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Amikacin Liposome Inhalation Suspension (ALIS) ALIS is a new formulation of the aminoglycoside amikacin, which allows for improved penetration in the lung with reduced toxicity. In the CONVERT study, treatment with amikacin liposome inhalation sus pension in addition to standard background regimen was associated with significantly increased culture conversion (29 vs 8.9%; $p < .0001$) by month 6 in patients with treatment-refractory MAC lung disease compared to standard background regimen alone. It is now approved for treatment of refractory MAC lung infection with persistent sputum positivity at 6 months while on appropriate background regimen. The typical dose is 590 mg (one vial once a day) for 6 months along with the standard three-drug regimen of macrolide, rifampin, and ethambutol. Dosage adjustments in patients with hepatic and renal dysfunction are not required. Half-life elimination typically occurs in ~5.9–9.5 h. Respiratory side effects such as bronchospasm, cough, dysphonia, and dyspnea are common. Monitoring for systemic aminoglycoside toxicity should be considered.

Imipenem Imipenem primarily inhibits cell-wall biosynthesis by binding to the penicillin-binding proteins. It is rapidly gaining impor tance for the treatment of M. abscessus, with a meta-analysis showing improved outcomes with its inclusion in a multidrug regimen. It is dosed at 500 mg to 1 g twice to three times a day as part of a combina tion regimen for the treatment of M. abscessus. Half-life of imipenem is ~1 h, and because it is metabolized in the kidneys, dosing adjustment is needed with renal dysfunction. Adverse effects include anemia, throm bocythemia, and liver dysfunction. Cefoxitin Cefoxitin is a second-generation parenteral cephalosporin with activity against rapidly growing NTM, particularly M. abscessus and M. chelonae. Its mechanism of action against NTM is unknown but may involve inactivation of cell-wall synthesis enzymes. High doses are used for treatment of NTM: 200 mg/kg IV three or four times per day, with a maximal daily dose of 12 g. The half-life of cefoxitin is ~1 h, with primary renal clearance that requires adjustment in renal insufficiency. Adverse effects are uncommon but include gastrointestinal manifesta tions, rash, eosinophilia, fever, and neutropenia. PART 5 Infectious Diseases Newer Drugs Three newer classes of drugs—the oxazolidinones, the glycylcyclines, and the ketolides—are currently being evaluated for possible use in the treatment of NTM infections, especially those caused by M. abscessus. Approximately 50% of M. abscessus isolates have shown some degree of susceptibility in vitro to linezolid, an oxazolidinone. Tigecycline, which is a glycylcycline and a tetracycline derivative, and telithromycin, a ketolide, also appear to have in vitro activity against M. abscessus. These drugs, however, have not yet been prospectively tested for NTM in patients. In addition, some anti-TB drugs, including clofazimine and beda quiline, are being evaluated as alternative agents for the treatment of refractory NTM infections. In particular, clofazimine appears to act synergistically in combination with amikacin, bedaquiline, or tigecy cline. The exact role of these agents in the treatment of refractory NTM infections remains unclear. Suppressive therapy with

periodic parenteral/ oral drugs to limit disease progression and control symptoms may be an appropriate alternative to curative treatment. CONCLUSION Treatment of mycobacterial infections requires multiple-drug regi mens that often exert significant side effects with the potential to limit tolerability. The prolonged duration of treatment has vastly improved results over those obtained in past decades, but drugs and regimens that will shorten treatment duration and limit adverse drug effects and interactions are needed. ■ ■FURTHER READING Collaborative Group for the Meta-Analysis of Individual Patient Data in Mdr-Tb Treatment–2017: Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculo sis: An individual patient data meta-analysis. Lancet 392:821, 2018.

Daley CL et al: Treatment of nontuberculous mycobacterial pulmo nary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 71:e1, 2020. Nahid P et al: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clini cal practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 63:e147, 2016. Sterling TR et al: Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Con trollers Association and CDC, 2020. MMWR Recomm Rep 69:1, 2020. World Health Organization: WHO consolidated guidelines on tuberculosis Module 4: Treatment, Drug-resistant tuberculosis treat ment Geneva: World Health Organization, 2022. Section 9 Spirochetal Diseases Sheila A. Lukehart

Syphilis DEFINITION Syphilis, a chronic systemic infection caused by Treponema pallidum subspecies pallidum, is usually sexually transmitted and is character ized by episodes of active disease interrupted by asymptomatic periods (latency). After an incubation period averaging 2–6 weeks, a primary lesion appears—often associated with regional lymphadenopathy—and then resolves without treatment. The secondary stage, with generalized mucosal and cutaneous lesions and generalized lymphadenopathy, also resolves spontaneously and is followed by a latent period of subclini cal infection lasting years or decades. Central nervous system (CNS) invasion may occur early in infection, and CNS involvement may be symptomatic or asymptomatic. In the preantibiotic era, one-third of untreated patients developed tertiary syphilis, characterized by destructive mucocutaneous, skeletal, or parenchymal lesions; aortitis; or late CNS manifestations. ETIOLOGY The Spirochaetales include five genera that are pathogenic for humans and for a variety of other animals: Leptospira species (leptospirosis, Chap. 189); Borrelia and Borreliella species (relapsing fever and Lyme disease, respectively; Chaps. 190 and 191); Brachyspira species (gastro intestinal infections); and Treponema species (syphilis and the endemic treponematoses; see also Chap. 188). The Treponema pallidum subspe cies include T. pallidum subsp. pallidum (venereal syphilis), T. pallidum subsp. pertenue (yaws), and T. pallidum subsp. endemicum (bejel).

T. carateum (pinta), for which no extant strains are available for molec ular studies, is still classified as a separate species. Historically, the pathogenic Treponema were distinguished by the clinical syndromes they produce, but phylogenetic analyses of whole genome sequences from several strains (excluding T. carateum) yield the three named subspecies groupings. Whether these groupings represent geographi cal variation or actual biological differences is unclear. The crossing of subspecies boundaries by some “molecular signatures” and the recent recognition of treponemes of the endemicum genotype in sexually acquired genital ulcers (chancres) and secondary rashes (Chap. 188) support the concept of a genetic and clinical “continuum” among strains and subspecies of the pathogenic treponemes. T. pallidum subspecies are thin spiral

organisms, with a cell body surrounded by a trilaminar cytoplasmic membrane, a delicate

peptidoglycan layer, and a lipid-rich outer membrane. Endoflagella wind around the cell body in the periplasmic space and are responsible for motility. Historically, T. pallidum subspecies could not be cultured in vitro, but long-term propagation of multiple strains of T. pallidum subsp. pallidum and one strain of subsp. endemicum in complex medium with eukaryotic cells is now possible. To date, the pertenue subspecies has not been cultured. All T. pallidum subspecies have severely limited metabolic capabilities and are highly dependent on host-derived amino acids, carbohydrates, and lipids. Genetic analyses have revealed the existence of a 12-member gene family (tpr) encoding outer-membrane antigens. One member, TprK, has discrete variable regions that undergo antigenic variation during infection, providing a mechanism for immune evasion and persistence. The only known natural host for T. pallidum subsp. pallidum (referred to hereafter as T. pallidum) is the human. T. pallidum can infect many mammals, but only humans, higher apes, and a few labora tory animals develop syphilitic lesions. Rabbits are used to propagate T. pallidum and serve as the animal model that best reflects human disease and immunopathology. TRANSMISSION AND EPIDEMIOLOGY Nearly all cases of syphilis are acquired by sexual contact with infec tious lesions (i.e., the chancre, mucous patch, skin rash, or condylo mata lata; see Fig. A1-20). T. pallidum DNA has also been detected in swabs of normal-appearing oral mucosa, in saliva, in urine, and in semen, raising the possibility of transmission by these routes, but the infectivity of these organisms has not been assessed. Less common modes of transmission include nonsexual skin contact, infection in utero, blood transfusion, and organ transplantation. ■ ■SYPHILIS IN THE UNITED STATES Following the introduction of penicillin therapy in the 1940s, the number of reported cases of syphilis of all stages in the United States declined 95% to a low of 31,575 cases in 2000, with 5979 reported cases of primary and secondary (P&S) syphilis. (P&S cases are infectious and are a better indicator of disease activity than total syphilis cases.) Since 2000, total cases have increased 6.6-fold to 207,255, and the number of P&S cases has increased tenfold, with 59,061 cases reported in 2022 (Fig. 187-1). Nationally, ~45% of these cases were in men who have sex with men (MSM), ~40% of whom are co-infected with HIV. In two years, from 2020 to 2022, P&S cases rose 31.7% among all men and 85.4% among women, with increases in all racial and ethnic groups and in all geographic regions of the United States. Because the incidence of congenital syphilis parallels that of infectious syphilis in women, the striking increase in early syphilis in women has resulted in a dramatic increase in congenital syphilis. In 2022, 3755 cases of congenital syphi lis were reported, resulting in 282 congenital syphilis-related stillbirths and deaths. In the last decade, the number of reported cases in infants

Men Women

Number of cases

FIGURE 187-1 Primary and secondary syphilis in the United States, 1990–2022, by sex. (Data from the Centers for Disease Control and Prevention.)

<1 year of age has increased from 334 to 3755, or elevenfold. The vast majority of these cases resulted from late or no prenatal care, but some were in women who had tested positive for syphilis but were not treated prior to delivery. A recent study of substance use in pregnant women with syphilis found that illicit use of opioids and other illicit nonprescription substances was six and

four times higher, respectively, in persons with a congenital syphilis outcome than in those without a congenital syphilis outcome. Other risk factors include homelessness and unstable housing, transactional sex, and incarceration.

The populations at highest risk for acquiring syphilis have changed over time, with outbreaks among MSM in the pre-HIV era of the late 1970s and early 1980s, as well as at present. The current dramatic decade-long increase in syphilis and other sexually transmitted infec tions in MSM may be due to unprotected sex between persons who are HIV concordant and to disinhibition facilitated by highly effective antiretroviral therapy (ART) or pre- and postexposure prophylaxis (PrEP and PEP). Many MSM diagnosed with syphilis have had syphilis previously, and reinfections may be asymptomatic in persons with multiple past episodes. Thus, more frequent (every 3 months) screen ing for syphilis and other sexually transmitted infections is warranted in high-risk populations. Cases of P&S syphilis among African Americans increased 5.5-fold between 2002 and 2022, and the rate (44.4 per 100,000 population) remains higher than rates for other racial/ethnic groups except American Indians/Alaska Natives (67 per 100,000). Of individuals named as sexual contacts of persons with early syphi lis, some will have developed manifestations of syphilis when they are first seen, and others will develop infectious syphilis if not treated; overall, ~30–60% of persons exposed to P&S syphilis will develop syphilis if not treated. Thus, identification and treatment of all recently exposed sexual contacts continue to be important aspects of syphilis control. Recent data suggest that PEP with 200 mg of doxycycline (Doxy-PEP), taken within 72 h of exposure, will significantly reduce the likelihood of syphilis (and other) infections in MSM. Data from a single study of Doxy-PEP in women have been disappointing, but these results may be due to lack of compliance in the test population. Concerns have been raised that widespread use of Doxy-PEP (perhaps misused as PrEP) may result in selection for resistance in sexually transmitted infection pathogens. CHAPTER 187 Syphilis ■ ■GLOBAL SYPHILIS Syphilis remains a significant health problem globally; the number of new infections is estimated at ~8 million per year, with 22.3 million prevalent cases. The regions most affected include sub-Saharan Africa, South America, and central and south Asia. Rates of P&S syphilis have increased dramatically among MSM in many European, Asian, and South American countries. Globally, although efforts by the World Health Organization (WHO) reduced the incidence of congenital syphilis in the 2010s, that progress is being lost as recent increases are reported in nearly all regions of the world. In 2022, there were an estimated 700,000 cases of congenital syphilis and 390,000 adverse birth outcomes: 150,000 early fetal deaths and stillbirths, 70,000 neo natal deaths, 55,000 preterm or low-birth-weight infants, and 115,000 infants with clinical evidence of infection. NATURAL COURSE AND PATHOGENESIS OF UNTREATED SYPHILIS T. pallidum rapidly penetrates intact mucous membranes or microscopic abrasions in skin and, within a few hours, enters the lymphatics and blood to produce systemic infection and metastatic foci long before the appearance of a primary lesion. Blood from a patient with incubating or early syphilis is infectious. The generation time of T. pallidum during early disease is estimated to be ~33 h, and the incubation period of syphi lis is inversely proportional to the number of organisms transmitted. The 50% infectious dose for intradermal inoculation in humans has been calculated to be 57 organisms, and the treponeme concentration gener ally reaches 107/g of tissue before a clinical lesion appears. The median incubation period in humans (~21 days) suggests an average inoculum of 500–1000 infectious organisms for naturally acquired disease; the incubation period rarely exceeds 6 weeks.

The primary lesion appears at the site of inoculation, usually persists for 4–6 weeks, and then heals spontaneously. Histopathologic exami nation shows perivascular infiltration, chiefly by CD4+ and CD8+

T lymphocytes, plasma cells, and macrophages, with capillary endo thelial proliferation and subsequent obliteration of small blood vessels. The cellular infiltration produces a TH1-type cytokine profile, consis tent with the activation of macrophages. Phagocytosis of opsonized organisms by activated macrophages ultimately causes their destruc tion, resulting in spontaneous resolution of the chancre and later the secondary rash.

The generalized parenchymal, constitutional, mucosal, and cutane ous manifestations of secondary syphilis usually appear ~6–12 weeks after infection, although primary and secondary manifestations may occasionally overlap. In contrast, some patients may enter the latent stage without ever recognizing secondary lesions. The histopathologic features of secondary maculopapular skin lesions include hyperkera tosis of the epidermis, capillary proliferation with endothelial swelling in the superficial dermis, and—in the deeper dermis—perivascular infiltration by CD8+ and CD4+ T lymphocytes, macrophages, and variable numbers of plasma cells. T. pallidum disseminates during the first days to weeks of infection, invading many tissues, including the CNS; cerebrospinal fluid (CSF) abnormalities can be detected in as many as 40% of patients during the secondary stage. Clinical hepatitis and immune complex–induced glomerulonephritis are rare, but recognized, manifestations of secondary syphilis. Generalized nontender lymphadenopathy is noted in 85% of patients with second ary syphilis. The paradoxical appearance of secondary manifestations, even after the development of an immune response that clears primary lesions, likely results from immune evasion due to antigenic variation of exposed portions of the TprK surface protein. Secondary lesions generally subside within 2–6 weeks, and the infection enters the latent stage, which is detectable only by serologic testing. In the preantibiotic era, up to 25% of untreated patients experienced at least one cutaneous relapse of secondary lesions, usually during the first year. Therefore, identification and examination of sexual contacts are most important for patients with syphilis of <1 year in duration. PART 5 Infectious Diseases In the preantibiotic era, about one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease, the most common types being the gumma (a usually benign granulomatous lesion); cardiovascular syphilis (usually involving the vasa vasorum of the ascending aorta and resulting in aneurysm); and late symptomatic neurosyphilis (tabes dorsalis and paresis). In Western countries today, specific treatment for early and latent syphilis and coincidental therapy (i.e., therapy with antibiotics active against treponemes, but given for other conditions) have nearly eliminated tertiary syphilis. Asymptom atic CNS involvement, however, is still demonstrable in up to 40% of persons with early syphilis and 25% of patients with late latent syphi lis, and modern cases of general paresis and tabes dorsalis are being reported from China. The factors that contribute to the development and progression of tertiary disease are unknown. The course of untreated syphilis was studied retrospectively in a group of nearly 2000 patients with primary or secondary disease diagnosed clinically (the Oslo Study, 1891–1951) and was assessed prospectively in 431 African-American men with seropositive latent syphilis of ≥3 years in duration (the notorious Tuskegee Study, 1932–1972). In the Oslo Study, serious late complications were nearly twice as common among men as among women. In the Tuskegee Study, untreated syphilis increased the death rate 17% compared to uninfected subjects, largely due to cardiovascular syphilis. The ethical issues eventually raised by the Tuskegee Study, begun in the pre-penicillin era

but continuing into the early 1970s, had a major influence on the development of current guide lines for protection of human subjects and still contribute to a reluctance of some African Americans to participate in clinical research. CLINICAL MANIFESTATIONS ■ ■PRIMARY SYPHILIS The typical primary chancre usually begins as a single painless pap ule that rapidly erodes and becomes indurated, with a characteristic

FIGURE 187-2 Primary syphilis with a firm, nontender chancre. cartilaginous consistency on palpation of the edge and base of the ulcer. Multiple primary lesions are seen in a minority of patients. In heterosexual men, the chancre is usually located on the penis, where it is readily seen (Fig. 187-2; see also Fig. A1-17), but in MSM, it may also be found in the anal canal, rectum, or mouth. Oral sex has been identified as the source of infection in some MSM. In women, com mon primary sites are the cervix, vaginal wall, and labia, as well as anal canal and mouth. Consequently, primary syphilis goes unrecognized in women and MSM more often than in heterosexual men. Atypical primary lesions are common, and may be multiple, small, or partially resolved. Therefore, syphilis should be considered in the evaluation of trivial or atypical dark-field-negative genital lesions. The lesions that most commonly must be differentiated from those of pri mary syphilis include those caused by herpes simplex virus infection (Chap. 197), chancroid (Chap. 162), traumatic injury, and donovano sis (Chap. 178). Regional (usually inguinal) lymphadenopathy accom panies the primary syphilitic lesion, appearing within 1 week of lesion onset. The nodes are firm, nonsuppurative, and painless. Inguinal lymphadenopathy is bilateral and may occur with anal as well as with genital chancres. The chancre generally heals within 4–6 weeks (range, 2–12 weeks), but lymphadenopathy may persist for months. ■ ■SECONDARY SYPHILIS The classical manifestations of the secondary stage include mucocu taneous or cutaneous lesions and generalized nontender lymphade nopathy. The healing primary chancre may still be present in ~15% of cases—more frequently in persons with concurrent HIV infection. The skin rash consists of macular, papular, papulosquamous, and occasion ally pustular syphilides; often more than one form is present simulta neously. The eruption may be very subtle, and 25% of patients with a discernible rash may be unaware that they have dermatologic manifes tations. Initial lesions are pale red or pink, nonpruritic, discrete mac ules distributed on the trunk and extremities; these macules progress to papular lesions that are distributed widely and that frequently involve the palms and soles (Fig. 187-3; see also Figs. A1-18 and and A1-19). Rarely, severe necrotic lesions (lues maligna) may appear and are more commonly reported in HIV-infected individuals with low CD4+ T-cell counts. Involvement of the hair follicles may result in patchy alopecia of the scalp hair, eyebrows, or beard in up to 5% of cases.

FIGURE 187-3 Secondary syphilis. Left: Maculopapular truncal eruption. Middle: Papules on the palms. Right: Papules on the soles. (Photos courtesy of Jill McKenzie and Christina Marra.) In warm, moist, intertriginous areas (commonly the perianal region, vulva, and scrotum), papules can enlarge to produce broad, moist, pink or gray-white, highly infectious lesions (condylomata lata; see Fig. A1-20) in 10% of patients with secondary syphilis. Superficial mucosal erosions (mucous patches) occur in 10–15% of patients and commonly involve the oral or genital mucosa (see Fig. A1-21). The typical mucous patch is a painless silver-gray erosion surrounded by a red periphery. T. pallidum DNA has been detected in oral mucosal swabs from persons with early and latent syphilis, but who have no vis ible oral lesions. The implications of this finding for transmission are unclear but warrant further research. Constitutional signs and symptoms that may accompany or precede secondary syphilis include sore throat (15–30%), fever (5–8%), weight loss (2–20%), malaise (25%),

anorexia (2–10%), headache (10%), and meningismus (5%). Acute meningitis occurs in only 1–2% of cases, but CSF cell and protein concentrations are increased in up to 40% of early syphilis cases, and viable T. pallidum organisms have been recovered from CSF during primary and secondary syphilis in 30% of cases, sometimes without other CSF abnormalities. Persons with current or recent secondary syphilis may present with ocular or otic manifestations. Ocular findings include pupillary abnormalities and optic neuritis as well as the classic iritis or uveitis. The diagnosis of ocular syphilis is often considered in affected patients only after they fail to respond to topical steroid therapy. Anterior uve itis has been reported in 5–10% of patients with secondary syphilis, and T. pallidum has been demonstrated in aqueous humor from such patients. Permanent blindness may result without prompt diagnosis and treatment. Otic syphilis may present as sensorineural hearing loss, vertigo, or tinnitus, and deafness may result if untreated. The publica tion of several reports of ocular and otic syphilis reminds clinicians to inquire about neurologic manifestations in all stages of syphilis infection. In a recent study, 7.9% of patients with syphilis, when asked, reported recent vision or hearing changes, and more than half of those had abnormal CSF or ophthalmologic findings consistent with syphilis. Less often recognized complications of secondary syphilis include hepatitis, nephropathy, gastrointestinal involvement (hypertrophic gastritis, patchy proctitis, or a rectosigmoid mass—sometimes mis takenly assumed to be malignant), arthritis, and periostitis. Hepatic involvement is common in syphilis; although it is usually asymptom atic, up to 25% of patients may have abnormal liver function tests. Frank syphilitic hepatitis is rare. Renal involvement usually results from immune complex deposition and produces proteinuria associ ated with an acute nephrotic syndrome. Like those of primary syphilis, most manifestations of the secondary stage resolve spontaneously, usually within 1–6 months. ■ ■LATENT SYPHILIS Positive serologic tests for syphilis, together with a normal CSF exami nation and the absence of clinical manifestations of syphilis, indicate a diagnosis of latent syphilis in an untreated person. The diagnosis may be made following routine serologic screening or may be suspected due to a history of primary or secondary lesions, a history of exposure to

syphilis, or the delivery of an infant with congenital syphilis. A previous nonre active serologic test or clear history of lesions or exposure may help to estab lish the duration of infection, which is an important factor in the selection of appropriate therapy. Early latent syphilis is limited to the first year after infection, whereas late latent syphilis is defined as that of ≥1 year in duration or unknown duration. The classical definition of early latent syphilis could include an asymp tomatic person whose secondary rash has resolved, as well as a person whose chancre has healed but who has not yet developed secondary manifestations. Accordingly, the Centers for Disease Control and Prevention (CDC) have revised the case definitions for surveillance and reporting purposes to better reflect the recognition that some clinical presentations may be seen at several stages of infec tion. These definitions include the traditional primary and secondary stages, as well as “syphilis, early nonprimary nonsecondary,” describing infections of <12 months in duration, and “syphilis, unknown duration or late,” encompassing the previous late latent and late (tertiary) clas sifications. In this new scheme, neurologic, ocular, otic, and late clinical manifestations are reported separately in the context of their separate primary, secondary, early nonprimary nonsecondary, and unknown duration or late categories.

CHAPTER 187 It was previously thought that untreated late latent syphilis had three possible outcomes: (1) persistent lifelong infection; (2) development of tertiary syphilis; or (3) spontaneous cure, with reversion of serologic tests to negative. Although progression to clinically evident late

syphilis is very rare today, the occurrence of spontaneous microbiologic cure is in doubt. Syphilis Because T. pallidum continues to be present throughout untreated infection, it may seed the bloodstream intermittently during the latent stage, and a pregnant woman with latent syphilis may infect the fetus in utero. Moreover, syphilis has been transmitted through blood transfu sion or organ donation from patients with latent syphilis. ■ ■REINFECTION SYPHILIS A growing number of individuals, particularly MSM, acquire multiple episodes of syphilis, with important implications for clinical presenta tion and serologic testing. Although no national data are available, 32% of enrollees (mostly MSM) in an 18-year longitudinal study of CNS involvement were known to have had multiple episodes of syphilis. It is well recognized that, after treatment, persons with past syphilis are less likely to revert to nonreactive in the Venereal Disease Research Labora tory (VDRL)/rapid plasma reagin (RPR) tests than persons with first episode syphilis, and treponemal tests will remain reactive. However, several recent studies also indicate that subsequent episodes of syphilis are more likely to be asymptomatic than initial episodes, less likely to have T. pallidum identified in blood or CSF, and less likely to have laboratory-defined neurosyphilis. These cases would be detectable only by serologic screening, reinforcing the utility of frequent screening in high-risk populations to identify reinfection. ■ ■INVOLVEMENT OF THE CNS Traditionally, neurosyphilis has been considered a late manifestation of syphilis, but this view is inaccurate. CNS syphilis represents a con tinuum encompassing early invasion (usually within the first weeks of infection), months to years of asymptomatic involvement, and, in some cases, development of early or late neurologic manifestations. Early neurosyphilis includes asymptomatic or symptomatic meningitis and meningovascular syphilis; late neurosyphilis includes tabes dorsalis and general paresis. Asymptomatic Neurosyphilis The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs but who have CSF abnormalities, including mononuclear

pleocytosis, increased protein concentration, or reactivity in the CSF VDRL test. CSF abnormalities are demonstrated in up to 40% of cases of untreated primary or secondary syphilis and in 25% of cases of untreated latent syphilis. T. pallidum has been recovered by inocula tion into rabbits of CSF from up to 30% of patients with primary or secondary syphilis but less frequently from patients with syphilis of

> 1 year in duration. The presence of T. pallidum in CSF is often asso ciated with other CSF abnormalities, but organisms can be recovered from patients with otherwise normal CSF. Although the prognostic implications of these findings in early syphilis are uncertain, it may be appropriate to conclude that even patients with early syphilis who have CSF abnormalities do indeed have asymptomatic neurosyphilis and should be treated for neurosyphilis; such treatment is particularly important in patients with concurrent untreated HIV infection. Before the advent of penicillin, the risk of development of clinical neurosyphi lis in untreated asymptomatic persons was roughly proportional to the intensity of CSF changes. In several large studies, neurosyphilis was associated with a serum RPR titer of ≥1:32, regardless of clinical stage or HIV infection status. Most experts agree that clinical neurosyphilis is more common among persons with untreated HIV infection, and that the immune reconstitution

> seen with effective ART may have a protective effect against development of clinical neurosyphilis in some HIV-infected persons with syphilis. Nonetheless, RPR titer ≥1:32 is still associated with reactive CSF VDRL, even in persons taking effec tive ART. HIV-uninfected persons with untreated latent syphilis and normal CSF probably run a very low risk of subsequent neurosyphilis. Symptomatic Neurosyphilis The major clinical categories of symptomatic neurosyphilis include early meningeal and meningovas cular and late parenchymatous syphilis. The last category includes gen eral paresis and tabes dorsalis. The onset of symptoms usually occurs <1 year after infection for meningeal syphilis, up to 10 years after infection for meningovascular syphilis, at ~20 years for general paresis, and at 25–30 years for tabes dorsalis. Neurosyphilis is more frequently symptomatic in patients co-infected with untreated HIV, particularly those with low CD4+ T lymphocyte counts.

PART 5 Infectious Diseases Meningeal syphilis may present as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status. This condition may be concurrent with or may follow the sec ondary stage. Patients presenting with uveitis, iritis, or hearing loss often have meningeal syphilis, but these clinical findings can also be seen in patients with normal CSF. Meningovascular syphilis reflects meningitis together with inflam matory vasculitis of small, medium, or large vessels. The most common presentation is a stroke syndrome involving the middle cerebral artery of a relatively young adult. However, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often becomes manifest after a subacute encephalitic prodrome (with headaches, vertigo, insomnia, and psychological abnormalities), which is followed by a gradually progressive vascular syndrome. The manifestations of general paresis reflect widespread late paren chymal damage and include abnormalities corresponding to the mnemonic paresis: personality, affect, reflexes (hyperactive), eye (e.g., Argyll Robertson pupils), sensorium (illusions, delusions, hallucina tions), intellect (a decrease in recent memory and in the capacity for orientation, calculations, judgment, and insight), and speech. Tabes dorsalis is a late manifestation of syphilis that presents with symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia, including ataxia, foot drop, paresthesia, bladder disturbances, impotence, areflexia, and loss of positional, deep-pain, and temperature sensations. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommo dation but not to light. Optic atrophy also occurs frequently in associa tion with tabes. ■ ■OTHER MANIFESTATIONS OF LATE SYPHILIS The slowly progressive inflammatory process leading to tertiary dis ease begins early during infection, although these manifestations may not become clinically apparent for years or decades. Early syphilitic aortitis first becomes evident soon after secondary lesions subside, and

treponemes that trigger the development of gummas may have seeded the tissue years earlier. Cardiovascular Syphilis Cardiovascular manifestations, usually appearing 10–40 years after infection, are attributable to endarteritis obliterans of the vasa vasorum, which provide the blood supply to large vessels; T. pallidum DNA has been detected by polymerase chain reaction (PCR) in aortic tissue. Cardiovascular involvement results in uncomplicated aortitis, aortic regurgitation, saccular aneurysm (usu ally of the ascending aorta), or coronary ostial stenosis. In the prean

tibiotic era, symptomatic cardiovascular complications developed in ~10% of persons with untreated late syphilis. Today, cardiovascular syphilis is rarely seen in the developed world. Late Benign Syphilis (Gumma) Gummas are usually solitary lesions ranging from microscopic to several centimeters in diameter. Histologic examination shows a granulomatous inflammation, with a central area of necrosis due to endarteritis obliterans. T. pallidum in low numbers have been detected by PCR in these lesions, and penicillin treatment results in rapid resolution, confirming the treponemal stim ulus for the inflammation. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved. Gummas of the skin produce indolent, painless, indurated nodular or ulcerative lesions that may resemble other chronic granulomatous con ditions. Skeletal gummas may affect any bone or cartilage. Upper respi ratory gummas can lead to perforation of the nasal septum or palate. ■ ■CONGENITAL SYPHILIS Transmission of T. pallidum across the placenta from a pregnant per son with syphilis to the fetus may occur at any stage of pregnancy, but fetal damage generally does not occur until after the fourth month of gestation when fetal immunologic competence begins to develop. This timing suggests that the pathogenesis of congenital syphilis, like that of adult syphilis, depends on the host immune response rather than on a direct toxic effect of T. pallidum. The risk of fetal infection during untreated early maternal syphilis is ~75–95%, decreasing to ~35% for maternal syphilis of >2 years in duration. Adequate treatment of the woman before the 16th week of pregnancy should prevent fetal dam age, and treatment before the third trimester should adequately treat the infected fetus. Untreated maternal infection may result in a rate of fetal loss of up to 40% with second-trimester spontaneous abortion, stillbirth, prematurity, and neonatal death. Among infants born alive, only fulminant congenital syphilis is clinically apparent at birth, and these babies have a very poor prognosis. The most common clinical problem is the healthy-appearing baby born to a mother with a posi tive serologic test. Routine serologic testing for syphilis in early pregnancy is costeffective in virtually all populations, even in areas with a low pre natal prevalence of syphilis. Low-tech point-of-care tests have been developed and widely implemented to facilitate antenatal testing in resource-poor settings. Globally, congenital syphilis incidence has increased dramatically, particularly in Africa, South America, and the United States. Periodic lack of benzathine penicillin (BPG) availability in low- and middle-income countries and the current critical shortage in the United States and Europe complicate treatment of seropositive women. Globally, integration of programs to prevent congenital syphi lis with programs to prevent maternal transmission of HIV would be highly cost-effective but is often hampered by the restrictions placed on HIV-focused funds. All pregnant women should be serologically screened at their first antenatal visit. Where the prevalence of syphilis in women is high or when the patient is at high risk of reinfection, testing should be repeated at 28 weeks and at delivery. Those testing positive should be treated immediately, even before receiving results of confirmatory tests. During the current BPG shortage, many clinics are treating nonpreg nant patients with doxycycline, thus reserving BPG for seropositive pregnant women. Neonatal congenital syphilis must be differentiated from other generalized congenital infections, including rubella, cyto megalovirus or herpes simplex virus infection, and toxoplasmosis, as well as from erythroblastosis fetalis.

Manifestations of congenital syphilis may appear early (within the first 2 years of life, often at 2–10 weeks of age) or late (after 2 years). The earliest manifestations of congenital syphilis include rhinitis, or “snuffles” (23%); mucocutaneous lesions (35–41%); bone changes (61%), including periostitis detectable by x-ray examination of long bones; hepatosplenomegaly (50%); lymphadenopathy (32%); anemia (34%); jaundice (30%); thrombocytopenia; and leukocytosis. CNS

invasion by T. pallidum is detectable in 22% of infected neonates. Neonatal death is usually due to pulmonary hemorrhage, second ary bacterial infection, or severe hepatitis. Late congenital syphilis (untreated after 2 years of age) is subclinical in 60% of cases; the clini cal spectrum in the remainder of cases may include interstitial keratitis (which occurs at 5–25 years of age), eighth-nerve deafness, and recur rent arthropathy. Neurosyphilis was documented in about one-quarter of untreated patients with late congenital syphilis in the preantibiotic era. Gummatous periostitis occurs at 5–20 years of age and, as in bejel, tends to cause destructive lesions of the palate and nasal septum. Classic stigmata include Hutchinson's teeth (centrally notched, widely spaced, peg-shaped upper central incisors), "mulberry" molars (sixthyear molars with multiple, poorly developed cusps), saddle nose, and saber shins. LABORATORY EXAMINATIONS ■ ■DEMONSTRATION OF THE ORGANISM Historically, dark-field microscopy and immunofluorescence antibody staining have been used to identify T. pallidum in moist lesions such as chancres or condylomata lata, but these tests are rarely available outside of research laboratories. Sensitive and specific PCR tests have been developed but are not commercially available, although a number of laboratories perform in-house validated PCR testing. The recent advances in cultivation of T. pallidum in a tissue culture system have not yet been implemented in clinical laboratories. T. pallidum can be found in tissue by immunofluorescence or immu nohistochemical methods using specific monoclonal antibodies to

T. pallidum; some commercial polyclonal antibodies are cross-reactive with other spirochetes and should be avoided. Silver stains should be interpreted with caution because artifacts resembling T. pallidum are often seen. T. pallidum DNA has been detected by PCR in lesion swabs, tissue samples, blood, CSF, ocular fluid, urine, and oropharyngeal and rectal swabs. ■ ■SEROLOGIC TESTS FOR SYPHILIS Treponemal and Lipoidal Tests There are two types of serologic tests for syphilis: lipoidal (formerly called "nontreponemal") and trepo nemal. Both are reactive in persons with any treponemal infection, including syphilis, yaws, pinta, and bejel. The most widely used lipoidal antibody tests are the RPR and VDRL tests, which measure IgG and IgM directed against a cardiolipinlecithin-cholesterol antigen complex. The RPR test is easier to perform and uses unheated serum or plasma; it is the test of choice for rapid serologic diagnosis in a clinical setting. The VDRL test remains the standard for examining CSF and is superior to the RPR for this pur pose. Either test is recommended for screening and for quantitation of serum antibody. The titer generally reflects disease activity, rising during early syphilis, often exceeding 1:32 in secondary syphilis, and declining slowly thereafter without therapy. After treatment for early syphilis, a persistent fall by fourfold or more (e.g., a decline from 1:32 to 1:8) is considered an adequate response. VDRL titers do not cor respond directly to RPR titers, and sequential quantitative testing (as for response to therapy) must employ a single test. A reactive VDRL/ RPR screening test must be confirmed by a treponemal test to rule out a biological false-positive reaction. Treponemal tests measure antibodies to native or recombinant

T. pallidum antigens and include the fluorescent treponemal antibody– absorbed (FTA-ABS) test and the T. pallidum particle agglutination (TPPA) test, both of which are more sensitive for primary syphilis than the lipoidal tests. When used to confirm reactive lipoidal test results,

treponemal tests have a very high positive predictive value for diagno sis of syphilis.

Treponemal enzyme or chemiluminescence immunoassays (EIAs/ CIAs), based largely on reactivity to recombinant antigens, are auto mated and now used as screening tests by large laboratories. When these tests are used for screening, a high proportion of sera reactive by EIA/CIA are nonreactive by subsequent lipoidal tests. Such sera should be examined in the TPPA test, which includes different antigens and a different platform. If the TPPA test is nonreactive, the patient is unlikely to have syphilis; if it is reactive, the patient is likely to have current or past syphilis. Both lipoidal and treponemal tests may be nonreactive in early primary syphilis, although treponemal tests are slightly more sensitive (85–90%) during this stage than lipoidal tests (~80%). All tests are reactive during secondary syphilis. (Fewer than 1% of patients with high titers have a lipoidal test that is nonreactive or weakly reactive with undiluted serum but is reactive with diluted serum—the prozone phenomenon.) VDRL and RPR sensitivity and titers may decline in untreated persons with late latent syphilis, but treponemal tests remain reactive in late syphilis. After treatment for early syphilis, lipoidal test titers will generally decline or the tests will become nonreactive, whereas treponemal tests often remain reactive after therapy and are not helpful in determining the infection status of persons with past syphilis. There is some concern in the literature about persons in whom the lipoidal test titer fails to become nonreactive or remains reactive in low titer after treatment; this is more commonly seen in persons with repeated episodes of syphilis. The implications in such cases are unclear, but re-treatment rarely achieves the desired goal and is not recommended in the absence of clinical findings. CHAPTER 187 False-Positive Serologic Tests for Syphilis The lipid antigens of lipoidal tests are similar to those found in human tissues, and these tests may be reactive (usually with titers ≤1:8) in persons without treponemal infection, largely limited to persons with autoimmune conditions or injection drug use. Among patients being screened for syphilis because of risk factors, clinical suspicion, or history of expo sure, ~1% of reactive lipoidal tests are falsely positive. In a patient with a false-positive lipoidal test, syphilis is excluded by a nonreactive treponemal test. Syphilis False-positive reactions may also occur with treponemal tests, par ticularly the EIA/CIA tests. Screening a low-prevalence population for syphilis with a treponemal test may result in true-positive reactions being outnumbered by false-positive reactions, leading to unnecessary treatment. Thus, screening with lipoidal tests is highly recommended. ■ ■EVALUATION FOR NEURO-, OCULAR, AND

OTIC SYPHILIS Involvement of the CNS is detected by examination of CSF for mono nuclear pleocytosis (>5 white blood cells/μL), increased protein con centration (>45 mg/dL), or CSF VDRL reactivity. Elevated CSF cell counts and protein concentrations are not specific for neurosyphilis and may be confounded by HIV co-infection. Because CSF pleocytosis may also be due to HIV, some studies have suggested using a CSF white cell cutoff of 20 cells/μL as diagnostic of neurosyphilis in HIV-infected patients with syphilis. The CSF VDRL test is highly specific and, when reactive, is considered diagnostic of neurosyphilis; however, this test is insensitive and may be nonreactive even in cases of symptomatic neu rosyphilis. The RPR test should not be substituted for the VDRL test for CSF examination. The FTA-ABS test on CSF is reactive far more often than the CSF VDRL test in all stages of syphilis, but reactivity may reflect passive transfer of serum antibody into the CSF. A nonreactive FTA-ABS test on CSF, however, may be used to rule out asymptomatic neurosyphilis. All T. pallidum–infected patients with signs or symptoms consistent with neurologic disease (e.g., meningitis, hearing loss) should have a CSF examination, regardless of disease stage. Persons with suspected ophthalmic disease (e.g., uveitis, iritis) should have a thorough ocular examination, with cranial nerve evaluation. Hearing loss, which can occur at any stage of syphilis, may be an isolated finding or may be due

to neurosyphilis (involvement of the eighth cranial nerve). If there is no cranial nerve dysfunction in persons with ocular or otic manifesta tions, no CSF exam is required; conversely, a finding of cranial nerve involvement indicates the need for CSF examination. All persons with ocular or otic syphilis should nonetheless be treated as for neurosyphi lis regardless of CSF findings.

The appropriate management of asymptomatic persons is less clear. Lumbar puncture on all asymptomatic patients with untreated syphilis is impractical and unnecessary. Even at high doses, penicillin G ben zathine fails to result in treponemicidal drug levels in CSF, and viable

T. pallidum have been isolated from the CSF of patients (with and with out HIV infection) after penicillin G benzathine treatment for early syphilis. Therefore, it is important to identify persons at higher risk for having or developing neurosyphilis so that appropriate treatment may be given. Large-scale prospective studies have shown that patients with RPR titers of ≥1:32 are at higher risk of having neurosyphilis (11fold and 6-fold higher in HIV-infected and HIV-uninfected persons, respectively), as are HIV-infected patients with CD4+ T-cell counts of ≤350/μL. Persons with active tertiary syphilis and those in whom treatment failure is suspected should also have their CSF examined to determine appropriate therapy. ■ ■EVALUATION OF HIV-INFECTED PATIENTS FOR SYPHILIS Because persons at highest risk for syphilis are also at increased risk for HIV infection, these two infections frequently coexist. There is evidence that syphilis and other genital ulcer diseases are important risk factors for acquisition and transmission of HIV infection. Some manifestations of syphilis may be altered in patients with concurrent untreated HIV infection, and multiple cases of neurologic relapse after standard therapy have been reported in these patients. PART 5 Infectious Diseases Persons with newly diagnosed HIV infection should be tested for syphilis; conversely, all patients with newly diagnosed syphilis should be tested for HIV infection. Some authorities, persuaded by reports of persistent T. pallidum in CSF of HIV-infected persons after standard therapy for early syphilis, have recommended CSF examination for evidence of neurosyphilis for all co-infected patients, regardless of the stage of syphilis, with treatment for neurosyphilis if CSF abnormalities are found. Others, on the basis of their own clinical experience, think that standard therapy—without CSF examination—is sufficient for all cases of early syphilis in HIV-infected patients without neurologic signs or symptoms. All persons with HIV infection and early syphilis should receive careful neurologic, ophthalmic, and otologic examina tions, including cranial nerve assessment; if cranial nerve dysfunction or neurologic signs or symptoms are found, a CSF examination is war ranted to inform treatment. As described above, RPR titer and CD4+ T-cell count can be used to identify patients at higher risk of neurosyphilis who might benefit from lumbar puncture, although some cases of neurosyphilis will be missed even when these criteria are used. Serologic testing after treat ment is important for all patients with syphilis, particularly for those also infected with HIV. TREATMENT Syphilis TREATMENT OF ACQUIRED SYPHILIS The CDC’s 2021 guidelines for the treatment of syphilis are sum marized in Table 187-1 and are discussed below. Penicillin G is the drug of choice for all stages of syphilis. T. pallidum is killed by very low concentrations of penicillin G, although a long period of exposure to penicillin is required because of the unusually slow rate of multiplication of the organism. Penicillin G benzathine is the preferred treatment for uncomplicated syphilis, with aqueous peni cillin being used for ocular, otic, and neurosyphilis. The efficacy of penicillin against syphilis remains undiminished after 75 years of use, and there is no evidence of penicillin resistance in T. pallidum. The current (2023) extreme shortage of penicillin G benzathine

TABLE 187-1 Recommendations for the Treatment of Syphilisa PATIENTS WITHOUT PENICILLIN ALLERGY PATIENTS WITH CONFIRMED PENICILLIN ALLERGY STAGE OF SYPHILIS Primary, secondary, or early latent CSF normal or not examined: Penicillin G benzathine (single dose of 2.4 mU IM) CSF abnormal: Treat as neurosyphilis CSF normal or not examined: Doxycycline (100 mg PO bid) or tetracycline HCl (500 mg PO qid) for 2 weeks CSF abnormal: Treat as neurosyphilis Late latent (or latent of unknown duration), cardiovascular, or benign tertiary CSF normal or not examined: Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) CSF abnormal: Treat as neurosyphilis CSF normal and patient not infected with HIV: Doxycycline (100 mg PO bid) or tetracycline HCl (500 mg PO qid) for 4 weeks CSF normal and patient infected with HIV: Desensitize and treat with penicillin if compliance cannot be assured CSF abnormal: Treat as neurosyphilis Neurosyphilis, ocular syphilis, or otic syphilis Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days or Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days Desensitize and treat with penicillin Syphilis in pregnancy According to stage Desensitize and treat with penicillin aSee text for indications for CSF examination. Abbreviations: CSF, cerebrospinal fluid; mU, million units. Source: Adapted from the 2021 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention. Available from https://www. cdc.gov/std/treatment-guidelines/default.htm. has significantly complicated the management and control of the syphilis outbreak in the United States and elsewhere, increasing the need to use alternative antibiotics. Doxycycline, normally the second-line treatment, is now being used widely for men and non pregnant women with uncomplicated syphilis, reserving penicillin G benzathine for pregnant women. Other antibiotics effective in syphilis include the tetracyclines and the cephalosporins. Amino glycosides and spectinomycin inhibit T. pallidum only in very large doses, and the sulfonamides and most quinolones are inactive. Azithromycin showed significant promise as an effective oral agent against T. pallidum; however, strains harboring 23S rDNA muta tions that confer macrolide resistance are widespread. Such strains represent >99% of recent isolates from large U.S., European, and Chinese cities, although the prevalence of resistant strains varies by geographic location. Routine treatment of syphilis with azithromy cin is not recommended. Careful follow-up of any patient treated for syphilis with azithromycin must be assured. Several additional antibiotics are actively being tested for efficacy against human syphilis infection. Early Syphilis Patients and Their Contacts Penicillin G benza thine is the most widely used agent for the treatment of early syphi lis (2.4 million units; Table 187-1) and for preventive treatment of individuals exposed to infectious syphilis within the previous 3 months. The regimens recommended for prevention are the same as those recommended for early syphilis. Penicillin G benzathine cures >95% of cases of early syphilis, although clinical relapse can follow treatment, particularly in patients with untreated HIV infection. Because the risk of neurologic relapse may be higher in HIV-infected patients, CSF examination may be recommended for

HIV-seropositive individuals with syphilis of any stage, particularly those with a serum RPR titer of ≥1:32 or a CD4+ T-cell count of ≤350/μL. Therapy appropriate for neurosyphilis should be given if there is any evidence of CNS infection. Late Latent Syphilis or Syphilis of Unknown Duration If the CSF is normal or is not examined, the recommended treatment is penicillin G benzathine (7.2 million units total; Table 187-1). If CSF abnormalities are found, the patient should be treated for neurosyphilis. Tertiary Syphilis This category includes persons with gummas (“benign”), cardiovascular syphilis, or signs and symptoms of late neurosyphilis. CSF examination should be performed. If the CSF is normal, the recommended treatment is penicillin G benzathine (7.2 million

units total; Table 187-1). If CSF is abnormal, the patient should be treated for neurosyphilis. The clinical response to treat ment for benign tertiary syphilis is usually impressive, but responses in cardiovascular syphilis are not dramatic because aortic aneurysm and aortic regurgitation cannot be reversed by antibiotics. Syphilis in Penicillin-Allergic Patients For penicillin-allergic patients with syphilis, a 2-week (early syphilis) or 4-week (late or late latent syphilis) course of therapy with doxycycline or tetracy cline is recommended (Table 187-1). These regimens appear to be quite effective in early syphilis but have not been tested for late or late latent syphilis, and compliance may be problematic. Limited studies suggest that ceftriaxone (1 g/d, given IM or IV for 8–10 days) is effective for early syphilis, and there are reports of the suc cess of 2 g/d for ocular syphilis. These nonpenicillin regimens have not been carefully evaluated in HIV-infected individuals and should be used with caution. If compliance and follow-up are not assured, penicillin-allergic HIV-infected persons with late latent or late syphilis should be desensitized and treated with penicillin. Neurosyphilis Penicillin G benzathine, even at high doses, does not produce treponemicidal concentrations of penicillin G in CSF and should not be used for treatment of neurosyphilis. Asymp tomatic neurosyphilis may relapse as symptomatic disease after treatment with benzathine penicillin, and the risk of relapse may be higher in immunosuppressed HIV-infected patients. Both symp tomatic and asymptomatic neurosyphilis should be treated with aqueous penicillin (Table 187-1). Administration of either IV aque ous crystalline penicillin G or of IM aqueous procaine penicillin G plus oral probenecid in recommended doses is thought to ensure treponemicidal concentrations of penicillin G in CSF. The clinical response to penicillin therapy for meningeal syphilis is dramatic, but treatment of neurosyphilis with existing parenchymal damage may only arrest disease progression. No data suggest that additional therapy (e.g., penicillin G benzathine for 3 weeks) would be benefi cial after treatment for neurosyphilis. The use of antibiotics other than penicillin G for the treat ment of neurosyphilis has not been studied, although limited data suggest that 1−2 g/d of IV ceftriaxone for 10−14 days and oral doxycycline, 200 mg twice daily for 21 days, may be used. Until further studies confirm these regimens, for patients with confirmed penicillin allergy, desensitization and treatment with penicillin are recommended. Management of Syphilis in Pregnancy Every pregnant woman should undergo a lipoidal screening serologic test at the first pre natal visit and, if at high risk of re-exposure, again in the third trimester and at delivery. In the untreated pregnant patient with presumed syphilis, expeditious treatment appropriate to the stage of the disease is essential. Patients should be warned of the risk of a Jarisch-Herxheimer reaction, which may be associated with mild premature contractions but rarely results in premature delivery. Penicillin is the only recommended agent for the treatment of syphilis in pregnancy. If the patient has a documented penicillin allergy, desensitization and penicillin therapy should be undertaken according to the CDC’s 2021 guidelines. After treatment during early pregnancy, a quantitative lipoidal test should be repeated

8 weeks following treatment unless reinfection is suspected and again at delivery. Treated women may not achieve a fourfold decline in titer before delivery, but for those in whom antibody titers rise by fourfold, re-treatment is warranted, with careful evaluation of the neonate at birth. EVALUATION AND MANAGEMENT OF CONGENITAL SYPHILIS All infants born to women who are untreated or who were treated after a reactive lipoidal serologic test result should be carefully examined at birth for evidence of congenital syphilis. Samples from suspicious lesions and the placenta or umbilical cord should be examined (immunohistochemistry or Clinical Laboratory Improvement Amendments [CLIA]-validated PCR) for presence of T. pallidum. Long bone radiographs may provide evidence of the periostitis of congenital syphilis.

Whether or not they are infected, newborn infants of women with reactive serologic tests may themselves have reactive tests because of transplacental transfer of maternal IgG antibodies. If the neonatal titer is fourfold higher than the mother’s, infec tion is indicated and treatment is warranted; CSF examination is recommended. For asymptomatic infants born to women treated adequately with penicillin during the first or second trimester of pregnancy, regular quantitative lipoidal tests may be performed to monitor for appropriate reduction in neonatal antibody titers. Ris ing or persistent titers indicate infection, and the infant should be treated. Detection of neonatal IgM antibody is insensitive, and no commercially available test is currently recommended. CHAPTER 187 An infant born to a seropositive mother should be treated at birth if (1) the treatment status of the seropositive mother is unknown; (2) the mother received inadequate or nonpenicillin therapy; (3) the mother received penicillin therapy in the third trimester; or (4) the infant may be difficult to follow. The CSF should be examined to obtain baseline values before treatment. Penicillin is the only recom mended drug for the treatment of syphilis in infants. More detailed recommendations for the treatment of infants and older children are included in the CDC’s 2021 treatment guidelines. JARISCH-HERXHEIMER REACTION A dramatic although self-limited reaction consisting of fever, chills, myalgia, headache, tachycardia, and increased respiratory rate may follow the initiation of treatment for syphilis. This reaction is thought to be a response to lipoproteins released by dying T. pal lidum organisms. The Jarisch-Herxheimer reaction occurs in ~50% of patients with primary syphilis, 90% of those with secondary syphilis, and a lower proportion of persons with later-stage disease. Defervescence takes place within 12–24 h. In secondary syphilis, erythema and edema of cutaneous lesions may increase. Patients should be warned to expect such developments, which can be managed with symptom-based treatment; steroid therapy is not required for this mild transient reaction. Syphilis FOLLOW-UP EVALUATION OF RESPONSES TO THERAPY Efficacy of treatment should be assessed by clinical evaluation and monitoring of the quantitative VDRL or RPR titer for a fourfold decline (e.g., from 1:32 to 1:8). Patients with primary or secondary syphilis should be examined 6 and 12 months after treatment, and persons with latent or late syphilis at 6, 12, and 24 months. More fre quent clinical and serologic examination (3, 6, 9, 12, and 24 months) is recommended for patients concurrently infected with HIV, regard less of the stage of syphilis. After successful treatment of seropositive first-episode primary or secondary syphilis, the VDRL or RPR titer progressively declines; the test becomes nonreactive by 12 months in 40–75% of seroposi tive primary cases and in 20–40% of secondary cases. A minority of patients treated for early syphilis may experience a one-dilution titer increase within 14 days after treatment; however, this early ele vation does not significantly affect the serologic outcome at 6 months after treatment. In patients with HIV infection or a history of prior syphilis, VDRL and RPR tests are less likely to become nonreactive.

Revision #1
Created 2026-01-06 16:33:20 UTC by Omar Ayman
Updated 2026-01-06 16:33:20 UTC by Omar Ayman