

Case Report

Going Off-Script: Dilemmas in the Evaluation and Treatment of Syphilis in Four Patients

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Abstract: Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum*. Currently, rates of infection are increasing across all populations worldwide, with disproportionate impact on men who have sex with men, adolescents, and young adults. Syphilis is well-known for its variability in disease progression and clinical presentation, which complicates prompt and accurate diagnosis. Acute care settings have become the frontline in the battle against this syphilis surge, and providers must be prepared to recognize syphilis presentation, initiate appropriate testing, and establish contact tracing for individuals who may have been exposed. The purpose of this manuscript is to serve as a teaching tool for syphilis diagnosis and treatment, and we present four cases that showcase the risks and variable clinical presentation, discussing the challenges involved in managing each case. The authors then summarize key learning points related to diagnosis, treatment, and follow-up.

Keywords: syphilis; latent syphilis; screening test; confirmatory test; uncertainties in treatment



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1. Introduction

Both the incidence and prevalence of sexually transmitted syphilis are surging worldwide [1,2]. In the United States (US), collection of epidemiological data began in 1941, and, in 1947 alone, 93,545 cases of primary and secondary syphilis were reported [3]. Although initially considered a heterosexual disease, rates began to rise among men having sex with men (MSM) in the late 1980s and early 1990s [4]. Reported cases dropped to 6103 by 2000 due to widespread use of penicillin and the “Syphilis Elimination Effort” by the Centers for Disease Control and Prevention (CDC). However, since 2000, rates have resurged across all populations and age groups, increasing by 28.6% between 2020 and 2021, and reaching 176,713 cases in 2021 in the US [5]. The highest rates of increase were among the American Indian, Alaska Native, and African American populations. Currently, syphilis disproportionately affects MSM, adolescents, and young adults [5,6]. The number of cases is also rising among women [6].

Although treatment is relatively straightforward early in the infection, the variability in syphilis presentation, often mimicking other common diseases, makes diagnosis challenging. Acute care settings, such as urgent care clinics and free or low-cost community-based clinics, play a crucial role in combating the surge in syphilis infections [7], and clinicians must recognize the variability in presentation, provide early and accurate diagnosis, and

initiate contact tracing for potential exposures. This article provides a brief overview of the stages of syphilis and their respective symptoms, and then describes four cases in which healthcare providers were either surprised by the physical manifestations of syphilis infection or otherwise uncertain about how to interpret available data. We intend for this article to be a teaching tool for recognizing more challenging case presentations so that syphilis may be more promptly and accurately diagnosed and managed.

1.1. Syphilis Stages and Symptoms

Syphilis is a bacterial infection caused by the spirochete *Treponema pallidum*, an obligate human parasite with no other known animal or environmental reservoirs. Left untreated, syphilis is a chronic disease that progresses through multiple stages: primary, secondary, latent, and tertiary. Primary syphilis is characterized by the classic painless sore known as a chancre, which typically appears within three weeks of exposure but may take as long as three months. This chancre often begins as a macule or papule at the mouth, genital, or peri-anal area, eventually eroding to become an ulcer, and can easily go unnoticed, depending on the bodily location. On rare occasions, multiple painful sores may occur during primary syphilis.

Secondary syphilis occurs four to eight weeks after primary syphilis, and often presents with a spotty rash on the palms and soles—a result of the spirochete spreading systemically. This secondary-stage rash is most notorious for mimicking other diseases such as lichen planus, psoriasis, eczema, mycoses, Kaposi sarcoma, Rocky Mountain spotted fever, bacillary angiomatosis, leprosy, and sarcoidosis, earning syphilis the nickname “the great imitator” [8,9]. The cause of the variability in presentation of secondary syphilis is not clear; however, the balance between the affected individual’s humoral versus cellular immune response, co-infection with HIV (which impairs the cellular immune response), and antigenic variability among *T. pallidum* strains can affect presentation, progression, and clearance [10,11]. Transmission of the infection usually occurs during the primary stage via direct contact with a chancre, but can occur via contact with a secondary lesion as well.

Lesions seen in the primary and secondary stages resolve without treatment, and an asymptomatic period of latency follows. Roughly one-third of infected individuals will progress further to the tertiary stage, in which syphilis spreads to other organs. The most common forms are neurosyphilis, cardiovascular syphilis, and gummatous syphilis [1,11]. Pregnant individuals with untreated syphilis have an 80% chance of transmitting the infection to the fetus, resulting in various birth defects and a 40% chance of fetal death [4]. (For recent clinical reviews, see references [12,13]).

1.2. Syphilis Diagnosis and Treatment

The definitive test for syphilis is darkfield microscopy (DFM), but it is rarely performed due to its labor-intensive nature, and few clinical facilities, including urgent care centers, have the specialized microscope and skilled microscopist close enough to review the sample within 20 min of specimen collection. Instead, serological tests that show indirect evidence of infection are commonly used for diagnosis. Polymerase chain reaction (PCR), the laboratory technique of first amplifying DNA segments to better detect them, is of increasing interest in the diagnosis of various sexually transmitted infections (STIs), including gonorrhea (GC), chlamydia (CT), and HIV [14,15]. However, the US Food and Drug Administration (FDA) has not yet approved clinical diagnostic PCR assays for syphilis, and therefore they are not yet available to all clinicians or practice settings [16].

Non-treponemal serological tests (NTTs), such as rapid plasma reagin (RPR), are often used for initial screening, followed by treponemal-specific serological tests (TTs), such as *Treponema pallidum*-particle agglutination (TP-PA), for confirmation. This traditional algorithm of NTT first, then TT, remains the most common standard in resource-limited settings, since it is cost-effective [8]. However, “reverse algorithm” testing using automated treponemal-specific immunoassays, potentially followed by NTT and a different

TT, is considered more efficient, and is becoming more widely used in high-prevalence settings [17,18]. These screening algorithms are illustrated in Figure 1.

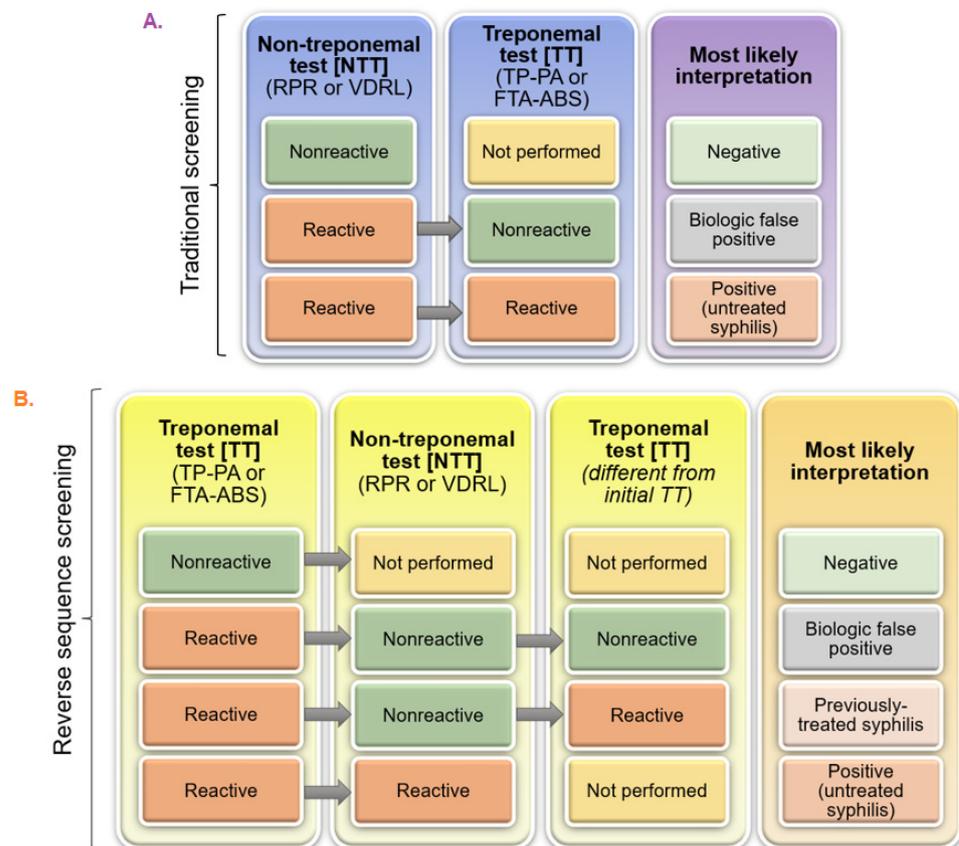


Figure 1. Traditional (A) and reverse sequence (B) screening algorithms for syphilis. RPR: rapid plasma reagin. VDRL: venereal disease research laboratory. TP-PA: *Treponema pallidum* particle agglutination. FTA-ABS: fluorescent treponemal antibody absorption.

Despite the convenience of treponemal-specific serological tests, anti-treponemal antibodies do not appear until 1–2 weeks following transmission [10], and this delay can complicate detection directly following known exposure, resulting in a false negative. Some individual laboratories have developed their own treponemal-specific PCR tests that allow for detection prior to seroconversion. While PCR-based detection may be especially helpful in early diagnosis of syphilis infection, such direct testing (like DFM) can be costly [16,19]. And given that PCR test kits are not yet commercially available in the US, PCR testing is not universally used as an initial screen. (For reviews regarding the current efficacy of PCR-based detection of syphilis, see references [20,21]).

Following seroconversion, anti-treponemal antibodies remain in the blood even after successful treatment; therefore, repeat infection is implied by an increase in NTT serum titer (e.g., a four-fold increase from 1:1 to 1:4) [22]. Moreover, maternal antibodies can be transferred through the placenta to the fetus. Thus, when evaluating a newborn for congenital syphilis, non-serologic testing, such as DFM or PCR, may be warranted. The “TORCH” acronym (Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes simplex—in which syphilis and Hepatitis B are relegated to the “Others” portion of the mnemonic) is often used to aid in the diagnosis of congenital infections [23]. However, since syphilis (the only bacterial agent) is not explicitly named, it is often forgotten as a potential differential.

According to the CDC’s 2021 STI treatment guidelines, treatment for primary, secondary, and early latent syphilis is penicillin G benzathine, 2.4 million units delivered intramuscularly (IM) as a one-time dose [24]. Late-latent syphilis (or latent syphilis of unknown duration) and tertiary syphilis are treated with the same agent, but it is given

once weekly for three weeks, for a total of 7.2 million units [24]. Though treatment of syphilis has remained largely unchanged for more than 75 years [25], the definition of early or late syphilis varies depending on professional standards: The CDC defines early syphilis as exposure within the past 12 months [25], whereas the World Health Organization (WHO) defines it as exposure within the past 24 months [26]. Neurosyphilis is most commonly treated with intravenous aqueous crystalline penicillin G, either every four hours or by continuous infusion, over 10–14 days [24]. It is important to note that treatment of neurosyphilis or ocular syphilis will halt disease progression, but will not repair damage.

2. Detailed Case Presentations

Syphilis infection can present in a wide range of ways, and potentially as co-infection with another STI. Partners of infected individuals should be treated empirically while testing is pending, and treatment should be considered even if their own test is negative. Titer analysis is important for determining reinfection, but can be a common point of confusion for generalists. In order to aid other clinicians in recognizing and managing syphilis infection, we share the following four cases in which the diagnosis could have been missed or treatment delayed due to an atypical presentation or other diagnostic pitfall.

2.1. Case 1: 39-Year-Old Male with Weight Gain and Edema

A 39-year-old cisgender man with no documented past medical history presented to an urgent care clinic for evaluation of accelerating and unintentional weight gain and edema. He reported gaining 20 pounds over the last month, with 10 pounds gained over the preceding week. The patient had noticed lower extremity edema, resulting in loss of muscle definition in his legs, and also facial and scrotal swelling, which led him to seek medical evaluation. He also endorsed chills, subjective fevers, and muscle aches. His last sexual contact had been about four months prior—unprotected and with a male partner. He had no known history of STIs, and had last been screened for STIs about a year prior to this visit. A urogenital exam revealed scrotal edema and a right-sided hydrocele, but no frank enlargement or tenderness of the testes. No lesions or rashes were noted.

A urine dipstick revealed significant proteinuria. Serologic testing was sent to a centralized lab, and the results were available the next day. HIV and hepatitis C were negative. The patient's syphilis screen by RPR was positive, with a high titer of 1:128 (reference range < 1:4). While awaiting the confirmatory test, the patient was treated with a single dose of penicillin G benzathine, 2.4 million units IM.

His TP-PA confirmatory syphilis testing was positive. In a follow-up phone call 12 days after his initial clinic visit, the patient reported his symptoms were improving. His presentation was ultimately attributed to a nephrotic syndrome resulting from secondary syphilis.

2.2. Case 2: 23-Year-Old Male with Genital Rash

A 23-year-old cisgender man with no documented past medical history presented to a primary care clinic for a vesicular rash on his genitals that had appeared four days earlier. The patient reported that his most recent sexual contact was approximately 10 days prior to the development of the skin rash. He denied known exposures to STIs, but also reported occasionally engaging in penetrative vaginal intercourse without a condom. He denied having noticed a chancre or rash in his palms and/or soles. No previous STI screening test results were available for reference at time of consultation. The patient stated that his sexual debut was at age 16 and that he had only ever been active with female partners, approximately five in total.

A viral swab of the skin lesions was positive for herpes simplex virus type 2 (HSV-2), and he was started on valacyclovir. GC/CT urine testing was negative, and serologic screening for HIV and hepatitis C were also negative. His RPR test was reactive with a titer > 1:64 (reference range < 1:4) and confirmatory TP-PA testing was positive as well. Since it could not be confirmed that he was infected with syphilis within the preceding one to two

years, he was treated for latent syphilis of unknown duration with penicillin G benzathine, 2.4 million units IM, weekly for three doses.

2.3. Case 3: 22-Year-Old Male with Syphilis-Positive Sexual Partner

A 22-year-old cisgender man with no documented past medical history presented to a primary care clinic after being told by a previous sexual partner that she tested positive for syphilis. The patient stated that he had had unprotected penetrative vaginal intercourse with this partner six weeks prior, but he denied any symptoms at time of consultation. Reportedly, she told him she had only one other sexual partner three years ago and she also denied any symptoms. The patient indicated his sexual debut was at age 18 and that he had only ever been sexually active with female partners, approximately six in total, and had always used a condom in those encounters. Past screening for HIV and hepatitis C was negative, but no other STI screening results were available for review. While awaiting the results of more comprehensive testing obtained at this encounter, the patient received a single dose of penicillin G benzathine, 2.4 million units IM. Urine and serologic screening, including GC/CT, RPR, and TP-PA, ultimately came back as negative/nonreactive.

2.4. Case 4: 24-Year-Old Female with History of Syphilis

A 24-year-old cisgender woman presented to an urgent care clinic for STI screening. She had previously been diagnosed with syphilis one year prior and, at the time, was treated with a single dose of penicillin G benzathine, 2.4 million units IM. Per chart review, she had presented several times for a palmar rash, and was repeatedly misdiagnosed prior to the confirmation of syphilis infection. She presented on this occasion for follow up to confirm successful treatment. She denied any other known medical issues or concerns, and was asymptomatic at the time of this clinical encounter. Per the institution's laboratory protocol, an NTT was performed first, followed by confirmation testing for treponemal antibodies. As would be expected in someone who had been diagnosed with syphilis, this treponemal testing was reactive. However, her RPR titer had decreased from 1:32 prior to treatment to 1:1. Given this interval improvement (and previous receipt of appropriate treatment), no further treatment was necessary. The patient was encouraged to follow-up with her primary care clinician to have her titers rechecked at six months and one year. She would not need re-treatment unless her titers were to rise again, or she were re-exposed or reinfected.

3. Discussion

Each of the four cases presented here highlight various issues in the diagnosis and tracking of syphilis. Unlike the canonical case involving the appearance of a primary chancre, neither of the newly diagnosed cases of syphilis involved discovery of a primary chancre nor the typical secondary palmar/plantar rash. In case #1, the patient's symptoms—weight gain, edema, and proteinuria—suggested nephrotic syndrome, which can be a consequence of secondary syphilis.

In case #2, the patient's presentation included a vesicular genital rash, thus warranting HSV testing and, due to the risk of co-infection, further STI screening. This additional screening resulted in the incidental discovery of syphilis, which underscores the importance of routine testing [27–29]. Since the duration of this patient's infection could not be determined, he was treated with the more aggressive three-dose regimen. The unknown duration also warrants contact tracing of 12 months of sexual history [30].

The patient in case #3 was treated due to a known exposure, even though his test results did eventually return as nonreactive. If it had been a more recent exposure (i.e., less than a week), the patient would not likely have seroconverted yet, and the tests would be negative regardless of actual exposure. However, in this instance, being six weeks post-exposure would have likely resulted in positive serology if he had been infected.

Lastly, in case #4, the patient presented for STI screening and had a known history of syphilis infection that had been treated with penicillin. Her RPR titers were 1:1 on repeat

testing. Her previous titers were 1:32, so this decrease in titers indicates that she was successfully treated. If the titers had increased to 1:64, for example, this would indicate reinfection or potentially inadequate treatment.

Teaching Points for Diagnosis and Treatment

In light of the four interesting cases of syphilis infection described above, below are teaching points to aid other healthcare providers in diagnosing and treating syphilis infection despite variability in presentation:

- As with other bacteria, previous infection with syphilis does not prevent future infections. Although treponemal antibodies can remain long after infection, NTT titers should decrease by four-fold in the 1–24 months following successful treatment [22,31]. Conversely, a four-fold increase in titer (i.e., two dilutions) likely indicates reinfection requiring further treatment [22].
- Latex condoms only protect as much skin as they cover. A patient who, within the previous three months, has had sexual contact with someone confirmed to have primary, secondary, or early latent syphilis should receive treatment regardless of their own test result or reported condom use [30].
- Effective social history taking can help to stratify a patient's risk of a syphilis infection. Risk factors include engaging in MSM sexual behavior, taking HIV pre-exposure prophylaxis (PrEP), being HIV+, and having sexual contact with a partner who has tested positive for syphilis [32]. Other groups at risk include pregnant women, men under the age of 29, and individuals engaged in transactional sex [27]. However, the lack of these risk factors does not rule out syphilis infection. When faced with a constellation of nonspecific symptoms, providers should have a wide differential that includes syphilis.
- Although the traditional testing algorithm of first using a non-specific screening test (e.g., RPR, VDRL) followed by a confirmatory test (e.g., TP-PA, FTA-ABS) is still widely used, automated treponema-specific immunoassays are becoming more popular as an initial screen, followed by non-treponemal and different treponemal testing, if necessary [8]. PCR testing is also available in some locations.
- Penicillin remains the mainstay of treatment for syphilis across stages, populations, and age groups. Patients with a penicillin allergy should undergo desensitization. This is especially true in pregnant patients. If desensitization is contraindicated, other antibiotics may be acceptable for certain disease stages (e.g., doxycycline for primary and secondary syphilis), assuming close post-treatment monitoring can be assured [24].
- Latent syphilis is diagnosed if the patient tests positive without symptoms of primary, secondary, or tertiary disease. Early latent syphilis, defined by the CDC as seroconversion (or having exposure) within the last year, can be treated with one IM dose of penicillin G benzathine. However, late latent syphilis and latent syphilis of unknown duration require three weekly IM doses of penicillin G benzathine.

4. Conclusions

Syphilis infection can present in unexpected ways, as evidenced by the four cases shared here. Its reemergence may be influenced by changing attitudes towards sex (e.g., certain smartphone apps that can increase one's social and/or sexual network, and/or the advent of PrEP for HIV, which does not protect against other STIs). Even though the treatment of syphilis has remained unchanged for decades, failure to recognize the multitude of ways in which the infection can manifest has been a tripping point for many clinicians. Prompt diagnosis and treatment is critical for reducing transmission and preventing long-term complications associated with untreated syphilis.

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