autoimmune conditions or injection drug use. The prevalence of false-positive results increases with advancing age, approaching 10% among persons >70 years old. In a patient with a false-positive nontreponemal test, syphilis is excluded by a nonreactive treponemal test.

False-positive reactions may also occur with the treponemal tests, particularly the new, very sensitive EIA/CIA tests. When a low-prevalence population for syphilis is screened, the number of false-positive reactions may outnumber true positives, leading to unnecessary treatment. Although the precise reason is not known, it has been shown that sera from patients with periodontal disease react with antigens used in the EIA/CIA tests, presumably as a result of cross-reactive epitopes in the many treponemes that infect the gingival crevices during periodontal disease.

Evaluation for Neurosyphilis Involvement of the CNS is detected by examination of CSF for pleocytosis (>5 white blood cells/μL), increased protein concentration (>45 mg/dL), or 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 neurosyphilis. The FTA-ABS test on CSF is reactive far more often than the VDRL test on CSF 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. The utility of measuring CXCL13 in CSF to distinguish between neurosyphilis and HIV-related CSF abnormalities has been demonstrated.

Clearly, all *T. pallidum*–infected patients who have signs or symptoms consistent with neurologic disease (e.g., meningitis, hearing loss) or ophthalmic disease (e.g., uveitis, iritis) should have a CSF examination, regardless of disease stage. The appropriate management of asymptomatic persons is less clear. Lumbar puncture on all asymptomatic patients with untreated syphilis is impractical and unnecessary. Because standard therapy with penicillin G benzathine fails to result in treponemicidal drug levels in CSF, however, it is important to identify those persons at higher risk for having or developing neurosyphilis so that appropriate therapy may be given. Viable *T. pallidum* has been isolated from the CSF of several patients (with and without concurrent HIV infection) after penicillin G benzathine therapy for early syphilis. Large-scale prospective studies have now provided evidence-based guidelines for determining which syphilis patients may benefit most from CSF examination for evidence of neurosyphilis. Specifically, patients with RPR titers of ≥1:32 are at higher risk of having neurosyphilis (11-fold 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. Guidelines for CSF examination are shown in Table 206-1.

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 HIV infection, and multiple cases of neurologic relapse after standard therapy have been reported in these patients.

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, recommend 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, believe that standard therapy—without CSF examination—is sufficient for all cases of early syphilis in HIV-infected patients without neurologic signs or symptoms. As described above, RPR titer and CD4+ T cell count can be used to identify patients at higher risk of neurosyphilis for lumbar puncture, although some cases of neurosyphilis will be missed, even when these criteria are used. Table 206-1 summarizes guidelines suggested by published studies. Serologic testing after treatment is important for all patients with syphilis, particularly for those also infected with HIV.

TABLE 206-1 INDICATIONS FOR CEREBROSPINAL FLUID EXAMINATION IN ADULTS WITH ALL STAGES OF SYPHILIS

All Patients
Signs or symptoms of nervous system involvement (e.g., meningitis, hearing loss, cranial nerve dysfunction, altered mental status, ophthalmic disease [e.g., uveitis, iritis, pupillary abnormalities], ataxia, loss of vibration sense), ***or***
RPR or VDRL titer ≥1:32, *or*
Active tertiary syphilis, *or*
Suspected treatment failure
Additional Indications in HIV-Infected Persons
CD4+ T cell count ≤350/μL, *or*
All HIV-infected persons (recommended by some experts)

Source: Adapted from the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

TREATMENT SYPHILIS

TREATMENT OF ACQUIRED SYPHILIS

The CDC's 2010 guidelines for the treatment of syphilis are summarized in Table 206-2 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. The efficacy of penicillin against syphilis remains undiminished after 60 years of use, and there is no evidence of penicillin resistance in *T. pallidum*. Other antibiotics effective in syphilis include the tetracyclines and the cephalosporins. Aminoglycosides and spectinomycin inhibit *T. pallidum* only in very large doses, and the sulfonamides and the quinolones are inactive. Azithromycin has shown significant promise as an effective oral agent against *T. pallidum*; however, strains harboring 23S rRNA mutations that confer macrolide resistance are widespread; such strains represent >80% of recent isolates from Seattle and San Francisco and have now been identified in multiple North American and European sites. Macrolide resistance mutations have been identified in nearly all samples reported from some regions of China. In contrast, a study based in Madagascar documented the equivalence of benzathine penicillin and azithromycin for treatment of early syphilis, although a sample from one azithromycin clinical failure in that study showed the presence of a 23S rRNA resistance mutation. A more recent survey from South Africa showed a very low (1%) frequency of known 23s rRNA resistance mutations. In short, the prevalence of resistant strains varies widely by geographic location, and routine treatment of syphilis with azithromycin is not recommended. In all cases, careful follow-up of any patient treated for syphilis with azithromycin must be ensured.

Early Syphilis Patients and Their Contacts Penicillin G benzathine is the most widely used agent for the treatment of early syphilis; a single dose of 2.4 million units is recommended. Preventive treatment is also recommended for individuals who have been 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 concurrent HIV infection. Because the risk of neurologic relapse may be higher in HIV-infected patients, CSF examination is recommended in HIV-seropositive individuals with syphilis of any stage, particularly those with a serum RPR titer of ≥1:32 or a