Syphilis

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Key Points

- Syphilis is still a frequent sexually transmitted infection (STI), caused by *Treponema pallidum*, with very serious consequences not only for the index patient but sexual partners if the diagnosis is missed.
- There are authoritative guidelines for its treatment.
- The therapeutic guidelines by Centers for Disease Control (CDC) and Prevention for syphilis in adults in the different stages of the infection are followed in this chapter.

Syphilis is still a frequent sexually transmitted infection (STI) with very serious consequences not only for the index patient but sexual partners if the diagnosis is missed.

In Europe the incidence has increased in recent years. It has been realized over the last 50 years that it is common in men who have sex with men (MSM). In the last 30 years in MSM, its coexistence with HIV has been frequently found. When syphilis is diagnosed, HIV and hepatitis B and C should be screened for at the same time in all adults as well as other sexually transmitted infections. In heterosexuals it has become more frequent though unfortunately again often misdiagnosed. It has always been recognized in sex workers and their clients, but it is not infrequently found in "swinger" groups with multiple sexual partners and intravenous drug users.

There are authoritative guidelines for its treatment. Those of Centers for Disease Control (CDC) and Prevention, Atlanta, USA, are followed in this chapter.

Only syphilis in adults will be considered here.

Definition

Syphilis is a systemic disease caused by *Treponema pallidum*. On the basis of clinical findings, the disease has been divided into a series of overlapping stages, which are used to help guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and

This chapter is the copy of CDC guidelines. The copied part has been reported between brackets (all the chapter)

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lymphadenopathy), neurologic infection (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities, which might occur through the natural history of untreated infection), or tertiary infection (i.e., cardiac or gummatous lesions). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis might require a longer duration of therapy because organisms might be dividing more slowly; however, the validity of this concept has not been assessed.

Diagnosis

Dark-field examinations and tests to detect *T. pallidum* in lesion exudate or tissue are the definitive methods for diagnosing early syphilis (CDC). Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed PCR tests for the detection of *T. pallidum*. A presumptive diagnosis of syphilis is possible with the use of two types of serologic tests: (1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and (2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various EIAs, and chemiluminescence immunoassays). The use of only one type of serologic test is insufficient for diagnosis, because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use (Nandwani and Evans 1995; Association of Public Health Laboratories (APHL) 2009); therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers may correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Nontreponemal test titers usually decline after treatment and might become nonreactive with time; however, in some persons, nontreponemal antibodies can persist for a long period of time – a response referred to as the "serofast reaction." Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15–25 % of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years (Romanowski et al. 1991). Treponemal test antibody titers should not be used to assess treatment response.

Some clinical laboratories and blood banks have begun to screen samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (CDC 2008; Pope 2004). This strategy will identify both persons with previous treatment for syphilis and persons with untreated or incompletely treated syphilis. The positive predictive value for syphilis associated with a treponemal screening test result might be lower among populations with a low prevalence of syphilis.

Persons with a positive treponemal screening test should have a standard nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, then the laboratory should perform a different treponemal test (preferably one based on different antigens than the original test) to confirm the results of the initial test. If a second treponemal test is positive, persons with a history of previous treatment will require

no further management unless sexual history suggests likelihood of re-exposure. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection, previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative, further evaluation or treatment is not indicated.

For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and dark-field microscopy) should be considered.

Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment for neurosyphilis. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis. The VDRL in cerebrospinal fluid (CSF-VDRL), which is highly specific but insensitive, is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis; however in early syphilis, it can be of unknown prognostic significance (Lukehart et al. 1988). Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, and a reactive CSF-VDRL with or without clinical manifestations. Among persons with HIV infection, the CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm^3); using a higher cutoff (>20 WBC/mm^3) might improve the specificity of neurosyphilis diagnosis (Marra et al. 2004a). The CSF-VDRL might be nonreactive even when neurosyphilis is present; therefore, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; neurosyphilis is highly unlikely with a negative CSF FTA-ABS test (Jaffe et al. 1978).

General Principles of Treatment

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. Selection of the appropriate penicillin preparation is important, because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by some forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for the treatment of syphilis. Reports have indicated that practitioners have inadvertently prescribed combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) widely used in the United States. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the inappropriate combination therapy agent for treating syphilis (CDC 2005).

The effectiveness of penicillin for the treatment of syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, nearly all the recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but approximately 50 years of clinical experience.

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy").

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that usually occur within the first 24 h after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction occurs most frequently among patients who have early syphilis, presumably because bacterial burdens are higher during these stages. Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women, but this should not prevent or delay therapy (see section "Syphilis during pregnancy").

Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur only when mucocutaneous syphilitic lesions are present. Although such manifestations are uncommon after the first year of infection, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically and treated with a recommended regimen, according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) can be assumed to have early syphilis. For the purpose of determining a treatment regimen, however, serologic titers should not be used to differentiate early from late latent syphilis (see section "Latent syphilis," Treatment).
- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

Sexual partners of infected patients should be considered at risk and provided treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for patients diagnosed with primary syphilis, 6 months plus duration of symptoms for those with secondary syphilis, and 1 year for patients with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for more than 50 years to achieve clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). Substantially fewer data are available for non-penicillin regimens.

Recommended Regimen for Adults[a]

Benzathine penicillin G 2.4 million units IM in a single dose

[a]Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see sections "Syphilis among HIV-infected persons" and "Syphilis in pregnancy")

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis (primary, secondary, and early latent) do not enhance efficacy, regardless of HIV status (Figs. 94.1, 94.2, 94.3, 94.4, 94.5, 94.6, 94.7, 94.8, and 94.9).

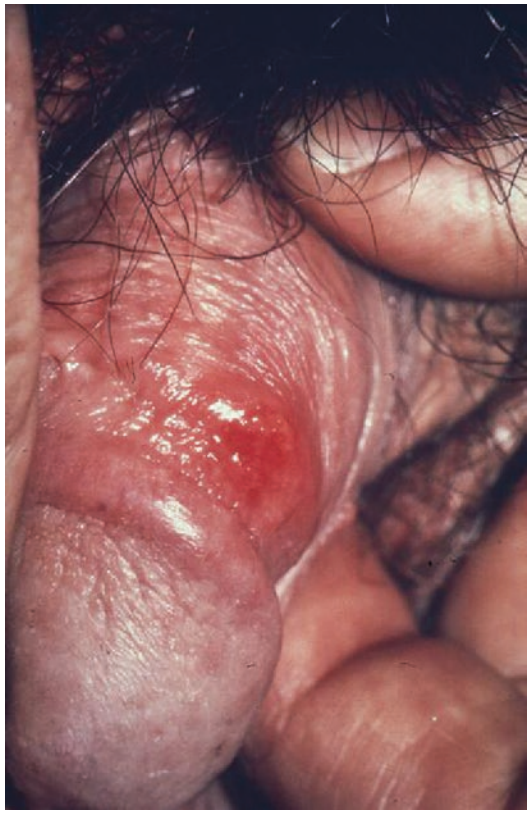

Fig. 94.1 Primary syphilis – chancre male

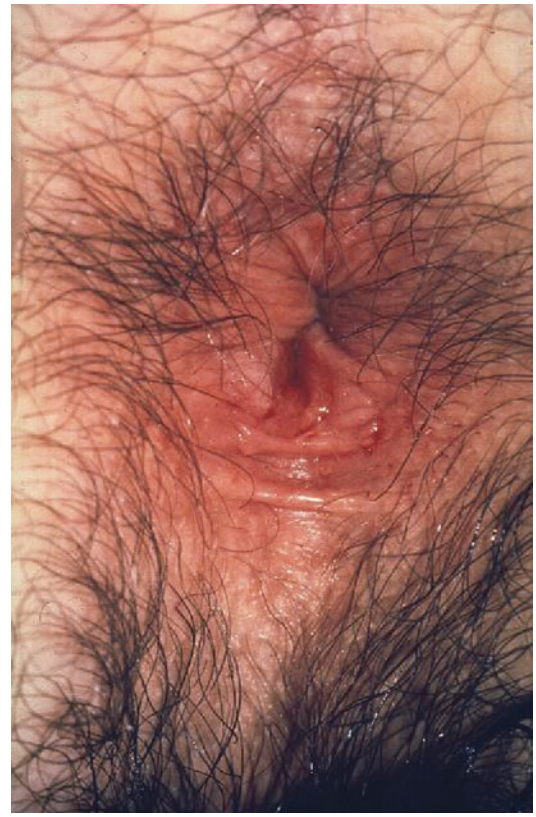

Fig. 94.3 Primary syphilis – chancre anus

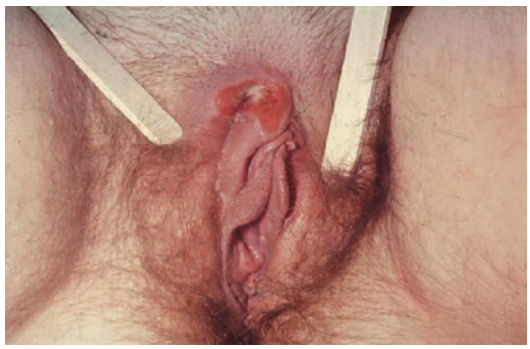

Fig. 94.2 Primary syphilis – chancre female

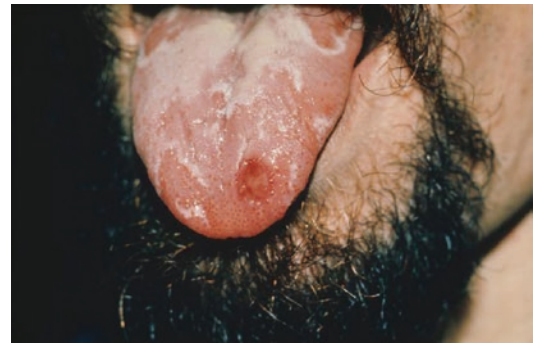

Fig. 94.4 Primary syphilis – chancre tongue

Other Management Considerations

All persons who have syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, persons who have primary syphilis should be retested for HIV after 3 months if the first HIV test result was negative.

Patients who have syphilis and symptoms or signs suggesting neurologic disease (e.g., meningitis and hearing loss) or ophthalmic disease

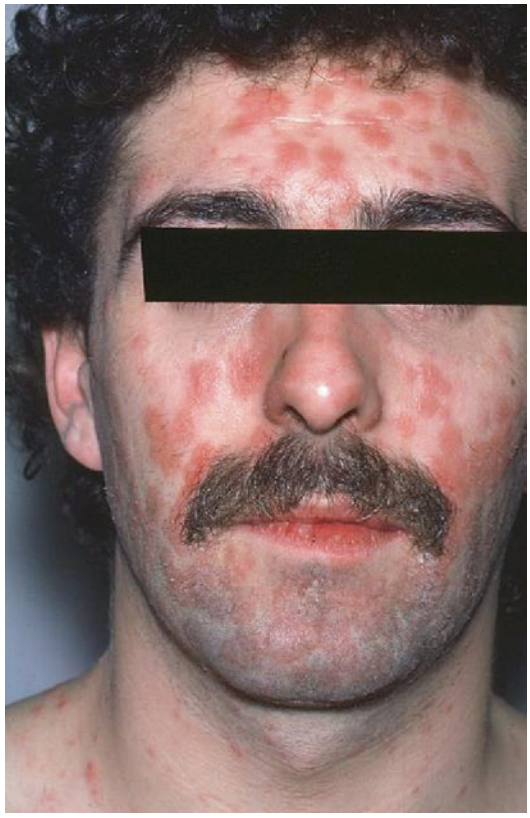

Fig. 94.5 Secondary syphilis – man's face

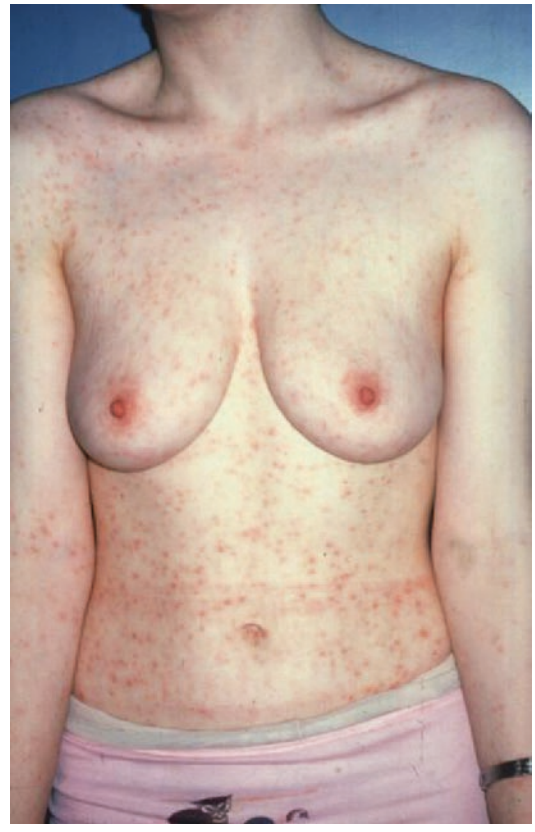

Fig. 94.6 Secondary syphilis – female trunk

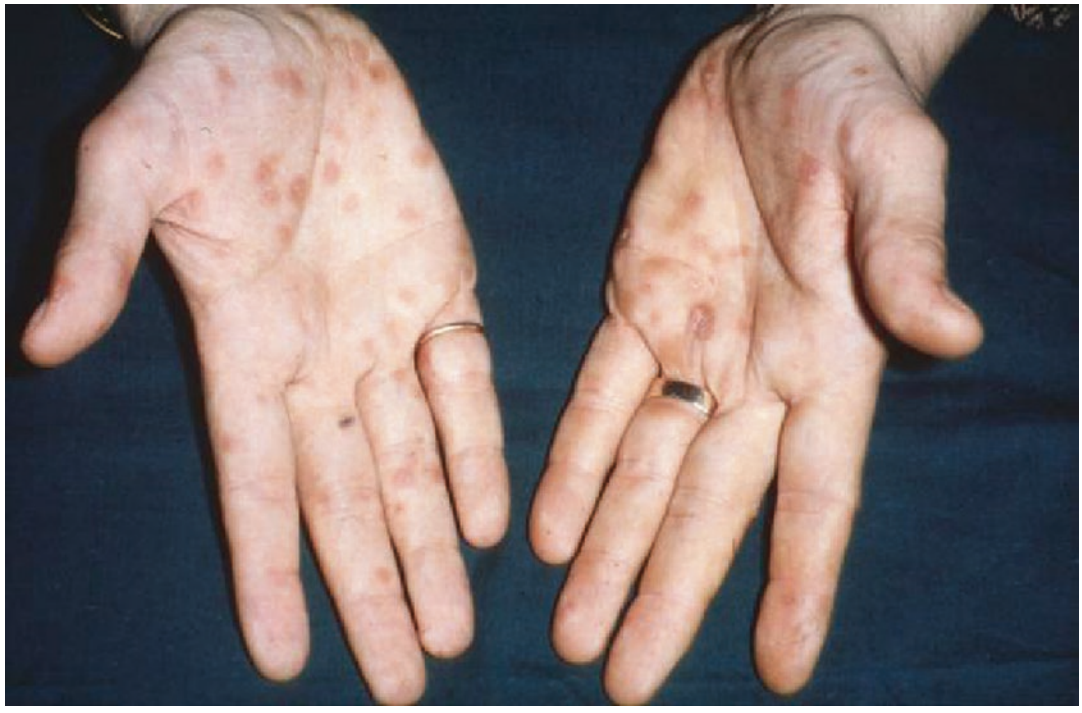

Fig. 94.7 Secondary syphilis – hands

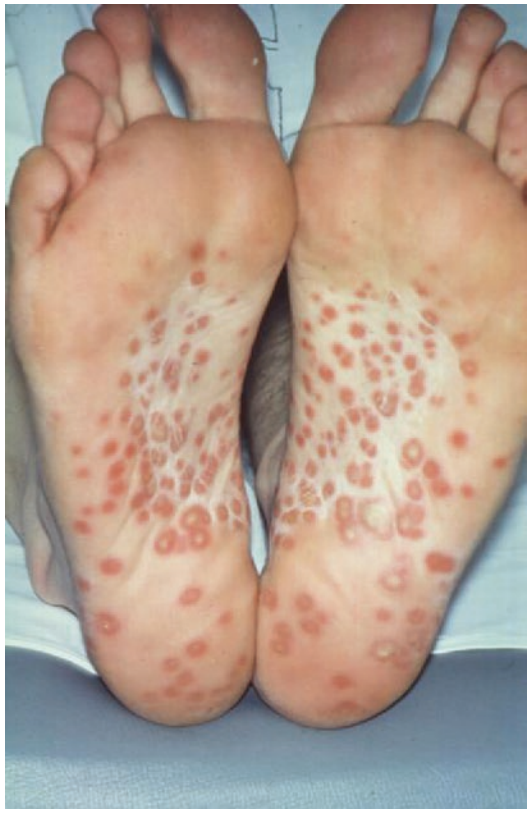

Fig. 94.8 Secondary syphilis – feet

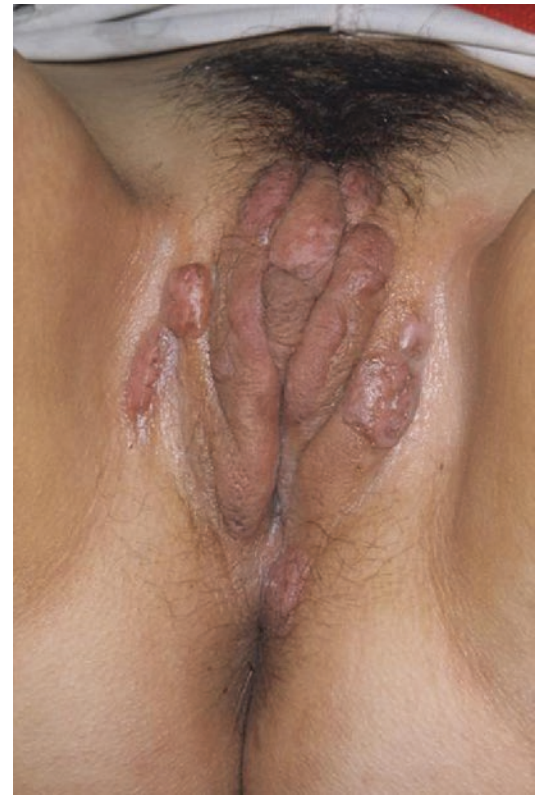

Fig. 94.9 Secondary syphilis – condylomata lata

(e.g., uveitis, iritis, neuroretinitis, and optic neuritis) should have an evaluation that includes CSF analysis, ocular slit-lamp ophthalmologic examination, and otologic examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis (Lukehart et al. 1988). Therefore, in the absence of clinical neurologic findings, no evidence exists to support variation from the recommended treatment regimen for early syphilis. Symptomatic neurosyphilis develops in only a limited number of persons after treatment with the penicillin regimens recommended for primary and secondary syphilis. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present or treatment failure is documented, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Treatment failure can occur with any regimen. However, assessing response to treatment frequently is difficult, and definitive criteria for cure or failure have not been established. In addition, nontreponemal test titers might decline more slowly for persons who previously have had syphilis (Ghanem et al. 2007). Clinical and serologic evaluation should be performed 6 and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e.,

compared with the maximum or baseline titer at the time of treatment) probably failed treatment or were reinfected. These patients should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis also should be performed.

Although failure of nontreponemal test titers to decline fourfold within 6–12 months after therapy for primary or secondary syphilis might be indicative of treatment failure, clinical trial data have demonstrated that >15 % of patients with early syphilis treated with the recommended therapy will not achieve the two-dilution decline in nontreponemal titer used to define response at 1 year after treatment (Rolfs et al. 1997). Persons whose titers do not decline should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients should receive additional clinical and serologic follow-up. If additional follow-up cannot be ensured, re-treatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations.

For re-treatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks are recommended, unless CSF examination indicates that neurosyphilis is present (see section "Neurosyphilis"). In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis. Doxycycline 100 mg orally twice daily for 14 days (Ghanem et al. 2006; Wong et al. 2008) and tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1 g daily either IM or IV for 10–14 days) is effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (Hook et al. 1988). Azithromycin as a single 2 g oral dose is effective for treating early syphilis (Riedner et al. 2005; Hook et al. 2002, 2010). However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States (Lukehart et al. 2004; Mitchell et al. 2006; Su et al. 2006) as well as some other countries. As such, the use of azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM or pregnant women. Close follow-up of persons receiving any alternative therapies is essential.

Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform the test adequately (see section "Management of patients who have a history of penicillin allergy").

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis. Patients' conditions can be diagnosed as early latent syphilis if, during the year preceding the evaluation, they had (1) a documented seroconversion or fourfold or greater increase in titer of a nontreponemal test, (2) unequivocal symptoms of primary or secondary syphilis, or (3) a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons whose only possible exposure occurred during the previous 12 months, reactive nontreponemal and treponemal tests are indicative of early latent syphilis. In the absence of these conditions, an asymptomatic person should be considered to have late latent syphilis or syphilis of unknown duration. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. All patients with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, perianal area, perineum and vagina in women, and underneath the foreskin in uncircumcised men) to evaluate for internal mucosal lesions. All patients who have syphilis should be tested for HIV infection.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating patients with this stage of disease is to prevent complications. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens.

The following regimens are recommended for penicillin nonallergic patients who have normal CSF examinations (if performed):

Recommended Regimens for Adults[a]

Early latent syphilis

Benzathine penicillin G 2.4 million units IM in a single dose

Late latent syphilis or latent syphilis of unknown duration

Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

[a]Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see sections "Syphilis among HIV-infected persons" and "Syphilis in pregnancy")

Available data demonstrate no enhanced efficacy of additional doses of penicillin G, amoxicillin, or other antibiotics in early syphilis, regardless of HIV status.

Other Management Considerations

Patients diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic (e.g., auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic signs or symptoms (e.g., iritis and uveitis)
- Evidence of active tertiary syphilis (e.g., aortitis and gumma)
- Serologic treatment failure

If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10–14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis. Pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if (1) titers increase fourfold, (2) an initially high titer (≥1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or (3) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, re-treatment for latent syphilis should be initiated. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might fail to decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

The effectiveness of alternatives to penicillin in the treatment of latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to therapies recommended as alternatives to penicillin for the treatment of primary and secondary syphilis (see section "Primary and secondary syphilis," Treatment). The only acceptable alternatives for the treatment of late latent syphilis or latent syphilis of unknown duration are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days. These therapies should be used only in conjunction with close serologic and clinical follow-up. Based on biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating late latent syphilis or syphilis of unknown duration. However, the optimal dose and duration of ceftriaxone therapy have not been defined, and treatment decisions should be discussed in consultation with a specialist. Some patients who are allergic to penicillin also might be allergic to ceftriaxone; in these circumstances, use of an alternative agent might be required. The efficacy of these alternative regimens in HIV-infected persons has not been well studied.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen:

Recommended Regimen

Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Other Management Considerations

Patients who have symptomatic late syphilis should be given a CSF examination before therapy is initiated. Some providers treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. These patients should be managed in consultation with an infectious disease specialist.

Follow-Up

Limited information is available concerning clinical response and follow-up of patients who have tertiary syphilis.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Patients allergic to penicillin should be treated in consultation with an infectious disease specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis. However, CSF laboratory abnormalities are common in persons with early syphilis, even in the absence of clinical neurological findings. No evidence exists to support variation from recommended treatment for early syphilis for patients found to have such abnormalities. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis), a CSF examination should be performed.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis and should be managed according to the treatment recommendations for neurosyphilis. Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the recommended regimen for neurosyphilis; those with eye disease should be managed in collaboration with an ophthalmologist. A CSF examination should be performed for all patients with syphilitic eye disease to identify those with abnormalities; patients found to have abnormal CSF test results should be provided follow-up CSF examinations to assess treatment response:

Recommended Regimen

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion for 10–14 days

If compliance with therapy can be ensured, the following alternative regimen might be considered:

Alternative Regimen

Procaine penicillin 2.4 million units IM once daily

PLUS

Probenecid 500 mg orally four times a day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

Other considerations in the management of patients who have neurosyphilis are as follows:

- All persons who have syphilis should be tested for HIV.
- Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven to be beneficial.

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months

until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important (Marra et al. 2004b, 2008). The leukocyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months or if the CSF cell count or protein is not normal after 2 years, re-treatment should be considered.

Limited data suggest that in immunocompetent persons and HIV-infected persons on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters (Marra et al. 2008).

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Limited data suggest that ceftriaxone 2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for patients with neurosyphilis (Hook et al. 1986; Shann and Wilson 2003). However, the possibility of cross-reactivity between ceftriaxone and penicillin exists. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, if concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, desensitization in consultation with a specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see section "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Although they are uncommon, unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports have involved serologic titers that were higher than expected, but false-negative serologic test results and delayed appearance of seroreactivity also have been reported (Kingston et al. 2005). Regardless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with *T. pallidum* and HIV.

When clinical findings are suggestive of syphilis but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, dark-field examination, and PCR of lesion material) might be useful for diagnosis. Neurosyphilis should be considered in the differential diagnosis of neurologic disease in HIV-infected persons.

Treatment

Compared with HIV-negative patients, HIV-positive patients who have early syphilis might be at increased risk for neurologic complications (CDC 2007) and might have higher rates of serologic treatment failure with currently recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients (Rolfs et al. 1997). Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment of primary and secondary syphilis among HIV-infected persons is benzathine

penicillin G, 2.4 million units IM in a single dose.

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis do not result in enhanced efficacy, regardless of HIV status (Rolfs et al. 1997).

Other Management Considerations

Most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown. Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤350 cells/mL and/or an RPR titer of ≥1:32 (Marra et al. 2004a; Libois et al. 2007; Ghanem 2009); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in HIV-infected persons with syphilis (Marra et al. 2008; Ghanem et al. 2008a, b).

Follow-Up

HIV-infected persons should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

HIV-infected persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and re-treatment). CSF examination and re-treatment also should be strongly considered for persons whose nontreponemal test titers do not decrease fourfold within 6–12 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM each at weekly intervals for 3 weeks is recommended.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

HIV-infected, penicillin-allergic patients who have primary or secondary syphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy"). The use of alternatives to penicillin has not been well studied in HIV-infected patients. These therapies should be used only in conjunction with close serologic and clinical follow-up.

Latent Syphilis Among HIV-Infected Persons

Treatment

HIV-infected persons with latent syphilis should be treated according to the stage-specific recommendations for HIV-negative persons:

- Treatment of early latent syphilis among HIV-infected persons is benzathine penicillin G, 2.4 million units IM in a single dose.
- Treatment of late latent syphilis or syphilis of unknown duration among HIV-infected persons is benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks.

Other Management Considerations

All HIV-infected persons with syphilis and neurologic symptoms should undergo immediate CSF examination. Some studies have demonstrated that clinical and CSF abnormalities

consistent with neurosyphilis are most likely in HIV-infected persons who have been diagnosed with syphilis and have a CD4 count of ≤350 cells/ml and/or an RPR titer of ≥1:32 (Marra et al. 2004a; Libois et al. 2007; Ghanem 2009); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

Follow-Up

Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If, at any time, clinical symptoms develop or nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. If during 12–24 months the nontreponemal titer does not decline fourfold, CSF examination should be strongly considered and treatment administered accordingly.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

The efficacy of alternative nonpenicillin regimens in HIV-infected persons has not been well studied. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy"). These therapies should be used only in conjunction with close serologic and clinical follow-up. Limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone might be effective (Dowell et al. 1992; Smith et al. 2004). However, the optimal dose and duration of ceftriaxone therapy have not been defined.

Neurosyphilis Among HIV-Infected Persons

Treatment

HIV-infected patients with neurosyphilis should be treated according to the recommendations for HIV-negative patients with neurosyphilis (see section "Neurosyphilis").

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to gauge response after therapy. Limited data suggest that changes in CSF parameters might occur more slowly in HIV-infected patients, especially those with more advanced immunosuppression (Marra et al. 2004b; Ghanem et al. 2008a). If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, re-treatment should be considered.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

HIV-infected, penicillin-allergic patients who have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis. Several small observational studies conducted in HIV-infected patients with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternate agent (Marra et al. 2000; Dowell et al. 1992; Smith et al. 2004).

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy. Most states mandate screening at the first prenatal visit for all women (Hollier et al. 2001); antepartum screening by nontreponemal antibody testing is typical, but in some settings, treponemal antibody testing is being used. Pregnant women with reactive treponemal screening tests should have confirmatory testing with nontreponemal tests with titers. In populations in which use of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time that pregnancy is confirmed (World Health Organization 2005). For communities and populations in which the prevalence of syphilis is high and for patients at high risk, serologic testing should be performed twice during the third trimester (ideally at 28–32 weeks' gestation) and at delivery. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis. No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined. Serofast low antibody titers might not require treatment; however, persistent higher titer antibody tests might indicate reinfection, and treatment might be required.

Treatment

Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection (Alexander et al. 1999). Evidence is insufficient to determine optimal, recommended penicillin regimens (Walker 2001):

Recommended Regimen

Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.

Other Management Considerations

Some evidence suggests that additional therapy can be beneficial for pregnant women in some settings (e.g., a second dose of benzathine penicillin G 2.4 million units IM administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis) (Wendel et al. 2002). When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (i.e., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (Hollier et al. 2001); such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations.

Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction (Klein et al. 1990). These women should be advised to seek obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment, but concern for this complication should not delay necessary treatment. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. Serologic titers should be repeated at 28–32 weeks' gestation and at delivery as recommended for the disease stage. Providers should ensure that the clinical and antibody responses

are appropriate for the patient's stage of disease, although most women will deliver before their serologic response to treatment can be assessed definitively. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, if clinical signs of infection are present at delivery, or if the maternal antibody titer at delivery is fourfold higher than the pretreatment titer. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

For treatment of syphilis during pregnancy, no proven alternatives to penicillin exist. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Oral stepwise penicillin dose challenge or skin testing might be helpful in identifying women at risk for acute allergic reactions (see section "Management of patients who have a history of penicillin allergy").

Tetracycline and doxycycline usually are not used during pregnancy. Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection nor treats an infected fetus (Walker 2001). Data are insufficient to recommend ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

HIV Infection

Placental inflammation from congenital infection might increase the risk for perinatal transmission of HIV. All HIV-infected women should be evaluated for syphilis and receive treatment as recommended. Data are insufficient to recommend a specific regimen for HIV-infected pregnant women (see section "Syphilis among HIV-infected patients").

Syphilis in Pregnancy

Pregnant women should be treated with the first line therapy option appropriate for the stage of syphilis and if allergic to penicillin should be desensitized (Janier et al. 2014).

General Principles Management of Sexual Partners

The Guidelines for contact tracing, management of sexual partners and notification of syphilis cases are detailed in 2014 European guideline on the management of syphilis (Janier et al. 2014).

References

Alexander JM, Sheffield JS, Sanchez PJ, et al. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol. 1999;93:5–8.

Association of Public Health Laboratories (APHL). Laboratory diagnostic testing for Treponema pallidum. Expert consultation meeting summary report, 13–15 Jan 2009, Atlanta. Available at: http://www.aphl.org/aphlprograms/ infectious/std/–Documents/LaboratoryGuidelinesTreponemapallidumMeetingReport.pdf.

CDC. Inadvertent use of Bicillin® C-R to treat syphilis infection – Los Angeles, California, 1999–2004. MMWR Morb Mortal Wkly Rep. 2005;54:217–9.

CDC. Symptomatic early neurosyphilis among HIV-positive men who have sex with men: four cities, United States, January 2002–June 2004. MMWR Morb Mortal Wkly Rep. 2007;56:625–8.

CDC. Syphilis testing algorithms using treponemal tests for initial screening – four laboratories, New York City, 2005–2006. MMWR Morb Mortal Wkly Rep. 2008;57:872–5.

CDC. Guidelines for the laboratory diagnosis of gonorrhea, chlamydia and syphilis. Available at: http://www.aphl.org/aphlprograms/infectious/std/Pages/std-testingguidelines.aspx.

Dowell ME, Ross PG, Musher DM, et al. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am J Med. 1992;93:481–8.

Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. Clin Infect Dis. 2009;49:162–3.

Ghanem KG, Erbelding EJ, Cheng WW, et al. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clin Infect Dis. 2006;42:e45–9.

Ghanem KG, Erbelding EJ, Wiener ZS, et al. Serological response to syphilis treatment in HIV-positive and

HIV-negative patients attending sexually transmitted diseases clinics. Sex Transm Infect. 2007;83:97–101.
Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS. 2008a;22:1145–51.
Ghanem KG, Moore RD, Rompalo AM, et al. Antiretroviral therapy is associated with reduced serologic failure rates for syphilis among HIV-infected patients. Clin Infect Dis. 2008b;47:258–65.
Hollier LM, Harstad TW, Sanchez PJ, et al. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol. 2001;97:947–53.
Hook III EW, Baker-Zander SA, Moskovitz BL, et al. Ceftriaxone therapy for asymptomatic neurosyphilis. Case report and Western blot analysis of serum and cerebrospinal fluid IgG response to therapy. Sex Transm Dis. 1986;13(3 Suppl):S185–8.
Hook III EW, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. J Infect Dis. 1988;158:881–4.
Hook III EW, Martin DH, Stephens J, et al. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis. 2002;29:486–90.
Hook III EW, Behets F, Van DK, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010;201:1729–35.
Jaffe HW, Larsen SA, Peters M, et al. Tests for treponemal antibody in CSF. Arch Intern Med. 1978;138:252–5.
Janier M, Hegyi V, Dupin N, et al. European guidelines on the management of syphilis. JEADV. 2014;28:1581–93.
Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. Arch Dermatol. 2005;141:431–3.
Klein VR, Cox SM, Mitchell MD, et al. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet Gynecol. 1990;75(3 Pt 1):375–80.
Libois A, De WS, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. Sex Transm Dis. 2007;34:141–4.
Lukehart SA, Hook III EW, Baker-Zander SA, et al. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. Ann Intern Med. 1988;109:855–62.
Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. N Engl J Med. 2004;351:154–8.
Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2000;30:540–4.
Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis. 2004a;189:369–76.
Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis. 2004b;38:1001–6.
Marra CM, Maxwell CL, Tantalo LC, et al. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis. 2008;47:893–9.
Mitchell SJ, Engelman J, Kent CK, et al. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. Clin Infect Dis. 2006;42:337–45.
Nandwani R, Evans DT. Are you sure it's syphilis? A review of false positive serology. Int J STD AIDS. 1995;6:241–8.
Pope V. Use of treponemal tests to screen for syphilis. Infect Med. 2004;21:399–402.
Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005;353:1236–44.
Rolfs RT, Joesoef MR, Hendershot EF, et al; The Syphilis and HIV Study Group. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. N Engl J Med. 1997;337:307–14.
Romanowski B, Sutherland R, Fick GH, et al. Serologic response to treatment of infectious syphilis. Ann Intern Med. 1991;114:1005–9.
Shann S, Wilson J. Treatment of neurosyphilis with ceftriaxone. Sex Transm Infect. 2003;79:415–6.
Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD AIDS. 2004;15:328–32.
Su JR, Hook E, Kenney K, et al. Prevalence of the 23S rRNA point mutation in *Treponema pallidum* in the United States and associated factors, 2006–2008. In: 18th International Society for Sexually Transmitted Diseases Research, London, #OS1.11.03. 2009.
Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database Syst Rev. 2001:(3);CD001143.
Wendel Jr GD, Sheffield JS, Hollier LM, et al. Treatment of syphilis in pregnancy and prevention of congenital syphilis. Clin Infect Dis. 2002;35 Suppl 2:S200–9.
Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. Am J Med. 2008;121:903–8.
World Health Organization. The global elimination of congenital syphilis: rationale and strategy for action. Geneva: WHO Department of Reproductive Health and Research; 2005.