CHAPTER 43

Syphilis

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Syphilis results from infection with the spirochete *Treponema pallidum*. Transmission of syphilis occurs most often through sexual contact. Mother-to-infant transmission also occurs, and infection via blood transfusion is possible. Although *T. pallidum* induces strong humoral and cell-mediated immune responses, untreated infections can persist for decades.

EPIDEMIOLOGY

Syphilis is transmitted only through human-to-human contact; there is no animal or environmental reservoir. The World Health Organization (WHO) estimated that 10.6 million new cases of syphilis occurred among adults worldwide in 2008. Although the infection has a global distribution, 90% of syphilis cases occur in developing countries, reflecting the lack of access to treatment and prevention programs for sexually transmitted infections in resource-poor settings.

In the United States, rates of syphilis declined rapidly in the late 1940s after the introduction of penicillin therapy and accompanying public health control programs. However, a resurgence occurred in the 1980s, coincident with an epidemic of crack-cocaine use, at which time most cases occurred in heterosexuals. Medical and public health efforts substantially reduced rates of syphilis by the mid-1990s, but a second resurgence, which is ongoing, began in the late 1990s to early 2000s. In North America and Europe today, syphilis is concentrated in populations of men who have sex with men (MSM), particularly MSM infected with human immunodeficiency virus (HIV). Among HIV-negative MSM, the diagnosis of early syphilis portends a high risk for subsequent HIV infection, and MSM with syphilis represent a high priority subgroup for HIV pre-exposure prophylaxis and other HIV prevention efforts. A substantial increase in syphilis occurred in Russia, other Eastern European countries, and China beginning in the early 1990s. The majority of syphilis cases globally occur in sub-Saharan Africa and South and Southeast Asia. Rates of congenital infection and stillbirth from syphilis remain unacceptably high in many settings in these areas.

Endemic, nonvenereal treponemal infections, such as yaws and pinta, remain a source of disability in affected areas, primarily tropical regions in Africa, Latin America, and Southeast Asia. Penicillin mass treatment programs in the 1950s and 1960s significantly decreased the worldwide prevalence of these infections, but eradication was not achieved. Impoverished, remote populations are disproportionately affected.

CLINICAL PRESENTATION

Numerous monographs have been written describing the protean manifestations of syphilis, and excellent, updated reviews are available in the major medical and infectious disease texts. This discussion will be limited to specific aspects of syphilis relevant to understanding and

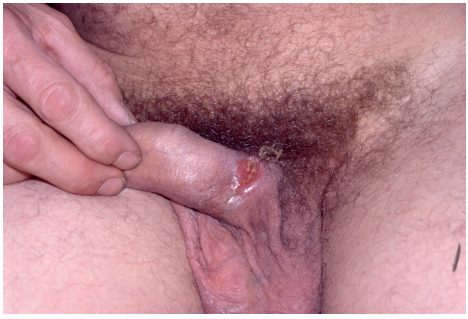

Fig. 43.1 Chancre of primary syphilis.

treating sexually transmitted infections among travelers and persons living in the developing world.

Primary Syphilis

The classic chancre of primary syphilis is a painless ulcer with an indurated margin and a clean base called a "chancre" that develops at the site of inoculation an average of 2-3 weeks post-infection (**Fig. 43.1**). Solitary lesions are typical, but multiple lesions can occur. The patient may not notice chancres, particularly in difficult-to-visualize areas such as the perianal area, labia, cervix, anus, rectum, and mouth. Secondary bacterial infection of these ulcers is rare. Unilateral or bilateral painless, nonsuppurative inguinal adenopathy follows appearance of the chancre by several days in 70-80% of cases. Spontaneous resolution of the chancre and adenopathy usually occurs within 6 weeks. Unfortunately, variation in the presentation of syphilitic ulcers makes clinical examination alone unreliable for the diagnosis of primary syphilis. Even clinicians experienced in diagnosis and management of sexually transmitted infections frequently misdiagnose the etiology of genital ulcers based on clinical examination. Use of laboratory diagnostics, when available, is crucial for appropriate etiologic diagnosis and treatment. In resource-poor settings, syndromic management of genital ulcer disease, including treatment for chancroid and syphilis, is commonly practiced.

Secondary Syphilis

Secondary syphilis is a systemic illness resulting from hematogenous dissemination of treponemes. The symptoms of secondary syphilis usually appear about 4-10 weeks after the appearance of the primary chancre. The manifestations of primary and secondary syphilis overlap in about 15% of cases. Clinical manifestations of secondary syphilis are extremely varied. The classic finding is a lacy, erythematous, maculopapular rash covering the trunk and abdomen. Palmar or plantar lesions, if present, are particularly suggestive of the diagnosis (**Fig. 43.2**). Cutaneous manifestations also include nodular, pustular, or follicular rashes, typically on the palms and soles but also more diffuse on the trunk; condylomata lata (nontender, sometimes moist, wart-like papules in the genital region), mucous patches in the mouth; and, less commonly, alopecia. The skin eruption is usually nonpruritic, but some patients complain of itching and present with excoriated lesions. Persons in the secondary stage of syphilis commonly have other manifestations of a systemic infection, including fever, generalized fatigue, and lymphadenopathy. Secondary syphilis must be considered in the differential diagnosis of *any* generalized skin eruption, particularly in MSM and pregnant women. The differential diagnosis for the rash of secondary syphilis includes viral exanthema, drug eruption, and primary HIV infection, among other etiologies. If untreated, approximately 25% of patients with secondary syphilis will have a relapse of active secondary syphilis, typically within 1 year.

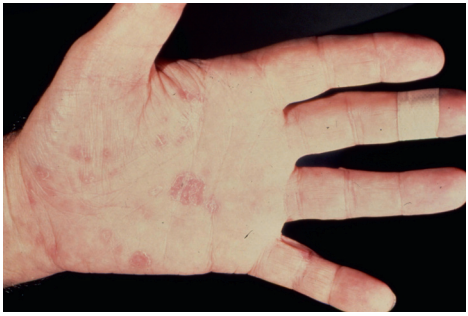

Fig. 43.2 Palmar rash of secondary syphilis.

Latent and Tertiary Syphilis

Untreated secondary syphilis spontaneously resolves after 3-12 weeks and is followed by latent, asymptomatic infection. Latent syphilis is defined by a positive serology in the absence of clinical disease. It is important to distinguish early latent syphilis from late latent syphilis to inform treatment decisions. Early latent syphilis is diagnosed only if the timing of infection can be confirmed as having occurred within the past year. Syphilis of unknown duration should be treated as late latent syphilis. Although syphilis is not transmitted through sexual contact during latent stages of the disease, symptoms of secondary syphilis can recur during the first year of infection. Pregnant women with latent syphilis are capable of transmitting the infection to the fetus. Elimination of congenital syphilis remains a global public health priority, and all pregnant women should be screened for syphilis at the first antenatal care visit. In the pre-antibiotic era, approximately one-third of individuals with late latent syphilis would eventually develop clinical disease, such as neurosyphilis, cardiovascular syphilis, or gummatous disease. However, the incidence of these manifestations has declined worldwide due to the widespread use of antibiotics that have some activity against latent syphilitic infection.

Neurosyphilis

Treponemal infection of the central nervous system (CNS) can occur during any stage of syphilis and is particularly common in the secondary stage. CNS infection in the setting of early syphilis (primary, secondary, and early latent) is distinct from, and much more common than, CNS manifestations in late syphilis, such as tabes dorsalis and the historic syphilis "madness" characterized by severe neurocognitive impairment. Early neurosyphilis presentations can range from subtle (e.g., headache) to severe (e.g., stroke resulting from meningovascular syphilis). All patients diagnosed with syphilis should be queried about symptoms of neurosyphilis, otosyphilis, and ocular syphilis. Changes in vision and hearing, in particular, should prompt cerebrospinal fluid (CSF) evaluation, if possible, and treatment with a neuropenetrative antibiotic regimen.

DIAGNOSIS

T. pallidum cannot be cultured. The definitive diagnostic procedure for primary and secondary syphilis is identification of spirochetes by darkfield microscopy or fluorescent monoclonal antibodies of serous exudate or scrapings obtained from lesions. Commensal spirochetes that reside in the oropharynx and intestinal tract can be difficult to differentiate from *T. pallidum* by morphologic criteria, making darkfield examination of oral and rectal lesions less reliable. However, darkfield microscopy is not widely available, requires specialized equipment and training, has limited sensitivity, and can be used only when cutaneous or

TABLE 43.1 Serologic Tests for Syphilis

Nontreponemal serologic tests
Venereal Disease Research Laboratory (VDRL) test
Rapid plasma reagin (RPR) test
Treponemal serologic tests
Enzyme immunoassay (EIA)
Chemiluminescence assay (CIA)
T. pallidum particle agglutination (TP-PA)
Fluorescent treponemal antibody absorption test (FTA-ABS)
Microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP)

mucosal manifestations of syphilis are present. Thus, most cases of syphilis are diagnosed through serologic testing.

Both nontreponemal and treponemal serologic tests are used for syphilis screening and diagnosis (**Table 43.1**). The "traditional sequence" testing algorithm begins with a nontreponemal test (e.g., the Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR] tests), which if positive, is followed by a treponemal test (e.g., *T. pallidum* particle agglutination [TP-PA]). Like most clinical screening activities, this algorithm begins with a highly sensitive test, which prompts follow-up with a higher specificity test if positive. In recent years, a "reverse sequence" testing algorithm has been used more commonly by some laboratories, beginning with a treponemal test (e.g., *T. pallidum* enzyme immunoassay [EIA] or chemiluminescence assay [CIA]), which, if positive, is followed by a nontreponemal test. If the results of the two tests are discordant, a second type of treponemal test is performed. Many laboratories switched to the reverse sequence algorithm as newer treponemal-specific tests became available that allow increased automation and reduced laboratory costs.

Interpretation of test results from either testing algorithm relies on recognition of two key features that differentiate treponemal-specific and nontreponemal-specific antibodies. First, nontreponemal antibodies are sensitive, but not specific, for *T. pallidum* infection. Second, treponemal-specific antibodies typically remain in the absence of active infection, either after treatment or in latent infection, whereas nontreponemal-specific antibodies decrease or disappear after resolution of clinically active syphilis.

Interpretation of test results with traditional testing is relatively straightforward (**Table 43.2**). A positive nontreponemal test with a positive treponemal test indicates syphilis; a positive nontreponemal test with a negative treponemal test indicates biologic false positivity. Numerous factors can cause biologic false positivity, including nonvenereal treponemal infections, other endemic tropical infections, and autoimmune diseases (**Table 43.3**). Interpretation of reverse sequence screening can be challenging due to the frequency of discordant test results (i.e., a positive treponemal test followed by a negative nontreponemal test). When the results of the treponemal and nontreponemal test are discordant, a second type of treponemal test is required. This is typically done reflexively in the laboratory without a clinician's order.

When the second treponemal test is negative, the results likely indicate a false positive. This can be due to either biologic or test factors, and in many instances, the false positive test reverts to negative on subsequent testing. Rarely, this pattern indicates very early infection because treponemal tests can become positive before the VDRL or RPR tests. This possibility should be considered in patients at high risk for recent syphilis infection and should prompt follow-up testing in approximately 1 month.

In the setting of discordant treponemal and nontreponemal results when the second type of treponemal-specific test is positive, additional clinical history is required to interpret the test. This pattern indicates a history of syphilis, either treated or untreated. If the patient

TABLE 43.2 Interpretation of Syphilis Testing Results

Test Results			Interpretation	Notes
TRADITIONAL SEQUENCE ALGORITHM				
Nontreponemal (RPR, VDRL)	**Treponemal-Specific (TP-PA, FTA-ABS)**			
NR	–		No syphilis[a]	
R	R		Syphilis	Clinical history and examination required to determine stage of infection and distinguish treated from untreated infection
R	NR		False positive	See Table 43.3 for a list of possible causes.
REVERSE SEQUENCE ALGORITHM				
Treponemal-Specific (EIA, CIA)	**Nontreponemal (RPR, VDRL)**	**Treponemal-Specific (TP-PA, FTA-ABS)**		
NR	–	–	No syphilis[a]	
R	R	–	Syphilis	Clinical history and examination required to determine stage of infection and distinguish treated from untreated infection
R	NR	R	Past syphilis[b]	Clinical history required to distinguish successfully treated infection from untreated infection. Treat for late latent syphilis if past treatment cannot be confirmed.
R	NR	NR	False positive[b]	May be due to factors related to the test technology or biologic false positivity (see Table 43.3)

[a]All serologic tests have limitations in detection of very early syphilis (primary or incubating). Patients with clinical symptoms of syphilis or known contact with syphilis should be treated for syphilis regardless of serologic results.
[b]Because treponemal tests can become positive before nontreponemal tests, this pattern can also indicate very early syphilis infection in a patient who is at risk for acquiring syphilis.
CIA, chemiluminescence assay; *EIA*, enzyme immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption test; *NR*, nonreactive; *R*, reactive; *RPR*, rapid plasma reagin test; *TP-PA*, *T. pallidum* particle agglutination; *VDRL*, Venereal Disease Research Laboratory test; –, test not performed

TABLE 43.3 Causes of Biologically False-Positive Tests for Syphilis

Spirochetal Diseases	Other Tropical Infections	Other Infections	Other Conditions
Yaws[a]	Leprosy	Varicella (chickenpox)	Connective tissue diseases
Pinta[a]	Malaria	Rubeola (measles)	Illicit drug use
Bejel[a]	Chancroid	Infectious mononucleosis	Advanced age
Leptospirosis	Lymphogranuloma venereum	Other viruses	Pregnancy
Rat-bite fever	Trypanosomiasis	Immunizations	Malignancy
Relapsing fever	Rickettsial infections	*Mycoplasma pneumoniae*	Cirrhosis
Lyme disease	Hepatitis		

[a]Nonvenereal treponematoses.

has been previously treated, this result pattern reflects successful treatment. If the patient has not been treated for syphilis, this result indicates late latent infection (in the vast majority of cases) or very early infection (rarely). All patients who have two positive treponemal tests in the setting of a negative nontreponemal test should be treated for late latent syphilis if past treatment cannot be confirmed. In areas in which endemic treponemal infections such as pinta, yaws, and bejel are prevalent, serologic cross-reactivity may complicate interpretation of syphilis testing, making the diagnosis of latent syphilis largely presumptive. These endemic treponemal infections cannot be distinguished from syphilis with clinically available tests. Because endemic treponemes are prevalent in the same regions that syphilis is prevalent, treatment for latent syphilis is indicated even if cross-reactivity is a consideration.

Serologic tests can be negative in primary syphilis and in the incubation period before chancre development. Patients who have genital ulcers and are at risk for recent syphilis infection and patients with known contact to a sexual partner with syphilis should be empirically treated for early syphilis because serologic testing will not rule out infection. Approximately 80% of patients with primary syphilis will be seropositive by VDRL or RPR test. Virtually 100% of patients with secondary syphilis will have a reactive VDRL or RPR test, and the titers of these tests are usually higher than for other stages of syphilis (i.e., typically ≥1 : 32). Antibody levels detected with the nontreponemal tests fall slowly following treatment, and sequential quantitative VDRL or RPR titers are used to assess response to therapy. However, they also fall slowly with time, even in the absence of treatment, and many patients with untreated late latent syphilis are no longer seropositive with nontreponemal tests (**Table 43.4**).

Point-of-care tests for syphilis are available, most of which are treponemal tests and accordingly have the limitations of treponemal testing in the absence of nontreponemal testing. That is, a positive rapid test in isolation cannot distinguish active clinical infection from past, treated infection. A dual treponemal and nontreponemal rapid syphilis test has recently been described in the scientific literature, but it is not clinically available at the time of this writing.

Diagnosis of Central Nervous System Syphilis

No single test is definitive for the diagnosis of neurosyphilis. Lumbar puncture with CSF examination is used to detect CNS involvement in syphilis. A CSF VDRL test is highly specific but insensitive. CSF pleocytosis and elevated protein are often present; follow-up of the CSF cell count is used to monitor response to treatment for neurosyphilis. However, CSF analysis is not recommended routinely for patients with primary or secondary syphilis. CDC guidelines recommend CSF examination for patients with syphilis and any of the

TABLE 43.4 Sensitivity and Specificity of Serologic Tests for Syphilis

	SENSITIVITY BY STAGE FOR UNTREATED SYPHILIS				
	Primary	**Secondary**	**Early Latent**	**Late Latent**	**Specificity**[a]
Nontreponemal serologic tests					
VDRL	78%	100%	96%	71%	98%
RPR	86%	100%	98%	73%	98%
Treponemal serologic tests					
EIA	93%	100%	100%	unknown	NA
FTA-ABS[b]	84%	100%	100%	96%	97%
MHA-TP	76%	100%	97%	94%	99%

[a]May not apply for patients from countries with endemic nonvenereal treponemal infections due to serologic cross-reactivity.
[b]FTA-ABS and TP-PA are equally sensitive for the detection of primary syphilis
EIA, Enzyme immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption test; *MHA-TP*, microhemagglutination assay for antibodies to *T. pallidum; NA*, not applicable; *RPR*, rapid plasma reagin test; *VDRL*, Venereal Disease Research Laboratory test.
Adapted from Larsen, S., Hunter, E., Kraus, S. (Eds.), 1990. A Manual of Tests for Syphilis. American Public Health Association, Washington, DC, with permission.

following: (1) neurologic or ophthalmologic signs or symptoms, (2) active tertiary disease (e.g., aortitis, gumma), (3) treatment failure of non-neurologic syphilis, or (4) late latent syphilis or syphilis of unknown duration in a patient with HIV infection. The absence of clinical symptoms or signs does not rule out the possibility of CNS involvement with syphilis, although the clinical significance of asymptomatic neurosyphilis is uncertain. Some experts recommend performing a lumbar puncture on anyone with latent syphilis as well as in all HIV-infected patients regardless of syphilis stage. In addition, CSF examination should be considered for individuals with latent syphilis and high titer (≥1:32) nontreponemal serologic results or for those in whom nonpenicillin therapy is planned. Importantly, CSF testing can be normal in cases of ocular syphilis and otosyphilis. For this reason, clinicians should consider additional ophthalmologic and audiologic evaluation, when possible, and empiric treatment with a neuropenetrative antibiotic regimen for patients with syphilis who report recent changes in vision or hearing.

TREATMENT

T. pallidum has remained exquisitely sensitive to penicillin, and parenteral penicillin therapy remains the treatment of choice for all forms of syphilis. A summation of current US and WHO recommendations is provided in **Table 43.5**.

Small studies have suggested that azithromycin, provided as a single oral dose of 2 g, may be effective for treatment of primary and secondary syphilis. However, case reports of treatment failure and documented resistance to azithromycin in some areas prevent formal recommendation of use of azithromycin for treatment of early syphilis. Azithromycin treatment is not appropriate for MSM in the United States, where more than half of *T. pallidum* strains are resistant to azithromycin.

Ceftriaxone has also been used for treatment of early and latent syphilis, as well as neurosyphilis, based on small clinical studies and pharmacokinetics. For early syphilis, a dose of 1 g ceftriaxone daily, by intramuscular injection or intravenous administration, for 8-10 days, has been used. For neurosyphilis, some have recommended a dose of 2 g daily, by intramuscular injection or intravenous administration, for 10-14 days. It is important to note, however, that optimal dosing and duration of ceftriaxone therapy have not been defined in formal guidelines, have not been studied in HIV-infected patients, and can be associated with allergic reactions due to cross-reactivity in patients with penicillin allergies.

TABLE 43.5 Treatment of Syphilis in Adults

Stage	Treatment
Primary, secondary, or early latent[a]	Recommended: benzathine penicillin G 2.4 million units by intramuscular injection, single dose
	Alternative regimen for penicillin-allergic, nonpregnant patients: doxycycline 100 mg by mouth, twice daily for 14 days *or* tetracycline 500 mg by mouth, four times daily for 14 days
	Second alternative (WHO Guidelines): procaine penicillin, 1.2 million units by intramuscular injection, daily for 10 consecutive days
Late latent, syphilis of unknown duration, and tertiary disease without neurologic involvement	Recommended: benzathine penicillin G 2.4 million units by intramuscular injection, once a week for 3 consecutive weeks
	Alternative regimen for penicillin-allergic, nonpregnant patients: doxycycline 100 mg by mouth, twice daily for 28-30 days *or* tetracycline 500 mg by mouth, four times daily for 28-30 days
	Second alternative (WHO Guidelines): procaine penicillin, 1.2 million units by intramuscular injection, daily for 20 consecutive days
Neurosyphilis[c]	Recommended: aqueous crystalline penicillin G 18-24 million units per day, administered intravenously in divided doses every 4 h or by continuous infusion, for 10-14 days
	Alternative: procaine penicillin G 1.2-2.4 million units by intramuscular injection daily *plus* probenecid[b] 500 mg by mouth, four times daily. Both for 10-14 days.
	Penicillin-allergic patients, including allergic pregnant patients, should undergo penicillin desensitization, followed by treatment with one of the above regimens.
	WHO guidelines suggest that doxycycline 200 mg by mouth, twice daily for 30 days or tetracycline 500 mg, by mouth, four times daily for 30 days may be considered alternatives for penicillin-allergic, nonpregnant patients, although these regimens have not been evaluated in systematic studies. Many experts do not endorse these regimens for neurosyphilis due to limited clinical experience and concerns about compliance.

[a]Latent syphilis is defined by seroreactivity without clinical evidence of disease. Early latent syphilis (defined as infection within 1 year by CDC guidelines and 2 years by WHO guidelines) requires at least one of the following: (1) documented seroconversion within the defined time period, (2) unequivocal symptoms of primary or secondary syphilis within the time period, or (3) a sex partner with primary, secondary, or early latent syphilis within the time period.
[b]Patients with serious allergies to sulfonamides should not be treated with a probenecid-containing regimen.
[c]Of note, some experts recommend treating patients with cardiovascular syphilis with a neurosyphilis regimen.

The optimal management strategies for late latent syphilis, neurosyphilis, and cardiovascular syphilis continue to be debated, and recommendations are based on clinical experience rather than controlled trials. In general, penicillin-based regimens for the appropriate stage of syphilis are recommended for treatment of pregnant women. WHO guidelines offer erythromycin-based regimens for penicillin-allergic, pregnant patients with syphilis without CNS involvement; however, erythromycin does not reliably cure infection in the fetus. Penicillin desensitization should be attempted, if possible. Infants born to mothers who have to be treated with erythromycin should receive penicillin after birth. The reader is encouraged to consult available experts and the Further Reading section for further details related to syphilis in pregnancy and management of congenital disease.

Finally, all patients treated for syphilis should be tested for HIV and other sexually transmitted diseases (e.g., gonorrhea and chlamydial infections).

ASSESSING THERAPEUTIC RESPONSE

Treatment failure can occur with any regimen given for any syphilis stage. All patients treated for syphilis require clinical and serologic follow-up at 6, 12, and, for those treated for latent syphilis, 24 months. Treatment failure is defined as persistent symptoms or signs or a sustained four-fold increase or failure to achieve a four-fold decrease in those with high-titer initial results (equivalent to a two-dilution change) in nontreponemal test titer. A lumbar puncture to evaluate for neurosyphilis should be considered when initial treatment is unsuccessful. Approximately 5-15% of patients with primary or secondary syphilis will not achieve an adequate serologic decline after initial therapy and require retreatment despite adequate serologic response to appropriate treatment. The same regimens recommended for initial treatment should be used for retreatment, unless the CSF is abnormal.

Many patients with latent syphilis, whether early or late, remain reactive by VDRL or RPR testing at a persistent low titer (1:1 to 1:8) for several years. These patients require careful follow-up with periodic testing: a four-fold (i.e., two dilution) increase in titer indicates treatment failure or reinfection.

As detailed above, lumbar puncture with CSF examination is recommended for patients with treated early syphilis whose titers do not fall adequately. Those treated for neurosyphilis should have repeat CSF examination at 3-6 months after therapy, and then 6-monthly thereafter until normalization of CSF findings. Failure to normalize CSF cell count by 2 years should prompt consideration of retreatment.

MANAGEMENT OF SEX PARTNERS

Sexual transmission of syphilis occurs when mucocutaneous lesions are present; the risk of sexual transmission is low from patients with untreated syphilis of >1 year duration. Nonetheless, sex partners of patients with syphilis of any stage should be evaluated clinically and serologically for syphilis. Presumptive treatment is recommended for those exposed within 90 days preceding a diagnosis of primary, secondary, or early latent syphilis in a sex partner, as serologic results may not yet become positive in such individuals.

HIV AND SYPHILIS

Persons with syphilis are at risk for HIV infection due to factors related to sexual behavior and biology. Ulcerative sexually transmitted infections such as syphilis appear to facilitate the acquisition and transmission of HIV. All persons with suspected or confirmed syphilis should be tested for HIV infection, and MSM with syphilis are a priority population for HIV pre-exposure prophylaxis. In patients with early syphilis and concurrent immunosuppression from HIV infection, aggressive or atypical manifestations may occur. HIV infection increases the risk of early or persistent CNS invasion. In general, syphilis in HIV-infected persons should be treated according to the standard guidelines for HIV-uninfected populations. Some specialists extend therapy for early syphilis in persons with HIV by providing weekly benzathine penicillin for 3 weeks, rather than just a single dose; this practice is controversial and is not endorsed in guidelines. HIV-infected patients with syphilis should be monitored closely for clinical and serologic response after treatment—CDC guidelines recommend follow-up at 3, 6, 9, 12, and 24 months after therapy.

FURTHER READING

Causer, L.M., Kaldor, J.M., Conway, D.P., et al., 2015. An evaluation of a novel dual treponemal/nontreponemal point-of-care test for syphilis as a tool to distinguish active from past treated infection. Clin. Infect. Dis. 61 (2), 184–191. Epub ahead of print.

Centers for Disease Control and Prevention, 2011. Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006–2010. MMWR 60, 133–137.

Chen, Z.Q., Zhang, G.C., Gong, X.D., et al., 2007. Syphilis in China: results of a national surveillance programme. Lancet 369, 132–138.

Golden, M.R., Marra, C.M., Holmes, K.K., 2003. Update on syphilis: resurgence of an old problem. JAMA 290, 1510–1514.

Larsen, S., Hunter, E., Kraus, S. (Eds.), 1990. A Manual of Tests for Syphilis. American Public Health Association, Washington, DC.

Lukehart, S.A., Hook, E.W., III, Baker-Zander, S.A., et al., 1988. Invasion of the central nervous system by *Treponema pallidum*. Ann. Intern. Med. 109, 855–862.

Lukehart, S.A., Godornes, C., Molini, B.J., et al., 2004. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. N. Engl. J. Med. 351, 154–158.

Musher, D.M., 1999. Early syphilis. In: Holmes, K.K., Sparlin, P.F.Mårdh, P.-A. (Eds.), Sexually Transmitted Diseases, third ed. McGraw-Hill, New York, pp. 479–485.

Park, I.U., Chow, J.M., Bolan, G., et al., 2011. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. J. Infect. Dis. 204, 1297–1304.

Pathela, P., Braunstein, S.L., Blank, S., et al., 2015. The high risk of an HIV diagnosis following a diagnosis of syphilis: a population-level analysis of New York City men. Clin. Infect. Dis. 61 (2), 281–287. Epub ahead of print.

Patton, M.E., Su, J.R., Nelson, R., et al., 2014. Primary and secondary syphilis—United States, 2005–2013. MMWR 9, 402–406.

Rolfs, R.T., Joesoef, M.R., Hendershoot, E.F., et al., 1997. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. N. Engl. J. Med. 337, 307–314.

Sparling, P.F., 1999. Natural history of syphilis. In: Holmes, K.K., Sparlin, P.F.Mårdh, P.-A. (Eds.), Sexually Transmitted Diseases, third ed. McGraw-Hill, New York, pp. 473–478.

Stoner, B.P., 2007. Current controversies in the management of adult syphilis. Clin. Infect. Dis. 44, S130–S146.

Swartz, M.N., Healy, B.P., Musher, D.M., 1999. Late syphilis. In: Holmes, K.K., Sparlin, P.F., Mårdh, P.-A. (Eds.), Sexually Transmitted Diseases, third ed. McGraw-Hill, New York, pp. 487–509.

Tichinova, L., Bonshenko, K., Ward, H., et al., 1997. Epidemics of syphilis in the Russian Federation: trends, origins and priorities for control. Lancet 350, 210–213.

Wasserheit, J., 1992. Epidemiological synergy. Interrelationships between human immunodeficiency virus and other sexually transmitted diseases. Sex. Transm. Dis. 19, 61–77.

Workowski, K.A., Berman, S., 2010. Sexually transmitted diseases treatment guidelines, 2010. MMWR 17, 1–110.

WHO. Global incidence and prevalence of selected curable sexually transmitted infections—2008. Available at <http://apps.who.int/iris/bitstream/10665/75181/1/9789241503839_eng.pdf> (accessed April 23, 2015).

Zetela, N.M., Klausner, J.D., 2007. Syphilis and HIV infection: an update. Clin. Infect. Dis. 44, 1222–1228.