Infectious Syphilis: The Return of the Great Imitator To Rhode Island

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SINCE 2010, RHODE ISLAND HAS SEEN A precipitous increase in the number of cases of infectious syphilis, particularly among HIV+ **men who have sex with men (MSM)**. As clinicians, we are charged with recognizing the protean manifestations of this ancient disease, often called "the Great Imitator," a task made difficult by the low prevalence of syphilis during our training and practice. Entire textbooks have been devoted to the topic of syphilis; this article is designed as a clinical primer on infectious syphilis for the practicing clinician in primary care, emergency medicine, dermatology, neurology, hepatology, and nephrology. In order to contribute to public health efforts to reduce the spread of syphilis (see accompanying article "Interrupting Transmission of HIV and Other Sexually Transmitted Infections in Rhode Island"), emphasis is placed on the diagnosis of infectious syphilis (primary, secondary and early latent) in adults.

ETIOLOGY

Syphilis is caused by *Treponema pallidum,* a slender, tightly coiled bacterium that cannot be cultivated in vitro. The genome of *T. pallidum* lacks apparent transposable elements, suggesting that the genome is extremely conserved and stable. This is the likely explanation of why *T. pallidum* has remained exquisitely sensitive to penicillin for more than 70 years and that there are few differences in DNA sequences among subspecies.[1]

HISTORY & EPIDEMIOLOGY

Syphilis has a long and storied past. Historians have speculated that Columbus brought syphilis back to Europe from the New World, perhaps leading to the "Great Pox" epidemic in Europe and Asia. In the United States, syphilis cases reached a peak during World War II, and declined steadily with the use of serologic testing and penicillin therapy until the late 1980s and early 1990s, when an increase in cases in heterosexual women and neonates was linked to exchange of sex for drugs, particularly crack cocaine.[2] After declining once again by 2000, a more recent rise in cases has been noted in men who have sex with men. In Rhode Island, the number of infectious syphilis cases per year rose from 25 in 2008 to 61 in 2010. In 2010, 93% of cases were in MSM and half of those were HIV-infected. Factors associated with syphilis infection included engagement in anonymous sex and finding sexual partners on the internet.[3] This epidemiology necessitates all physicians to complete a comprehensive assessment of sexual practices, and testing for HIV infection and other sexually transmitted diseases.[4]

Syphilis can be acquired by sexual contact, transplacental transfer, kissing or other close contact with an active lesion, transfusion of contaminated fresh human blood, or accidental direct inoculation (needlestick).[1]

CLINICAL MANIFESTATIONS

Primary Syphilis

The classic syphilitic chancre occurs at the site of inoculation of the spirochete, and may be seen as single or multiple genital, perianal, or oral lesions.[5] The chancre is characteristically indurated with a rolled edge and clean base, painless, and accompanied by regional lymphadenopathy. Lesions may be inapparent to the patient. The median incubation period before appearance of the chancre is 21 days, with a range from three to 90 days after acquisition.[6] Syphilitic chancres are not reliably diagnosed by any serologic test and, given the lack of ready availability of dark-field microscopy, these must be diagnosed clinically and managed presumptively (treatment, reporting, follow-up and partner management).[5]

Secondary Syphilis

The clinical presentation of secondary syphilis is protean, as one would expect from the wide dissemination of treponemes throughout the body during the spirochetemia of early infection. (Table 1) The presentation most easily remembered from medical school is a rash with the classic "palms and soles" distribution. (Figure 1)

Table 1. Multi-organ system manifestations of Secondary Syphilis (modified from Mandell PPID)[1]

| Skin		
Generalized rash	•	begins on the trunk, typically non-pruritic
	•	macules then papules, may be scaly, rarely pustular
	•	classically involves palms & soles
Condylomata lata	•	highly infectious
	•	painless, broad, moist, gray-white to erythematous plaques
	•	occur in warm, moist areas
Mucous patches	•	highly infectious
	•	silvery gray, superficial erosion with a red periphery
	•	occur on oral, genital, anal mucous membranes
Constitutional symptoms	•	low-grade fever, malaise, pharyngitis, laryngitis, anorexia, weight loss, arthralgias
Lymphadenopathy	•	generalized painless lymphadenopathy
	•	enlargement of the epitrochlear lymph nodes is a unique finding that should always suggest the diagnosis of syphilis
Neurologic	•	CNS involvement in up to 40% of patients.
	•	Headache and meningismus are common
Ocular syphilis	•	Anterior or posterior uveitis or panuveitis, episcleritis, vitreitis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment
	•	differential diagnosis includes tuberculosis, rheumatoid arthritis, sarcoidosis, toxoplasmosis, histoplasmosis, and ocular *Toxocara canis* infections.
Otic syphilis	•	sudden or progressive sensorineural hearing loss, tinnitus, vertigo, and dysequilibrium
Hepatic	•	high serum alkaline phosphatase level, a normal or moderately elevated serum bilirubin concentration
Kidney	•	immune complex glomerulonephritis, with subepithelial electron-dense deposits
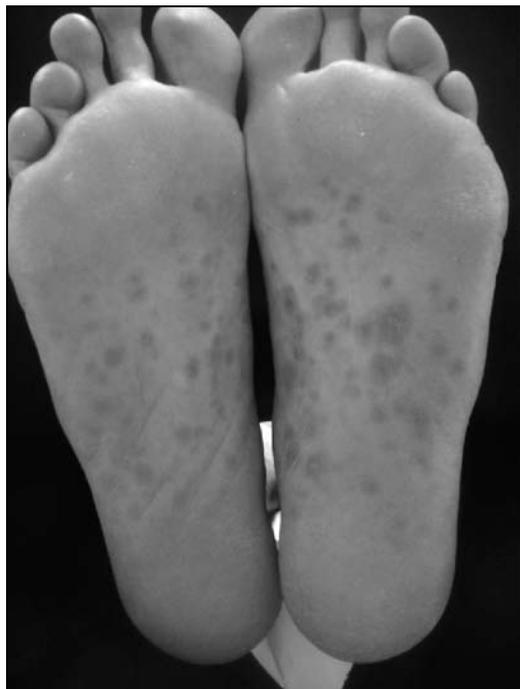
Figure 1. Lesions of secondary syphilis on the soles of the feet.

Patients may ascribe the rash to another etiology, and, though classically non-pruritic, they may present with the common "generalized pruritic rash" to their primary care provider. (Figure 2) The lesions typically begin as three to ten mm macules, symmetrically distributed first on the trunk and upper extremities, that may progress to papules, and less commonly, to pustules.[1] A fine scaly appearance is seen in papulosquamous rashes. The lesions on the palms and soles are typically reddish brown, flat or with a scaly appearance. A patchy alopecia or loss of eyebrows and beard may occur.[1,7] These skin lesions are not infectious to intact skin, though the use of gloves is recommended when examining any potentially infectious rash. Vesicular lesions occur only in congenital syphilis.[1]

Two highly infectious skin lesions are condylomata lata and mucous patches. **Condylomata lata** occur on warm, moist, intertriginous areas (perianal area, vulva, scrotum, inner aspects of the thighs, skin under pendulous breasts, nasolabial folds, cleft of the chin, axillary and antecubital folds, webs of the fingers and toes) as painless, broad, moist, grey-white to erythematous plaques.[1] Mucous membrane lesions, termed **mucous patches**, are silvery gray, superficial erosion with a red periphery, and may occur on lips, mouth, pharynx, tonsils, vulva, vagina, glans penis, inner prepuce, cervix, and anal canal.[1]

Constitutional symptoms may be prominent (or the presenting complaint), including fever, malaise, pharyngitis, anorexia, weight loss, and arthralgias. Generalized lymphadenopathy (particularly epitrochlear), hepatitis, and glomerulonephritis may accompany other manifestations. Seeding of the central nervous system may occur at any stage of syphilis, and early neurologic disease (syphilitic aseptic meningitis, ocular and otic syphilis) may occur.[1] Acute HIV infection is in the differential diagnosis of secondary syphilis, both due to overlapping clinical presentation and shared modes of transmission, and all patients diagnosed with syphilis should have HIV testing performed.

Early Latent Syphilis

Latent syphilis is by definition seroreactivity without other evidence of disease. Early Latent syphilis is defined as 1) documented seroconversion or fourfold rise in titer in the past year, or 2) unequivocal symptoms of primary or secondary syphilis (now resolved), or 3) a sex partner documented to have primary, secondary, or early latent syphilis.[6] Late Latent syphilis is defined as asymptomatic seroreactivity in the absence of these conditions. Early latent syphilis is considered "early" or "infectious" syphilis and treatment recommendations are identical to primary and secondary syphilis.

To LP or not to LP?

A common clinical dilemma is whether to perform an LP on a patient presenting with early syphilis.[8] This is particularly true for HIV-infected patients, in whom an increased likelihood of progression to symptomatic neurosyphilis has been described.[9] In HIV+ individuals, clinical and CSF abnormalities consistent with neurosyphilis are associated with an RPR titer > 1:32 and/or a CD4 cell count < 350 cells/μL.[11-13] However, no studies have demonstrated a change in clinical outcome if a lumbar puncture is performed and neurosyphilis is documented and treated.[8,14] Therefore, CDC does not recommend CSF examination in HIV-infected or -uninfected patients who lack neurologic signs or symptoms suggestive of neurosyphilis.[6] In clinical practice, therefore, a detailed history and physical examination to detect symptomatic neurosyphilis must be performed in all patients diagnosed with syphilis. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis), an evaluation that includes CSF analysis, ocular slit-lamp ophthalmologic examination, and otologic examination should be performed. Treatment should be guided by the results of this evaluation.[6]

Laboratory Diagnosis

The serologic diagnosis of syphilis relies on the use of non-treponemal (RPR, VDRL) and treponemal tests (FTA-ABS, EIA). In Rhode Island, an RPR/VDRL screening test can be performed rapidly in the clinical laboratory. All samples testing positive by the non-treponemal RPR/VDRL assay are confirmed by the treponemal FTA-ABS test.

The RPR/VDRL tests are subject to a false-negative "prozone effect," due to high antibody titers, particularly in secondary syphilis. In cases where syphilis is highly suspected, the lab should be asked to repeat

Figure 2. Diffuse macules and papules of secondary syphilis on the upper arm

the test using higher dilutions of serum. False positive RPR/VDRL tests may occur in collagen vascular disease, pregnancy, intravenous drug use, advanced malignancy, tuberculosis, malaria, viral and rickettsial diseases, and advanced age. A false positive FTA may result from cross-reactivity with other spirochetes, such as *Borrelia burgdorferi*, the etiologic agent of Lyme Disease.[1]

New rapid treponemal tests, such as the Syphilis EIA or chemiluminescence immunoassay, have been utilized to accomplish low-cost, automated, high-volume syphilis screening. If the rapid treponemal test is positive, an RPR/VDRL with titer must be performed to distinguish active from past infection.[15]

The laboratory diagnosis of neurosyphilis is made difficult by the lack of a standard definition.[8] A positive CSF VDRL, in the absence of substantial contamination of CSF with blood, is considered diagnostic of neurosyphilis.[16] However, this test is relatively insensitive, thus a negative CSF VDRL does not rule out neurosyphilis (i.e., helpful only if positive). Other diagnostic criteria include CSF pleocytosis (> 5 cells/mm³ in HIV uninfected, >10-20 cells/mm³ in HIV-infected) and elevated CSF protein.[17,18] In HIV patients who are not on antiretroviral therapy, these abnormalities are common, making it difficult to ascribe CSF abnormalities to neurosyphilis in the absence of a positive CSF VDRL.[14,17] The CSF FTA-ABS is highly sensitive but not specific, thus, if negative, neurosyphilis is highly unlikely (i.e., helpful only if negative).[6,14,19]

LABORATORY TESTING FOR OTHER STDS

Syphilis, HIV, gonorrhea and chlamydia are transmitted person-to-person by similar sexual practices.[20,21] Individuals testing positive for syphilis, therefore, should be screened for other STDs. Testing should target areas of exposure, i.e., urine gonorrhea and chlamydia (all patients), rectal gonorrhea and chlamydia (anal receptive patients), pharyngeal gonorrhea (oral receptive patients), vaginal trichomonas and bacterial vaginosis/cervical gonorrhea and chlamydia (vaginal receptive women). Patients may state they "always practice safe sex" but on specific questioning, may admit to unprotected oral sex; while this is less risky for transmission of HIV infection, the localization of syphilis organisms on external genitalia during primary and secondary syphilis provides ample opportunity for transmission during oral sex. This underscores the need to look for the lesions of primary syphilis in and around the mouth. Patients testing negative for HIV on this initial evaluation should be considered for re-testing in three months.

TREATMENT OF EARLY (INFECTIOUS) SYPHILIS

Early or Infectious syphilis includes primary syphilis, secondary syphilis and early latent syphilis, all of which are treated with the same regimen of one injection of Benzathine Penicillin G 2.4 MU intramuscularly. (Table 2) The CDC and RI Department of Health strongly recommend that clinicians always use Benzathine Penicillin whenever possible. In practice, this may require some investigation into the details of reported penicillin allergy and mandates penicillin desensitization for pregnant women and patients diagnosed with neurosyphilis. Alternative regimens for treatment of early syphilis in patients with a history of severe penicillin allergy are: Doxycyline 100 mg po BID x 14 days; Ceftriaxone 1 g IM or IV QD x 10-14 days; Azithromycin 2 g po x 1. All of these regimens have reduced efficacy, increasing resistance and/or a paucity of supporting clinical data, and should only be used when patients are unable to be treated with penicillin. HIV-negative patients should have follow-up RPR titers at six and twelve months post-treatment. HIV-infected persons should have clinical and serologic follow-up at three, six, nine, 12, and 24 months post-treatment.[6]

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that usually occur within the first 24 hours after the initiation of any therapy for syphilis. It occurs most frequently among patients who have secondary syphilis, due to high bacterial burden. Patients should be informed about this possible adverse reaction. Many clinicians pre-treat with 1 g acetominophen two hours prior to IM PCN, although this is not proven to prevent Jarisch-Herxheimer reaction.

Treatment of Exposed Partners

The CDC 2010 STD guidelines recommend that persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be **treated presumptively**. Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated

Table 2. Therapy for Early or Infectious Syphilis (Primary, Secondary and Early Latent)

Recommended:
• IM Benzathine Penicillin G 2.4 MU x 1
For Penicillin-allergic patients[1]
• Doxycycline 100 mg po BID x 14 days
• Ceftriaxone 1 g IM or IV QD x 10-14 days [2]
• Azithromycin 2 g orally x 1[3]

1. Patients receiving non-penicillin regimens must have close clinical & serologic follow-up.
2. Little clinical support. Optimal dose & duration not defined. Treatment failures documented.
3. Do not use in pregnant women or MSM. Chromosomal mutations conferring resistance documented.

Table 3. Take Home Points

Take Home Points
- syphilis is in the differential of many common clinical syndromes
- always test for other STDs – HIV, gonorrhea, chlamydia
- rule out symptomatic neurosyphilis by careful H&P in all stages of syphilis
- in the absence of signs or sx of neurosyphilis, CSF exam does not change clinical outcome
- always obtain day of treatment RPR titer
- sexual contacts should be empirically treated or tested twice (initially and in 3 months)

presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.[6]

Reporting and follow-up

All stages of syphilis are reportable diseases in RI, and laboratories report positive results directly to the RI Department of Health. Physicians are required to complete the RIDOH STD case report form (http://www.health.ri.gov/forms/reporting/cases/SexuallyTransmittedDiseases.pdf), and Disease Intervention Specialists from the RI Dept of Health will interview index cases. Many index cases will decline to give names of sexual contacts, preferring to notify their contacts to be tested by their own physician. Importantly, RPR testing may be negative in incubating or early syphilis, therefore, contacts testing negative initially must be re-tested three months after their last exposure. Preferably, however, CDC recommends empiric therapy of all recent contacts, as noted above. Counseling Syphilis Fact Sheets for patients and contacts are available on the CDC website.[22]

TREATMENT FAILURE OR REINFECTION

Signs or symptoms that persist or recur may suggest treatment failure or reinfection. The serologic definition of failure/reinfection is a sustained fourfold increase in RPR titer compared to the maximum or day of treatment titer. For this reason, it is imperative that a day of treatment titer be drawn, in addition to the initial blood draw that made the diagnosis. For treatment failure or reinfection, HIV testing should be repeated, and an evaluation for neurosyphilis, including lumbar puncture, should be performed.

The quantitative RPR/VDRL test should become nonreactive one year after successful therapy in primary syphilis and two years after successful therapy in secondary syphilis; most patients with late syphilis will be nonreactive by the fifth year after successful therapy.[23] The RPR titer may fail to decline fourfold by one year post-treatment in 15-20% of patients. For these patients, CDC recommends repeat HIV testing, close clinical and serologic follow-up, and consideration of lumbar puncture to rule out inadequately treated neurosyphilis. If conversion to negative does not occur, and active syphilis is ruled out, the test result is said to be be "serofast." It is unknown whether a serofast high titer has different clinical implication from a low titer.[8]

CONCLUSIONS

Rising rates of infectious syphilis in Rhode Island, particularly among men who have sex with men, compels all physicians to be aware of the varied manifestation of this disease, and the management of the infected patient and contacts. Physicians must be mindful of the superiority of benzathine penicillin as the drug of choice for infectious syphilis, and the need for careful evaluation and follow-up for coexisting sexually acquired diseases.

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Discussion of Off-Label Usage

Ceftriaxone, Azithromycin

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