

Perspective

The Great Imitator Revealed: Syphilis

Rates of syphilis and other sexually transmitted infections are on the rise in the United States. The lesions of early syphilis can be mistaken for those of other infections and conditions, and syphilis should be suspected in all sexually active patients presenting with a new skin rash or an oral or genital lesion. Rapid diagnosis and treatment of syphilis as well as rapid identification and treatment of sexual contacts are needed to reverse the trend of increasing incidence. Available data indicate success in reducing acquisition of syphilis with doxycycline pre- and postexposure prophylaxis. This article is based on a presentation by Jeffrey D. Klausner, MD, MPH, at the 2018 Clinical Conference at the National Ryan White Conference on HIV Care & Treatment in December 2018.

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Epidemiology

Rates of sexually transmitted infections (STIs) are increasing dramatically in the United States, including among newborns. As shown in Figure 1, rates of primary and secondary syphilis in the United States are the highest since 1994, a reversal of the dramatic decline observed with the emergence of HIV infection and resultant changes in many individuals' sexual behaviors.¹ The recent increase in syphilis rates is likely multifactorial, including increases in high-risk sexual behaviors, decreased fear of HIV infection, substantial declines in condom use among adults and adolescents, and a marked decline in public health prevention services. Many counties and jurisdictions no longer have sufficient staff or resources to perform follow-up of individuals with syphilis and their sexual contacts, to support prevention and education campaigns, or to promote syphilis testing in target populations.

Figure 2A shows the incidence of primary and secondary cases of syphilis (acquired in the past 6 months) in 37 states between 2013 and 2017. Cases of syphilis nearly doubled among men who have sex with men (MSM), and increased among women and among men who have sex with women. The increase in cases of syphilis among women translated into an increase in

babies born with congenital syphilis over the same period. Some of that increase is associated with the loss of local public health capacity. Although health care practitioners may be testing individuals for syphilis, positive test results are not being acted on in the same manner as in the past by local public health departments. Patients may not be coming back for treatment and sexual contacts are not being sought for testing and treatment.

Primary Syphilis

When a patient presents with a new oral or anogenital lesion, there must be suspicion for STIs such as primary syphilis, genital herpes, and chancroid, although the latter is rare in the United States. Other potential causes of genital ulcers include fixed drug eruptions (eg, reactions to drugs, such as doxycycline or nonsteroidal anti-inflammatory drugs), staphylococcal or streptococcal

infections, some autoimmune conditions, trauma, and malignancy.

When dark-field microscopy examination of a syphilis lesion reveals undulating treponemes (*Treponema pallidum* organisms, the cause of syphilis), a diagnosis of primary syphilis is likely. Figure 3 shows examples of clinical lesions positive for syphilis using dark-field microscopy that could be mistaken for genital herpes or chancroid. For uncircumcised individuals, it is important to roll back the foreskin and examine the coronal sulcus.

According to Centers for Disease Control and Prevention (CDC) STD treatment guidelines, early syphilis of less than 1-year duration (ie, primary, secondary, or early latent syphilis) should be treated with a single intramuscular (IM) injection of benzathine penicillin G 2.4 MU, regardless of HIV serostatus. However, 3 injections of benzathine penicillin G 2.4 MU are recommended for individuals who have had syphilis for more than 1 year. The efficacy of single-dose benzathine penicillin G for treatment of syphilis was reconfirmed in a study in Tanzania (more than half of participants had HIV infection), in which the proportion cured was 95% at 9 months.²

Any sexual contacts who may have been exposed within the past 90 days should receive prophylactic treatment with a single injection of benzathine penicillin G 2.4 MU. Medical practitioners should make a reasonable effort to notify all sexual contacts exposed

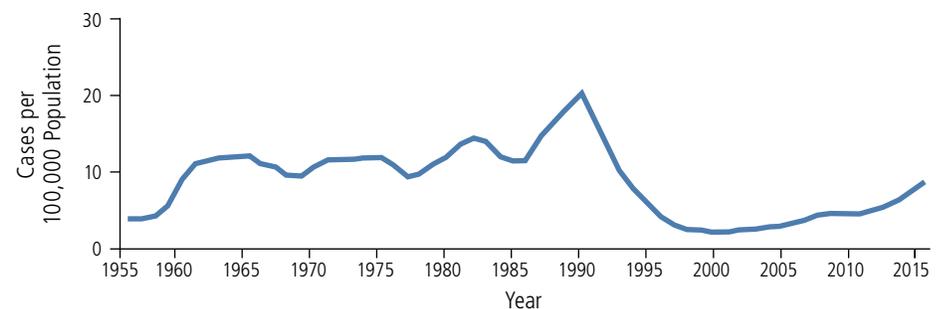


Figure 1. New cases of primary and secondary syphilis in the United States, 1956 to 2016. Adapted from Kojima et al.¹

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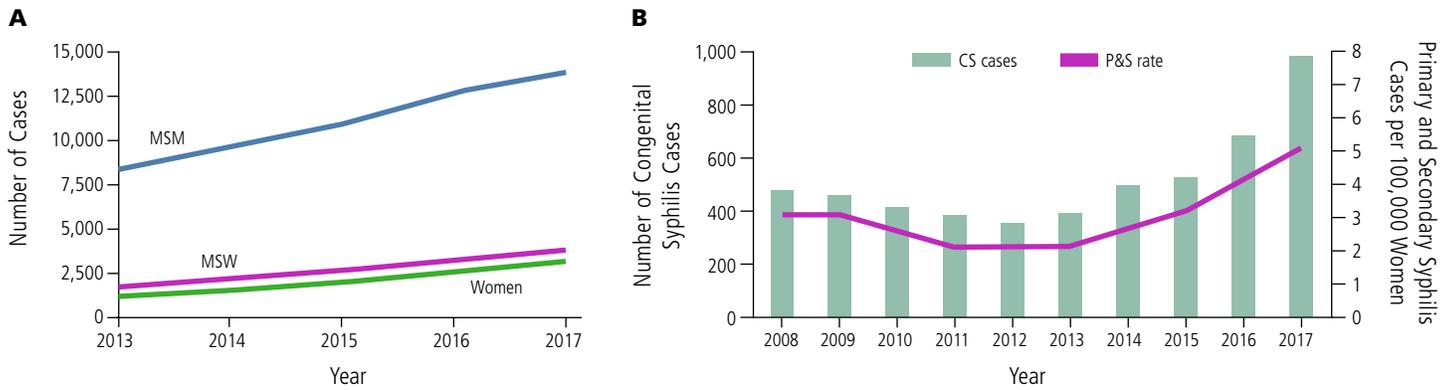


Figure 2. A: Cases of primary and secondary (P&S) syphilis in 37 states, 2013 to 2017. Of note, 37 states were able to classify 70% or more of reported cases of P&S syphilis as either men who have sex with men (MSM), men who have sex with women only (MSW), or women for each year between 2013 and 2017. **B:** Cases of P&S syphilis among women aged 15 to 44 years and cases of congenital syphilis (CS) in the United States, 2008 to 2017. Adapted from the US Centers for Disease Control 2017 Sexually Transmitted Disease Surveillance Report.

in the past 90 days. Although health departments have often performed such notifications in the past, some of them have been defunded or lost staff, and do not have the same resources they had 10 or 20 years ago.

Secondary Syphilis

Figure 4 shows a rash associated with secondary syphilis on the chest and back that consists of nonspecific maculopapular lesions. In addition to secondary syphilis, the differential diagnosis of such a trunk rash includes viral exanthem, including acute HIV infection; pityriasis rosea; drug eruption; lichen planus; psoriasis; and sarcoidosis. Examination of the palms and soles in Figure 4 shows classic erythematous, somewhat copper-colored lesions. Presence of a palmar-plantar rash is indicative of secondary syphilis. Other, rarer causes include erythema multiforme or Rocky Mountain spotted fever.

Oral and other secondary lesions in syphilis are shown in Figure 5, including split papules, “moth-eaten” alopecia, mucous patches, and condyloma lata. The split papule presentation can be mistaken for oral herpes labialis. The white plaque lesions can be mistaken for thrush or oral hairy leukoplakia.

Latent Syphilis

Latent syphilis presents with no signs, symptoms, or sores. It is possible—and

strongly recommended—to contact the county or state public health department and check if a patient with suspected latent syphilis is entered in the syphilis reactor registry, which may contain details of any prior reports on the patient.

According to CDC guidelines, the recommended treatment for latent syphilis of unknown duration is a weekly IM injection of benzathine penicillin G 2.4 MU for 3 weeks. Sexual contacts within the prior 90 days should be found and treated with prophylactic benzathine penicillin G, and contacts within the past 12 months should be notified and tested.

Given the absence of signs and symptoms in latent syphilis, diagnosis depends on syphilis testing. Nontreponemal tests, such as the rapid plasma reagin (RPR) and Venereal Disease Research Laboratory tests, detect antibody to cardiolipin, with levels rising and falling with infection and treatment over time. A 4-fold change in titer (1:2 to 1:8 or 1:64 to 1:16) is significant. Those tests have a specificity of 98%, with false-positive results seen in injection drug users, some autoimmune conditions, viral infections and in cases of recent vaccination.⁴

Treponemal tests are more specific, including the *T. pallidum* particle agglutination assay, fluorescent treponemal antibody absorption test, *T. pallidum* enzyme immunoassay (TP EIA), and rapid treponemal test, each of which detects antibody to treponemal antigen.

The rapid TP test is a 10-minute point-of-care assay that can be used in the clinic. It is more sensitive than and becomes positive earlier than an RPR test. Positive treponemal test results indicate past or current infection. Treponemal antibodies may remain detectable for life, although about 15% of people might actually become seronegative if treated early. In practice, it is prudent to order both a nontreponemal test and a treponemal test to ensure the best likelihood of obtaining serologic confirmation.

Neurosyphilis

Indications for analysis of cerebrospinal fluid (CSF) in CDC treatment guidelines include neurologic findings (including auditory findings); ocular abnormalities (including visual loss, uveitis); tertiary disease (eg, dementia, aortic disease, gumma); and treatment failure (lack of 4-fold decline at 6 [early], 12 [late or HIV-infected early], or 24 [HIV-infected late] months). The CSF can serve as a sanctuary for untreated infection. Neurosyphilis in early disease can cause meningovascular syndrome and stroke. The most common presentations of neurosyphilis are the different manifestations of ocular syphilis, with the primary complaint of red eye, blurry vision or decreased visual acuity followed by hearing loss. CSF analysis helps rule out other conditions and provides a baseline for following CSF titers to determine if there is improvement during treatment. Unfortunately,

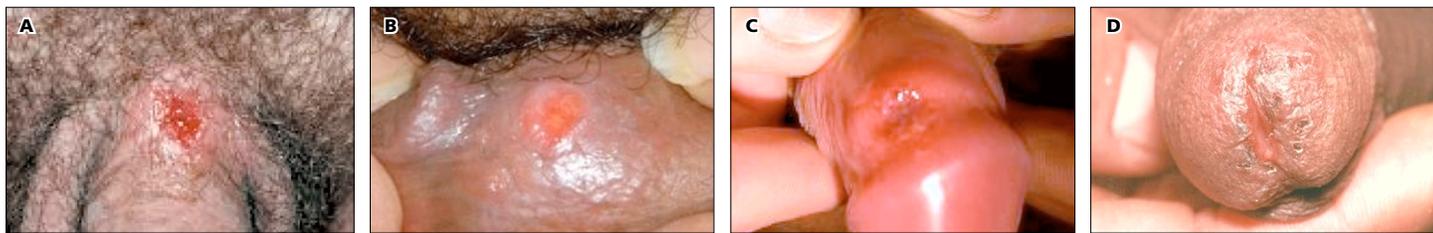


Figure 3. Images of primary syphilis penile chancres that could be mistaken for genital herpes or chancroid. Images A, C, and D courtesy of Joseph Engelman, MD; San Francisco Department of Health.

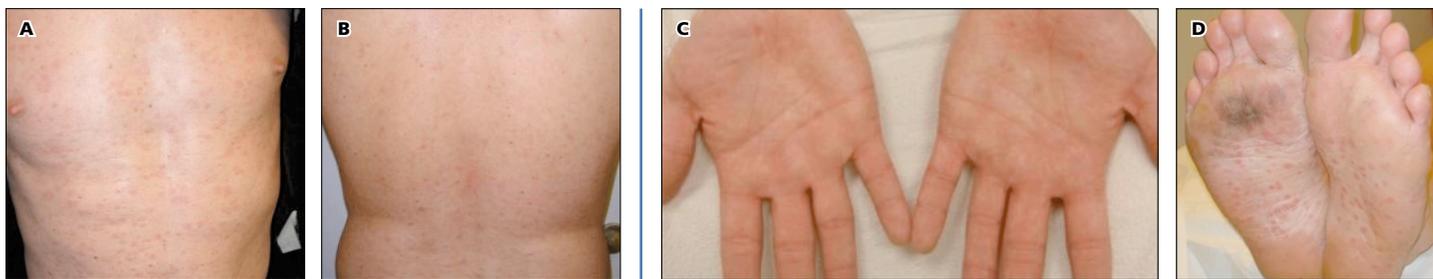


Figure 4. Left: Rash on the chest and back consisting of nonspecific maculopapular lesions in a patient with secondary syphilis. Right: Erythematous lesions on palms and soles of the same patient are highly characteristic of secondary syphilis. Image A courtesy of Joseph Engelman, MD; San Francisco Department of Health.



Figure 5. Oral and other manifestations of secondary syphilis. **A** shows a split papule; **B**, mucous patch; **C**, condyloma lata; **D**, mucous patch; **E**, moth-eaten alopecia. Images courtesy of Joseph Engelman, MD; San Francisco Department of Health (A, D) and the US Centers for Disease Control and Prevention (B, C, E).¹⁰



Figure 6. Syphilis in a patient with HIV infection manifesting as numerous herpesvirus-like chancres. Image courtesy of Joseph Engelman, MD; San Francisco Department of Health.

approximately 25% to 30% of individuals with hearing loss or ocular abnormalities and vision loss have some persis-

tent deficits after treatment. Thus, it is important to remember that although syphilis is curable, it can have serious consequences.

The recommended treatment for neurosyphilis is 14 days of intravenous penicillin G 18 to 24 MU followed by IM benzathine penicillin G 2.4 MU on day 14.

Syphilis and HIV Infection

Unique features of syphilis in the context of HIV infection have been observed. Patients may present with numerous chancres that resemble herpesvirus infection (Figure 6). Patients may also present with overlapping primary and secondary manifestations (eg, chancre with rash, adenopathy, or fever).

Serology results are rarely abnormal in individuals with HIV infection with syphilis. However, in a few cases titers may decline more slowly, and it is unknown whether this is associated with HIV infection, other immune suppression, or prior history of syphilis. Because of the potential slower decline in reactivity, outcome timelines for treatment success (ie, a 4-fold decline in RPR titer) are somewhat extended. In patients with HIV infection, treatment success is determined at 12 months for early syphilis and 24 months for late syphilis. Individuals with HIV infection have increased risk of early neurosyphilis. Approximately 2% to 3% of individuals with HIV infection who contract syphilis may have some neurologic involvement within the first 6 months of infection.

Table 1. US Centers for Disease Control and Prevention Screening Recommendations for Syphilis.

Pregnancy
<ul style="list-style-type: none"> • First visit • Repeat at 28 to 32 weeks in high-prevalence areas
Men who have sex with men
<ul style="list-style-type: none"> • Every year • More frequently (every 3 months) if <ul style="list-style-type: none"> - Have more than 1 sex partner in the past 12 months - Meet sex partners online or in sex venues - Have sex in conjunction with illicit drug use (especially methamphetamine) - Have sex partners who participate in any of the above activities

Adapted from the 2015 Sexually Transmitted Diseases Treatment Guidelines.⁶

Further, syphilis can increase HIV viral load and reduce CD4+ cell counts in individuals with HIV infection.⁵ Such findings have been made in persons with HIV infection with fully suppressed virus, as well as in those not receiving antiretroviral therapy.

Prevention

Syphilis prevention efforts are needed at the individual and population levels. At the individual level, there is need to reduce exposure (eg, by reducing number of sex partners), to reduce risk of infection after exposure (eg, by treating sexual contacts prophylactically), and to reduce sequelae of infection (eg, by treating infection early in order to reduce long-term sequelae). At the population level, the objective is to reduce the basic reproduction number—the number of new infections caused by a single case. Early case identification and timely treatment reduce the duration of infection, an essential intervention to decrease the basic reproduction number.

The 2015 CDC recommendations for screening for syphilis are shown in Table 1. It is recommended that pregnant women in areas with a high prevalence of syphilis have repeat testing during their third trimester. For MSM, screening is recommended at least every year and more frequently in those with such risk factors as numerous sexual contacts and sex in conjunction with illicit drug use. In the clinic setting, including syphilis testing in every blood test is an optimal screening ap-

proach. In those with a prior positive treponemal test result, repeat screening for infection should be with a non-treponemal test (ie, RPR), since a positive treponemal test result indicates past infection. Public programs in San Francisco, California in the early 2000s designed to increase awareness of syphilis risk and the need for frequent testing successfully increased testing rates. In a study in Australia, more frequent testing led to a reduction in incidence in secondary syphilis between 2007 and 2014.⁷

There is evidence that chemoprophylaxis is effective in reducing syphilis acquisition in MSM. In a pilot study in Los Angeles, California, use of doxycycline 100 mg daily resulted in a 73% reduction in the acquisition of syphilis over a 1-year period.⁸ In a study of postexposure prophylaxis in France, use of doxycycline 200 mg once after sex also resulted in a 73% reduction in risk of syphilis acquisition over 1 year.⁹ Trials are ongoing that may provide additional evidence of the efficacy and safety of syphilis prophylaxis.

Summary

The most important elements in effective management of syphilis are frequent screening, treating patients with syphilis quickly, identifying and treating sexual contacts, and rescreening. Prevention at the population level is highly effective but must be adequately funded. Doxycycline for syphilis prophylaxis is a highly promising prevention approach. 

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References

1. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. *Curr Epidemiol Rep*. 2018;5(1):24-38.
2. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med*. 2005;353(12):1236-1244.
3. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2017 - Syphilis. <https://www.cdc.gov/std/stats17/syphilis.htm>. Accessed on January 31, 2019.
4. Klausner JD. *Current Diagnosis and Treatment of Sexually Transmitted Diseases*. 1 ed. McGraw-Hill Education/Medical, 2007.
5. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18(15):2075-2079.
6. Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. <https://www.cdc.gov/std/tg2015/default.htm>. Accessed on February 1, 2019.
7. Chow EPF, Callander D, Fairley CK, et al. Increased syphilis testing of men who have sex with men: greater detection of asymptomatic early syphilis and relative reduction in secondary syphilis. *Clin Infect Dis*. 2017;65(3):389-395.
8. Bolan RK, Beymer MR, Weiss RE, et al. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. 2015;42(2):98-103.
9. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis*. 2018;18(3):308-317.
10. US Centers for Disease Control and Prevention. STD Picture Cards. <https://www.cdc.gov/std/training/picturecards.htm>. Accessed on April 12, 2019.

Top Antivir Med. 2019;27(2):71-74.

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