

## Case Series

# Interpretation of Syphilis Serology: Implications for Clinical Practice and Improved Diagnosis

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## Introduction

Syphilis, an affliction induced by the bacterium *Treponema pallidum*, is classified as (STIs) that progresses through distinct stages. Early detection and treatment of syphilis disease are crucial to prevent severe systemic complications. Serological tests play a vital role in diagnosing syphilis, monitoring treatment response, and distinguishing between ongoing active or resolved or re-infection [1].

## Syphilis Serology Tests

Syphilis serology encompasses the utilization of both non-

## Abstract

### Background

This series comprises a comprehensive clinical examination of eight cases of syphilis, presenting a diverse array of symptoms and varying serological test outcomes among patients seeking primary care. Syphilis exhibits a wide spectrum of clinical manifestations, contingent upon the infection stage, progressing through distinct phases marked by specific clinical features. Primary syphilis is characterized by the presence of non-painful, well-defined, circular or oval ulcers known as chancres at the site of infection. Secondary syphilis presents with a cutaneous rash on the palms of accompanied by constitutional symptoms, sporadic alopecia aerata, and flu-like manifestations. In contrast, latent syphilis is asymptomatic, while tertiary syphilis is associated with the development of severe systemic complications.

**Aims:** The primary aims are to conduct a methodically rigorous investigation of case series. The emphasis is placed on elucidating the clinical manifestations, potential predisposing risk factors and the consequent implications for proper diagnosis and implement best evidence therapeutic strategies related to the various stage of syphilis.

**Methods:** The clinical evaluation of the patients encompassed a comprehensive assessment of their medical history, physical examination, and a through battery of laboratory analysis. This series provides valuable insights into the clinical management of different serological tests combined with the variable clinical manifestations of syphilis disease, aiding in the accurate identification and judicious treatment of patients with similar presentations.

**Results:** Patient management necessitated a dual therapeutic approach, incorporating the administration of antibiotic regimens in conjunction with empathetic measures aimed at relieving symptomatic discomfort. Safe sexual behaviors were highlighted as a preventive measure against STIs, These findings have significant implications for physicians, offering valuable insights into the clinical presentation, diagnosis, and management of different syphilitic cases, particularly in primary care settings.

**Keywords:** Syphilis Serology; Best Practice; Diagnostic Interpretation

treponemal and treponemal tests. Nontreponemal tests, exemplified by the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) assays, serve as primary screening tests. These tests are designed to identify antibodies produced in response to syphilis infection. Reactive outcomes in nontreponemal tests signify the presence of syphilis antibodies, necessitating further confirmatory evaluation [2,3].

In contrast, treponemal tests, including the Fluorescent Treponemal Antibody Absorption (FTA-ABS) and *Treponema Pallidum* Particle Agglutination (TPPA) assays, function as con-

firmatory examinations to corroborate positive nontreponemal findings. These tests are geared towards the detection of specific antibodies directed against *Treponema pallidum*, the causative agent of syphilis. A positive outcome in both nontreponemal and treponemal tests serves to confirm an active syphilis infection [4]

### Clinical Practice Implications:

Prudent interpretation of syphilis serology outcomes assumes paramount importance in the realm of effective clinical management and transmission prevention. The following are pivotal implications of syphilis serology in clinical practice:

**1 - Diagnosis and Screening:** Syphilis serology tests are pivotal for both initial diagnoses and screening, notably in high-risk demographics. High risk group including sex workers, organ donor recipient, drug abusers, expectant delivered mothers, and STIs patients, particularly in cases of concurrent HIV infection. Opportunistic screening is recommended in these contexts [5,6].

**2 - Treatment Monitoring:** Syphilis serology stands as an indispensable tool for gauging the efficacy of treatment. A decrement in nontreponemal titers over time signifies a favorable response to treatment. Conversely, persistently elevated, or ascending titers may indicate treatment inadequacy or reinfection, warranting further assessment and therapeutic adjustments [4].

**3 - Discerning Infection Phases:** Syphilis serology aids in the differentiation of distinct infection phases. Nontreponemal tests, in conjunction with their titration, offer valuable insights into disease progression and therapeutic response. During the primary stage of syphilis, serological tests are often non-reactive or yield false-negative results. Instead, diagnosis primarily relies on clinical symptoms.

Though, in the secondary stage, non-treponemal tests (VDRL and RPR) become reactive and are usually the first to indicate the presence of the infection. Treponemal tests may also become positive at this stage. The combination of a reactive non-treponemal test with a reactive treponemal test confirms the diagnosis of syphilis. Furthermore, in the latent phase, the non-treponemal tests remain reactive, while the treponemal tests also continue to be positive. This indicates the persistence of the infection in the absence of clinical symptoms. While, in tertiary syphilis is characterized by the presence of both non-treponemal and treponemal tests typically remain positive.

**4 - Serofast Reactors:** In some cases, patients may become "serofast reactors," where the non-treponemal tests remain positive despite successful treatment. This condition is often observed in latent syphilis and is indicative of a sustained immune response.

Overall, the differentiation of distinct phases of syphilis infection is based on the combination of non-treponemal and treponemal serological test results, clinical manifestations, and the patient's history. Serology aids in confirming the diagnosis and monitoring the progression or resolution of the infection over time. [5].

**5 - Challenges and Considerations:** The interpretation of syphilis serology findings can be inherently complex due to various factors. The propensity for false-positive outcomes, particularly in nontreponemal tests, necessitates the conduct of confirmatory treponemal testing. Additionally, the timing of serological assessments concerning symptom onset and the disease stage holds significance in influencing serological out-



**Figure 1:** Single chancre on the penis of primary syphilis.

comes [6].

Syphilis serology occupies a pivotal role within the diagnostic and management framework for syphilis. Proficiency in comprehending serology result interpretation and its applications in clinical practice is an imperative for healthcare practitioners. Ongoing research initiatives and the enhancement of point-of-care testing in primary care settings have the potential to advance early diagnosis, treatment, and syphilis prevention, thereby contributing to the alleviation of the global health burden posed by disease progression [1,4].

### Case 1

**A 23-year-old male patient exhibited a singular, diminutive, and painless papule, which swiftly evolved into an indurated ulcer over the course of four days. The ulcer featured mildly raised borders surrounding its central lesion (Figure 1) and was concomitant with non-tender inguinal lymphadenopathy on the right side.**

**1 Which serological assays are recommended for the evaluation of syphilis during the initial presentation of a genital lesion?**

During the assessment of a patient presenting with a genital ulcer, it is advisable to conduct serological testing for syphilis, encompassing assays such as RPR, EIA, and FTA-ABS tests at the time of the lesion's appearance.

Nevertheless, in this particular case, all serological tests for syphilis yielded negative outcomes. It is crucial to emphasize that negative results should not preclude the consideration of early syphilis. Consequently, repeat testing after a few weeks may be warranted to conclusively establish or rule out the diagnosis [7].

**1.2- In the aforementioned clinical scenario, what is the recommended course of action in terms of initiating treatment and following best medical practices?**

In this scenario, the recommended course of action entails initiating treatment for syphilis. The initial treatment protocol for syphilis involves administering a single parenteral injection of penicillin G, with a dosage of 2.4 million units administered intramuscularly.

In cases where the patient exhibits a penicillin allergy, alter-

native treatment options such as doxycycline, erythromycin, or azithromycin may be prescribed for a duration of 14 days. It is imperative to counsel the patient on the importance of refraining from any sexual activity until syphilis tests have been completed, and all syphilis-related sores or lesions have completely healed. Additionally, it is advised to conduct screenings for other STIs as part of the comprehensive care plan [7].

### 1.3- What does a positive EIA and reactive VDRL test with a dilution greater than 8 in a repeated syphilis serologic test conducted after one month suggest?

When a repeated syphilis serologic test, performed one month later, yields a positive EIA result and a reactive VDRL test with a dilution exceeding 8, it may signify the initial treatment's ineffectiveness or potential reinfection. In such instances, it is prudent to reinstate treatment with an appropriate antibiotic regimen, tailored to the syphilis stage and the patient's specific allergic history. Regular follow-up assessments and syphilis serologic tests are strongly recommended to monitor the patient's treatment response. Additionally, consideration should be given to ongoing screening for other STIs [7].

#### Case 2

A 33-year-old male patient presented with multiple asymptomatic lesions on the glans penis, which had been apparent for a duration of 10 days. The patient reported no prior history of urethral discharge, dysuria, or painful induration. Furthermore, there was no evidence of bilateral inguinal lymphadenopathy. In light of the suspicion of primary syphilis with the presence of multiple chancre lesions (Figure 2), serological tests for syphilis were promptly conducted. The EIA result returned as positive, and VDRL tests exhibited reactivity with a dilution of less than 8 titer.

### 2.1- What is the advised timeline for conducting follow-up investigations to monitor alterations in the VDRL titer subsequent to the initial serological testing?

It is recommended to initiate follow-up investigations aimed at monitoring changes in the VDRL titer after a 2-week interval. A VDRL titer escalation exceeding 16 dilution level signifies an ongoing, active syphilis infection [8,10].

### 2.2- What are the potential differential diagnoses to consider in cases featuring multiple chancre ulcers?



Figure 2: Multiple chancres on the penis of primary syphilis.

Multiple chancre ulcers, though uncommon, necessitate a comprehensive evaluation to consider and exclude alternative diagnostic possibilities.

These encompass conditions such as Herpes Simplex Virus (HSV) infection, chancroid, fixed drug eruptions, lymphogranuloma venereum, granuloma inguinale (donovanosis), traumatic ulceration, furunculosis (boils), and multiple aphthos ulcers [9].

### 2.3- What constitutes the recommended therapeutic approach for managing multiple chancres?

The preferred treatment protocol for multiple chancre ulcers of syphilitic origin involves a singular injection of penicillin, administered at a dose of 2.4 million units.

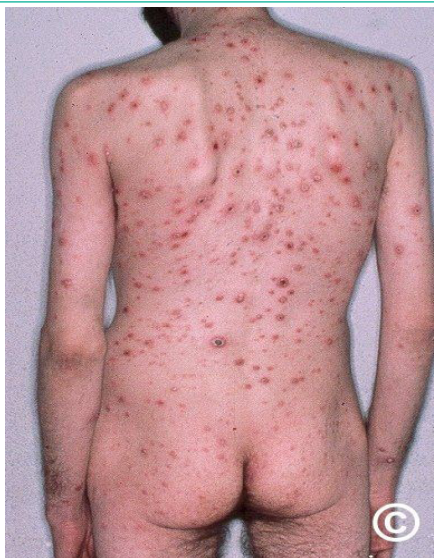


Figure 3 & 4: Secondary generalized syphilitic rash.

However, in cases where there is a documented history of penicillin allergy, an alternative treatment regimen should be judiciously employed [9].

#### Case 3

A 44-year-old male, who identifying as homosexual, sought medical attention due to the presence of a widespread, non-pruritic skin rash affecting his abdomen, back, palms, and soles of both feet (Figure 3-5). It is noteworthy that the patient had previously received a prescription for topical betamethasone steroid cream, which failed to yield any discernible improvement. This individual displayed a notable pattern of frequent visits to the healthcare facility, specifically seeking a battery of screening tests for STIs. His syphilis serological evaluation yielded positive results on the EIA test, with a weakly positive VDRL titer, registering at dilution levels lower than 8.

### 3.1- What is the recommended timeframe for follow-up in-

## vestigations?

In this particular case, it is advisable to schedule a follow-up assessment, including the repetition of syphilis serology tests, after a two-week interval. Additionally, it is recommended to conduct comprehensive screening tests for STIs for both the patient and their partner [11,12].

### 3.2- What specific types of lesions serve as diagnostic indicators for secondary syphilis?

The distinctive lesions pivotal for the diagnosis of secondary syphilis manifest as diffuse macular exanthema, typically measuring 1-2 cm in diameter, and predominantly appear on the trunk and extremities. These lesions are characterized by



**Figure 5:** Secondary syphilitic generalized skin rash distributed over palms and feet.

their scaly macular or papular nature, exhibiting a red-brown or 'ham colored' hue. Furthermore, the co-occurrence of syphilis papules on the palms and soles, accompanied by the presence of Bielt's collarette (manifesting as a white ring of scaling at the periphery of their central surface), serves as a highly diagnostic feature indicative of secondary diffuse syphilitic rash [11,12].

### 3.3- What treatment strategy is advisable for a patient diagnosed with secondary syphilis?

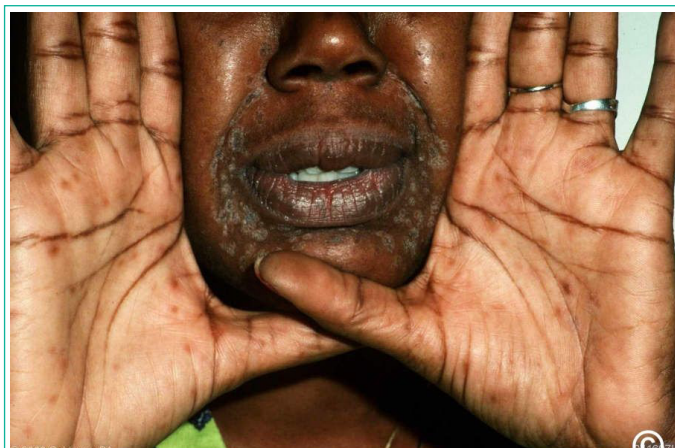
The recommended therapeutic regimen for secondary syphilis aligns with the protocol established for primary syphilis, entailing a singular intramuscular administration of penicillin G benzathine at a dose of 2.4 million units. In circumstances where a documented penicillin allergy is present, it is incumbent upon the clinician to judiciously deliberate alternative therapeutic modalities [10,11].

#### Case 4

A 35-year-old female expatriate underwent a pre-employment medical assessment, reporting a rash on her palms and perioral region that had been present for a duration of 10 days (Figure 6 & 7). An oral examination unveiled multiple scattered lesions on her gingiva and lip areas, including painful aphthous ulcers characterized by grey ulcerations with irregular whitish margins (Figure 8). The patient's medical and social history disclosure was limited, primarily due to her apprehension of potential stigmatization related to syphilis, and patient's misconception of its potential impact on her employment prospects.

#### 4.1- What are the suggested steps to be taken during her pre-employment medical evaluation?

During her pre-employment medical evaluation, it is recommended to take the following steps: conduct a comprehensive



**Figure 6 & 7:** Secondary syphilis on the palms and perioral rash.



**Figure 8:** Oral gingival and lips lesion.

serological testing for syphilis and screen for other STIs. If a suspected syphilis case is identified, promptly initiate the appropriate treatment regimen. Provide the patient with essential education and reassurance, emphasizing that syphilis is a treatable and curable condition and will not impede her eligibility for employment. In the specific case described, the syphilis serological findings revealed a faintly positive result in the EIA test, and the VDRL test exhibited reactivity with a titer surpassing 8-fold dilution [12,13]. These findings underscore the importance of early detection and intervention in managing the condition effectively.

#### 4.2- How should the results of the syphilis serological tests be interpreted? What is the appropriate timeline for conduct-



Figure 9: Moth-eaten alopecia aerates on scalp hair.

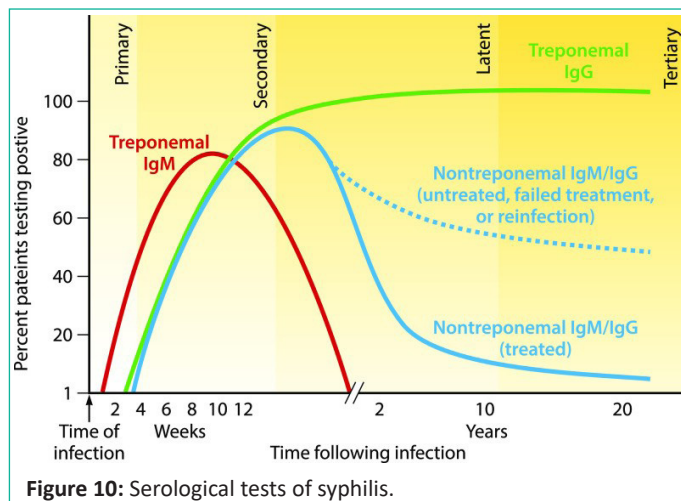


Figure 10: Serological tests of syphilis.

The medical diagnosis in this case is secondary active syphilis, and the recommended treatment entails either a solitary injection of penicillin G benzathine or an appropriate alternative therapeutic regimen, as per established medical guidelines [11,14].

### Case 6

A 24-year-old male patient exhibited multiple discrete patches of alopecia areata on his scalp (Figure 9). Following consultation with a dermatologist, the professional diagnosis was secondary syphilis with established alopecia areata was established. The patient subsequently underwent syphilis treatment and was referred to the local health center for further follow-up assessment.

#### 6.1 What is the recommended follow-up schedule for a patient with secondary syphilis and no HIV?

For patients without HIV, regular follow-up should include history taking and examination after 6 and 12 months, along with serial checking of non-treponemal VDRL or RPR titers. Treponemal tests are expected to remain persistently positive [11].

#### 6.2 How often should a patient with HIV and secondary syphilis be screened for treponemal tests?

In HIV-positive patients with secondary syphilis, screening should be more frequent, occurring at 3, 6, 9, 12, and 24 months [11,14].

#### 6.3 What is the significance of a fourfold decline or increase in nontreponemal test titers in patients with syphilis?

A fourfold decline in nontreponemal test titers (e.g., from 1:8 to 1:2) indicates successful treatment, while a fourfold increase (e.g., from 1:2 to 1:8) suggests reinfection or therapy failure [11,14].

#### 6.4 What is the different syphilis serological tests and their time following infection?

Serological tests for syphilis include treponemal IgM, IgG, and nontreponemal IgM and IgG. These antibodies can appear within weeks or years following infection (Figure 10).

### Case 7

A 28-year-old male with a positive serology test for syphilis and no known penicillin allergy underwent sensitivity testing and subsequently received 2.4 mega units of penicillin intramuscularly. Four hours following the initiation of penicillin treatment, he developed symptoms including fever (38.2°C), severe myalgia, tachycardia (110 beats per minute), tachypnea (24 breaths per minute), the presence of a cutaneous rash, and malaise.

### ing follow-up investigations?

In this particular case, the syphilis serological tests indicate a potential diagnosis of either primary or secondary syphilis, with a strong clinical implication towards secondary syphilis due to the presence of cutaneous and oral manifestations. Consequently, it is advisable for the healthcare provider to schedule a repeat syphilis serological test for follow-up purposes, with the retesting to be performed after a 2-week interval [12,13].

### Case 5

A 28-year-old female, in the first trimester of pregnancy at 6 weeks, presented with a constellation of clinical symptoms, including fever, sore throat, anorexia, nausea, a notable weight loss of 4 kilograms, headache, and persistent fatigue. Physical examination revealed an elevated body temperature of 38°C, generalized lymphadenopathy, primarily manifesting in the cervical and axillary regions, mild throat congestion, and notably, an absence of any skin rash. Her Complete Blood Count (CBC) demonstrated leukocytosis, with a white blood cell count of 18,000, characterized by neutrophilia at 70%. Despite a negative result from the monospot test, the EIA test returned positive, and the VDRL test exhibited reactivity, revealing a titer exceeding 16 dilution level.

#### 5.1- In accordance with best-practice guidelines, what is the advisable course of action for the physician to follow in this case?

In alignment with evidence-based medical practices, it is recommended that the physician elucidates the implications of the positive VDRL test result, obtains a comprehensive sexual history, arranges for confirmatory diagnostic assessments, and promptly initiates the administration of penicillin G benzathine injections for pregnant women diagnosed with syphilis. Furthermore, the physician should offer comprehensive counseling on partner treatment, the adoption of safe sexual practices, and the importance of scheduled follow-up evaluations. Vigilant monitoring of both the patient and her fetus throughout the duration of her pregnancy is of paramount importance [11,14].

#### 5.2- What is the medical diagnosis, and what constitutes the advised treatment strategy in this case?

### 7.1- What is the precise medical diagnosis for the patient's condition?

The patient is experiencing a Jarisch-Herxheimer reaction, a phenomenon observed in approximately 50% of cases. The presenting symptoms do not align with a penicillin hypersensitivity reaction characterized by cytokine induction. Ongoing clinical monitoring and appropriate intervention will be instituted as deemed necessary [13,15].

### 7.2- What are the distinguishing signs and symptoms of penicillin allergy and the Jarisch-Herxheimer reaction?

Penicillin allergy may manifest as mild cutaneous rashes or severe anaphylaxis, featuring symptoms such as facial, tongue, or throat swelling, pruritus, and respiratory distress, necessitating immediate medical attention. Conversely, the Jarisch-Herxheimer reaction may elicit systemic manifestations, including fever, chills, cephalalgia, myalgia, and cutaneous rash, which can sometimes be confused with an allergic response but is attributed to either release of bacterial toxins or presence of antigens subsequent to antibiotic therapy. Accurate differentiation can be achieved through comprehensive evaluation involving patient history, laboratory assessments, and skin tests. In cases where distinction remains challenging, consultation with an allergist or immunologist is advisable for precise diagnosis and management [13,15].

### 7.3- What is the recommended therapeutic approach for managing the patient's current condition?

The management of the Jarisch-Herxheimer reaction supportive care and involves the administration of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and acetaminophen. It is imperative for the physician to maintain close vigilance over the patient's blood pressure, as a decline in blood pressure can lead to acute end-organ damage and failure [14].

## Case 8

**An asymptomatic 30-year-old patient with positive serological tests indicative of syphilis was identified during opportunistic pre-employment screening.**

### 8.1- How can a physician ascertain the specific stage of the syphilis infection in this asymptomatic patient?

The determination of the stage of syphilis infection hinges on an amalgamation of nontreponemal and treponemal test outcomes, complemented by the consideration of clinical manifestations. The staging of syphilis, in relation to corresponding serological and clinical findings, can be outlined as follows [16]:

I. Primary syphilis: Characterized by the emergence of a painless chancre at the infection site. Nontreponemal test results are typically negative or exhibit low titers, whereas treponemal test results remain positive.

II. Secondary syphilis: Recognized by the presence of a secondary rash affecting various body regions, mucous membrane lesions, and systemic symptoms encompassing fever and malaise. Nontreponemal test titers typically register as high, while treponemal test results persist as positive.

III. Latent syphilis: This stage is asymptomatic and may endure for several years. Nontreponemal test titers may appear low or be non-reactive, but treponemal test results continue to be positive.

IV. Tertiary syphilis: Characterized by the development of gummas, which are chronic granulomatous lesions that can affect multiple organs. Nontreponemal test titers may present as low or non-reactive, while treponemal test results remain positive.

### 8.2- What constitutes the recommended therapeutic strategy for each presumed stage of syphilis infection?

For cases of primary and secondary syphilis, the favored treatment approach involves a single intramuscular injection of benzathine penicillin G, administered at a dosage of 2.4 million units [16].

For patients with early latent, late latent, or tertiary syphilis, the recommended therapeutic regimen entails three successive intramuscular injections of benzathine penicillin G, each administered on a weekly basis [16].

It is imperative for healthcare professionals to account for the individual patient's medical history, potential drug allergies, and to refer to the most current syphilis treatment guidelines to ascertain the most suitable treatment plan [16].

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