neonates. Neonatal death is usually due to pulmonary hemorrhage, secondary bacterial infection, or severe hepatitis.

Late congenital syphilis (untreated after 2 years of age) is subclinical in 60% of cases; the clinical spectrum in the remainder of cases may include interstitial keratitis (which occurs at 5–25 years of age), eighth-nerve deafness, and recurrent arthropathy. Bilateral knee effusions are known as *Clutton's joints*. Neurosyphilis was present 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 nonvenereal endemic syphilis, 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 (sixth-year molars with multiple, poorly developed cusps), saddle nose, and saber shins.

LABORATORY EXAMINATIONS

Demonstration of the Organism *T. pallidum* cannot be detected by culture. Historically, dark-field microscopy and immunofluorescence antibody staining have been used to identify this spirochete in samples from 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.

T. pallidum can be found in tissue with appropriate silver stains, but these results should be interpreted with caution because artifacts resembling *T. pallidum* are often seen. Tissue treponemes can be demonstrated more reliably in research laboratories by PCR or by immunofluorescence or immunohistochemical methods using specific monoclonal or polyclonal antibodies to *T. pallidum*.

Serologic Tests for Syphilis There are two types of serologic test for syphilis: nontreponemal and treponemal. Both are reactive in persons with any treponemal infection, including yaws, pinta, and endemic syphilis.

The most widely used nontreponemal antibody tests for syphilis are the RPR and VDRL tests, which measure IgG and IgM directed against a cardiolipin-lecithin-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 purpose. The RPR and VDRL tests are recommended for screening or for quantitation of serum antibody. The titer reflects disease activity, rising during the evolution of early syphilis, often exceeding 1:32 in secondary syphilis, and declining 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 correspond directly to RPR titers, and sequential quantitative testing (as for response to therapy) must employ a single test. As will be discussed (see "Evaluation for Neurosyphilis," below), the RPR titer may be useful in determining which patients will benefit from CSF examination.

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 previously used hemagglutination tests. The *T. pallidum* hemagglutination (TPHA) test is widely used in Europe but is not available in the United States. When used to confirm positive nontreponemal test results, treponemal tests have a very high positive predictive value for diagnosis of syphilis. Treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), based largely on reactivity to recombinant antigens, have also been developed and are now widely used as screening tests by large laboratories. In a screening setting, however, treponemal tests give false-positive results at rates as high as 1–2%, and the rate is higher with the EIA/CIA tests. Treponemal tests are likely to remain reactive even after adequate treatment and cannot differentiate past from current *T. pallidum* infection. Figure 206-4 provides a suggested algorithm for management of such cases.

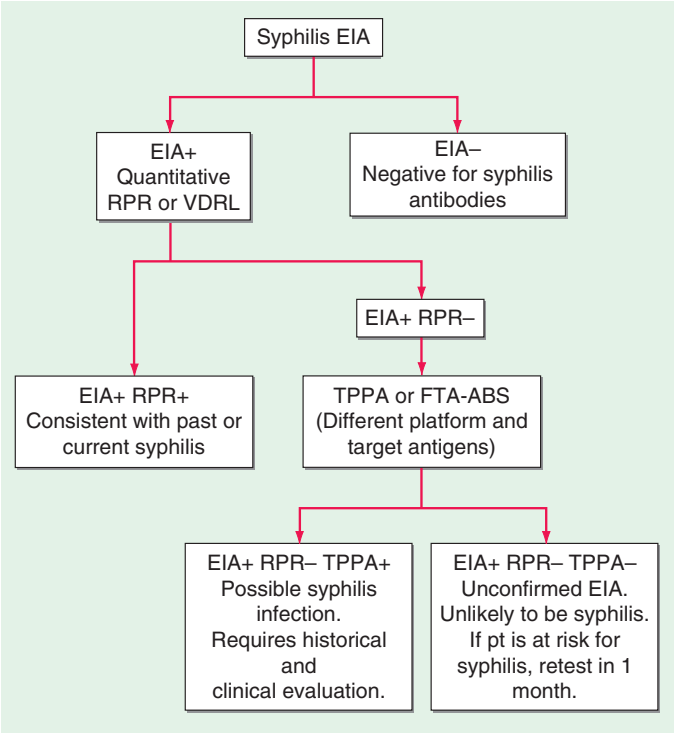

FIGURE 206-4 Algorithm for interpretation of results from syphilis enzyme immunoassays (EIAs) used for screening. FTA-ABS, fluorescent treponemal antibody–absorbed; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory. *(Based on the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.)*

Both nontreponemal and treponemal tests may be nonreactive in early primary syphilis, although treponemal tests are slightly more sensitive (85–90%) during this stage than nontreponemal tests (~80%). All tests are reactive during secondary syphilis. (Fewer than 1% of patients with high titers have a nontreponemal 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 sensitive in these stages. After treatment for early syphilis, nontreponemal 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.

For practical purposes, most clinicians need to be familiar with three uses of serologic tests for syphilis recommended by the Centers for Disease Control and Prevention (CDC): (1) screening or diagnosis (RPR or VDRL), (2) quantitative measurement of antibody to assess clinical syphilis activity or to monitor response to therapy (RPR or VDRL), and (3) confirmation of a syphilis diagnosis in a patient with a reactive RPR or VDRL test (FTA-ABS, TPPA, EIA/CIA). Studies have not demonstrated the utility of IgM testing for adult syphilis. Whereas IgM titers appear to decline after therapy, the presence or absence of specific IgM does not strictly correlate with *T. pallidum* infection. Moreover, no commercially available IgM test is recommended, even for evaluation of infants with suspected congenital syphilis.

False-Positive Serologic Tests for Syphilis The lipid antigens of nontreponemal tests are similar to those found in human tissues, and the tests may be reactive (usually with titers ≤1:8) in persons without treponemal infection. Among patients being screened for syphilis because of risk factors, clinical suspicion, or history of exposure, ~1% of reactive tests are falsely positive. Modern VDRL and RPR tests are highly specific, and false-positive reactions are largely limited to persons with