Conferences and Reviews

Syphilis
A Tale of Twisted Treponemes

JUDY L. FLORES, MD, *San Francisco, California*

Based on a discussion presented at Medical Grand Rounds in the University of California, San Francisco, School of Medicine, this article has been edited by Nathan M. Bass, MD, PhD, Associate Professor, Department of Medicine.

Despite the widespread availability of effective treatment, the incidence of primary and secondary syphilis in the United States is on the rise. In addition, syphilis is occurring in a substantial number of patients infected with the human immunodeficiency virus (HIV), thus adding to the complexities of diagnosis and treatment. Primary syphilis represents a disseminated infection, often accompanied by abnormalities of the cerebrospinal fluid, that may pass unrecognized and progress to the myriad manifestations of secondary syphilis. The diagnosis of syphilis in patients with mucosal or skin lesions may be made by darkfield examination; once lesions have resolved, serologic tests are required. Patients with latent syphilis may have asymptomatic neurosyphilis and risk progression to tertiary disease. The diagnosis of asymptomatic neurosyphilis is necessary to determine the optimal treatment of patients with latent disease. The diagnosis of active neurosyphilis generally requires an inflammatory cerebrospinal fluid profile and a reactive cerebrospinal fluid VDRL test. Syphilis is common in HIV-infected patients, who may have an altered antibody response to infection and an apparent increased incidence of neurologic complications. The preferred treatment at all stages is penicillin, which is also the only recommended therapy for neurosyphilis. The optimal treatment of syphilis in HIV-infected patients is unknown.

(Flores JL: Syphilis—A tale of twisted treponemes. West J Med 1995; 163:552-559)

Why should we be concerned today about syphilis, a disease that is readily cured by a widely available, inexpensive medication? After an initial precipitous decline in the number of cases after the development of penicillin, there has been an overall slow but sustained increase in the incidence of primary and secondary syphilis in the United States, which has only recently begun to decline (Figure 1).[1] In the 1970s and early 1980s, this increase occurred predominantly in the male homosexual community; with behavioral changes after the recognition of human immunodeficiency virus (HIV) transmission, rates have declined in this group.[2] More recently, the incidence of syphilis in heterosexual men and women has increased rapidly; concomitantly, the incidence of congenital syphilis has risen substantially over the past ten years.

Syphilis, therefore, is on the rise. This increase, and the added complexities of diagnosing and treating syphilis in the rising number of HIV-infected patients, makes review of this topic particularly timely.*

*See also the editorial by S. A. Lukehart, PhD, "Modern Syphilis—Still a Shadow on the Land," on pages 587-588 of this issue.

Early Syphilis

Syphilis is usually, but not exclusively, transmitted by sexual contact. Three to four weeks after exposure, 50% to 60% of patients will have a chancre at the site of inoculation (primary syphilis).[3] This characteristic ulcerative lesion is usually solitary and painless, with a clean, indurated base. Before any lesion appears, however, the causative agent, *Treponema pallidum*, is already widely disseminated. In fact, by the time primary syphilis is diagnosed, almost 25% of patients may have cerebrospinal fluid (CSF) abnormalities attributable to the infection.[4]

Because chancres are typically painless and heal in three to six weeks without treatment, primary syphilis infection may pass unnoticed. Virtually all untreated patients progress to secondary syphilis within four to ten weeks of the initial exposure. This stage is famous for its vast array of manifestations; symptoms commonly include fever, generalized lymphadenopathy, and a diffuse rash that typically involves the palms and soles. Mucosal lesions of secondary syphilis include condylomata lata, papular lesions in intertriginous areas covered by a grayish exudate teeming with treponemes,

From the Department of Medicine, Veterans Affairs (VA) Medical Center, University of California, San Francisco (UCSF), School of Medicine.
Reprint requests to Judy L. Flores, MD, VA Medical Center, Box 111A, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control and Prevention
CNS = central nervous system
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption [test]
HIV = human immunodeficiency virus
RPR = rapid plasma reagin [test]

and equally infectious mucous patches. Cerebrospinal fluid abnormalities are not uncommon, even in neurologically asymptomatic patients; *T pallidum* has been isolated from CSF in 30% of patients with primary or secondary syphilis.[5] Early symptomatic neurosyphilis—aseptic meningitis, cranial nerve palsies, eye manifestations—is also well known to occur in patients with secondary syphilis.[6]

Should the disease escape detection and treatment during this phase, all these manifestations, including central nervous system (CNS) involvement, will generally follow an initially benign course.[7] Patients will pass into "early latency," defined as the period of time during the first year of infection after all manifestations other than serologic markers have resolved. During this year, untreated patients are at risk for relapse: secondary syphilis will recur in about 25%.[8] Patients in this stage are, therefore, still potentially infectious. Primary, secondary, and early latent stages of infection are referred to together as early or infectious syphilis.

Diagnosing Early Syphilis

Darkfield examination is useful for making the diagnosis of syphilis in a patient with a chancre or mucosal lesion. *Treponema pallidum* is identified by its characteristic "corkscrew" structure and motility. This technique should not be used for oral lesions because the presence of nonpathogenic treponemes may result in a false-positive test. Although it has not been studied recently, the darkfield examination is widely regarded as both sensitive (95% in 1 series of seronegative patients with primary syphilis)[9(pp516-518)] and specific; however, the usefulness of the test depends on the experience of the observer and adequacy of the specimen. Also, the use of antibiotics topically or parenterally may result in a false-negative test. For these reasons, a darkfield examination should not be reported as negative until it has been repeated two or three times, especially in a patient with a suspicious lesion.

Patients with latent disease by definition have no cutaneous or mucosal lesions. Diagnosis rests on serologic tests, as shown in Figure 2. In all of these, antigen is provided to bind with antibody produced in response to syphilitic infection. Various mechanisms are then used to detect the formation of antigen-antibody complexes, such as flocculation in the VDRL and rapid plasma reagin (RPR) tests, fluorescence in the fluorescent treponemal antibody-absorption (FTA-ABS) test, or hemagglutination in the microhemagglutination-*T pallidum* test.

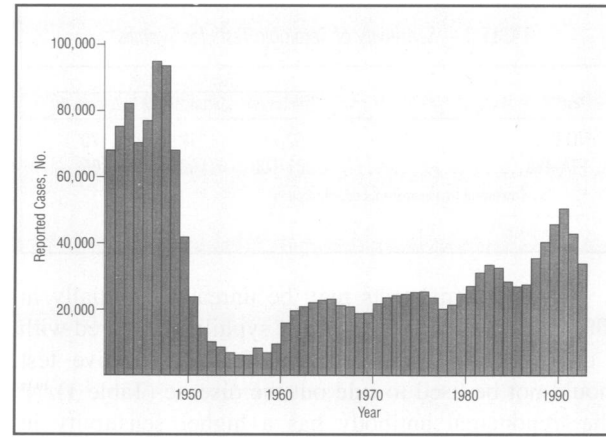

Figure 1.—The graph shows the number of cases of primary and secondary syphilis in the United States from 1941 through 1992.

Antibodies generated in response to syphilis fall into two broad categories. The first are the "reaginic" or nontreponemal antibodies. These antibodies, which react with cardiolipin, also reflect evidence of treponemal infection, an adventitious discovery that formed the basis of the Wassermann test, as well as the currently used VDRL and RPR tests. Titers of these antibodies generally reflect disease activity and are used to monitor response to treatment. Whereas either the VDRL or the RPR test may be assessed serially to monitor response, the titers of these two tests are not interchangeable; therefore, the same test should be used throughout follow-up.

Treponemal tests are conceptually simple: they are antibodies directed against *T pallidum* antigens. Most commonly used are the FTA-ABS and the microhemagglutination-*T pallidum* tests. The major use of these tests is to confirm positive nontreponemal tests because treponemal tests are positive in the vast majority of infected patients, whatever the stage.

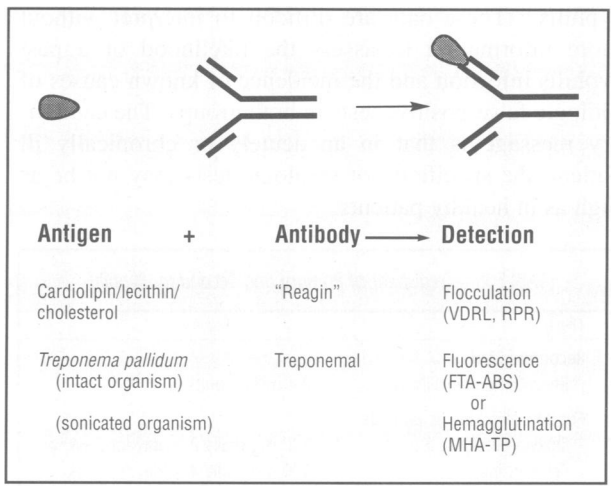

Figure 2.—Serologic tests for syphilis are shown. FTA-ABS = fluorescent treponemal antibody absorption, MHA-TP = microhemagglutination-*Treponema pallidum*, RPR = rapid plasma reagin

TABLE 1.—*Sensitivity of Serologic Tests for Syphilis**

Test	Stage of Infection		
	Primary, %	Secondary, %	Tertiary, %
VDRL	62-75	99	70
FTA-ABS	81-100	100	100

FTA-ABS = fluorescent treponemal antibody-absorption

*From Hart.[10]

Nontreponemal tests may be unreactive initially in 30% to 40% of cases of primary syphilis compared with a darkfield gold standard; therefore, a negative test should not be used to rule out the disease (Table 1).[10,11] The treponemal antibody has a higher sensitivity in primary syphilis.[10] By the time of secondary syphilis, virtually all patients produce both treponemal and nontreponemal antibodies. In an untreated patient, the nontreponemal antibody response can diminish over time, but the treponemal antibody response should remain positive essentially lifelong.

Assessing the specificity of these serologic tests is problematic: the difficulty, of course, is in finding a population with a near-zero probability of syphilis to ensure that a positive test is actually false-positive. An innovative study tested 250 nuns with a stated history of no infectious or congenital syphilis; in some cases the nuns' mothers were interviewed for completeness.[12] In this group, the VDRL test was 100% specific, whereas the FTA-ABS test had a 1.2% false-positive rate. The three false-positive tests included one in a person with active pulmonary tuberculosis and another in a person with a history of rheumatoid arthritis. In another study, better than 99% specificity was found for the VDRL and FTA-ABS tests in more than 1,000 healthy volunteers, but substantially lower specificity was reported for both tests in hospitalized patients with no known history of syphilis.[13] These data are difficult to interpret without more information to assess the likelihood of a past syphilis infection and the incidence of known causes of biologic false-positive tests in both groups. The cautionary message is that in an acutely or chronically ill patient, the specificity of serologic tests may not be as high as in healthy patients.

TABLE 2.—*Treatment of Primary and Secondary Syphilis*

Therapy	Regimen
Recommended	
Benzathine penicillin G	2.4 million units IM in 1 dose
For penicillin-allergic patients	
Doxycycline	100 mg orally 2 ×/day for 2 wk, or
Tetracycline	500 mg orally 4 ×/day for 2 wk
Third-line therapy	
Erythromycin	500 mg orally 4 ×/day for 2 wk

IM = intramuscularly

Treatment of Early Syphilis

Treatment is the same for all phases of early disease—primary, secondary, and early latency (Table 2). The treatment of choice is the administration of benzathine penicillin G, 2.4 million units intramuscularly, shown to be at least 95% effective in large studies.[14,15] Whereas the use of benzathine penicillin is highly effective, it achieves negligible CSF levels.[16] Remember that a substantial number of patients with early syphilis have asymptomatic CSF involvement; the vast majority, however, are able to resolve early infection with treatment that does not provide treponemicidal CSF levels. The clearance of the CSF does appear to require an intact immune response even with appropriate antibiotics.[17]

For penicillin-allergic patients, doxycycline is the best alternative therapy; erythromycin has less than 90% efficacy.[14] Ceftriaxone sodium achieves excellent CSF penetration, but data are too limited to recommend it as an effective alternative therapy.

Treatment response is gauged by a fall in nontreponemal antibody titers, because early clinical manifestations resolve without treatment. According to previous guidelines, patients treated for early syphilis should show a nontreponemal antibody titer decline of at least fourfold (2 tubes) at three months and eightfold (3 tubes) at six months.[18] A slower or smaller decline in the titer has been considered worrisome for possible treatment failure. A fourfold rise in antibody titer or a return of clinical manifestations indicates treatment failure or reinfection.

A recent study from Canada has revised these general guidelines. In more than 1,000 patients treated for early syphilis and observed for as long as three years, the observed rate of nontreponemal antibody titer decline was much slower than previously expected.[19] In fact, many patients considered cured in this study by their eventual titer decline would be considered treatment failures by the previous criteria. Patients with early latent syphilis had a slower and smaller drop in titer (fourfold decrease at 12 months) than patients with primary and secondary syphilis (fourfold decrease at 6 months and eightfold decrease at 12 months). Given these results, at least a fourfold antibody titer decline within 6 months for primary and secondary syphilis and within 12 months for early latent syphilis can be considered evidence of a treatment response. A return to negative serologic tests ("seroreversion") is too stringent a test for cure because only 63% of the treated study patients seroreverted in three years. In addition, despite previous teaching that treponemal antibodies persist even after adequate treatment, in this study about 25% of treated patients became treponemal antibody-negative over the three-year period. Of note, all patients who seroreverted in this study had a first episode of infection, and most had primary syphilis.

Latent Syphilis and Asymptomatic Neurosyphilis

From such studies as the infamous Tuskegee study and a large study in Oslo,[8] we know that undetected or

inadequately treated syphilis will progress to "late latency," a phase of disease occurring at least a year after infection and detectable only by serologic tests. Most untreated patients will persist in latency for life, although some will lose serologic markers. About a third, however, go on to manifest tertiary disease, which can take a variety of forms: neurologic, including general paresis and tabes dorsalis; cardiovascular, with aortitis, aortic regurgitation, and aortic aneurysm; and gummatous, characterized by granulomatous-like lesions infiltrating the skin, soft tissues, bone, liver, or any organ in the body.

All patients with latent or tertiary syphilis require treatment. Our goal in treating patients with latent disease is to identify those who need more intensive treatment for asymptomatic neurosyphilis. The usual clinical question is, "Does my asymptomatic patient with positive syphilis serologies really need a lumbar puncture to rule out asymptomatic neurosyphilis, or can he or she be simply treated presumptively for latent disease?" In attempting to answer this question, we will start by considering the prevalence of asymptomatic neurosyphilis in patients with late latent infection.

Historical data from large series suggest that 5% to 10% of patients with late latent syphilis may have asymptomatic neurosyphilis.[20(pp72-73)] Two studies have found 0% prevalence in a small number of patients.[21,22] A study of CSF abnormalities in patients with syphilis, however, found that 3 of 15 patients (20%) with late latent syphilis had a positive CSF-VDRL test.[5] Taking all of these studies into account, we may infer that the prevalence of asymptomatic neurosyphilis is likely low, but not negligible. The prevalence in HIV-infected patients, however, appears to be substantially higher, as I will discuss.

Do any other factors predict a risk of asymptomatic neurosyphilis? Age, or more precisely, the duration of infection, may be helpful. In the long-term natural history study from Oslo, none of 169 patients with latent syphilis for more than 30 years had asymptomatic neurosyphilis. Presumably, neurologic involvement eventually becomes symptomatic, so that after 30 years no patient is left with asymptomatic neurologic involvement. We cannot assume, however, that because a patient is elderly, the infection must have been acquired many years ago. A recent study from Hartford described the cases of 35 patients older than 60 with early syphilis[23]; consistently, 2.5% to 3% of cases of primary and secondary syphilis in the US are diagnosed in patients older than 55 years.[1]

In addition, CSF abnormalities in early syphilis have long been recognized as prerequisite for the development of neurosyphilis in untreated patients.[6] Patients with normal CSF during the first two years of infection have a negligible risk of having symptomatic neurologic involvement in late disease.[6]

A decision-analysis model compared the strategies of lumbar puncture in patients with asymptomatic late syphilis to diagnose and treat neurosyphilis versus simply treating patients for presumed uncomplicated latent disease.[24] Outcome estimates for cure using the two strategies slightly favored the one using lumbar puncture (99.75% versus 99.95%); however, the rate of complications in the group having lumbar puncture (0.3%) was estimated to exceed the marginal benefit.

TABLE 3.—*Criteria for Cerebrospinal Fluid Examination in Latent Syphilis*

Neurologic or ophthalmic signs or symptoms
Evidence of tertiary syphilis—aortitis, gummas
Failure of treatment of early syphilis
Nonpenicillin therapy planned
Serum nontreponemal antibody titer >1:16 (unless duration of infection is <1 yr)
Human immunodeficiency virus infection

If, as this analysis suggests, it is not necessary to subject indiscriminately all asymptomatic patients with latent syphilis to lumbar puncture, who then should be screened (Table 3)? Any patient with untreated syphilis for less than 30 years but longer than a year should be considered for screening. Infection for less than a year, even with asymptomatic CSF abnormalities, is well treated with intramuscular benzathine penicillin in a normal host, despite a lack of "adequate" CNS penetration. Patients must also consent to and be able to tolerate lumbar puncture. These two criteria together form the most conservative guidelines for CSF examination in late latent syphilis.

Because nonpenicillin regimens have not been well documented to treat neurosyphilis, it is prudent to rule out asymptomatic neurosyphilis in patients with latent disease who would otherwise be treated with alternative therapy. Other evidence of late infection like cardiovascular or gummatous disease mandates an evaluation for neurosyphilis, as does concurrent HIV infection. Patients in whom the treatment of early syphilis has failed are at increased risk for CNS involvement and should undergo lumbar puncture before retreatment. The Centers for Disease Control and Prevention (CDC) recommends that patients who have a VDRL or RPR titer of 1:32 or greater after a year of infection should also be evaluated with a lumbar puncture, as they may also be at increased risk for neurosyphilis.[25]

Diagnosing Asymptomatic Neurosyphilis

Once the decision to screen is made, the immediate problem is to identify asymptomatic neurosyphilis if it is present. Unfortunately, no practical treatment standard exists for diagnosing this disorder. Instead, we are faced with using a variety of tests in combination, none with ideal sensitivity and specificity (Table 4). There is consensus in the literature that a positive serum treponemal antibody test is absolutely required for making the diagnosis.[7] Unfortunately, treponemal antibody in the CSF is not diagnostic for neurosyphilis, as it may represent only passive diffusion of treponemal antibody from the blood into the CSF rather than active CNS infection.[26]

TABLE 4.—*Criteria for the Diagnosis of Neurosyphilis*

Reactive serum treponemal antibody test (FTA-ABS or MHA-TP)
Reactive cerebrospinal fluid (CSF) VDRL test*
CSF pleocytosis (>5 leukocytes × 10^6/liter) with or without elevated protein level

FTA-ABS = fluorescent treponemal antibody absorption, MHA-TP = microhemagglutination-*Treponema pallidum*

*In some instances, an unreactive CSF-VDRL test may be consistent with a diagnosis of neurosyphilis. See text.

The CSF-VDRL test is extremely specific: a patient who has a positive test should be treated for neurosyphilis. The sensitivity of this test, however, varies in the literature from 30% to 90%.[5,10] Why is this range so broad? Historically, the sensitivity of the CSF-VDRL test has been assessed in patients with symptomatic neurosyphilis. Unfortunately, during the period when neurosyphilis was relatively prevalent and the classic studies were carried out, several common neurologic syndromes were not well understood. In these studies, neurologic symptoms were likely ascribed to neurosyphilis in patients with other evidence of syphilis infection.[27] For this reason, patients with carotid artery disease, viral meningoencephalitis, lacunar syndromes, or basilar artery insufficiency, to name a few unrecognized diagnoses, who had serologic evidence of syphilis but a negative CSF-VDRL test, were undoubtedly labeled with "seronegative" neurosyphilis. The VDRL test, then, may be much more sensitive than historical data suggest; in fact, some experts require a CSF-VDRL test for the diagnosis of asymptomatic or symptomatic neurosyphilis. It is well known, however, that *T pallidum* can be isolated from CSF that is negative on the VDRL test[5]; in addition, cases have been described of patients with a negative CSF-VDRL test who have clinical evidence of neurosyphilis and who respond to penicillin therapy. The CSF-VDRL sensitivity is, therefore, almost certainly better than reported in the historical literature, but likely not 100%.

Finally, CSF pleocytosis and an elevated protein level are nonspecific findings that may be associated with neurosyphilis. Many patients with primary and secondary syphilis manifest CSF abnormalities early on; those with abnormalities persisting into late latency are at risk for progressing to symptomatic neurosyphilis.[6] Therefore, unexplained CSF pleocytosis or elevated protein concentration in a patient with serologic evidence of syphilis should be taken as presumptive evidence of asymptomatic neurosyphilis.

Symptomatic Neurosyphilis

How do we determine if neurologic abnormalities in a patient with evidence of syphilis infection actually represent neurosyphilis? First, the diagnosis requires the presence of serum treponemal antibody. The CSF-VDRL test, as discussed earlier, is specific and reasonably sensitive in these patients. Unlike in patients with asymptomatic neurosyphilis, however, CSF pleocytosis with or without an elevated CSF protein level should be present if the disease is active.[7,27] In fact, without both a positive CSF-VDRL test and CSF pleocytosis, active neurosyphilis should be diagnosed only after a thorough search for alternative diagnoses. A symptomatic patient with unexplained CSF pleocytosis and a positive serum treponemal antibody test without a positive CSF-VDRL test could be treated presumptively for neurosyphilis, though that diagnosis must be a cautious one in such a patient.[27]

Manifestations of Neurosyphilis

As pointed out in a review, neurosyphilis is not one disease, but a collection of syndromes that span all stages of syphilis, from within weeks of infection to 50 or more years.[7] The classic late manifestations of neurosyphilis, general paresis and tabes dorsalis, are now exceedingly uncommon. Although also rare, the early forms—syphilitic meningitis and meningovascular syphilis—are currently of greater concern, especially in patients with HIV infection.

Syphilitic meningitis occurs in patients with early infection; in 10% of patients, it develops while the rash of secondary syphilis is still present.[7] Its symptoms are those of meningitis: headache, confusion, and meningeal signs. Cranial nerve abnormalities may occur and typically involve cranial nerves III, V, or VIII. These symptoms generally resolve even if untreated, although patients may be left with cranial nerve palsies. Worse, such patients remain at risk for the recrudescence of neurosyphilis. With treatment, symptoms will resolve in a few days to weeks. Meningovascular syphilis also occurs early, usually in the first months to a few years after infection. Unlike stroke syndromes, which usually occur with full neurologic deficits at the outset, meningovascular syphilis may present with a prodrome of nonspecific symptoms such as headache, psychiatric changes, or vertigo before focal neurologic deficits appear.[7]

Late neurosyphilis was common before the development of penicillin: in the early part of this century, general paresis of the insane accounted for 20% of psychiatric hospital admissions in the United States. Its symptoms are those of dementia and psychosis, and if untreated, it is fatal within months to a few years. Tabes dorsalis also occurs late in infection and is characterized by a triad of symptoms (lightning pains, dysuria, and ataxia) and a triad of signs (Argyll Robertson pupil, loss of reflexes, and loss of proprioception). Both general paresis and tabes dorsalis are extremely uncommon since the introduction of penicillin.

Treatment of Late Latent Syphilis and Neurosyphilis

Late latent syphilis is best treated with benzathine penicillin G, 2.4 million units given intramuscularly each week for three weeks (Table 5).[25] The use of doxycycline and erythromycin are less well studied; recommendations for their use in latent disease are

TABLE 5.—*Treatment of Late Latent Syphilis or Syphilis of Unknown Duration*

Therapy	*Regimen*
Recommended	
Benzathine penicillin G.....	2.4 million units IM as 1 dose/wk for 3 wk
For penicillin-allergic patients	
Doxycycline	100 mg orally 2 ×/day for 4 wk, or
Tetracycline.....	500 mg orally 4 ×/day for 4 wk

IM = intramuscularly

simply extensions of recommendations for treating early syphilis.

Penicillin, administered intravenously or intramuscularly, remains the drug of choice for treating neurosyphilis (Table 6).[25] The effectiveness of alternative therapies is unproved. Administering amoxicillin in high doses (2 grams 3 times a day) along with probenecid (500 mg 4 times a day) to raise drug concentrations appears effective in a small number of patients and may prove to be an outpatient treatment alternative.[28] Because of the large dosage required, this regimen can be difficult for patients to tolerate. Ceftriaxone sodium remains an unproven therapy to date, with notable rates of treatment failure reported in HIV-infected patients.[29]

How do we monitor the treatment response in patients with latent syphilis or neurosyphilis? As in early syphilis, the serum titer must be measured to ensure that it declines at least fourfold, although the decline is slower the longer the duration of infection. The titer may not revert to zero even with adequate treatment. Rising titers indicate treatment failure or reinfection.

In patients with neurosyphilis, follow-up CSF examinations should be done at six-month intervals over the first two years, or until the CSF becomes normal.[25] Resolving pleocytosis is generally the first measure of improvement and should occur over about six months.[30] Elevated protein levels, if present, will begin to decline during the first six months, but can take up to two years to return to normal. The CSF-VDRL titer should decline (fourfold within a year) if it is initially high, but it may take years to revert to negative.[30] A persistent, low CSF-VDRL titer after a course of treatment may warrant retreatment; however, if CSF pleocytosis and elevated protein levels have resolved and the serum VDRL titer is not increased, additional therapy is unlikely to be beneficial.[27]

TABLE 6.—*Recommended Treatment of Neurosyphilis**

Drug	*Regimen*
Aqueous penicillin G.....	2-4 million units IV every 4 hr, for 10-14 days, or
Procaine penicillin	2.4 million units IM a day, plus probenecid, 500 mg orally 4 ×/day, both for 10-14 days

IM = intramuscularly, IV = intravenously

*Some experts follow either regimen with 1 to 3 weekly dose(s) of benzathine penicillin G, 2.4 million units IM.

The goal of therapy for neurosyphilis, particularly general paresis and tabes dorsalis, is to halt the progression of disease. Symptoms of meningitis, and to some extent meningovascular syphilis, should resolve with therapy, but general paresis and tabes dorsalis are much less likely to abate. Neurologic signs or symptoms attributed to syphilis in the absence of CSF pleocytosis are unlikely to respond to therapy.[7]

Syphilis and Human Immunodeficiency Virus Infection

With the increasing prevalence of HIV as well as syphilis, the interaction of these two infections has become a topic of current interest and clinical importance. In studies controlled for known HIV risk factors such as number of sexual partners, male homosexual activity, and injection-drug use, syphilis emerges as an independent risk factor for HIV infection.[31] Not surprisingly, then, the prevalence of syphilis in patients with HIV infection is high: 14% to 36% in various studies, depending on the background rate in the community.[31,32]

A frequently noted concern is that the antibody response to syphilis may be delayed or impaired in HIV-infected patients. Are the serologic tests on which we rely for the diagnosis and follow-up of syphilis still useful in patients with HIV infection? A widely quoted report described the case of a patient with the acquired immunodeficiency syndrome (AIDS) who initially had seronegative secondary syphilis; a VDRL test did eventually become positive, although not until at least 20 days after the onset of a syphilitic rash.[33] Despite this report, there is little other evidence so far that seronegative syphilis poses an important diagnostic problem in patients with HIV.

Is the rate of false-positive serologic tests for syphilis substantially increased? Polyclonal B-cell activation is recognized to occur early in HIV infection, possibly leading to an increased rate of false-positive tests. A study of more than 4,800 patients found that the false-positive RPR rate in patients with HIV was about 4%, whereas in HIV-negative patients, the rate was slightly less than 1%.[11] Thus, although the number of false-positive tests does appear to be increased, the overall rate remains manageably low.

Other studies have found that higher titers of nontreponemal antibody develop in patients with HIV and early syphilis than in HIV-negative patients. A study from New York found a median RPR titer of 1:128 in a group of HIV-infected patients compared with 1:32 in a group of non–HIV-infected patients.[34] These higher titers have raised concern for the "prozone effect": false-negative serologic tests due to vast antibody excess. In such cases, positive serologic tests can be detected by diluting the specimen. Despite this concern, so far the prozone effect appears to be of predominantly theoretical rather than clinical importance in patients with HIV.

Finally, treponemal antibody seroreversion may be more frequent in patients with HIV. The rate of seroreversion was compared in patients without HIV, with

early asymptomatic HIV, and with symptomatic HIV, and it was found that the rate of seroreversion progressively increased with worsening immune function.[35] No HIV-negative patients lost the treponemal antibody response after treatment, but 7% with asymptomatic HIV and 38% with symptomatic HIV became seronegative. The clinical importance of this difference is unclear because all patients in the study had been treated, and it is known that healthy patients treated for syphilis may become treponemal antibody-negative.[19] Despite these caveats—a higher incidence of false-positive tests and higher rate of seroreversion after treatment—the serologic response to syphilis is generally preserved and remains useful in diagnosing syphilis in patients with HIV infection.

Clinical Manifestations of Syphilis in Patients Infected With the Human Immunodeficiency Virus

Are the clinical manifestations of syphilis altered in patients with HIV infection? Researchers in New York who evaluated patients with syphilis who did or did not have HIV infection found no significant differences in clinical presentation, course of disease, or response to treatment.[34] A number of studies, however, have reported the prevalence of neurosyphilis in HIV-infected patients. One remarkable study found that 9% of HIV-infected patients had a positive CSF-VDRL test; overall, 39% of the patients in this study had abnormal CSF findings that might be attributed to neurosyphilis.[36] In other studies, the prevalence of neurosyphilis (defined as a positive CSF-VDRL test) in unselected patients with HIV has ranged from 1.5% to 2%.[37,38] Reports of cases of symptomatic neurosyphilis in patients with HIV describe the manifestations of early neurosyphilis: meningitis with cranial nerve abnormalities and meningovascular syphilis with focal neurologic deficits, even polyradiculopathy.[39-41] Ocular involvement has been described, involving almost any part of the eye and including retinitis resembling cytomegalovirus infection. Cranial nerve VIII is also commonly involved with syphilitic meningitis. All these manifestations are well known to occur in non-immunocompromised patients; whether these neurologic syndromes are more severe in patients with HIV infection is unknown.

There is increasing evidence that HIV-infected patients may not respond as well as non-immunocompromised patients to standard treatment of early syphilis. In one study, three patients with secondary syphilis and HIV infection were treated appropriately for secondary syphilis with a single dose of benzathine penicillin.[5] All three had viable *T pallidum* recovered from the CSF after treatment. A recent review found that of 42 reported patients with HIV presenting with symptomatic neurosyphilis, 16 had received standard therapy with penicillin for earlier stages of syphilis.[42] Historically, the risk of early neurosyphilis ("neurorecurrence") is higher in partially treated patients. If standard therapy for early syphilis is more likely to fail for HIV-infected patients, the patients may be at increased risk for the development of early neurosyphilis after receiving usual treatment.[17]

The optimal evaluation of patients with HIV and early syphilis remains unclear. Because early asymptomatic CNS involvement is a risk factor for later symptomatic neurosyphilis, early CSF abnormalities may be important to recognize in patients infected with HIV. For this reason, some experts recommend lumbar puncture for all stages of syphilis in HIV-infected patients; others reserve CSF examination for patients with secondary or latent syphilis. Patients infected with HIV who have latent syphilis definitely require CSF examination to rule out neurosyphilis before treatment.[25]

The diagnosis of neurosyphilis is complicated in HIV-infected patients by the frequency of CSF abnormalities—pleocytosis and elevated protein levels—resulting from HIV infection itself.[43] It remains difficult to determine whether these nonspecific CSF findings should be attributed to neurosyphilis in HIV-infected patients with evidence of syphilis infection. Until better methods of diagnosis are developed, HIV-infected patients with evidence of syphilis and unexplained CSF pleocytosis or elevated protein levels, as well as those with a positive CSF-VDRL test, should be treated with a regimen appropriate for neurosyphilis.

Treatment of Syphilis in Patients Infected With the Human Immunodeficiency Virus

For HIV-infected patients with early syphilis, no change in standard therapy is currently recommended by the CDC. Some experts suggest treating with a more intensive antibiotic course early in the course of infection (such as 3 weekly doses of benzathine penicillin rather than a single dose), given evidence of treatment failures with standard therapy, although data to support or refute this approach are lacking.[42]

Penicillin remains the most reliable therapy for neurosyphilis; patients with a penicillin allergy should be desensitized for treatment. The use of ceftriaxone sodium cannot currently be recommended.[29] Although until recently, no treatment failures had been documented in HIV-infected patients who received standard penicillin therapy for neurosyphilis, a number of cases have now been reported in which such patients failed to respond to the recommended regimen.[44,45] Penicillin treatment of early syphilis had previously failed in some of the same patients. These reports strongly suggest that there may be no reliable cure for neurosyphilis in these patients.

Follow-up after the treatment of early syphilis consists of a clinical evaluation and serologic tests at intervals of 1, 2, 3, 6, 9, and 12 months to ensure that titers are declining appropriately—at least fourfold in 3 to 6 months. If the VDRL or RPR titer has not changed after six months, it is appropriate to reevaluate the patient, including examination of the CSF, before retreatment.

Evaluating the response to treatment of neurosyphilis requires the same measures, along with serial CSF examinations at six-month intervals over two years or

until CSF results return to normal. The appropriate rate of the resolution of CSF abnormalities in these patients is not established; generally, the same guidelines as for non–HIV-infected patients are followed: pleocytosis resolution over six months, with a slower decline in an elevated CSF protein level and the CSF-VDRL titer. Patients with persistently abnormal CSF values or inadequate serum RPR or VDRL titer response to treatment may be candidates for retreatment. Given the possibility of treatment failure, these patients require even greater than usual vigilance to ensure an adequate treatment response.

Conclusion

With its recent resurgence in the United States, syphilis has been transformed from a primarily historical disease to an important public health concern. The treatment of choice in all stages of infection is penicillin; doxycycline is a reasonable alternative for early syphilis. In patients with late latent disease, distinguishing asymptomatic neurosyphilis from late latency is necessary to determine the optimal treatment. Symptomatic neurosyphilis now presents mainly as meningitis and meningovascular syphilis, manifestations that may be more common in patients infected with HIV. Despite some limitations, serologic testing remains useful in patients with HIV infection. Finally, clinical and serologic follow-up is crucial in all patients, especially those with concurrent HIV infection, to detect treatment failures and thus prevent the occurrence of late complications.

REFERENCES

1. Division of STD/HIV Prevention: Sexually Transmitted Disease Surveillance, 1992. Atlanta, Ga, Centers for Disease Control, 1992

2. Rolfs RT, Nakashima AK: Epidemiology of primary and secondary syphilis in the United States, 1981 through 1989. JAMA 1990; 264:1432-1437

3. Schober PC, Gabriel G, White P, Felton WF, Thin RN: How infectious is syphilis? Br J Vener Dis 1983; 59:217-219

4. Moore J: Asymptomatic neurosyphilis—V. A comparison of early and late asymptomatic neurosyphilis. Arch Dermatol Syph 1928; 18:99-108

5. Lukehart SA, Hook EW 3d, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH: Invasion of the central nervous system by *Treponema pallidum*: Implications for diagnosis and treatment. Ann Intern Med 1988; 109:855-862

6. Merritt H: The early clinical and laboratory manifestations of syphilis of the central nervous system. N Engl J Med 1940; 223:446-450

7. Simon RP: Neurosyphilis. Arch Neurol 1985; 42:606-613

8. Clark E, Danbolt N: The Oslo study of the natural course of untreated syphilis: An epidemiologic investigation based on a re-study of the Boeck-Bruusgaard material. Med Clin North Am 1964; 48:613-623

9. Stokes JH, Beerman H, Ingraham NR Jr: Modern Clinical Syphilology. Philadelphia, Pa, WB Saunders, 1944

10. Hart G: Syphilis tests in diagnostic and therapeutic decision making. Ann Intern Med 1986; 104:368-376

11. Rompalo AM, Cannon RO, Quinn TC, Hook EW 3d: Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis 1992; 165:1124-1126

12. Goldman JN, Lantz MA: FTA-ABS and VDRL slide test reactivity in a population of nuns. JAMA 1971; 217:53-55

13. Wentworth BB, Thompson MA, Peter CR, Bawdon RE, Wilson DL: Comparison of a hemagglutination treponemal test for syphilis (HATTS) with other serologic methods for the diagnosis of syphilis. Sex Transm Dis 1978; 5:103-114

14. Schroeter AL, Lucas JB, Price EV, Falcone VH: Treatment for early syphilis and reactivity of serologic tests. JAMA 1972; 221:471-476

15. Smith C, Kamp J, Olansky S, Price E: Benzathine penicillin G in the treatment of syphilis. Bull WHO 1956; 15:1087-1096

16. Mohr JA, Griffiths W, Jackson R, Saadah H, Bird P, Riddle J: Neurosyphilis and penicillin levels in cerebrospinal fluid. JAMA 1976; 236:2208-2209

17. Musher DM, Hamill RJ, Baughn RE: Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann Intern Med 1990; 113:872-881

18. Brown ST, Zaidi A, Larsen SA, Reynolds GH: Serological response to syphilis treatment—A new analysis of old data. JAMA 1985; 253:1296-1299

19. Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ: Serologic response to treatment of infectious syphilis. Ann Intern Med 1991; 114:1005-1009

20. Merritt H: Neurosyphilis. New York, NY, Oxford University Press, 1946

21. Traviesa DC, Prystowsky SD, Nelson BJ, Johnson KP: Cerebrospinal fluid findings in asymptomatic patients with reactive serum fluorescent treponemal antibody absorption tests. Ann Neurol 1978; 4:524-530

22. Dans PE, Cafferty L, Otter SE, Johnson RJ: Inappropriate use of the cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) test to exclude neurosyphilis. Ann Intern Med 1986; 104:86-89

23. Berinstein D, DeHertogh D: Recently acquired syphilis in the elderly population. Arch Intern Med 1992; 152:330-332

24. Wiesel J, Rose DN, Silver AL, Sacks HS, Bernstein RH: Lumbar puncture in asymptomatic late syphilis—An analysis of the benefits and risks. Arch Intern Med 1985; 145:465-468

25. Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines. MMWR 1993; 42:27-46

26. Jaffe H, Kabins S: Examination of cerebrospinal fluid in patients with syphilis. Rev Infect Dis 1982; 4:S842-S846

27. Jordan KG: Modern neurosyphilis—A critical analysis. West J Med 1988; 149:47-57

28. Faber WR, Bos JD, Rietra PJ, Fass H, Van Eijk RV: Treponemicidal levels of amoxicillin in cerebrospinal fluid after oral administration. Sex Transm Dis 1983; 10:148-150

29. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE: Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am J Med 1992; 93:481-488

30. Dattner B, Thomas E, De Mello L: Criteria for the management of neurosyphilis. Am J Med 1951; 10:463-467

31. Quinn TC, Cannon RO, Glasser D, et al: The association of syphilis with risk of human immunodeficiency virus infection in patients attending sexually transmitted disease clinics. Arch Intern Med 1990; 150:1297-1302

32. Hutchinson CM, Rompalo AM, Reichart CA, Hook EW 3d: Characteristics of patients with syphilis attending Baltimore STD clinics—Multiple high-risk subgroups and interactions with human immunodeficiency virus infection. Arch Intern Med 1991; 151:511-516

33. Hicks CB, Benson PM, Lupton GP, Tramont EC: Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma—A diagnostic dilemma. Ann Intern Med 1987; 107:492-495 [erratum published in Ann Intern Med 1987; 107:946]

34. Gourevitch MN, Selwyn PA, Davenny K, et al: Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. Ann Intern Med 1993; 118:350-355

35. Haas JS, Bolan G, Larsen SA, Clement MJ, Bacchetti P, Moss AR: Sensitivity of treponemal tests for detecting prior treated syphilis during human immunodeficiency virus infection. J Infect Dis 1990; 162:862-866

36. Holtom PD, Larsen RA, Leal ME, Leedom JM: Prevalence of neurosyphilis in human immunodeficiency virus-infected patients with latent syphilis. Am J Med 1992; 93:9-12

37. Berger JR: Neurosyphilis in human immunodeficiency virus type 1-seropositive individuals—A prospective study. Arch Neurol 1991; 48:700-702

38. Katz DA, Berger JR: Neurosyphilis in acquired immunodeficiency syndrome. Arch Neurol 1989; 46:895-898

39. Johns DR, Tierney M, Felsenstein D: Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. N Engl J Med 1987; 316:1569-1572

40. Feraru ER, Aronow HA, Lipton RB: Neurosyphilis in AIDS patients: Initial CSF VDRL may be negative. Neurology 1990; 40(pt 1):541-543

41. Berry CD, Hooton TM, Collier AC, Lukehart SA: Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. N Engl J Med 1987; 316:1587-1589

42. Musher DM: Syphilis, neurosyphilis, penicillin, and AIDS. J Infect Dis 1991; 163:1201-1206

43. Hollander H: Cerebrospinal fluid normalities and abnormalities in individuals infected with human immunodeficiency virus. J Infect Dis 1988; 158:855-858

44. Gordon SM, Eaton ME, George R, Larsen S, Lukehart SA: The response of symptomatic neurosyphilis to high-dose penicillin G in patients with human immunodeficiency virus infection. N Engl J Med 1994; 331:1469-1473

45. Horowitz H, Valsamis MP, Wicher V, et al: Brief report: Cerebral syphilitic gumma confirmed by the polymerase chain reaction in a man with human immunodeficiency virus infection. N Engl J Med 1994; 331:1488-1491