JARISCH-HERXHEIMER REACTION

A dramatic although usually mild reaction consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, increased circulating neutrophil count, and vasodilation with mild hypotension may follow the initiation of treatment for syphilis. This reaction is thought to be a response to lipoproteins released by dying *T. pallidum* 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 patients with secondary syphilis, erythema and edema of the mucocutaneous lesions may increase. Patients should be warned to expect such symptoms, which can be managed with symptom-based treatment. Steroid or other anti-inflammatory therapy is not required for this mild transient reaction.

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 frequent clinical and serologic examination (3, 6, 9, 12, and 24 months) is recommended for patients concurrently infected with HIV, regardless of the stage of syphilis.

After successful treatment of seropositive first-episode primary or secondary syphilis, the VDRL or RPR titer progressively declines, becoming negative by 12 months in 40–75% of seropositive primary cases and in 20–40% of secondary cases. Patients with HIV infection or a history of prior syphilis are less likely to become nonreactive in the VDRL or RPR test. Rates of decline of serologic titers appear to be slower, and serologically defined treatment failures more common, among HIV-infected patients than among those without HIV co-infection; however, effective antiretroviral therapy may reduce these differences. Re-treatment should be considered if serologic responses are not adequate or if clinical signs persist or recur. Because it is difficult to differentiate treatment failure from reinfection, the CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal. A minority of patients treated for early syphilis may experience a one-dilution titer increase within 14 days after treatment; however, this early elevation does not significantly affect the serologic outcome at 6 months after treatment. Patients treated for late latent syphilis frequently have low initial VDRL or RPR titers and may not have a fourfold decline after therapy with penicillin. In such patients, re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear. Because treponemal tests may remain reactive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.

The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment. Repeat CSF examinations should be performed every 6 months until the cell count is normal. An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients. The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure. Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years. In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective antiretroviral therapy.

IMMUNITY TO SYPHILIS

The rate of development of acquired resistance to *T. pallidum* after natural or experimental infection is related to the size of the antigenic stimulus, which depends on both the size of the infecting inoculum and the duration of infection before treatment. Both humoral and cellular responses are considered to be of major importance in immunity and in the healing of early lesions. Cellular infiltration, predominantly by T lymphocytes and macrophages, produces a T_H1 cytokine milieu consistent with the clearance of organisms by activated macrophages. Specific antibody enhances phagocytosis and is required for macrophage-mediated killing of *T. pallidum*. Recent studies demonstrate antigenic variation of the TprK protein, which may lead to persistence of infection and determine susceptibility to reinfection with another strain. Comparative genomic studies have revealed some sequence variations among *T. pallidum* strains, which can be differentiated by molecular typing methods. Possible correlations between molecular type and clinical manifestations are being examined.