REVIEW ARTICLE

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The Modern Epidemic of Syphilis

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Syphilis was first recognized in Europe in the late 15th century[1]; its cause, *Treponema pallidum* subspecies *pallidum*, was identified four centuries later. The advent of penicillin, together with effective public health measures, was responsible for a marked decline in syphilis in the United States and Europe. Today, however, the incidence of syphilis in the United States has returned to levels not seen in more than 20 years, and the numbers of cases reported to the Centers for Disease Control and Prevention (CDC) increased by 81% from 2014 to 2018.[2] Recognition of syphilis, with its versatile presentations, can challenge even the most experienced clinician, and the natural history of both untreated and treated disease can be unpredictable.

Epidemiology

Syphilis has had a major effect on several at-risk populations over time. Since 2000, for example, the increase in rates of primary and secondary syphilis in the United States has been largely attributable to an increase in rates among men by a factor of more than 3; in 2018, men accounted for 86% of all patients with syphilis.[2] More than half of men with incident syphilis reported having sex with men, and 42% of those men were infected with the human immunodeficiency virus (HIV), a finding that highlights the strong association between incident syphilis and an increased risk of HIV infection, which can also be accompanied by other sexually transmitted infections. Similar increases in syphilis among men who have sex with men have been reported in Europe[3] and China.[4] A second, more recent epidemic in the United States is affecting heterosexual men and women. Rates of primary and secondary syphilis among women more than doubled between 2014 and 2018.[2] Alarmingly, the number of incident syphilis cases rose by a factor of 6 among women who used methamphetamine, heroin, or other injected drugs or who had sex with a person who injected drugs.[5] The remarkable increase in the number of cases of primary and secondary syphilis among women of childbearing age is mirrored by increasing numbers of congenital syphilis cases and increasing infant mortality.[2] All stages of syphilis in pregnant women pose a risk of transmission to the fetus, but the risk is considerably higher with early syphilis than with later stages of disease. These data suggest a link between illicit drugs and the rise of congenital syphilis in the United States.

Natural History and Clinical Recognition of Syphilis

T. pallidum disseminates within days after infection, resulting in early invasion of distant tissues, including the central nervous system (CNS), and transplacental infection of the fetus in a pregnant woman.[6] The primary stage of syphilis may be manifested clinically as a solitary chancre, indurated and ulcerative, with a clean

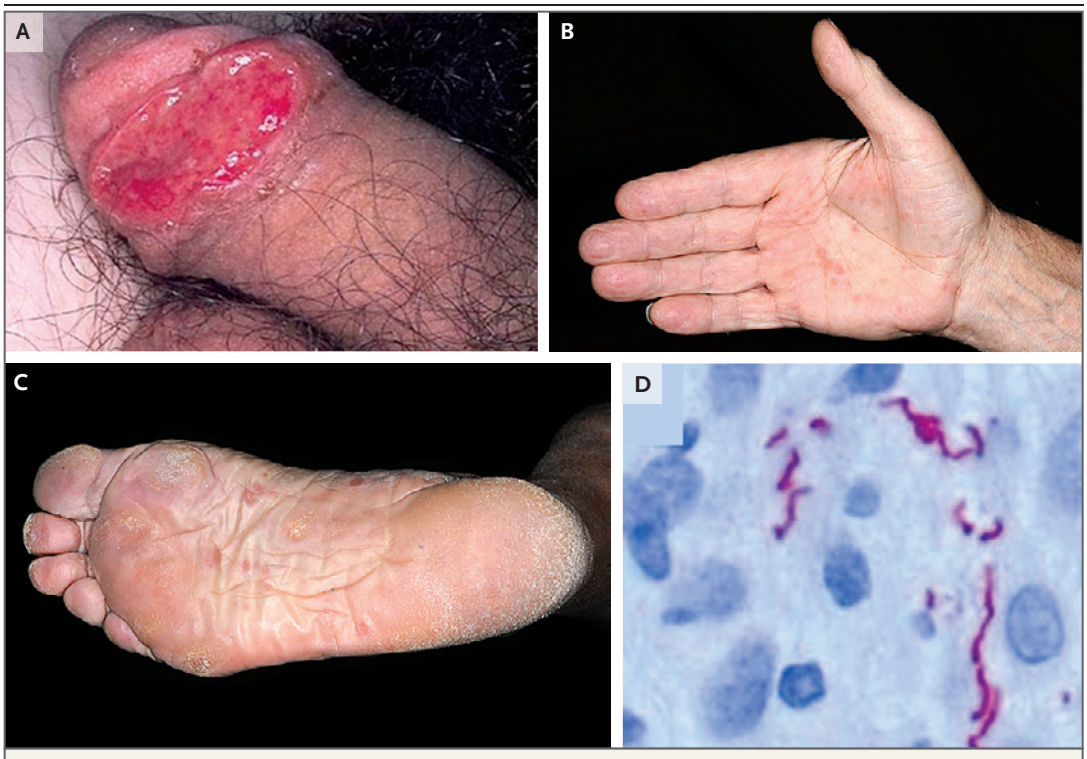

Figure 1. Primary and Secondary Lesions of Syphilis.

Panel A shows a syphilitic chancre with a clean base and heaped-up margins. Panels B and C show scaly plaque on the palm and sole, respectively, of a patient with syphilis. Panel D shows bacteria with a corkscrew appearance, which is characteristic of *Treponema pallidum*, on immunohistopathological examination of a biopsy sample from a lesion. The images in Panels B, C, and D are from Schön and Bertsch.[7]

base (Fig. 1A), which typically appears at the site of contact with the sex partner's infectious lesion.[8] The chancre is usually painless and may occur at extragenital sites such as the perirectal area, the rectum itself, or the oral cavity. Multiple painful anogenital ulcers may also occur.[9]

Clinical manifestations of secondary syphilis include a mild, nonpruritic rash, particularly on the palms and soles (Fig. 1B and 1C); fever; lymphadenopathy; mucosal lesions (e.g., mucous patches or condyloma latum); alopecia; periostitis; and occasionally hepatitis (often with high alkaline phosphatase values but minimally elevated aminotransferase levels) or nephritis. All these manifestations have a broad differential diagnosis. Primary syphilis and secondary syphilis are the sexually transmissible stages of infection.

Early latent syphilis, an asymptomatic stage, can occur between the primary and secondary stages and can also occur after the resolution of secondary-stage lesions. In up to 24% of patients, early latent syphilis is interrupted by relapse with recurrent, infectious secondary lesions (Fig. 2).[10-13] The high proportion of cases of early latent syphilis suggests that primary syphilis and secondary syphilis frequently go unnoticed or are misidentified. The CDC uses a 1-year cutoff point for the duration of infection to demarcate early latent from late latent syphilis because most relapses occur within 1 year[14]; thus, syphilis may also be infectious in the early latent phase.

Asymptomatic or symptomatic neurologic involvement may occur during any stage of syphilis.[13,15] Certain treponemal types (e.g., strain type 14d/f) may have an enhanced propensity to invade the CNS.[16] CNS invasion by treponemes is accompanied by abnormal cerebrospinal fluid (CSF) findings in up to 50% of persons after early infection, even in the absence of clinical features (termed asymptomatic neurosyphilis). These CSF abnormalities typically resolve after recommended therapy for early syphilis. Early

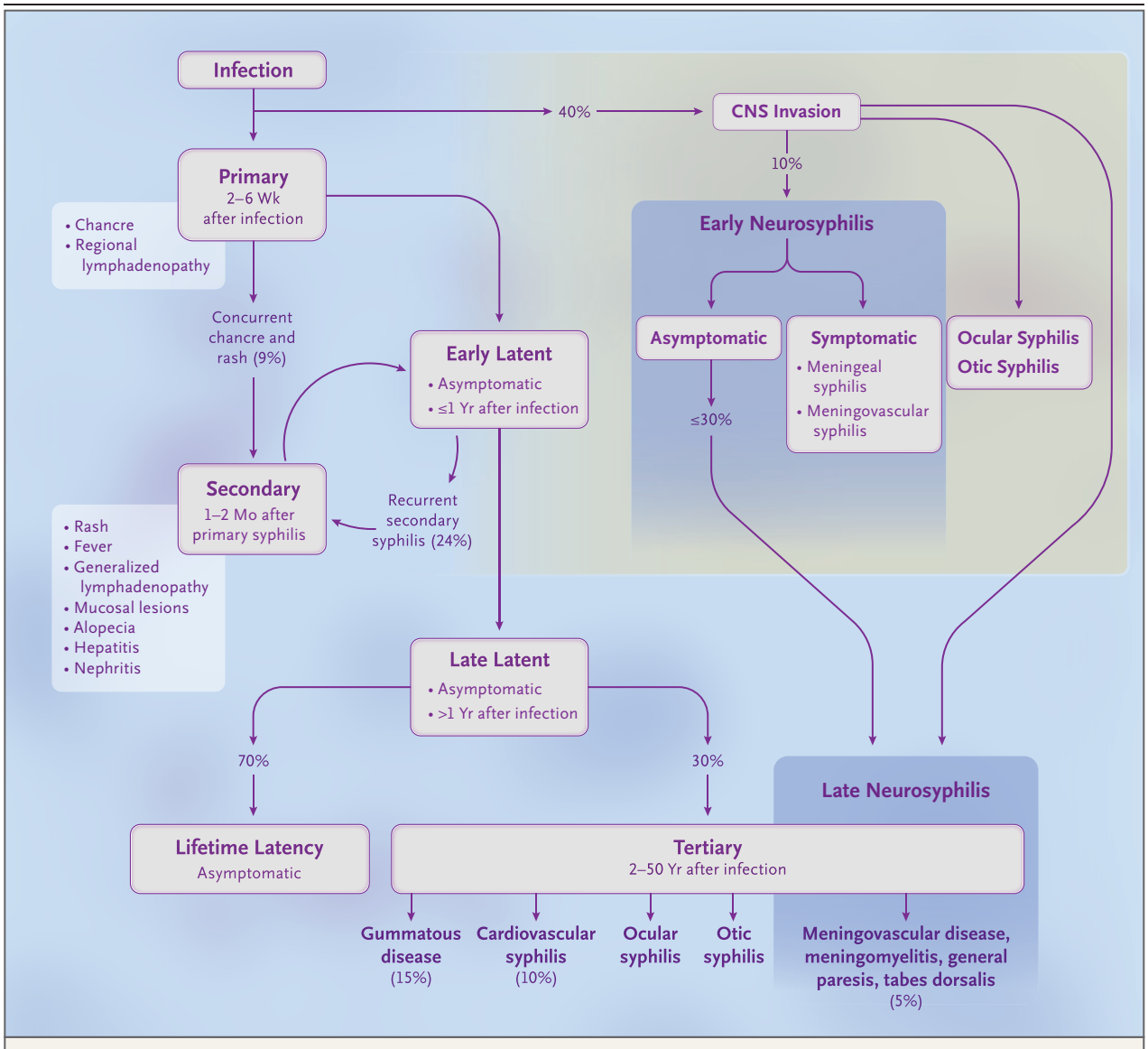

Figure 2. Natural History of Untreated Syphilis.

The time intervals between stages of syphilis are shown, along with the approximate percentages of persons progressing to the indicated stages. Invasion of the central nervous system (CNS) by treponemes may not be a necessary prerequisite for the development of certain forms of ocular syphilis. Adapted from Ho and Lukehart.[10]

clinical findings (i.e., early neurosyphilis or "neurorecurrence") include meningitis, often a basilar form resulting in cranial-nerve abnormalities.[13] The tertiary (i.e., late) neurologic manifestations of syphilis are either meningovascular or parenchymatous.[13] Meningovascular syphilis usually occurs 5 to 12 years after initial infection but can occur earlier or later; manifestations may include hemiplegia, aphasia, and seizures. The vessels of the spinal cord may also be involved, resulting in meningomyelitis and spinal vascular syphilis. The parenchymatous forms, general paresis and tabes dorsalis, tend to occur later (>15 years after infection). Manifestations of general paresis include irritability and cognitive and memory impairments, followed by emotional lability, delusions, and paranoia. Manifestations of tabes dorsalis include lightning pains, ataxia, bladder disturbances, visceral crises, and rectal incontinence.

Neurologic deficits, including recent visual or hearing changes, may be subtle and are often overlooked unless the clinician makes a specific inquiry.[17] Ocular syphilis and otic syphilis are, technically, distinct entities from neurosyphilis but may occur concomitantly. Like neurosyphilis, they can occur during any stage of infection. Clusters of cases of ocular syphilis have been reported in the past 5 years throughout the United States.[18,19] Ocular syphilis may affect any part of the eye (uveitis is the most common clinical presentation), and there are generally no pathognomonic characteristics to help guide the clinical diagnosis.[20] Patients with otic syphilis usually present with hearing loss, tinnitus, or both.[21] If either ocular or otic syphilis is suspected, the patient should be referred to a specialist for immediate evaluation in order to minimize long-term sequelae.

In addition to the neurologic manifestations, cardiovascular disorders and gummas are the other tertiary manifestations of syphilis.[8] Cardiovascular syphilis occurs 15 to 30 years after infection and may lead to the development of aortic aneurysms (often involving the ascending aorta), aortic insufficiency, coronary-artery stenosis, and myocarditis. Gummatous syphilis (also called late benign syphilis) represents a proliferative granulomatous process that can occur in any tissue, including the brain.

DIAGNOSTIC TESTS

Most clinical settings lack the capacity to perform direct detection of *T. pallidum* with darkfield microscopy when lesions are present. Nucleic acid amplification tests to detect *T. pallidum* from lesions are not approved by the Food and Drug Administration (FDA) but may be used to diagnose primary, secondary, or congenital syphilis.[22] However, a negative nucleic acid amplification test does not rule out the infection. When tissue sections are available, immunohistopathological identification of organisms is the preferred method for detecting *T. pallidum* (Fig. 1D).

The majority of syphilis cases are diagnosed by means of serologic testing. Two algorithms are commonly used, and both require two-stage testing.[23] The algorithms vary only in the order in which the tests are performed. The standard screening algorithm begins with a nontreponemal test (e.g., a rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test), with reactivity confirmed with the use of a highly sensitive and specific treponemal test (e.g., the *T. pallidum* particle-agglutination test or an automated enzyme or chemiluminescence immunoassay). With the reverse screening algorithm, the treponemal test is used initially; reactive serum samples are then reflex-tested with the nontreponemal test, providing titers that are necessary for clinical management. If the nontreponemal test is nonreactive, further testing is necessary with a confirmatory treponemal test that uses antigens distinct from those in the initial treponemal test. The interpretation of serologic test results is the same, irrespective of the testing algorithm used (Table 1, and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Performance characteristics of the algorithms are influenced by the prevalence of syphilis (Fig. S2).

A few important properties of serologic tests for syphilis can help with the interpretation of the algorithm results. Serologic results are nonreactive in up to 30% of persons with primary syphilis, and testing should therefore be repeated in 2 weeks if the initial test result is nonreactive. Nontreponemal test titers often decline rapidly after treatment but may also decline, although more slowly, in the absence of treatment. Treponemal tests remain reactive irrespective of the treatment history, but up to 24% of patients treated in the early stage of syphilis have seroreversion years after therapy[24] (Fig. 3).

Several serologic point-of-care tests that detect treponemal antibodies, nontreponemal antibodies, a combination of treponemal and nontreponemal antibodies, or a combination of HIV and treponemal antibodies are available worldwide.[27] Only one point-of-care test that detects treponemal antibodies has been approved by the FDA. Although the potential value of point-of-care tests could be substantial in some clinical settings (e.g., resource-limited antenatal care[28]), the data on their performance characteristics in the field are limited, and their use should be accompanied by a robust quality-assurance program.

There are no standard tests for the diagnosis of neurosyphilis, so a combination of laboratory tests and clinical signs and symptoms is used. A reactive CSF nontreponemal test is highly predictive of neurosyphilis, although it is less than 80% sensitive. A CSF treponemal test can be

Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*

Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse-sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse-sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse-sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse-sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

* The traditional algorithm starts with a nontreponemal test (NTT) followed, if reactive, by a confirmatory treponemal test (TT). The reverse-sequence algorithm starts with a TT (e.g., fluorescent treponemal-antibody absorption test, *Treponema pallidum* particle agglutination test, or automated enzyme or chemiluminescence immunoassay), followed, if reactive, by an NTT. RPR denotes rapid plasma reagin, and VDRL Venereal Disease Reference Laboratory.

† The confirmatory TT should be different from the TT performed initially.

‡ The likely or most likely interpretation of test results is noted for each algorithm.

§ Causes of a biologic false positive NTT include older age, autoimmune diseases, infections (e.g., human immunodeficiency virus infection), and drug use; pregnancy as a cause is controversial.

¶ Causes of a biologic false positive TT include infections (e.g., Lyme disease), autoimmune diseases, and older age.

sensitive, but it lacks specificity owing to passive transfer of serum treponemal IgG antibodies across the blood–CSF barrier or to traces of blood in the CSF. Although not usually recommended, a CSF treponemal test may be useful to rule out neurosyphilis when the pretest probability is moderate to low.[29] A polymerase-chain reaction assay of CSF for *T. pallidum*, although specific, is insensitive.[22] Pleocytosis (>5 cells per cubic millimeter; >20 cells per cubic millimeter in HIV-infected patients who are not receiving antiretroviral therapy) is a sensitive but not a specific marker for neurosyphilis. CSF protein levels may be elevated in patients with neurosyphilis, but this finding has limited sensitivity and specificity.

MANAGEMENT OF SYPHILIS

CSF EXAMINATION

The CDC does not recommend routine CSF examination for persons with early syphilis, irrespective of HIV status, unless neurologic signs are present.[14] A CSF examination is necessary in all patients with neurologic signs or symptoms and in neurologically asymptomatic patients with evidence of tertiary syphilis.[14] In addition, a CSF examination may be considered in neurologically asymptomatic patients with inadequate serologic responses on nontreponemal testing after therapy (see the discussion below).[14] Risk factors for neurosyphilis in HIV-infected patients include a serum RPR titer of 1:32 or higher, a peripheral-blood CD4 count of 350 cells per cubic millimeter or lower, and an absence of antiretroviral therapy.[30,31] The estimated risk of neurosyphilis (asymptomatic or symptomatic) in this population is not well defined, partly because of inconsistencies in the definition of neurosyphilis among studies. Evidence that identification of asymptomatic neurosyphilis predicts treatment failure is insufficient, even in patients with HIV infection.[32] Some experts recommend CSF examination in such patients, but support from high-quality data is lacking. A CSF examination is not necessary to diagnose ocular or otic syphilis in patients with reactive serologic tests because up to 30% of patients with ocular syphilis[33]

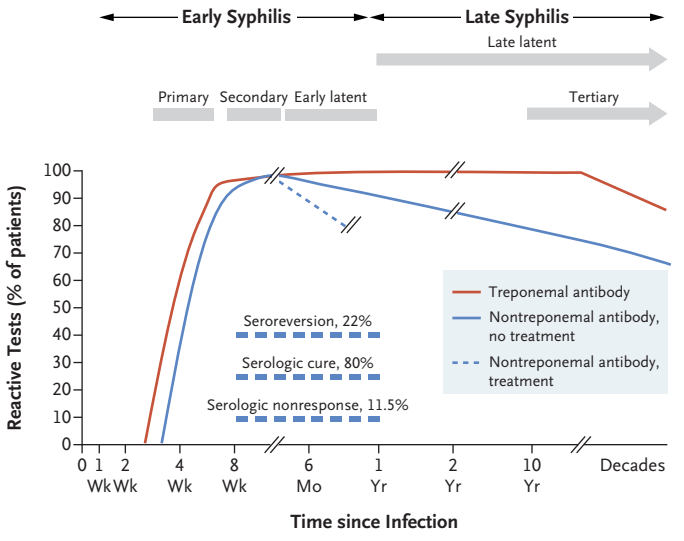

Figure 3. Serologic Responses (in Serum) throughout the Natural History of Treated and Untreated Syphilis.

We assume that treatment occurred in the secondary stage and that outcomes are measured at 1 year, on the basis of information from Romanowski et al.[24] Seroreversion of the nontreponemal test (NTT) titer occurs in 22% of patients who are treated; a decrease in the NTT titer by a factor of 4 or more is associated with serologic cure in 80%, and a decrease in the NTT titer by a factor of less than 4 is associated with serologic nonresponse in 11.5%. Treponemal antibodies that are detected by means of treponemal tests, with the exception of the fluorescent treponemal-antibody absorption test, are in general more sensitive than nontreponemal antibodies (detected by means of NTTs) in patients with primary syphilis.[25,26] Up to 24% of patients treated in the early stage of syphilis show seroreversion of their treponemal tests years after therapy (not shown). The gray bars and blue dashed bars indicate time ranges.

and up to 90% of patients with otic syphilis[34] have a normal CSF examination.

ANTIMICROBIAL AGENTS

Penicillin is highly effective for all stages of syphilis and is the drug of choice.[35] Resistance to penicillin has not been observed in *T. pallidum*. A single dose of 2.4 million units of long-acting penicillin G benzathine, given intramuscularly, sustains treponemicidal drug levels in blood for 7 to 10 days and is effective in the treatment of uncomplicated early syphilis (Table 2).[14] Late latent syphilis is treated with a total of three doses of penicillin G benzathine, given at weekly intervals. Although 7 days is the ideal interval between doses, up to 10 days between doses may be acceptable in nonpregnant adults.[36] Recent shortages of penicillin G benzathine underscore the importance of establishing alternative treatment regimens, particularly in pregnant women. Persons with neurosyphilis or ocular or otic syphilis are treated with intravenous aqueous penicillin G because of the inability to achieve measurable levels of penicillin G benzathine in the CSF.[37] For persons with a documented penicillin allergy, desensitization and treatment with penicillin are recommended. Limited data preclude the use of alternative antibiotic agents, which should be considered only when treatment with penicillin is not possible or is absolutely contraindicated.

Studies in the 1950s suggested that tetracycline was effective in treating early syphilis.[38] Subsequently, small retrospective analyses have shown that the efficacy of oral doxycycline is similar to that of penicillin G benzathine.[39,40] Limited data have shown that doxycycline administered for 28 days is also effective for late latent syphilis in persons with or without HIV infection.[41]

Ceftriaxone has been shown to have efficacy similar to that of penicillin in all stages of syphilis, although the data are restricted to observational studies.[42,43] Ceftriaxone penetrates the CNS well and is an option for treating neurosyphilis in nonpregnant adults with penicillin allergy in whom desensitization is not possible. Ampicillin and amoxicillin are treponemicidal in a rabbit model of syphilis[44] and in treponemal loss-of-motility assays in vitro,[45] but the use of these agents as alternatives for management is not yet supported by robust evidence.[46]

Azithromycin has been shown to be effective for the treatment of early syphilis in several randomized trials.[47] However, resistance to azithromycin and other macrolides (A→G mutations at position 2058 or 2059 in 23S ribosomal DNA) has been detected globally.[48,49] Azithromycin should no longer be used for the treatment of syphilis in most clinical settings.[50]

SCREENING DURING PREGNANCY

All women should be screened for syphilis early in pregnancy. Women at high risk for infection should be screened again at 28 weeks of gestation and at delivery. Although there is a critical need for alternatives to parenteral penicillin regimens during pregnancy, data supporting the use of alternative regimens are insufficient at this time.[51] Despite the lack of evidence, some experts recommend an additional dose of peni-

cillin G benzathine 1 week after the first dose for the treatment of early syphilis because of an increase in the volume of distribution. For the treatment of late latent infection in pregnant women, the full course of penicillin G benzathine should be repeated if the interval between doses is more than 7 days.[14,52]

TESTING IN ELDERLY PERSONS WITH REACTIVE SEROLOGIC TESTS AND COGNITIVE DECLINE

Although serologic testing for syphilis in elderly patients undergoing an evaluation for dementia is not routinely recommended in most clinical settings,[53] such testing is frequently performed. Consequently, patients may be found to have reactive serologic tests (a reactive treponemal test accompanied by either a reactive or a nonreactive nontreponemal test). Information about a history of syphilis, treatment, and nontreponemal titers may be valuable but is rarely available. Before CSF testing is performed, clinicians should estimate the probability of syphilis (by noting the presence or absence of symptoms consistent with general paresis, for example), as opposed to another diagnosis, as a cause of the observed neurologic findings. If the pretest probability is moderate or high, a CSF examination is warranted. If the pretest probability is low and no information about prior treatment is available, clinicians may elect to forgo a CSF examination and provide treatment with three weekly doses of penicillin G benzathine.[54] Despite the lack of consistent treponemicidal concentrations in the CSF, three weekly doses of penicillin G benzathine was an approved alternative regimen for the treatment of neurosyphilis until the early 1980s and was reasonably effective.[55,56]

NONTREPONEMAL TITER RESPONSES AFTER THERAPY

The major goal of treatment for syphilis is a clinical and serologic cure. In the preantibiotic era, the complete seroreversion of nontreponemal titers from reactive to nonreactive was often considered to constitute a serologic cure. That definition was used because patients with early syphilis in whom nontreponemal titers did not serorevert (often referred to as "serofast" titers) were more likely to have subsequent neurologic complications. With the availability of antibiotics and more sensitive nontreponemal tests, serologic cure now refers to a decline by a factor of 4 or more in nontreponemal titers 6 to 12 months after therapy for early syphilis and 12 to 24 months after therapy for late syphilis. This definition of a serologic cure is based, surprisingly, on scant objective data[24,57] but on more than 70 years of clinical experience.

When treatment does not result in the expected decline by a factor of 4 or more in nontreponemal titers and reinfection is deemed unlikely, the term "serologic nonresponse" is used. About 20% of patients with early syphilis have a serologic nonresponse at 6 months; this proportion declines to 11.5% at 12 months.[58] The implications of a serologic nonresponse, however, are not well defined.[59] Clinically, it is unclear whether patients with a serologic nonresponse are at increased risk for disease progression — hence, the current recommendation to consider a CSF examination.[14] Studies assessing the risks of neurosyphilis among persons with a serologic nonresponse have yielded mixed findings, depending on the population being studied.[60,61]

Table 2. Treatment Guidelines for Antimicrobial Management of Syphilis.*

For primary and secondary syphilis in nonpregnant adults, including HIV-infected adults:
Penicillin G benzathine, 2.4 million units in a single IM dose
Doxycycline, 100 mg orally twice a day for 14 days (first alternative)
Ceftriaxone, 1–2 g daily, IM or IV, for 10–14 days (second alternative)

For latent syphilis in nonpregnant adults, including HIV-infected adults:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals
Doxycycline, 100 mg orally twice a day for 28 days (alternative)

For late syphilis (gummas and cardiovascular manifestations) but not neurosyphilis:
Penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

For neurosyphilis and ocular syphilis:
Aqueous crystalline penicillin G, 18–24 million units per day, administered in IV doses of 3–4 million units every 4 hr or as a continuous infusion, for 10–14 days
Penicillin G procaine, 2.4 million units in a single IM dose daily, plus probenecid, 500 mg administered orally four times a day, both for 10–14 days (alternative)

For primary and secondary syphilis in pregnancy:
Penicillin G benzathine, 2.4 million units in a single IM dose†

For latent syphilis in pregnancy:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

* Treatment guidelines are from the Centers for Disease Control and Prevention (Workowski and Bolan[14]). IM denotes intramuscular, and IV intravenous.
† Some experts recommend an additional IM dose of 2.4 million units of penicillin G benzathine, given 1 week later.

Whether additional antibiotic therapy is warranted in patients with syphilis and a serologic nonresponse is unclear.[58,62] A controlled study did not reveal improved serologic outcomes in patients who received additional antibiotic therapy.[63] No studies have assessed long-term clinical outcomes. Consequently, clinicians should wait a full 12 months after therapy for early syphilis and 24 months after therapy for late syphilis before considering whether a CSF examination, additional therapy, or both are warranted. Serologic responses in HIV-infected persons are slower.[64] The use of the term "serofast" is confusing because it has been used to suggest a serologic nonresponse (which has unknown clinical significance), a decline in nontreponemal titers by a factor of 4 or more but lack of seroreversion (which represents a serologic cure), or a combination of the two. Today, in the antibiotic era, the only meaningful definition of serofast is a serologic nonresponse.

FOLLOW-UP FOR PATIENTS WITH NEUROSYPHILIS

Current guidelines recommend repeating the CSF examinations at 6-month intervals until CSF measures (e.g., pleocytosis) normalize.[14] Two studies suggest that appropriate declines in nontreponemal titers after therapy for neurosyphilis predict improved CSF measures in both immunocompetent persons and persons with HIV infection who are receiving effective antiretroviral therapy.[65,66] Thus, repeat CSF examinations may not be necessary in most patients who have clinical and serologic responses.

PREVENTION OF SYPHILIS

The classic approach to prevention, outlined by Parran in the 1930s[67] and consisting of screening (Table S1), treatment, health services for sexual partners, and education, remains the basis for syphilis control by public health authorities.[68] These interventions, however, must adapt to the modern world. Sexual-partner services in the era of geosocial networking apps have become more challenging because of the increased anonymity of encounters and the lack of physical social meeting spaces that are important for the identification of contacts.[69] Rates of serologic screening are lagging even among the highest-risk groups.[70] Preexposure HIV prophylaxis, a highly effective HIV prevention strategy, may increase rates of syphilis.[71]

FUTURE DIRECTIONS

Vaccines for the prevention of syphilis are needed, and although progress has been made on this front,[72] a viable candidate is years away. Recent data from two relatively small studies have provided preliminary evidence that a biomedical approach to prevention may be possible. In a study in Los Angeles, doxycycline administered prophylactically at a dose of 100 mg daily reduced the combined odds of syphilis, gonorrhea, and chlamydia infection by 73% in a group of 30 HIV-infected men who have sex with men.[73] An open-label study involving 116 men who have sex with men showed that postexposure prophylaxis with doxycycline (200 mg given orally within 24 hours after a sexual encounter) resulted in a 73% reduction in the risk of incident syphilis over a mean follow-up period of 8.7 months.[74] Further studies are under way to establish the usefulness of such interventions and better define the associated risks (antibiotic resistance, as well as alterations in the microbiome and their consequences) in groups at high risk for syphilis. Thus, the routine use of doxycycline prophylaxis is not yet recommended but may become a useful biomedical preventive strategy in the near future.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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