

Syphilis in the Urgent Care Center

Urgent message: Seeking information beyond the stated history can prompt important information that informs the true diagnosis. This is especially true in patients with a complicated or potentially embarrassing history.

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Case Presentation

A 59-year-old female with a past medical history of type 2 diabetes and hypertension presents to an urgent care facility with complaints of abdominal pain. She is well known to the urgent care staff. She is consistently noncompliant with medical care. Her hypertension and diabetes are both uncontrolled. She has a right below-knee amputation and is wheelchair-bound. She has been flagged in the past for drug-seeking behavior, often requesting opiates or loperamide (Imodium). She was recently treated for a urinary tract infection. She has had multiple urinary tract infections over the course of the past year. On the initial examination, she does not endorse any additional complaints but does request pain medication for her chief complaint of abdominal pain.

Her physical exam reveals a rash on her right leg but was otherwise normal. Evaluation of the right inguinal area, right thigh, and labia majora demonstrate a well-circumscribed ulceration on the right labia majora, another ulceration in the right groin, and erythematous and inflamed skin on the medial right thigh. This prompts questions about her recent sexual history. She notes a recent isolated, unwanted sexual encounter with a man. She denied any other sexual encounters. She noted that the one sexual encounter she had was approximately one month prior to her presentation to the urgent care facility. She denied any drug or alcohol use. Lab testing came back positive for syphilis without any co-infections. She is treated with a single dose of IM benzathine penicillin G.

On subsequent follow-up, her repeat titers show resolution of the disease burden.

Introduction/Epidemiology

Syphilis is a sexually transmitted disease caused by the



Treponema pallidum bacterium, and poses serious health risks if not treated properly. It is transmitted through intimate contact, typically by direct contact with a syphilitic chancre through oral, vaginal, or anal sex. The occurrence has been steadily increasing across the U.S. over the past several years.

According to the Centers for Disease Control and Prevention, syphilis reached its nadir in 2015, increasing by 19% from 2014 and by 27% in women, regardless of sexual orientation.¹ The U.S. saw an increase in primary and secondary syphilis, from 7.4 cases per 100,000 people in 2015 to 8.7 cases per 100,000 people in 2016.² The Western region of the country reported the highest levels of

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primary and secondary syphilis, with 11.4 cases per 100,000 people.² Overall, this is the highest reported incidence of syphilis since historic lows in 2000 and 2001.

The age group most susceptible to infection is 20-24 (men and women, though men have a higher incidence of infection than women).² Of all men who contract syphilis, men who have sex with men comprise 83% of reported cases of primary and secondary syphilis.² There has been an increase in the number of early and late latent syphilis cases. The rate of early latent syphilis rose by 19.7% and late latent syphilis rose by 17.2%. This indicates more people overall are going untreated.²

Stages of Syphilis

Syphilis progresses through four stages: primary, secondary, latent, and tertiary. The progression of each stage can last for weeks or years at a time. The major characteristics of each stage are described here:

- **Primary:** The primary stage is marked by a chancre which is often unnoticed and heals regardless of treatment. It occurs at the sight of inoculation and can range in size from 0.3 mm to 3 cm. This ulcer is generally painless and often resolves without treatment. If the patient presents to an urgent care center with a painless ulcer in the genital area, the diagnosis becomes more straightforward; they should be tested and treated at that time. The incubation period can last from 3 to 90 days prior to the appearance of the chancre, but usually lasts 21 days.³ The disease transitions to the secondary stage as the initial ulceration heals.
- **Secondary:** During the secondary stage, a diffuse rash can develop. This stage of syphilis is often called “the great imitator” because it can easily be misdiagnosed as psoriasis, eczema, or a viral exanthem. The rash can be macular to maculopapular and occasionally pustular. A palmar rash is a distinctive feature of secondary syphilis. In untreated patients, the rash will heal after several weeks. Other symptoms include low-grade fever, headache, general malaise, sore throat, nausea, gen-

eralized lymphadenopathy, condyloma lata, alopecia, and occasional vomiting. These symptoms can easily be mistaken for other common illnesses.⁴

- **Latent:** The latent stage has no noticeable symptoms and can last for many years; 60%-85% of people will remain asymptomatic for years without any treatment.³ During the latent phase, the symptoms from the secondary stage disappear until treatment is received or the symptoms manifest into the tertiary stage. The latent stage lasts 1 to 2 years in most people, but may last longer.⁴
- **Tertiary:** The tertiary stage affects multiple organ systems and is often fatal if left untreated.⁵ Symptoms vary depending on the organ system affected. Cardiovascular syphilis often occurs 10-30 years after the initial infection and can cause aortic aneurysms and heart failure. The tertiary phase can also manifest as neurosyphilis where cerebrospinal fluid undergoes invasion by the *T pallidum* bacteria. Clinical findings may include headaches, confusion, stiff neck without fever, and ocular abnormalities including optic neuritis. As these symptoms progress, they are sometimes misdiagnosed as dementia or a psychiatric illness.⁴

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History and Examination

The history involves directed questions about sexual orientation, the most recent sexual encounter, alcohol use, and drug use. This is in addition to questions about the chief complaint (if unrelated) and associated symptoms. Patients at high risk for infection should be questioned about their sexual and social history at every urgent care visit. The provider needs to question the patient about prior syphilis infections if it is suspected and the patient will be getting tested for syphilis. Some laboratory tests will return positive results if the patient has ever had syphilis, even if they were treated appropriately. Accurate and honest histories play a vital role in capturing these patients because the disease burden isn’t always obvious.

The physical exam is directed to finding a painless chancre in patients with primary syphilis, a rash with secondary syphilis, and neurologic or cardiac symptoms with tertiary syphilis. Symptoms, like fever and malaise, may be indicators of secondary syphilis and should

prompt further questioning of the patient's sexual and social history.

When syphilis is suspected in the differential diagnosis, a thorough skin exam needs to be performed. Evaluation for a chancre should not be limited to the genitalia because chancres can arise in the mouth, around the anus, or within the vaginal canal (among other sites). The chancre simply develops at the site of inoculation. Multiple chancres may also be present, and should immediately prompt the provider to test for HIV co-infection.

Secondary syphilis most classically presents with a rash. However, 20% of patients with secondary syphilis may not even notice their symptoms.⁶ Again, a thorough skin exam is warranted in the evaluation of secondary syphilis. Because secondary syphilis can affect multiple organ systems, a full physical exam is warranted.

The evaluation for tertiary syphilis should include thorough neurologic and cardiac exams. Auscultation of the heart may reveal a murmur. General paresis or tabes dorsalis are two ways that neurosyphilis can present. The physical exam will include a detailed neurologic exam looking at pupillary response, sensation, motor function, gait, and reflexes.⁶

Laboratory Testing

If the history and physical examination do not reveal a definitive diagnosis, the fol-

lowing higher risk groups may be candidates for testing: men who have sex with men, patients with high-risk sexual activity, HIV-infected individuals, and patients with a sexual partner who tested positive for syphilis.⁶

Nontreponemal and direct treponemal testing are used to detect the presence of *T pallidum*. Typically, a combination of both types of tests is used in the diagnosis of syphilis. The nontreponemal tests include the RPR and VDRL tests. These measure the amount of antibodies (IgM and IgG) present in the serum to a cardiolipin-cholesterol-lecithin antigen and not directly to a treponemal protein.⁶ These tests are generally reported as titers (eg, 1:32, etc.).⁶ The sensitivity of the RPR test is 92.7% and the VDRL is 72.5%.⁶ Seroconversion typically occurs around 3 weeks, but can take up to 6 weeks,

which contributes to the false negative rate.⁷ The titers can also wane over time without treatment of syphilis.^{1,6} A decrease in the level of the titers is used to determine response to treatment (eg, from 1:64 to 1:8).

The treponemal tests have typically been used as a confirmatory test when the nontreponemal tests are positive.⁶ The available tests include the fluorescent treponemal antibody absorption test (FTA-ABS), microhemagglutination test for antibodies to *T pallidum* (MHA-TP), *T pallidum* particle agglutination assay (TPPA), *T pallidum* enzyme immunoassay (TP-EIA), and the chemiluminescence immunoassay (CIA).⁶ The tests detect antibodies to specific treponemal antigens.⁶ The FTA-ABS test is the most sensitive test in diagnosing primary syphilis, with a sensitivity of 98.2%. The TP-EIA

has nearly the same sensitivity for primary syphilis as the FTA-ABS and has become the favored test in labs.⁶ Using the treponemal tests as the initial screening modality is affected by the prevalence in the population. These tests have a good negative predictive value in the general population. However, in high-risk populations such as patients with HIV, the positive predictive value of the treponemal tests rises significantly. Lately, there has been a trend toward "reverse screening" where the treponemal tests are being used as the initial screening test for syphilis.^{6,7} This is a

result of these tests becoming more automated and easier to use. However, these tests are resultated as reactive or nonreactive and once positive will remain positive for life.⁶ The treponemal tests are qualitative, which still leaves a role for the nontreponemal tests in monitoring response to treatment.

There are also direct detection methods for syphilis and some point-of-care (POC) tests including PCR, direct fluorescent antibody testing, and dark field microscopy.⁷ Use of these tests is limited by their cost and complexity. The newer PCR technique may be viable in the future, but is not recommended as a screening test due to its lower sensitivity in blood and CSF samples compared with specimens collected from mucosal sites.⁶ POC testing is currently approved for use under an FDA waiver. The

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sensitivities of these POC tests are ranging from approximately 75% to 90%; the specificities range from 92% to 100%.⁶ There still needs to be further evaluation of the POC testing but, if approved, this could streamline testing in the urgent care.

After initial laboratory testing, providers should ensure appropriate follow-up for repeat serologic testing. If the initial serology is negative, but the suspicion remains high, empirically treat and repeat the serology 1 week after treatment.³ Ideally, patients with primary or secondary syphilis will be re-examined at 1 week to ensure symptom improvement and undergo repeat titers at 6 and 12 months. A fourfold decrease in titers is considered significant and should be seen between 6 and 12 months for HIV-negative patients and 12-24 months for HIV-positive patients.³

For HIV-positive patients, titers should also be repeated more frequently at 3, 6, 9, 12, and 24 months. HIV-negative patients with latent syphilis should have repeat titers at 6, 12, and 24 months, while HIV-positive patients with latent syphilis should get repeat titers at 6, 12, 18, and 24 months.³ Pregnant patients with syphilis should have titers at 28 and 32 weeks of gestation and at the delivery of the child; high-risk patients can even have monthly titers drawn.³ Most women will deliver before the appropriate serologic response can be detected.

Treatment

After diagnosing syphilis, benzathine penicillin G is given as a long-acting dose of 2.4 million units administered intramuscularly. This treatment will eradicate the bacteria while in the primary, secondary, or early latent stages. During the late latent or tertiary stages, the patient should receive benzathine penicillin G on a weekly basis for 3 weeks. The optimal interval between doses is 7-9 days, and the maximum allowable interval between doses of benzathine penicillin G is 14 days.³ While this treatment will cure the disease, it cannot reverse any previous damage.⁸ To date, there has been no reported resistance to penicillin, but there are cases of treatment failure.⁹ Cases of treatment failure likely stem from immunocompro-

mised states, treatment with alternative agents, and undiagnosed neurosyphilis.⁹ If the patient is found to have neurosyphilis, the treatment becomes IV penicillin G.³

Reported penicillin allergies are commonly encountered in urgent care centers. While 10% of the U.S. population reports a penicillin allergy, <1% of the population is truly allergic.¹⁰ Patients without a true penicillin allergy should be treated with benzathine penicillin G. Patients with a reported delayed hypersensitivity reaction (ie, rash) can be challenged with penicillin or sent for allergy skin testing.⁹ Lastly, patients with immediate hypersensitivity reactions should be treated with an alternative regimen or undergo desensitization therapy.⁹ For patients with an immediate hypersensitivity reaction and early syphilis, use doxycycline, ceftriaxone, or tetracycline for the initial treatment. However, data to support the use

of these alternatives are limited and patients need to be monitored closely for clinical response. If they fail treatment with one of the alternative medications, are pregnant, or have neurosyphilis and/or symptoms of cardiovascular syphilis they should be tested for penicillin allergy and desensitized if required.⁹

Penicillin is the only acceptable treatment for syphilis during pregnancy because the other medications are either contraindicated, don't cross the placenta, or lack efficacy data.¹¹ If the woman has a doc-

umented penicillin allergy, then desensitization therapy should be undertaken. Desensitization therapy entails treatment in an inpatient setting. Oral desensitization therapy is the preferred method as it is safer and simpler than IV desensitization therapy.¹¹ It typically takes 4 hours to complete, and most adverse reactions can be managed without discontinuing the treatment.¹¹

Another reason to make quick and accurate diagnoses of syphilis is that, if left untreated, it can be transmitted from pregnant mother to fetus in the form of congenital syphilis. Congenital syphilis can be transmitted during intrauterine development or at the time of birth.^{11, 12} Symptoms include fever, failure to thrive, and diffuse rash. More serious complications include blindness, deafness, and facial deformities. Treatment for congenital syphilis is also benzathine penicillin G and can be given

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to the mother before birth and to the infant after birth. Treatment before birth decreases the chances of a stillbirth; however, it is not a guaranteed cure.¹³

The Jarisch-Herxheimer reaction is an acute febrile reaction that usually occurs in the first 2–8 hours after the administration of benzathine penicillin G, but can occur up to 24 hours later; it can include symptoms of headache, myalgias, and rash and is most commonly seen in primary and secondary syphilis.³ The provider should not confuse this with a penicillin allergy. If systemic symptoms are present in addition to a rash, the Jarisch-Herxheimer reaction should be considered the more likely diagnosis over a penicillin allergy.

While penicillin is affordable through most insurance companies, due to the current national shortage, the price for patients without insurance can be high. It should also be taken into consideration that in late stages, at least three intramuscular injections are generally required for adequate treatment. This may not always be the most practical option for the patient in an urgent care setting, so appropriate follow-up must be stressed to the patient, and the provider should make every attempt to ensure follow-up. The way arrangements are made will of course vary depending on the site. Providers should ensure the first follow-up is scheduled in 7 days from the initial treatment.

Ideally, follow-up should occur with the patient's primary care physician. However, it can also take place at the same urgent care facility in which they were originally seen, at local STI clinics, if available, or anywhere else that ultimately gives the best chance for follow-up and completing the treatment course.

Conclusion

Although recognition of syphilis can be complicated depending on when the patient presents, diagnostic testing and treatment are fairly simple. Providers in the urgent care setting should be direct in their questioning with patients and aware that syphilis is becoming a more

prevalent sexually transmitted disease. As was seen in the initial case presentation, the patient may not be coming in because of their chancre or rash. Patients may not even realize that they have a chancre or rash characteristic of primary or secondary syphilis. Providers should be aware of the prevalence of this disease in the area they work and know what high-risk groups require further investigation in an effort to capture and treat all patients that present with this infection. Careful consideration should also be given to the course of treatment that will be best for the patient when considering medication availability, cost, and follow-up. With cases of syphilis continuing to increase, providers in primary care clinics, urgent care clinics, and emergency departments need to be thorough and effective in their attempts to diagnose and treat the reemergence of this disease. ■

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