It is teeming with spirochetes and should be considered extremely infectious. It is rare for a primary chancre to be absent, but it may go unnoticed. The chancre spontaneously heals without treatment over several weeks.

Secondary syphilis usually manifests as a diffuse, maculopapular rash that classically involves the palms and soles. However, a wide range of early skin manifestations exists, including macular, papular, pustular, vesicular, or any combination of these. Vesicular lesions may easily be confused with other STIs, including herpes simplex. Syphilis may also have late skin manifestations, including nodular, squamous, or gummous appearances.

The rash typically develops a few weeks after the chancre and results from dissemination of the organism. Up to 80% of patients have some cutaneous manifestations of disease. The rash is usually symmetrical and pink, with no pain or burning, and it usually spares the face. It resolves on its own over weeks to months and may be confused with pityriasis rosea, erythema multiforme, drug rashes, tinea, measles, and seborrheic dermatitis. The maculopapular rash of secondary syphilis is considered noninfectious, although lesions in axillary or inguinal folds or other regions exposed to chaffing may erode and become infectious.

Syphilis then enters a latent stage, during which an infected individual has no symptoms but does have positive serologic test results (Table 100-2). Tertiary syphilis may then develop at any point from years to decades after the initial infection.

Approximately 30% to 40% of individuals with untreated syphilis infection develop tertiary disease, which can include neurosyphilis, cardiovascular syphilis, and gummatous disease. Neurosyphilis has classically been thought of as a complication of tertiary syphilis. However, *T. pallidum* may invade and cause symptoms of the central nervous system at the time of initial infection. Early neurosyphilis may be characterized by signs and symptoms of meningitis and milder symptoms, including headache. Other manifestations of neurosyphilis include otosyphilis (i.e., hearing loss) and ocular syphilis, which is classically characterized as posterior uveitis. Late neurosyphilis may manifest with general paresis (i.e., progressive dementia, forgetfulness, psychiatric disease, and personality change), Argyll-Robertson pupils (i.e., no response to light but normal accommodation), and tabes dorsalis (i.e., ataxia and lancinating pains). The most common finding in late neurosyphilis is irregular pupils.

Gummas, a result of immune system activation, may develop in any tissue or organ in the body. Classic cardiovascular symptoms of syphilis include aortitis, which often affects the ascending thoracic aorta causing a tree-bark appearance with dilation and aortic valve regurgitation.

TABLE 100-2 SEROLOGIC TESTING FOR SYPHILIS

FEATURES	NONTREPONEMAL	TREPONEMAL
Technique	Antibody to cardiolipin-lecithin (RPR, VDRL)	Antibody to *Treponema pallidum* (FTA-ABS, EIA)
Indications	Screening and assessing response to therapy; should be quantified by diluting serum and reporting in titers	Confirmatory test; usually remains positive for life; may be used as a screening test in some settings
Positive for syphilis		
Primary	77%	86%
Secondary	98%	100%
Early latent	95%	99%
Late latent	73%	96%
False positives	1-2% of the population may have a false-positive RPR/VDRL; common in pregnancy, recent immunization, autoimmune diseases, acute infectious illness, HIV, chronic liver disease, prozone reaction (negative result due to high antibody titers)	Borderline positive is common in pregnancy, and test should be repeated

EIA, Enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption test; HIV, human immunodeficiency virus infection; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory test.

Diagnosis and Differential Diagnosis

The diagnosis of syphilis is limited by the inability of *T. pallidum* to grow on standard laboratory media. Diagnostic testing for syphilis relies on the direct and indirect measurement of antibodies against treponema. Nontreponemal tests such as the rapid plasma regain (RPR) and venereal disease research laboratory (VDRL) test rely on anticardiolipin antibodies, which usually resemble antibodies against treponema. These tests are usually sensitive but nonspecific, and false-positive results are relatively common, especially in individuals with other autoimmune diseases or who are pregnant. Nontreponemal tests report antibodies in terms of dilutions; a titer of 1 : 2 is extremely low compared with a titer of 1 : 1024. This measurement can be used as a general representation of spirochete load in the patient. With treatment, nontreponemal test results often revert to nonreactive.

Treponemal tests such as the fluorescent treponemal antibody absorption (FTA-ABS) test rely on antibodies that directly target the organism and are therefore more specific. Tests results may be positive or negative, and a positive result usually remains so for life. The normal testing algorithm employs the sensitive, nontreponemal tests, followed by a more specific, treponemal test to confirm the diagnosis. The inherent limitation of antibody testing results in many cases of unclear diagnoses.

Several mistakes may be made by clinicians in the diagnosis of syphilis. In primary syphilis, the initial nontreponemal test result may be negative. A patient with a lesion suspicious for syphilis should undergo repeat testing or empirical treatment regardless of the serologic results. In the event of a recent exposure, a patient should be counseled that a syphilis test and HIV antibody test may be negative. A patient who is treated early in the course of disease may never develop an antibody response and may therefore never have a positive test result.

After successful treatment, patients with an initial episode of syphilis should see a fourfold decrease in nontreponemal titers at 6 months. Titers may never return to normal and should be followed periodically. For MSM, CDC guidelines suggest yearly STI testing and more frequent testing (3 to 6 months) for patients with multiple partners, anonymous partners, or other risk factors for infection.