Clinical Infectious Diseases

STATE OF THE ART REVIEW

State-of-the-Art Review: Neurosyphilis

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We review key concepts in the diagnosis, treatment, and follow-up of individuals with neurosyphilis. We describe the epidemiology of syphilis in the United States, highlight populations that are markedly affected by this infection, and attempt to estimate the burden of neurosyphilis. We describe the cardinal clinical features of early and late (tertiary) neurosyphilis and characterize the clinical significance of asymptomatic neurosyphilis in the antibiotic era. We review the indications for cerebrospinal fluid (CSF) examination and the performance characteristics of different CSF assays including treponemal and lipoidal antibodies, white cell count, and protein concentration. Future biomarkers and the role of imaging are briefly considered. We review preferred and alternative treatments for neurosyphilis and evidence for their use, including evidence for the use of enhanced intramuscular benzathine penicillin G to supplement intravenous penicillin.

Keywords. syphilis; neurosyphilis; *Treponema pallidum*; lumbar puncture; cerebrospinal fluid.

For 21 years, rates of syphilis have increased in the United States. Between 2011 and 2021, the primary and secondary syphilis (PSS) rates per 100 000 among women and men increased by 711% (from 0.9 to 7.3) and 174% (from 9.2 to 25.2), respectively [1]. Disparities abound. In 2021, the highest rate per 100 000 of reported cases of PSS was among non-Hispanic American Indians or Alaska Natives (46.7; 74% increase from 2020), followed by non-Hispanic Black or African Americans (41.9). The former group had the greatest 5-year increase in rates of reported cases of PSS (11 to 46.7; 324.5% increase from 2017) [1].

With increasing rates of syphilis, cases of neurosyphilis have likely increased. While syphilis is a nationally reportable infection, accurate surveillance for neurosyphilis requires documentation of neurological symptoms on a case report. Inconsistent reporting often occurs when neurological symptoms are not communicated to the public health department, even if noted in the patient's medical record [2]. Consequently, the true rates of neurosyphilis in the United States are unknown. In a study of 468 persons diagnosed with all stages of syphilis in King County, Washington, 7.9% (95% confidence interval [CI]: 5.8–10.5) had vision or hearing changes, and 3.5% (95% CI: 2.2–5.4) had both symptoms and either abnormal cerebrospinal fluid (CSF) or an abnormal ophthalmologic examination [3]. In a recent study, among 41 187 syphilis cases in 16 US jurisdictions, any neurological, ocular, or otic manifestation was reported in 2% of cases, with a slightly higher prevalence among people with human immunodeficiency virus (HIV; PWH) [4]. Assuming neurological, ocular, and otic complications occur in 3%–5% of people with syphilis, in 2021, there were 5100–8600 cases of neurosyphilis, ocular syphilis, and otosyphilis in the United States.

This review focuses on neurosyphilis with particular attention to clinically relevant questions. While we did not focus on ocular and otic syphilis, entities distinct from neurosyphilis, we have included some information about these diagnoses to highlight relevant distinctions with neurosyphilis.

CLINICAL MANIFESTATIONS OF NEUROSYPHILIS

Asymptomatic Neurosyphilis

Treponema pallidum, the bacterium responsible for syphilis, disseminates quickly and may invade the central nervous system (CNS) within days (Figure 1) [5, 6]. Neuroinvasion, which is often asymptomatic, occurs in up to 30% of persons with early syphilis and is also documented in the later stages [5, 7]. Neurologically asymptomatic persons with syphilis who have CSF abnormalities (eg, reactive CSF Venereal Disease Research Laboratory (VDRL) test, elevated protein concentrations, and/or pleocytosis) not attributable to other etiologies are deemed to have asymptomatic neurosyphilis. In a seminal study [7], CSF was collected from 58 participants, including 16 PWH. Overall, among those with primary and secondary syphilis, *T. pallidum* was detected in CSF in approximately 30%. Among those with secondary syphilis, *T. pallidum* was isolated from 50% (3 of 6) and 26% (7 of 27) of participants with and without neurological signs or symptoms, respectively. More than 30% (4 of 12) with *T. pallidum*–positive CSF did not have any CSF abnormalities [7]. In another study, 15%–27% of persons with early syphilis without CSF abnormalities

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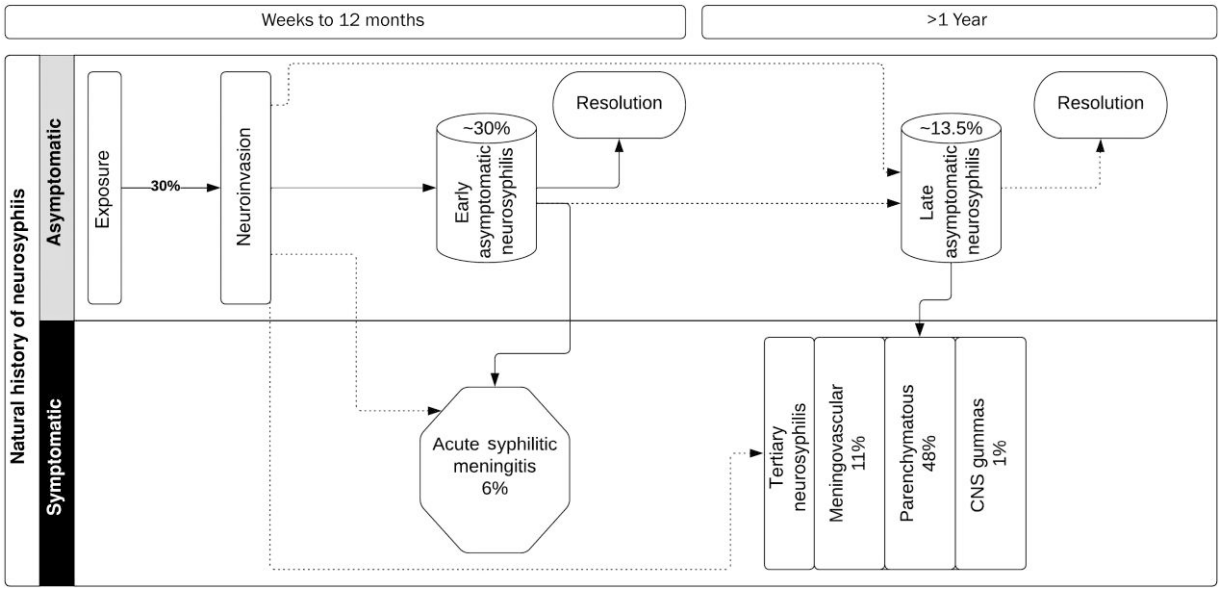

Figure 1. Summary of the natural history of neurosyphilis. Data are based on pre-antibiotic era estimates. Dotted lines suggest a possible relationship; solid lines represent an established relationship. Following exposure, at least 30% of persons will experience neuroinvasion [7, 8]. Early asymptomatic neurosyphilis has been documented in 25%–35% of persons with early syphilis [10] (Moore p. 347, Fig 51) [9]. These cerebrospinal fluid abnormalities will resolve in most persons without treatment. Among those with late syphilis (excluding symptomatic neurosyphilis), 13.5% have asymptomatic neurosyphilis [12]. It is not known whether all persons with late asymptomatic neurosyphilis had early asymptomatic neurosyphilis or if only a subset. Persons with early asymptomatic neurosyphilis may develop symptoms, and their presentation is often that of acute syphilitic meningitis, which represented 6% of all cases of neurosyphilis in the pre-antibiotic era (some with acute syphilitic meningitis may never have had early asymptomatic neurosyphilis). Tertiary neurosyphilis, whether meningovascular (representing 11% of all cases of neurosyphilis), parenchymatous (48%), or CNS gummas (1%), likely progresses from late asymptomatic neurosyphilis; however, some cases may not have experienced antecedent asymptomatic neurosyphilis. Neuroinvasion may not lead to CSF abnormalities and proceed to spontaneous resolution bypassing early symptomatic neurosyphilis. Abbreviation: CNS, central nervous system.

had *T. pallidum*–positive CSF [8]. Consequently, neuroinvasion is presumably necessary but not synonymous with CSF abnormalities that define asymptomatic neurosyphilis. The proportion of persons with persistent neuroinvasion and its relationship to early vs late asymptomatic neurosyphilis are poorly defined (Figure 1). In the pre-antibiotic era, asymptomatic neurosyphilis was documented in 25%–35% of persons with early syphilis [9, 10] and 13.5% of those with late syphilis [11, 12]. In the antibiotic era, the clinical significance of asymptomatic neurosyphilis is not clear. Current national guidelines recommend CSF examinations to diagnose asymptomatic neurosyphilis in patients with tertiary syphilis and in some patients with serological nonresponse or serological failure despite a paucity of data demonstrating improved outcomes with CSF examinations in these populations [13].

Symptomatic Neurosyphilis

Guidelines recommend intensive treatment of symptomatic neurosyphilis, which may occur during any syphilis stage [14]. PWH may be at increased risk for symptomatic neurosyphilis; increased reports of early symptomatic neurosyphilis increased with the advent of the HIV epidemic [15]. Early symptomatic neurosyphilis (within 12 months post-infection) usually manifests as acute meningitis, often basilar. Meningeal inflammation can lead to cranial nerve abnormalities and arteritis, leading to thrombosis of cerebral vessels. Hydrocephalus with increased intracranial pressure has also been described (Table 1). Tertiary manifestations of symptomatic neurosyphilis tend to be either meningovascular (typically 5–12 years post-infection) or parenchymatous (typically >15 years post-infection; Table 1). In meningovascular syphilis, endarteritis of CNS blood vessels can lead to thrombosis with infarction, resulting in stroke and its associated manifestations depending on the location of the infarct. Spinal meningomyelitis or spinal vascular infarct syndromes can also occur [5, 16–18]. Parenchymatous neurosyphilis tends to occur later and manifests either as general paresis (on average, 15–20 years after infection) or tabes dorsalis (on average, 20–25 years after infection) [17, 19]. General paresis is the result of chronic, slowly evolving meningoencephalitis. The onset may be insidious with symptoms of dementia, emotional lability, and a host of psychiatric manifestations and may progress over time until the patient becomes bedridden. Tabetic neurosyphilis results from chronic degeneration of the posterior roots and columns of the spinal cord with various resultant symptoms (Table 1) [5, 11, 16–19]. Rarely, in tertiary syphilis, gummas (tumor-like masses that consist of granulomatous inflammation surrounding a focus of infection) can occur in different parts of the body, including the brain and spinal

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Table 1. Major Clinical Manifestations of Symptomatic Neurosyphilis

Type of Symptomatic Neurosyphilis	Typical Timeframe for Manifestations After Infection	Possible Clinical Syndromes	Possible Symptoms	Possible Findings on Clinical Exam
Meningeal; acute syphilitic meningitis [5, 16–20]	Within 12 mo, though may occur later	Meningitis, often basilar; cranial nerve palsies; involvement of multiple CNs, (especially 3, 6, 7, 8, which may be the result of extensive basilar meningitis); hydrocephalus	Headache, photophobia, nausea, vomiting, confusion, seizure, and manifestations of cranial nerve palsies, for example, double vision or blurry vision, facial droop, ptosis (for vestibular or otic symptoms related to CN 8 palsies, see otic syphilis below)	Findings consistent with meningitis and/or increased intracranial pressure, for example, meningismus, altered mental status, papilledema, cranial nerve abnormalities; more rarely aphasia, hemiplegia; fever is often only low-grade or absent
Meningovascular; can have cerebral or spinal forms [5, 16–20]	5–12 y post-infection	Cerebral: stroke due to endarteritis and infarction of cerebral blood vessels Spinal: meningomyelitis or spinal vascular; chronic spinal meningitis with endarteritis or blood vessel infarct can result in parenchymatous degeneration of cord or vascular thrombosis, leading to cord infarct	Symptoms of cerebral stroke vary based on location of thrombosis, for example, aphasia, hemiparesis, hemiplegia, seizure Symptoms of spinal cord involvement vary according to location/extent, for example, weakness, pain, or paresthesias, usually of lower extremities; can progress to paraparesis, paraplegia, or urinary or fecal incontinence; abrupt onset of symptoms consistent with transection of the spinal cord, for example, paraplegia, urinary retention, loss of sensation may occur; diverse subtle psychiatric or neurologic symptoms may occur for months prior to onset of stroke syndrome	Multiple potential findings consistent with stroke depending on which cerebral vessels are involved Multiple potential findings depending on location/extent of spinal cord involvement, for example, muscle atrophy, leg weakness and spasticity, hyperreflexive deep tendon reflexes, ankle clonus, loss of position or vibratory sense; can see acute onset of flaccid paraplegia, sensory level and urinary retention
Parenchymatous; general paresis [5, 16–20]	15–20 y post-infection	Chronic progressive meningoencephalitis; may be complicated by communicating hydrocephalus in a few cases due to impairment of cerebrospinal fluid absorption by chronic meningitis and meningeal fibrosis	Early: irritability, memory loss, personality changes, headaches, insomnia, difficulty with concentration, carelessness in appearance Late: defective judgment, lack of insight, confusion, disorientation, emotional lability (depression, agitation, euphoria), delusions of grandeur, paranoia, seizures; patients may experience progressive deterioration and become bedridden; patients may manifest symptoms related to hydrocephalus as well	Memory loss, disorientation, slurred speech, tremors, impaired handwriting and speech, expressionless faces, reflex abnormalities; signs related to hydrocephalus may occasionally be seen as well
Parenchymatous; tabes dorsalis [5, 11, 16–21]	20–25 y post-infection	Degeneration of posterior roots and columns of the spinal cord	Ataxia, paresthesias, lancinating or "lightning" pain (sudden severe stabbing pains that last a few minutes and usually occur in the lower extremities), "visceral crises" (episodes of severe pain in the epigastrum often accompanied by nausea/vomitting, bladder disturbances, rectal incontinence)	Gait disturbances, diminished touch, pain, vibratory or position sense, lack of deep tendon reflexes, positive Romberg sign, broad-based or stomping gait, Charcot joints (enlargement of individual joints, sometimes with effusion)
CNS gummas [5, 11, 16–20]	2–40 y post-infection	Benign cerebral or spinal cord tumors	May be asymptomatic or variable depending on location; manifestations of space-occupying lesion	Variable depending on size and location; reflect space-occupying CNS lesion; spinal cord lesions can lead to compression and result in paraplegia, motor or sensory loss, and urinary and fecal incontinence
Ocular syphilis [5, 11, 16–20, 22, 23]	At any time after infection and may overlap with other syphilis stages or other manifestations of neurosyphilis	Diverse; includes, but not limited to, anterior and posterior uveitis, optic neuritis, optic nerve atrophy/ neuropathy, chorioretinitis, interstitial keratitis, retinal vasculitis	Diverse; any part of the eye can be affected including, but not limited to, vision loss, eye pain, floaters, flashing lights, eye pressure, photophobia	Diverse; includes, but not limited to, pupillary abnormalities, for example, Argyll Robertson pupil, decreased visual acuity, uveitis

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Table 1. Continued

Type of Symptomatic Neurosyphilis	Typical Timeframe for Manifestations After Infection	Possible Clinical Syndromes	Possible Symptoms	Possible Findings on Clinical Exam
Otic syphilis [5, 11, 16–20, 24]	At any time after infection and may overlap with other syphilis stages or other manifestations of neurosyphilis	Sensorineural or conductive hearing loss	Hearing loss, dizziness, tinnitus, vertigo, balance issues	Gait instability, hearing loss

Abbreviations: CN, cranial nerves; CNS, central nervous system.

cord [11, 17, 18]. Finally, ocular syphilis and otic syphilis are considered a subset of neurosyphilis, but the syndromes may not completely overlap, and ocular/otic manifestations may coexist with any form of neurosyphilis and occur during any stage of syphilis. Thus, ocular, otic, and neurological signs and symptoms should be assessed with any stage of syphilis. Developmentally, certain parts of the eye may be distinct from the CNS, and in ocular syphilis, any portion of 1 or both eyes can be involved. Thus, the clinical presentations are variable [22, 23]. With otosyphilis, persons often experience sensorineural hearing loss, though conductive hearing loss may also be present. Hearing loss may be bilateral in 50%. Persons may also experience tinnitus or vestibular abnormalities, including vertigo, balance issues, or gait instability [5, 24].

PATHOGENESIS

The pathogenesis of neurosyphilis is incompletely understood. For decades, experts have debated the role of direct CNS invasion by the spirochete and the role of immune responses to CNS invasion [25]. The histopathological changes in neurosyphilis include perivascular lymphocytic and plasma cell infiltration with loss of nerve cells [25]. In vasculitis, endothelial cell swelling progresses to endarteritis obliterans [26]. In tabes dorsalis, the dorsal roots and posterior spinal column are demyelinated [27]. These may be the consequence of immune dysregulation associated with delayed onset hypersensitivity reactions mediated by antibody–antigen complexes, neutrophil hyperactivation, cytotoxic T-cell activation, or strong humoral responses [27].

DIAGNOSIS OF NEUROSYPHILIS

No single laboratory test can secure or refute a diagnosis of neurosyphilis in all clinical scenarios. Current best practice for diagnosing neurosyphilis relies on clinical history, physical examination findings, serum antibody tests for syphilis including treponemal tests (TTs) and lipoidal (or antiphospholipid) nontreponemal tests (NTTs), CSF analysis, and occasionally imaging [14, 28]. Many studies use different definitions of a "gold standard" for neurosyphilis, which is a challenge when assessing the performance characteristics of syphilis biomarkers [29].

Who Should Undergo a CSF Examination?

CSF examination is necessary to diagnose neurosyphilis. In the pre-antibiotic era, a CSF examination was performed on all persons diagnosed with syphilis because it provided important prognostic information. Neurologically asymptomatic persons with syphilis and CSF abnormalities consistent with neurosyphilis had a 30%–70% risk (depending on the extent of abnormalities) of future neurological complications compared with 5% if CSF parameters were normal [9]. Those with underlying asymptomatic neurosyphilis required more intensive therapy [9]. Once penicillin was introduced and rates of neurosyphilis decreased, clinicians questioned the need for routine CSF examination in all patients with syphilis, and the practice declined [30, 31]. Indeed, clinical experience would suggest that most neuroinvasion and CSF abnormalities in asymptomatic persons likely resolve or do not progress with nonneurosyphilis antibiotic regimens given that symptomatic neurosyphilis in the antibiotic era is rare even in the absence of universal CSF examinations [30, 32].

The current recommendations for a CSF examination are more focused than in prior years (Figure 2). First, persons with syphilis and neurological signs and symptoms should always undergo CSF examination. CSF examinations, however, are not recommended for persons who present with ocular or otic signs and symptoms alone because approximately 30% of persons with ocular syphilis [33] and at least approximately 30% of persons with otic syphilis [34] (estimates for otic syphilis are unstable because most case series are small) will have normal CSF parameters [14]. Occasionally, clinicians may encounter a patient with both ocular (or otic) and neurological findings. Such patients should undergo a CSF examination given that it is an important component of the diagnostic evaluation, that is, understanding whether syphilis or an alternate diagnosis is causing the neurological findings.

Second, the Centers for Disease Control and Prevention (CDC) Guidelines recommend that individuals without neurological symptoms who are diagnosed with gummatous or cardiovascular syphilis should also undergo a CSF examination as it may change their treatment course. Up to 30% of these persons have concomitant asymptomatic neurosyphilis and should

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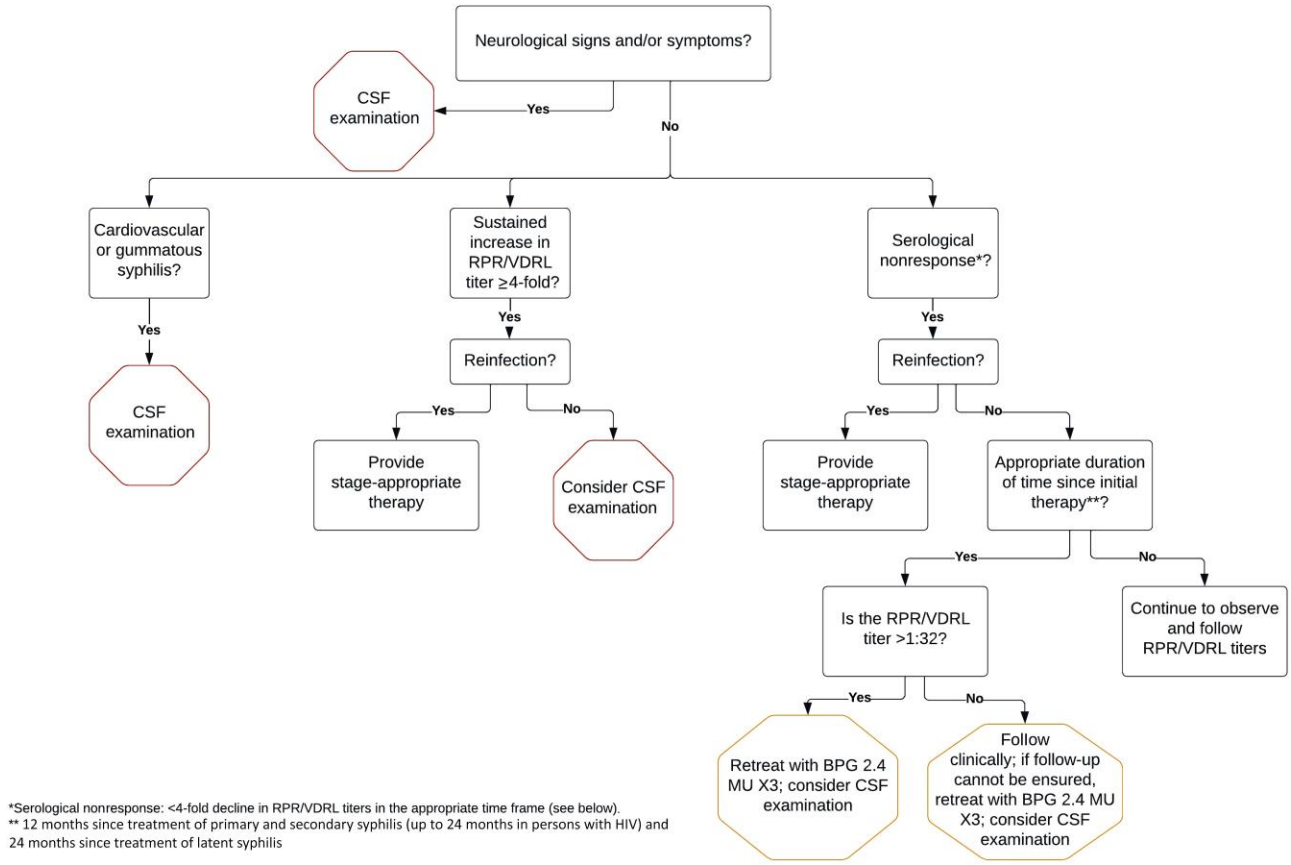

Figure 2. When to perform a CSF examination. Algorithm that summarizes the current guidelines for performing a CSF examination in persons with serological or clinical evidence of syphilis. These recommendations are based on the 2021 Centers for Disease Control and Prevention STI Treatment Guidelines [14]. Abbreviations: BPG, long-acting benzathine penicillin G; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; RPR, rapid plasma regain; VDRL, Venereal Disease Research Laboratory.

receive treatment with IV penicillin rather than 3 intramuscular (IM) doses of 2.4 MU of long-acting benzathine penicillin G (BPG) [14]. Whether intravenous (IV) penicillin results in improved outcomes in these individuals is not known.

Third, the CDC Guidelines recommend that a CSF examination be considered in patients whose lipoidal serological titers exhibit a sustained (checked approximately 2 weeks after the initial test) 4-fold increase following stage-appropriate therapy in the absence of reinfection, as the titer increase may reflect an asymptomatic neurological relapse. The prevalence of asymptomatic neurosyphilis in the setting of increasing serological titers is not well defined in the antibiotic era, and it is not known if the treatment of asymptomatic neurosyphilis with IV penicillin leads to better long-term outcomes [14].

Finally, a CSF examination may be considered in some persons whose lipoidal NTT serological titers fail to decline 4-fold (ie, serological nonresponse) following stage-appropriate therapy [14] and after waiting for an appropriate duration for the response to occur, that is, 12 months and 24 months following treatment of PSS and latent stages, respectively. For PWH, waiting for up to 24 months following treatment of PSS is acceptable, given slower declines in titers. In the pre-antibiotic era, persons whose lipoidal serologies remained reactive (ie, "lack of seroreversion") had a 30% prevalence of underlying asymptomatic neurosyphilis compared with 5% among those whose serologies seroreverted [9]. Several recent studies have attempted to define the prevalence of asymptomatic neurosyphilis in the setting of serological nonresponse. In a study of immunocompetent participants with all stages of syphilis whose titers either did not decline more than 4-fold following therapy (ie, serological nonresponse) or did decline but failed to completely serorevert (ie, serofast), 89 of 324 (27.5%; 95% CI: 22.7–32.7) participants were found to have CSF abnormalities consistent with asymptomatic neurosyphilis [35]. In multivariable modeling, the main risk factors were serological nonresponse and having a post-treatment rapid plasma reagin (RPR) titer >1:32. The titer cutoff of >1:32 was subsequently confirmed as an independent risk factor [36]. In a study of 22 participants experiencing serological nonresponse (most with late latent syphilis), 3 of 22 (13.6%; 95% CI: 2.9–34.9) had CSF abnormalities [37]. Currently, persons who experience serological nonresponse and whose titers are >1:32 should

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receive 3 doses of BPG, and a CSF examination should be considered. Again, it is not known if the treatment of asymptomatic neurosyphilis with IV penicillin leads to better long-term outcomes. Those with titers ≤1:32 should be followed carefully, and retreatment and CSF examination may be considered (Figure 2) [14]. If retreatment is administered, no additional therapy is recommended if asymptomatic serological nonresponse persists.

Persons with HIV

The need for routine CSF examinations in asymptomatic PWH was a critical question during the early HIV era due to increasing neurosyphilis rates [28]. In the antibiotic era, no trial has assessed whether universal CSF examination and treatment of asymptomatic neurosyphilis leads to better long-term outcomes. One small study enrolled participants with early syphilis to compare the efficacy of standard vs enhanced early syphilis therapy [29]. Baseline and 6-month follow-up CSF examinations were attempted in a subset. Sixty-one percent (28 of 46) of PWH and 40% (39 of 97) of those without HIV had CSF abnormalities, and 26% (11 of 43) of PWH and 24% (21 of 88) of those without HIV had *T. pallidum*–positive CSF at baseline. Of those who had repeat CSF examinations, 46% (6 of 13) in whom *T. pallidum* was detected before treatment remained positive after treatment, with no difference by HIV status or treatment arm. During 12-month follow-up, no participant developed neurological symptoms, and only 1 developed clinical treatment failure, leading authors to suggest that CSF abnormalities and *T. pallidum* detection in asymptomatic persons, regardless of HIV status, might not be clinically relevant. However, the numbers were very small, the resolution of CSF abnormalities was not reported, and follow-up time was limited [29]. Despite no robust data, the 2021 CDC STI Treatment Guidelines state that in PWH and syphilis, "CSF examination should be reserved for those with an abnormal neurologic examination" [14]. While PWH have a higher risk of neurosyphilis, overall, that risk is still likely small. This is particularly true in the antiretroviral therapy (ART) era, where prevalence of advanced immunosuppression in PWH has declined [3, 4, 38]. Additionally, more than 30 years of clinical experience suggest that the majority of asymptomatic PWH who do not undergo CSF examinations experience good clinical outcomes. While none of these factors are definitive, they are reassuring. Clinicians should remember, however, that guidelines target a general population rather than an individual patient. Given the lack of definitive data, a CSF examination among asymptomatic PWH may be warranted in specific circumstances in the setting of shared decision-making with the patient. For example, one may consider a CSF examination in an asymptomatic PWH experiencing homelessness with advanced immunosuppression and high RPR titers, who may face-challenges with maintaining routine healthcare follow-up.

Laboratory Testing of CSF

CSF Antibodies

The goal when making a diagnosis of neurosyphilis is to identify intrathecally produced antibodies. A reactive CSF antibody test can represent transudation (passive spillover) of antibodies from the blood into the CSF via the blood–brain barrier or intrathecal production in response to replication of *T. pallidum*. The predominant humoral response pattern in neurosyphilis is immunoglobulin (Ig) G–dominant, with low frequencies of IgM and the absence of IgA [39]. Available diagnostics cannot reliably distinguish intrathecal from blood compartment IgG production.

CSF Lipoidal Antibodies

NTTs use a complex antigen that consists of cardiolipin, lecithin, and cholesterol [40]. These tests detect a mixture of heterophile IgG and IgM [41]. They are simple to perform, inexpensive, and, when correctly performed, have a relatively high sensitivity [40]. The CSF VDRL test has long been the gold standard to establish a diagnosis of neurosyphilis and is the only NTT recommended by the CDC in the United States. VDRL test is specific but lacks sensitivity (Table 2). Outside of the United States, the RPR and the toluidine red unheated serum test are used. The CSF RPR assay is less sensitive than the VDRL test [42].

CSF NTTs, which are produced in lower concentrations than TT intrathecally, have higher specificity (less spillover) but lower sensitivity (less intrathecal production) [67]. Visibly blood-stained CSF is unsuitable for assessment because it is impossible to determine if the antibodies detected are blood or CSF in origin; the amount of whole blood contamination that renders CSF VDRL test reactive is inversely proportional to the serum NTT titer [41]. Blood-stained CSF is pink–red in appearance and may be grossly bloody when the red blood cell count exceeds 6000/uL [68].

CSF Treponemal Antibodies

The CSF fluorescent treponemal antibody (FTA) test and the CSF *Treponema pallidum* particle agglutination (TPPA) assay are the only CSF TTs included in the CDC Guidelines [14]. The CSF FTA test is sensitive but lacks specificity; a nonreactive CSF FTA test may rule out neurosyphilis (Table 2) [28, 32, 45, 54, 61, 63, 64, 69–71]. The sensitivity of CSF TPPA assay and CSF FTA test did not differ significantly in a study of participants at risk for neurosyphilis: 63.0% (95% CI: 55.2–70.8)–95% (95% CI: 89.5–100.0) and 66.7% (95% CI: 52.9–80.4)–95% (95% CI: 95–100), respectively [44]. The specificity of CSF TPPA titers of ≥1:640 was high at 93.3% (95% CI: 90.4–96.2)–97.0% (95% CI: 95.2–98.8) and was not significantly different from CSF VDRL test 90.2% (95% CI: 86.7–93.6). Additionally, if a CSF TPPA titer of 1:640 was used, in addition to a reactive CSF VDRL test, an additional 10 cases (21.3%) of neurosyphilis would have been diagnosed [44]. Other serum

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Table 2. Performance Characteristics of Different Cerebrospinal Fluid Antibody Tests for Neurosyphilis

Cerebrospinal Fluid Test/Diagnosis	Sensitivity (%)	Specificity (%)
Neurosyphilis		
VDRL test[a,b]	27–98.3 [42, 43]	74–100 [43, 44]
FTA-ABS[a]	22.2–100 [45, 46]	55–100 [7, 47]
TPPA[a]	12.8–100 [48–50]	42–100 [49, 51]
TPPA/TPHA titer ≥1:640	12.8–98.3 [48, 52]	81.5–96.3 [44, 52]
RPR[b]	51.5–100 [42, 49]	82.6–100 [42, 48, 50]
Toluidine red unheated serum test[b]	58.9–94.7 [50, 53]	93.1–100 [50, 53]
EIA	96.0–100 [54]	46.4–100 [54, 55]
TP-ELISA	94.7–100 [51, 56]	38.7–100 [54, 56, 57]
	92.9 [55]	100 [55]
Maxi-Syph	100 [55]	100 [55]
INNO-LIA	92.3–100 [55]	13.0–100 [55]
IgM ELISA[b]	100 [58]	98.0 [58]
Ocular syphilis		
FTA	0.0–100 [59, 60]	…
VDRL test	0.0–70.1 [59, 61, 62]	…
RPR	27.3–100 [63, 64]	…
Otic syphilis		
VDRL test	5.4–5.9 [24, 65]	0.0 [65, 66]

The definitions of neurosyphilis in these studies varied widely and included both symptomatic and asymptomatic neurosyphilis defined using various combinations of CSF VDRL test, pleocytosis, raised protein, and symptoms.

Abbreviations: EIA, enzyme immunoassay; FTA, fluorescent treponemal antibody; FTA-ABS, fluorescent treponemal antibody-absorption; IgM, immunoglobulin M; INNO-LIA, Innogenetics-line immunoassay; RPR, rapid plsma reagin; TP-ELISA, Treponema pallidum-enzyme linked immunoassay; TPHA, Treponema pallidum hemeagglutination; TPPA, Treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory.

[a]In the Centers for Disease Control and Prevention Guidelines.

[b]For symptomatic neurosyphilis: VDRL test sensitivity, 48.1%–87.5% [44, 49] and specificity, 78.2%–90.2% [44]; RPR sensitivity, 51.5%–100% [42, 49] and specificity, 89.7%–90.2% [42, 44]; IgM ELISA sensitivity, 100%; toluidine red unheated serum test sensitivity, 94.7% and specificity, 100% [53].

TTs have also been evaluated on CSF and identified additional cases of neurosyphilis compared with CSF VDRL test [54, 55].

The sensitivity of TTs in CSF is high due to high intrathecal production, but the specificity is low due to spillover from the systemic circulation [39, 67]. A 2001 study described CSF IgG decay after successful treatment of neurosyphilis in 7 patients; declines in intrathecal synthesis of IgG continued out to 18 years post-treatment [39]. This observation challenges the usefulness of CSF IgG assays in the diagnosis of neurosyphilis, remaining positive decades after successful treatment. It is reasonable to consider CSF TTs as serum TT analogs; they are sensitive tests for the initial diagnosis of neurosyphilis but unhelpful in managing relapse or subsequent episodes [72]. Tests, including the CSF TPHA/TPPA index, that attempt to assess blood–meningeal barrier disruption have been used to evaluate intrathecal synthesis of antitreponemal antibodies but are not yet validated [52]. Direct comparisons across studies are extremely limited because of differences in populations, case selection, definitions of neurosyphilis, and the gold standard tests used.

CSF Pleocytosis

Up to 5 white blood cells (WBCs) and 5 red blood cells per microliter are considered normal in the CSF of adults [73, 74]. CSF pleocytosis (>5 WBC/μL) is reported as being highly sensitive but not specific to neurosyphilis. However, the degree of pleocytosis varies depending on the type of neurosyphilis, gold standard diagnostic used, definition of pleocytosis, and HIV status [36, 75]. Thus, the true sensitivity and specificity of CSF pleocytosis are difficult to estimate. The degree of pleocytosis is typically an order of magnitude lower than for other bacterial causes of CNS infection [76]; indeed, neurosyphilis can occur with a CSF WBC count <5 μL [77]. When pleocytosis occurs, lymphocytes are typically observed in CSF. In PWH, it has been suggested that using the higher cutoff of 20 cells improves specificity for neurosyphilis. In a 2004 study in PWH, CSF B cells of >9% in fresh CSF were 100% specific but insensitive at 40%–43% [45]. CSF may be normal in up to 30% of cases of ocular syphilis and at least 30% with otic syphilis [13, 24].

CSF Protein Concentrations

Raised CSF protein is nonspecific and arguably the least discriminating CSF parameter. However, it may be supportive of a diagnosis of neurosyphilis. Many guidelines [78] and studies [36, 79] use a CSF protein cutoff of >0.45 g/L. However, the protein cutoff varies between laboratories [17]. In one study, normal (≤45 mg/dL) CSF protein concentrations were identified in 47%, 34%, 25%, and 12% of those with tabes dorsalis, vascular syndromes including stroke, general paresis, and syphilitic meningitis, respectively [80]. Of 40 participants with untreated PSS, 6 of 12 (50%) where *T. pallidum* was isolated from CSF had raised (>0.40 g/L) CSF protein compared with 6 of 28 (21%) where *T. pallidum* was not isolated [7]. Even in CSF samples where the presence of *T. pallidum* was incontrovertible, half of individuals, independent of HIV status, had normal protein. In one study, the mean CSF protein was 53 mg/dL in 54 healthy persons with previous syphilis and 103 mg/dL in 60 persons with active neurosyphilis. The mean CSF protein values in tabes dorsalis, meningovascular syphilis, and general paresis were 91, 100, and 108 mg/dL, respectively [52]. Both CSF WBC and protein may be raised in PWH in the absence of syphilis [14]. An isolated elevated protein concentration in CSF in the absence of any other abnormality should be interpreted cautiously.

CSF Polymerase Chain Reaction for T. pallidum

Polymerase chain reaction (PCR) is highly sensitive for diagnosing syphilis from primary and moist secondary lesions; however, it does not have correspondingly high sensitivity on CSF. PCR on CSF is not cleared by the US Food and Drug Administration. In a systematic review, the sensitivity and specificity of PCR for definite neurosyphilis ranged from 40% to

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70% and 60% to 100%, respectively. The PCR assay targeting Tp47 had an overall sensitivity and specificity of 68% and 91.9%, respectively [81].

Future Biomarkers

While some biomarkers hold promise, none are sufficiently developed to be implemented for clinical use [82]. Most are not specific for *T. pallidum*; they measure immunological responses to infection. The CSF chemokine (C-X-C motif) ligand CXCL13, a B-cell chemoattractant, has been most extensively studied as a biomarker for neurosyphilis [45, 83]. In a study of 199 PWH, the odds of symptomatic neurosyphilis were 2.23-fold higher for every log increase in CSF CXCL13 concentration [83]. Reported sensitivity of CSF CXCL13 at ≥10 pg/mL was 90% (95% CI: 73–98), but the specificity was only 37% (95% CI: 29–45); performance characteristics changed depending on the CXCL13 cutoff. Additional studies are necessary to better define the optimal cutoff and role that CXCL13 should play in the diagnosis of neurosyphilis. Other biomarkers proposed for neurosyphilis include light and heavy neurofilament levels, CSF interleukin (IL)-17, interferon-γ, and IL-10 [84]. *Treponema pallidum*–specific biomarkers are needed, and it will be critical to define the precise role of each biomarker in diagnosing and managing neurosyphilis.

Imaging in Neurosyphilis

Many patients undergo brain imaging during the workup of their neurological complaints. In one study, magnetic resonance imaging (MRI) was more sensitive than computed tomography in detecting brain infarcts associated with meningovascular neurosyphilis [85]. A 2013 MRI study of neurosyphilis classified patients into 3 groups based on clinical manifestations: neuropsychiatric, meningovascular, and myelopathic [86]. Those with neuropsychiatric predominant symptoms had specific findings including diffuse cerebral atrophy and infarcts; the meningovascular type was predominantly associated with infarcts on imaging; and the myelopathic group had findings of long-segment signal changes and dorsal column involvement. In persons diagnosed with general paresis, MRI showed high signal intensity on T2-weighted images involving the frontotemporal lobes, hippocampus, and periventricular area [86]. Radiological examinations are generally not required as part of a neurosyphilis workup unless another pathology is suspected or there is evidence of raised intracranial pressure.

TREATMENT OF NEUROSYPHILIS

Recommendations for first-line treatment of neurosyphilis are based mainly on case series, retrospective studies, pharmacokinetic/pharmacodynamic data, and clinical experience (Table 3). A Cochrane review [87] that assessed antibiotic therapy for adults with neurosyphilis described a single, small, randomized, controlled trial (RCT) [88] that compared ceftriaxone and IV penicillin G. The optimal duration of therapy for neurosyphilis has not been studied in a clinical trial. Clinical experience suggests that 10–14 days of penicillin is adequate (courses as short as 8 days have been reported [89]). No studies have directly compared 10 vs 14 days. We routinely use 10 days of antibiotics. Finally, the role of corticosteroids in the management of neurosyphilis is unclear. The CDC does not recommend the routine use of steroids when treating neurosyphilis [14]. We have occasionally used steroids to help manage signs and symptoms of ocular and otic syphilis in the absence of contraindications. There are no controlled studies to define their optimal dose and duration.

Table 3. Centers for Disease Control and Prevention Guidelines: Recommended Therapies for Neurosyphilis

Treatment options	Medications
First line	Aqueous crystalline penicillin G, 18–24 million units/d, administered as 3–4 million units IV every 4 h or continuous infusion for 10–14 d
Alternative	Procaine penicillin G, 2.4 million units IM once daily *plus* Probenecid, 500 mg orally 4 times/day, both for 10–14 d
Limited data	Ceftriaxone, 1–2 g IV/IM daily for 10–14 d

Abbreviations: IM, intramuscularly; IV, intravenously.

Penicillin

No regimen other than penicillin should be used to treat neurosyphilis unless an absolute contraindication exists. No other regimen should be used during pregnancy. Aqueous crystalline penicillin G is the preferred treatment regimen for all adults with neurosyphilis, ocular syphilis, or otosyphilis (Table 3). If compliance can be ensured, an alternative regimen is procaine penicillin plus probenecid (APPG-P) [14]. In addition to clinical experience, the efficacy of this alternative regimen was supported by a study [90] that compared the normalization of CSF abnormalities in 32 participants treated with IV penicillin and 118 treated with APPG-P; no between-group difference in the likelihood of normalization of CSF and serum measures regardless of HIV status was found.

Ceftriaxone

The CDC recommends the use of IV or IM ceftriaxone (Table 3) as an alternative treatment for neurosyphilis, though this is based on limited data [14, 91, 92]. The only RCT included 30 PWH randomized to either 10 days of ceftriaxone 2 g intravenously daily or penicillin G 4 MU intravenously every 4 hours. Blood and CSF were collected before and 14–26 weeks after therapy. There was no statistically significant difference in the proportion of each group whose CSF measures improved; a larger proportion of the ceftriaxone recipients had a decline in serum RPR titers [87, 88]. A recent retrospective cohort study compared 42 participants with neurosyphilis treated with ceftriaxone (2 g IV daily) to 166 treated with IV penicillin; 55%

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of the ceftriaxone group and 48% of the penicillin group were PWH. The study found a 98% clinical response rate in the ceftriaxone group vs a 76% rate in the penicillin group, and serological response at 6 months did not differ between the 2 groups [92]. No differences in subgroup analyses were seen by HIV status. Ceftriaxone appears to be a reasonable alternative in nonpregnant adults if penicillin cannot be used.

Long-acting Benzathine Penicillin G (BPG) in the Treatment of Neurosyphilis

Single-drug therapy with 3 doses of IM long-acting BPG was recommended for the treatment of neurosyphilis until this was eliminated as an option in the 1989 CDC STD Guidelines [93]. This regimen was used for decades with adequate clinical effectiveness [89, 94, 95]. In the 1970s, studies demonstrated that this regimen did not achieve reliable treponemicidal concentrations of penicillin in the CSF [96]. When HIV emerged in the 1980s, case reports of BPG treatment failures followed [97], so the CDC removed the BPG regimen from its recommendations despite decades of success. The accompanying background article to the 1989 CDC Guidelines explained the reasoning [98]: "Although the actual failure rate is unknown, sufficient failures have been reported to suggest that BPG should no longer be used alone to treat neurosyphilis." In certain limited situations, some clinicians may still consider using 3 doses of BPG if neurosyphilis is relatively low on the differential and the risk-to-benefit ratio does not favor a CSF examination; for example, an immunocompetent elderly patient with dementia whose serologies are reactive for syphilis, whose past history cannot be ascertained, and (after careful clinical and historical evaluation) whose probability of having neurosyphilis as a cause of the dementia is felt to be low. However, every patient must be evaluated individually, and a careful history and clinical assessment must be done to inform any decision to use alternative treatment.

Long-acting Benzathine Penicillin G (BPG) to Supplement IV Penicillin Treatment of Neurosyphilis

The 1982 CDC Treatment Guidelines introduced 3 doses of BPG to supplement IV or IM penicillin therapy for neurosyphilis [99]. The decision to add 3 doses of BPG to the short-acting regimens was not data-driven but was explained by Greene, "Since it is generally agreed that syphilis of long duration requires relatively prolonged therapy, regimens of short-acting penicillins should be supplemented with benzathine penicillin G in order to ensure prolongation of treatment" [97]. Surprisingly, and despite no new data, the CDC reversed course in its 1989 Guidelines [100] by modifying the recommendation for additional doses of BPG following IV or IM penicillin so that it became optional. Zenker and Rolfs explained: "It has been suggested that spirochetes in late disease divide more slowly, requiring a longer duration of therapy, but few data exist to substantiate this theory… no failures have been reported with 10 days of high-dose penicillin treatment (often supplemented with BPG)" [98]. This option has remained in all subsequent updates to the CDC Guidelines including the 2021 update. There are no animal data that define the *T. pallidum* replication rate or optimal duration of antibiotic therapy in late syphilis, only early syphilis [100, 101]. Thus, the option of using up to 3 additional doses of BPG lacks supportive experimental or observational clinical data. If a clinician decides to give additional doses of BPG following standard neurosyphilis therapy of 10–14 days, then a single dose in most patients is enough to achieve a duration of serum treponemicidal concentrations that parallel durations recommended to treat late latent syphilis [102].

Doxycycline

Doxycycline is not recommended as neurosyphilis treatment by the CDC or in European guidelines [14, 40]. UK guidelines suggest high-dose oral doxycycline at 200 mg orally twice daily for 28 days as an alternative therapy for neurosyphilis [78]. This recommendation is based on data from a 1985 study of 5 participants, only 2 of whom had neurosyphilis. In a 2021 UK study, 87 participants were treated for early neurosyphilis with either oral doxycycline 200 mg twice daily for 28 days (N = 16) or IM procaine penicillin/oral probenecid (N = 71) for 14 days. There were no statistically significant differences in clinical or serological responses between the groups [103]. While these data are encouraging, they are far from definitive, and larger, controlled trials are needed. We do not recommend offering oral doxycycline as an option to any patient diagnosed with neurosyphilis unless they absolutely refuse CDC-endorsed treatment regimens. This regimen should only be used in the setting of shared decision-making between the patient and their healthcare provider with the understanding that efficacy data are lacking.

FOLLOW-UP, GOALS OF TREATMENT, MANAGING EXPECTATIONS, AND SHARED DECISION-MAKING

There are many gray areas in neurosyphilis management; treatment decisions are frequently based on clinical experience, not rigorous controlled studies [104]. The necessity of lumbar puncture, the type and duration of therapy, and the decision to use long-acting BPG at the end of short-acting penicillin therapy represent some of these uncertainties. Where evidence is lacking, shared decision-making facilitates an informed decision on the part of the patient.

Follow-up should follow stage-specific guidelines [13]. Repeat CSF examination is not routinely required in individuals with appropriate clinical and serological responses unless they are PWH and not on ART [14, 105, 106]. The goal of therapy is to prevent progression of neurological damage and to reverse signs

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and symptoms. However, signs and symptoms of neurosyphilis may not resolve after appropriate therapy [66, 107]; therefore, setting expectations at the outset through patient–provider dialogue is key. Symptom resolution depends on the anatomic site of injury, the extent of the pathology, and the duration of time from symptom onset until completion of treatment. Early treatment is critical to preventing disease progression and reducing the risk of permanent disability [108].

PREVENTION

Data are emerging on the efficacy of syphilis prevention using doxycycline as pre- or post-exposure prophylaxis (PrEP/PEP) [105, 106]. Doxycycline PEP taken as 200 mg of oral doxycycline within 72 hours of potential exposure reduces incident syphilis by approximately 70%. Preventing syphilis will prevent neurosyphilis. However, to date, data only support the use of this intervention in people assigned male at birth, and there are unanswered questions about potential harms of doxycycline prophylaxis, including antimicrobial resistance in sexually transmitted infection and in other organisms, and microbiome disruptions. To interrupt transmission and reverse the epidemic of syphilis, bold new strategies to harness new techniques in vaccinology including proteomics and bioinformatics [109], advances in diagnostics beyond serology and lesion-based PCR [110], evaluation of prognostic biomarkers with true clinical end points, and innovative clinical trial design to bolster or disrupt existing treatment paradigms are needed.

There are major disparities in access to diagnostics and treatment for syphilis, mediated through stigma [103], intrinsic inequities, and systemic racism [104]. Much work is needed to address health disparities at all stages of the healthcare continuum. Attention to the numerous challenges posed by syphilis, including policy, diagnostics, treatment, and prevention, is required to reduce the burden of infection and associated neurological sequelae.

Note

Potential conflicts of interest. M. M. H. reports royalties from UpToDate, consulting fees from GSK, and writing fees from DynaMed. K. G. G. reports royalties from UpToDate. S. T. reports serving as a consultant for Biofire Diagnostics, Roche Molecular Diagnostics, and Luca Biologics; royalties from UpToDate; speaker honoraria from Roche Molecular Diagnostics and Medscape/WebMD; an unpaid role as a board member for the American Sexually Transmitted Diseases Association; and receipt of donated test kits to institution from Hologic. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control and Prevention. Centers for Disease Control sexually transmitted diseases surveillance 2020. Available at: https://www.cdc.gov/std/statistics/2020/. Accessed 12 March 2023.
2. Burghardt NO, Nelson LN, Tang EC, Plotzker RE, Jacobson K, Murphy RD. Neurosyphilis surveillance: exploring the use of multiple data sources to better understand morbidity in California. Sex Transm Dis **2021**; 48(8S):S11–S3.
3. Dombrowski JC, Pedersen R, Marra CM, Kerani RP, Golden MR. Prevalence estimates of complicated syphilis. Sex Transm Dis **2015**; 42:702–4.
4. Jackson DA, McDonald R, Quilter LAS, Weinstock H, Torrone EA. Reported neurologic, ocular, and otic manifestations among syphilis cases—16 states, 2019. Sex Transm Dis **2022**; 49:726–32.
5. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. N Engl J Med **2020**; 382:845–54.
6. Lukehart S. Biology of treponemes. In: Holmes KK, Sparling PF, Stamm WE, et al, eds. Sexually transmitted diseases. New York: McGraw Hill, **2008**:647–59.
7. Lukehart SA, Hook EW 3rd, 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**; 109:855–62.
8. Chesney AM Kemp JE. Incidence of *Spirochaeta pallida* in cerebrospinal fluid during early stage of syphilis. JAMA **1924**; 83:1725–8.
9. Moore JE, Kemp JE, Eagle H, Padget P, Goodwin MS, Reynolds FW. The modern treatment of syphilis, 2nd ed. Springfield, IL: Charles C. Thomas, **1943**.
10. O'Leary PA Cole HN, Moore JE, et al. Cooperative clinical studies in the treatment of syphilis: asymptomatic neurosyphilis. Vener Dis Inf **1937**; 18:45–65.
11. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. USA: Oxford University Press, **1947**.
12. Moore JE, Faupel M. Asymptomatic neurosyphilis: V. A comparison of early and late asymptomatic neurosyphilis. Arch Dermatol **1928**; 18:99–108.
13. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep **2021**; 70:1–187.
14. Workowski KA, Bachmann LH. Centers for Disease Control and Prevention's sexually transmitted diseases infection guidelines. Clin Infect Dis **2022**; 74(74 Suppl 2):S89–94.
15. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002-June 2004. MMWR Morb Mortal Wkly Rep **2007**; 56:625–8.
16. Ropper AH. Neurosyphilis. N Engl J Med **2019**; 381:1358–63.
17. Ghanem KG. REVIEW: neurosyphilis: a historical perspective and review. CNS Neurosci Ther **2010**; 16:e157–68.
18. Swartz MN, Healy BP, Musher DM. Late syphilis. In: Holmes KK, Sparling PF, Mardh PA, et al, eds. Sexually transmitted diseases, 3rd ed. USA: McGraw Hill, **1999**:487–511.
19. Sparling P. Natural history of syphilis. In: Holmes KK, Sparling PF, Mardh PA, et al, eds. Sexually transmitted disease, 3rd ed. USA: McGraw Hill, **1999**:473–8.
20. Sparling PF, Swartz MN, Musher DM, Healy BP. Clinical manifestations of syphilis. In: Holmes KS, Sparling PF, Stamm WE, et al, eds. Sexually transmitted diseases, 4th ed. New York: McGraw-Hill, **2008**:P661–83.
21. Gimenez-Roldan S, Martin M. Tabetic lightning pains: high-dosage intravenous penicillin versus carbamazepine therapy. Eur Neurol **1981**; 20:424–8.
22. Woolston SL, Dhanireddy S, Marrazzo J. Ocular syphilis: a clinical review. Curr Infect Dis Rep **2016**; 18:36.
23. Tuddenham S, Ghanem KG. Ocular syphilis: opportunities to address important unanswered questions. Sex Transm Infect **2016**; 92:563–5.
24. Yimtae K, Srirompotong S, Lertsukprasert K. Otosyphilis: a review of 85 cases. Otolaryngol Head Neck Surg **2007**; 136:67–71.
25. Gager WE, Israel CW, Smith JL. Presence of spirochaetes in paresis despite penicillin therapy. Br J Vener Dis **1968**; 44:277–82.
26. Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers **2017**; 3:17073.
27. Carlson JA, Dabiri G, Cribier B, Sell S. The immunopathobiology of syphilis: the manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. Am J Dermatopathol **2011**; 33:433–60.
28. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. Clin Infect Dis **2020**; 71(Suppl 1):S21–42.
29. Hamill MM, Mbazira KJ, Kiragga AN, et al. Challenges of rapid plasma reagin interpretation in syphilis screening in Uganda: variability in nontreponemal results between different laboratories. Sex Transm Dis **2018**; 45:829–33.
30. Perdrup A, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark: A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. Acta Derm Venereol Suppl (Stockh) **1981**; 96:1–14.
31. 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**; 145:465–8.
32. Tuddenham S, Ghanem KG. Neurosyphilis: knowledge gaps and controversies. Sex Transm Dis **2018**; 45:147–51.

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33. Vadboncoeur J, Labbe AC, Fortin C, et al. Ocular syphilis: case series (2000–2015) from 2 tertiary care centres in Montreal, Canada. Can J Ophthalmol **2020**; 55:30–7.
34. Theeuwen H, Whipple M, Litvack JR. Otosyphilis: resurgence of an old disease. Laryngoscope **2019**; 129:1680–4.
35. Weng W, Hou J, Song B, Zhang M, Zhang T, Gao Y. Identification of the factors associated with post-treatment asymptomatic neurosyphilis in HIV-negative patients with serological non-response syphilis: a retrospective study. Int J STD AIDS **2021**; 32:331–5.
36. Cui W, Yan J, Weng W, Gao Y, Zhu W. Factors associated with neurosyphilis in patients with syphilis treatment failure: a retrospective study of 165 HIV-negative patients. Front Med (Lausanne) **2022**; 9:757354.
37. Zhang X, Shahum A, Yang LG, et al. Outcomes from re-treatment and cerebrospinal fluid analyses in patients with syphilis who had serological nonresponse or lack of seroreversion after initial therapy. Sex Transm Dis **2021**; 48:443–50.
38. Flood JM, Weinstock HS, Guroy ME, Bayne L, Simon RP, Bolan G. Neurosyphilis during the AIDS epidemic, San Francisco, 1985–1992. J Infect Dis **1998**; 177:931–40.
39. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci **2001**; 184:101–22.
40. Janier M, Unemo M, Dupin N, Tiplica GS, Potocnik M, Patel R. 2020 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol **2021**; 35:574–88.
41. Kaplan IV, Levinson SS. When is a heterophile antibody not a heterophile antibody? When it is an antibody against a specific immunogen. Clin Chem **1999**; 45: 616–8.
42. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis **2012**; 39:453–7.
43. Davis LE, Schmitt JW. Clinical significance of cerebrospinal fluid tests for neurosyphilis. Ann Neurol **1989**; 25:50–5.
44. Marra CM, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC. Cerebrospinal fluid *Treponema pallidum* particle agglutination assay for neurosyphilis diagnosis. J Clin Microbiol **2017**; 55:1865–70.
45. Marra CM, Tantalo LC, Maxwell CL, Dougherty K, Wood B. Alternative cerebrospinal fluid tests to diagnose neurosyphilis in HIV-infected individuals. Neurology **2004**; 63:85–8.
46. Escobar MR, Dalton HP, Allison MJ. Fluorescent antibody tests for syphilis using cerebrospinal fluid: clinical correlation in 150 cases. Am J Clin Pathol **1970**; 53:886–90.
47. Gonzalez H, Koralnik IJ, Huhn GD, et al. A dual-platform point-of-care test for neurosyphilis diagnosis. Sex Transm Dis **2021**; 48:353–6.
48. Marra CM. Alternatives to the cerebrospinal fluid venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis **2021**; 48(8S):S54–S7.
49. Castro R, Prieto ES, Aguas MJ, et al. Evaluation of the *Treponema pallidum* particle agglutination technique (TP.PA) in the diagnosis of neurosyphilis. J Clin Lab Anal **2006**; 20:233–8.
50. Zhu L, Gu X, Peng RR, et al. Comparison of the cerebrospinal fluid (CSF) toluidine red unheated serum test and the CSF rapid plasma reagin test with the CSF venereal disease research laboratory test for diagnosis of neurosyphilis among HIV-negative syphilis patients in China. J Clin Microbiol **2014**; 52:736–40.
51. Li YLJ, Liu Y, Feng X, Wei H, Sun L. Analysis of laboratory examination results of cerebrospinal fluid in suspected neurosyphilis patients. Beijing Med J **2020**; 42:500–3.
52. Luger AF, Schmidt BL, Kaulich M. Significance of laboratory findings for the diagnosis of neurosyphilis. Int J STD AIDS **2000**; 11:224–34.
53. Jiang Y, Chen X, Ma X, Yang Y, Peng F, Hu X. The usefulness of toluidine red unheated serum test in the diagnosis of HIV-negative neurosyphilis. Sex Transm Dis **2011**; 38:244–5.
54. Xie JW, Wang M, Zheng YW, Lin Y, He Y, Lin LR. Performance of the nontreponemal tests and treponemal tests on cerebrospinal fluid for the diagnosis of neurosyphilis: a meta-analysis. Front Public Health **2023**; 11:1105847.
55. Guarner J, Jost H, Pillay A, et al. Evaluation of treponemal serum tests performed on cerebrospinal fluid for diagnosis of neurosyphilis. Am J Clin Pathol **2015**; 143:479–84.
56. Su ZY, Gong AH, Sui Q, Zhang ZG, Le HY, Li CH. Value of TP-ELISA, TRUST and VDRL on cerebrospinal fluid to diagnosis of neurosyphilis. Chin J Microecol **2014**; 26:1411–3.
57. Su ZY Sui Q, Gong AH, Liu XY. Comparison of the application of VDRL and RPR in the detection of neurosyphilis. Med Forum **2018**; 22:3928–30.
58. Lee JB, Farshy CE, Hunter EF, Hambie EA, Wobig GH, Larsen SA. Detection of immunoglobulin M in cerebrospinal fluid from syphilis patients by enzyme-linked immunosorbent assay. J Clin Microbiol **1986**; 24:736–40.
59. Kim Y, Yu SY, Kwak HW. Non-human immunodeficiency virus-related ocular syphilis in a Korean population: clinical manifestations and treatment outcomes. Korean J Ophthalmol **2016**; 30:360–8.
60. Kesserwani H. Decomplexifying serum and cerebrospinal fluid (CSF) serologic testing of neurosyphilis: a case report of ocular syphilis and highlights of the principles of serologic testing. Cureus **2020**; 12:e11533.
61. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis—eight jurisdictions, United States, 2014–2015. MMWR Morb Mortal Wkly Rep **2016**; 65:1185–8.
62. Spoor TC, Ramocki JM, Nesi FA, Sorscher M. Ocular syphilis 1986. Prevalence of FTA-ABS reactivity and cerebrospinal fluid findings. J Clin Neuroophthalmol **1987**; 7:191–5, 6–7.
63. Hamill MM, Seppings L, Kit V, Antao S. Concurrent primary chancre and ocular syphilis in an human immunodeficiency virus-negative man. Sex Transm Dis **2018**; 45:e109–e12.
64. Shen J, Feng L, Li Y. Ocular syphilis: an alarming infectious eye disease. Int J Clin Exp Med **2015**; 8:7770–7.
65. Dobbin JM, Perkins JH. Otosyphilis and hearing loss: response to penicillin and steroid therapy. Laryngoscope **1983**; 93:1540–3.
66. Gleich LL, Linstrom CJ, Kimmelman CP. Otosyphilis: a diagnostic and therapeutic dilemma. Laryngoscope **1992**; 102:1255–9.
67. Ghanem KG. Cerebrospinal fluid treponemal antibody titres: a breakthrough in the diagnosis of neurosyphilis. Sex Transm Infect **2020**; 96:391–2.
68. Jurado R, Walker HK. Cerebrospinal fluid. In: Walker HK, Dallas Hall W, Hurst JW, eds. Clinical methods: the history, physical, and laboratory examinations, 3rd ed. Boston: Butterworths, **1990**:P375.
69. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. Sex Transm Dis **2012**; 39:291–7.
70. Gao ZX, Gou Y, Liu XQ, Peng LW. Advances in laboratory diagnostic methods for cerebrospinal fluid testing for neurosyphilis. Front Public Health **2022**; 10: 1030480.
71. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. Clin Infect Dis **2020**; 71(Suppl 1): S13–20.
72. Izzat NN, Bartruff JK, Glicksman JM, Holder WR, Knox JM. Validity of the VDRL test on cerebrospinal fluid contaminated by blood. Br J Vener Dis **1971**; 47:162–4.
73. Lyons S, O'Kelly B, Woods S, et al. Seizure with CSF lymphocytosis as a presenting feature of COVID-19 in an otherwise healthy young man. Seizure **2020**; 80: 113–4.
74. Tattevin P, Tchamgoue S, Belem A, Benezit F, Pronier C, Revest M. Aseptic meningitis. Rev Neurol (Paris) **2019**; 175:475–80.
75. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis **2004**; 189:369–76.
76. Spanos A, Harrell FE Jr., Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. JAMA **1989**; 262: 2700–7.
77. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. JAMA **1972**; 219:726–9.
78. Kingston M, French P, Higgins S, et al. UK national guidelines on the management of syphilis 2015. Int J STD AIDS **2016**; 27:421–46.
79. Pastuszczak M, Jakiela B, Wojas-Pelc A. Association of interleukin-10 promoter polymorphisms with serofast state after syphilis treatment. Sex Transm Infect **2019**; 95:163–8.
80. Simon RP. Neurosyphilis. Arch Neurol **1985**; 42:606–13.
81. Marks M, Lawrence D, Kositz C, Mabey D. Diagnostic performance of PCR assays for the diagnosis of neurosyphilis: a systematic review. Sex Transm Infect **2018**; 94:585–8.
82. Lorenz Z, Nijhar S, Caufield-Noll C, Ghanem KG, Hamill MM. The utility of biomarkers in the clinical management of syphilis: a systematic review. Sex Transm Dis **2023**; 50:472–8.
83. Marra CM, Tantalo LC, Sahi SK, Maxwell CL, Lukehart SA. CXCL13 as a cerebrospinal fluid marker for neurosyphilis in HIV-infected patients with syphilis. Sex Transm Dis **2010**; 37:283–7.
84. Pastuszczak M, Jakiela B, Wielowieyska-Szybinska D, Jaworek AK, Zeman J, Wojas-Pelc A. Elevated cerebrospinal fluid interleukin-17A and interferon-gamma levels in early asymptomatic neurosyphilis. Sex Transm Dis **2013**; 40:808–12.
85. Khamaysi Z, Bergman R, Telman G, Goldsher D. Clinical and imaging findings in patients with neurosyphilis: a study of a cohort and review of the literature. Int J Dermatol **2014**; 53:812–9.
86. Nagappa M, Sinha S, Taly AB, et al. Neurosyphilis: MRI features and their phenotypic correlation in a cohort of 35 patients from a tertiary care university hospital. Neuroradiology **2013**; 55:379–88.

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87. Buitrago-Garcia D, Marti-Carvajal AJ, Jimenez A, Conterno LO, Pardo R. Antibiotic therapy for adults with neurosyphilis. Cochrane Database Syst Rev **2019**; 5:CD011399.
88. Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis **2000**; 30:540–4.
89. Idsoe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis. The experience of three decades. Bull World Health Organ **1972**; 47(Suppl):1–68.
90. Dunaway SB, Maxwell CL, Tantalo LC, Sahi SK, Marra CM. Neurosyphilis treatment outcomes after intravenous penicillin G versus intramuscular procaine penicillin plus oral probenecid. Clin Infect Dis **2020**; 71:267–73.
91. Shann S, Wilson J. Treatment of neurosyphilis with ceftriaxone. Sex Transm Infect **2003**; 79:415–6.
92. Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. Lancet Infect Dis **2021**; 21:1441–7.
93. Centers for Disease Control and Prevention. 1989 sexually transmitted diseases treatment guidelines. MMWR Suppl **1989**; 38:1–43.
94. Short DH, Knox JM, Glicksman J. Neurosyphilis, the search for adequate treatment. A review and report of a study using benzathine penicillin G. Arch Dermatol **1966**; 93:87–91.
95. Smith CA, Kamp M, Olansky S, Price EV. Benzathine penicillin G in the treatment of syphilis. Bull World Health Organ **1956**; 15:1087–96.
96. Ducas J, Robson HG. Cerebrospinal fluid penicillin levels during therapy for latent syphilis. JAMA **1981**; 246:2583–4.
97. Greene BM, Miller NR, Bynum TE. Failure of penicillin G benzathine in the treatment of neurosyphilis. Arch Intern Med **1980**; 140:1117–8.
98. Zenker PN, Rolfs RT. Treatment of syphilis, 1989. Rev Infect Dis **1990**; 12(Suppl 6):S590–609.
99. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 1982. MMWR Morb Mortal Wkly Rep **1982**; 31(Suppl 2): 33S–60S.
100. Eagle H, Magnuson HJ, Fleischman R. Relation of the size of the inoculum and the age of the infection to the curative dose of penicillin in experimental syphilis, with particular reference to the feasibility of its prophylactic use. J Exp Med **1947**; 85:423–40.
101. Cumberland MC, Turner TB. The rate of multiplication of *Treponema pallidum* in normal and immune rabbits. Am J Syph Gonorrhea Vener Dis **1949**; 33:201–12.
102. Collart P, Poitevin M, Milovanovic A, Herlin A, Durel J. Kinetic study of serum penicillin concentrations after single doses of benzathine and benethamine penicillins in young and old people. Br J Vener Dis **1980**; 56:355–62.
103. Girometti N, Junejo MH, Nugent D, McOwan A, Whitlock G, Dean Street Collaborative Group. Clinical and serological outcomes in patients treated with oral doxycycline for early neurosyphilis. J Antimicrob Chemother **2021**; 76:1916–9.
104. Ghanem KG. Management of adult syphilis: key questions to inform the 2015 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis **2015**; 61(Suppl 8):S818–36.
105. Xiao Y, Tong ML, Lin LR, et al. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. Sci Rep **2017**; 7:9911.
106. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis **2008**; 47:893–9.
107. Zoller M, Wilson WR Jr, Nadol JB. Treatment of syphilitic hearing loss. Combined penicillin and steroid therapy in 29 patients. Ann Otol Rhinol Laryngol **1979**; 88:160–5.
108. Gu X, Gao Y, Yan Y, et al. The importance of proper and prompt treatment of ocular syphilis: a lesson from permanent vision loss in 52 eyes. J Eur Acad Dermatol Venereol **2020**; 34:1569–78.
109. Kojima N, Konda KA, Klausner JD. Notes on syphilis vaccine development. Front Immunol **2022**; 13:952284.
110. Chen W, Luo H, Zeng L, et al. A suite of PCR-LwCas13a assays for detection and genotyping of *Treponema pallidum* in clinical samples. Nat Commun **2022**; 13:4671.

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