patients with treatment failure who have neurologic findings, or who have no neurologic findings and no sexual exposure during the previous year, a CSF examination is recommended.[3] Treatment depends on CSF findings. Among persons with no neurologic findings after neurologic examination and who are sexually active, treatment with weekly injections of BPG 2.4 MIU IM for 3 weeks is recommended.

In this case, as the patient is able to attend follow-up visits, it would be appropriate to continue follow-up serology and clinical examination annually or more frequently based on changes in sexual exposures, to evaluate for new syphilis symptoms.

Vignette 4: Neurosyphilis

A 68-year-old woman with a past medical history of well-controlled hypertension and a transient ischemic attack 10 years earlier presents to clinic with her family. She has a 3-year history of increasing forgetfulness with personality change and now regularly misplaces objects at home and has subsequently stopped driving. She endorses

intermittent, stabbing bilateral lower extremity pains associated with numbness. She endorses vision changes which had been previously attributed to cataracts. On physical examination, she has right-sided anisocoria and reduced sensation to pinprick and light touch in her bilateral lower extremities with diminished reflexes. Eye examination is limited by bilateral cataracts; a formal ophthalmologic examination reveals no additional findings.

She is found to have a reactive TT with an RPR titer of 1:2. She cannot recall prior treatment for syphilis and the local health department does not have a record of prior syphilis treatment. She reports no sexual encounters within the past year.

After a shared decision-making conversation with the patient and her family, an examination of her cerebrospinal fluid (CSF) is obtained and is notable for lymphocytic pleocytosis (36 white blood cells per microliter) and a CSF total protein of 56 mg/dL; CSF-VDRL is nonreactive. She was treated with aqueous crystalline penicillin 24 MIU intravenously per day for a total of 14 days. On day 14, she received a subsequent dose of 2.4 MIU of intramuscular BPG. At 12 and 24 months follow-up, the RPR was nonreactive. Her forgetfulness had not worsened; the pain in her legs had resolved and there were no new visual complaints. A repeat CSF examination was not obtained per guidelines.

Discussion

This patient had late neurosyphilis as manifested by general paresis and tabes dorsalis. Neurologic syphilis encompasses a vast spectrum of clinical manifestations and importantly can occur at any point during infection with TP. Patients with early neurosyphilis (typically within 1 year of infection) are more likely to present with meningitis, stroke, and cranial nerve palsies. Late neurosyphilis (initial infection occurred greater than 1 year ago or is unknown) is a tertiary manifestation of infection and classically includes the progressive dementia known as general paresis as well as posterior spinal column disease, termed tabes dorsalis. Of note, ocular and otic syphilis can occur at any stage of syphilis infection, in conjunction with neurosyphilis or in isolation, and are often considered distinct entities.

The diagnosis of neurosyphilis is challenging; there is no single test with robust enough characteristics alone to confirm or refute the diagnosis in all scenarios. CSF findings include lymphocytic pleocytosis, an elevated CSF protein, and a reactive CSF-VDRL. The CSF-VDRL lacks sensitivity (estimated to be 49%–87.5%) and can be negative in those who otherwise are considered to have neurosyphilis.[6] In individuals with a negative CSF-VDRL and suspected neurosyphilis, CSF FTA-ABS may be conducted. The CSF FTA-ABS is up to 100% sensitive but less specific than CSF-VDRL.[17,18] Some experts believe that a negative CSF-FTA-ABS excludes neurosyphilis, particularly in a person with nonspecific neurologic symptoms.

Primary care providers are routinely the first to identify and attempt to establish an etiology for cognitive decline in our communities. It is therefore important to note that syphilis serologies are not universally recommended as a means of screening for all patients in this setting.[19] Instead, we recommend that exposure history, epidemiologic factors, and associated neurologic signs and symptoms are considered before the initiation of testing.

Regardless, the primary care provider may be tasked with determining if CSF examination for an elderly patient with reactive serologies is truly necessary. Patients with neurologic signs and symptoms (ie, cranial nerve deficits, meningitis, stroke, altered mental status, cognitive decline, loss of vibration sense, or proprioception) in the context of reactive syphilis serologies should undergo CSF testing. As outlined in our case, we recommend that a shared decision-making model is used when

considering a CSF examination for an elderly patient, taking into account both the procedure and the potential treatment.

In patients with isolated ocular or otic symptoms who have no evidence of neurosyphilis (ie, headache, altered mental status, cranial nerve deficit), CSF testing can be avoided. Instead, focused ophthalmologic or otologic evaluation should be pursued. As many as 30% of patients with ocular syphilis and 90% with otic syphilis have normal CSF.[20,21]

Vignette 5: Syphilis in Pregnancy

A 28-year-old primigravida presents for routine prenatal care at 30 weeks gestation. She recently moved and is attending a new clinic in a different state. She has no significant medical history, no history of syphilis, and prenatal fetal anomaly scans were normal. She has had one male sexual partner for the past 4 years. HIV, RPR via traditional testing algorithm, chlamydia, and gonorrhea were nonreactive or negative at her first prenatal visit.

Her laboratory results from this visit reveal a reactive TT by the reverse sequence algorithm, which is the standard of care in her new jurisdiction. Reflex RPR was nonreactive and a second, different TT was also reactive. On further evaluation, she has no signs or symptoms of syphilis and the physical examination is normal. Her partner tested negative for syphilis. With her testing results, she is diagnosed with syphilis of unknown duration and treated (starting at 31-week gestation) with 2.4 MIU of BPG on days 0, 7, and 14. A repeat fetal ultrasound is normal. She delivers a healthy female neonate at 40 weeks. Maternal RPR remains negative at delivery. The neonate has a normal physical examination and nonreactive serum RPR.

Discussion

Syphilis diagnosed in pregnancy must prompt additional evaluation of the fetus for CS. The diagnosis of CS is based on a combination of factors: maternal syphilis serology interpretation, adequacy of maternal treatment and timing before delivery, presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate, and comparison of maternal (at delivery) and neonatal NTT titers. These factors guide classification of CS and management.[3] CS is more likely to occur if the pregnant person has primary or secondary syphilis. However, it can occur at any stage of syphilis in the pregnant person, including during latent infection. CS is preventable by providing adequate access to screening and treatment during pregnancy. Parenteral penicillin is the only acceptable treatment in pregnancy. Pregnant people who are allergic to penicillin should be desensitized and receive stage-appropriate treatment.

This case demonstrates the challenges associated with using an alternate syphilis diagnostic algorithm during prenatal care. If the patient had ongoing prenatal care in her previous jurisdiction and continued to be tested with the RPR, a diagnosis of syphilis in pregnancy would have been missed. It has been observed that screening with the reverse algorithm identifies additional true positives and false positives, though the proportions vary by population disease prevalence.[9]

Fortunately, this patient was diagnosed at 30 weeks and completed stage-appropriate treatment by week 34. Her neonate was born more than 30 days after she completed therapy, thereby avoiding an automatic diagnosis of CS.[3] A more challenging scenario is when a pregnant person, with a nonreactive RPR, is tested for the first time using the reverse algorithm late in the third trimester or at delivery; there is insufficient opportunity to complete stage-appropriate treatment before delivery. States have implemented varied recommendations for the frequency of screening for syphilis during pregnancy; clinicians should be familiar with the requirements in their jurisdiction.[22]

Vignette 6: Biologic False Positive

A 50-year-old woman attends a routine gynecology appointment for preventive care. She has never been diagnosed with an STI and has not been sexually active since her last testing 5 years ago, when her syphilis screening (via reverse algorithm) was nonreactive. She undergoes Pap testing that is normal and STI screening, which includes syphilis testing by the traditional sequence algorithm. The RPR is reactive, with a titer of 1:4, and a TP-PA is nonreactive. Tests for *N gonorrhea, C trachomatis*, and HIV are nonreactive. She is referred for mammography, is identified with a breast mass and is diagnosed with locally advanced breast cancer. Her primary care provider conducts a careful examination which is normal, reviews the patient's sexual history, RPR and TP-PA results, and determines that no syphilis treatment is needed.

Discussion

This patient has discrepant NTT and TT results performed by the traditional algorithm. In the absence of signs/symptoms suggestive of syphilis, or recent exposure, this patient's combination of results in the traditional algorithm is consistent with a "biologic false positive (BFP)." See **Table 3**, for a summary of possible interpretations of TT and NTT combinations.

BFP results are observed among NTT and TT. The prevalence of BFP results depends on the population tested but has been reported to account for 11% to 40% of reactive NTTs in surveillance data (including people with indications for screening)[23] and at much lower rates in the general population (<1%).[24]

A variety of epidemiologic factors and clinical conditions has been associated with BFPs, though the presence of BFP does not require association with any condition and does not portend an occult condition; in the absence of suggestive symptoms or epidemiologic exposures, no additional workup is required. BFP NTT has been associated with older age, female sex, autoimmune conditions (classically systemic lupus erythematosus), hematologic conditions, malignancy, HIV, and hepatitis C.[23–26] Infections (including Lyme disease), autoimmune conditions, and older age have been associated with BFP TT.[10] BFP association with pregnancy is controversial and every effort should be made to exclude syphilis in a pregnant person; expert consultation is recommended.

Attribution of reactive NTT or TT as a BFP should occur when other clues to a potential syphilis infection have been assessed and excluded. In this case, the patient has no

Table 3
Summary of treponemal test and non-treponemal test results and possible interpretations

Non-treponemal RPR (or VDRL)	Treponemal (FTA, TP-PA, and EIA)	Possible Interpretation
Reactive	Nonreactive	Biologic false-positive NTT False-negative TT
Reactive	Reactive	New diagnosis—requires treatment Old case – adequately treated Old case—inadequately treated Previously treated—reinfected Congenital Other treponematoses (eg, Yaws)
Nonreactive	Reactive	Primary syphilis before NTT are positive Old case—treated or untreated Prozone reaction (uncommon)
Nonreactive	Nonreactive	No syphilis Incubating syphilis/seronegative primary syphilis

recent sexual exposure, no clinical signs of syphilis, and a potential underlying condition (malignancy) that could be related to the BFP. In situations where the concern for syphilis is elevated based on epidemiologic factors, exposure, or examination findings, some experts may complete a second, different TT, following the reactive RPR and nonreactive TT completed in the traditional algorithm. If the second TT is reactive, the patient should be assessed and treated for syphilis consistent with the clinical stage.

SUMMARY

This series of vignettes highlights the concepts in syphilis serologic interpretation. Even with this guidance, the interpretation of syphilis serologies is complex and can be ambiguous; definitive criteria for cure or failure by serologic assessment have not been well established.[3] Several resources are available to assist clinicians in syphilis management. The 2021 CDC Sexually Transmitted Infection (STI) Treatment guidelines outline screening, interpretation, and treatment recommendations.[3] The National STD Curriculum (std.uw.edu) is a free educational Web site with self-study lessons and a question bank. The CDC National Network of STI Clinical Prevention Training Centers (NNPTCs) offer a free STI Clinical Consultation Service (stdccn.org) that provides expert advice over email or telephone on specific patient scenarios. For health care professionals in the United States, the NNPTCs offer training on STI prevention topics (https://www.cdc.gov/std/projects/nnptc.htm). Local health departments play a vital role in maintaining testing and treatment histories for reportable conditions, including syphilis. Clinicians should familiarize themselves with their local health department contacts to retrieve records and get assistance with requests from other jurisdictions. Finally, infectious diseases clinicians will have experience in the interpretation of syphilis serology and should be consulted for advice when appropriate.

CLINICS CARE POINTS

- Interpretation of syphilis serology can be challenging even for experienced providers.
- Diagnosis of syphilis relies on reactive treponemal-specific and non-treponemal antibody testing and clinical assessment.
- Serologic antibody testing may be nonreactive early in infection, leading to false-negative results.
- Ensure adequate time has passed (12 months for primary and secondary syphilis, 24 months for latent syphilis) before making a decision about serologic treatment success.
- Lumbar puncture is only indicated in specific scenarios, such as when a patient has neurologic symptoms or non-treponemal test titers increase $\geq$4-fold in the absence of reexposure.
- Local health departments can often provide a syphilis testing and treatment history
- Remember to test for HIV and offer HIV pre-exposure prophylaxis to patients with syphilis.

DISCLOSURE

The authors have no financial disclosures or conflicts of interest to disclose.

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