

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 (203). 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 (204). 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 (205).

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 peni-

cillin (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 (206).

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 Management of Patients Who Have a History of Penicillin Allergy).

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 hours 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 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 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*

Benzathine penicillin G 2.4 million units IM in a single dose

* Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see 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.

Recommended Regimen for Infants and Children

Infants and children aged ≥ 1 month diagnosed with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether such children have congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children) and treated by using the following pediatric regimen.

Recommended Regimen for Infants and Children

Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

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 (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 (203). Therefore, in the absence of clinical neuro-

logic 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 (207). Clinical and serologic evaluation should be performed 6 months 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 (208). 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, retreatment is recommended. Because treatment failure might be the result of

unrecognized CNS infection, CSF examination can be considered in such situations.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present (see 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 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 (209,210) 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 (211). Azithromycin as a single 2-g oral dose is effective for treating early syphilis (212–214). However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States (215–217). 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 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 Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See 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*
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
<small>* Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see Syphilis among HIV-Infected Persons and Syphilis in Pregnancy).</small>

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

Infants and children aged ≥ 1 month who have been diagnosed with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis (see Congenital Syphilis). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens (see Sexual Assault or Abuse of Children). These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.

Recommended Regimens for Children
Early Latent Syphilis
Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose
Late Latent Syphilis or Latent Syphilis of Unknown Duration
Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

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); or
- 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 ($\geq 1:32$) 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, retreatment 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 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 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 Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See 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 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 Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See 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 hours or continuous infusion, 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 (219,220). 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, retreatment 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 (220).

Management of Sex Partners

See 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 (221,222). 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 Syphilis During Pregnancy).

HIV Infection

See 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 (223). Regardless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfecting 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, darkfield 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 (224) 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 (208). 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 (208).

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 $\geq 1:32$ (204,225,226); 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 (220,227,228).

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 retreatment). CSF examination and retreatment 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 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 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 $\geq 1:32$ (204,225,226); 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 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 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 (229,230). 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 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 (219,227). If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered.

Management of Sex Partners

See 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 (218,229,230).

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 (231); 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 (232). 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 (233). Evidence is insufficient to determine optimal, recommended penicillin regimens (234).

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 2.4 million units IM administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis) (235). 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 (231); 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 (236). 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 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 step-wise penicillin dose challenge or skin test-

ing might be helpful in identifying women at risk for acute allergic reactions (see 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 or treats an infected fetus (234). 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 Syphilis Among HIV-Infected Patients).

B. Penicillin Allergy

Management of Persons Who Have a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Penicillin also is recommended for use, whenever possible, in HIV-infected patients. Of the adult U.S. population, 3%–10% have experienced an immunoglobulin E (IgE)-mediated allergic response to penicillin (238,239), such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension). Readministration of penicillin to these patients can cause severe, immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic patients, unless they undergo acute desensitization to eliminate anaphylactic sensitivity.

Although an estimated 10% of persons who report a history of severe allergic reactions to penicillin continue to remain allergic their entire lives, with the passage of time, most persons who have had a severe reaction to penicillin stop expressing penicillin-specific IgE (238,239). These persons can then be treated safely with penicillin. Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for penicillin reactions (238,239). Although these reagents are easily generated and have been available for more than 30 years, only benzylpenicilloyl poly-L-lysine (Pre-Pen [i.e., the major determinant]) and penicillin G have been available commercially. These two tests identify an estimated 90%–97% of the currently allergic patients. However, because skin testing without the minor determinants would still miss 3%–10% of allergic patients and because serious or fatal reactions can occur among these minor-determinant-positive patients, caution should be exercised when the full battery of skin-test reagents is not available (Box 2). Manufacturers are working to ensure better availability of the Pre-Pen skin test reagent as well as an accompanying minor determinant mixture.

Recommendations

If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), patients who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Skin-test–positive patients should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using benzylpenicilloyl poly-L-lysine (i.e., the major determinant) and penicillin G. Patients who have positive test results should be desensitized. One approach suggests that persons with a history of allergy who have negative test results should be regarded as possibly allergic and desensitized. Another approach in those with negative skin-test results involves test-dosing gradually with oral penicillin in a monitored setting in which treatment for anaphylactic reaction can be provided.

If the major determinant (Pre-Pen) is not available for skin testing, all patients with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. In patients with reactions not likely to be IgE-mediated, outpatient-monitored test doses can be considered.

Penicillin Allergy Skin Testing

Patients at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis, asthma, or other diseases that would make anaphylaxis more dangerous or 2) are being treated with beta-adrenergic blocking agents, should be tested with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. In these situations, patients should be tested in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, the patient should not have taken antihistamines recently (e.g., chlorpheniramine maleate or fexafenadine during the preceding 24 hours, diphenhydramine HCl during the preceding 4 days, or hydroxyzine or phenothiazines during the preceding 3 weeks).

Procedures

Dilute the antigens either 100-fold for preliminary testing (if the patient has had a life-threatening reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year).

Epicutaneous (Prick) Tests

Duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood. An epicutaneous test is positive if the average wheal diameter after 15 minutes is ≥ 4 mm larger than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to ensure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal Test

If epicutaneous tests are negative, duplicate 0.02-mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm by using a 26- or 27-gauge needle on a syringe. The margins of the wheals induced by the injections should be marked with a ball point pen. An intradermal test is positive if the average wheal diameter 15 minutes after injection is >2 mm larger than the initial wheal size and also is >2 mm larger than the negative controls. Otherwise, the tests are negative.

Desensitization

Patients who have a positive skin test to one of the penicillin determinants can be desensitized (Table 1). This is a straightforward, relatively safe procedure that can be performed orally or IV. Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur. Desensitization usually can be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, patients must be maintained on penicillin continuously for the duration of the course of therapy.

Box 2. Skin-test reagents for identifying persons at risk for adverse reactions to penicillin*

Major Determinant

- Benzylpenicilloyl poly-L-lysine (PrePen) (AllerQuest, Plainville Connecticut) (6 x 10⁻⁵M).

Minor Determinant Precursors[†]

- Benzylpenicillin G (10⁻²M, 3.3 mg/mL, 10,000 units/mL)
- Benzylpenicilloate (10⁻²M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) (10⁻²M, 3.3 mg/mL)

Positive Control

- Commercial histamine for intradermal skin testing (1.0 mg/mL)

Negative Control

- Diluent (usually saline) or allergen diluent

* Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204–15. Reprinted with permission from G.N. Beall and *Annals of Internal Medicine*.

[†] Aged penicillin is not an adequate source of minor determinants. Penicillin G should be freshly prepared or should come from a fresh-frozen source.

C. Urethritis

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include discharge of mucopurulent or purulent material, dysuria, or urethral pruritis. Asymptomatic infections are common. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis (240–243). If clinic-based diagnostic tools (e.g., Gram-stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia. Further testing to determine the specific etiology is recommended because both chlamydia and gonorrhea are reportable to health departments and a specific diagnosis might improve partner notification and treatment. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Culture and hybridization tests require urethral swab specimens, whereas NAATs can be performed on urine specimens. Because of their higher sensitivity, NAATs are preferred for the detection of *C. trachomatis* (197).

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID) on urethral smear is indicative of gonorrhea infection, which is frequently accompanied by chlamydial infection. Nongonococcal urethritis (NGU), which is diagnosed when examination findings or microscopy indicate inflammation without GNID, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men (244). Complications of NGU among males infected with *C. trachomatis* include epididymitis and Reiter's syndrome. Documentation of

chlamydial infection is essential because of the need for partner referral for evaluation and treatment.

In most cases of nonchlamydial NGU, no pathogen can be detected. *M. genitalium*, which appears to be sexually transmitted, is associated with both symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (240–243). *T. vaginalis*, HSV, and adenovirus also can cause NGU, but data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent (244–247). Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis, genital lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (244).

Confirmed Urethritis

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if clinic-based diagnostic tools (e.g., Gram-stain microscopy) are not available, patients should be treated with drug regimens effective against both gonorrhea and chlamydia.

Urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucopurulent or purulent discharge on examination.
- Gram stain of urethral secretions demonstrating ≥ 5 WBC per oil immersion field. The Gram stain is the preferred rapid diagnostic test for evaluating urethritis and is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing GNID.

TABLE 1. Oral desensitization protocol for patients with a positive skin test*

Penicillin V suspension dose [†]	Amount [§] (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Note: Observation period was 30 minutes before parenteral administration of penicillin.

* Reprinted with permission from the New England Journal of Medicine (Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985;312:1229–32.).

[†] Interval between doses, 15–30 minutes; elapsed time, 4–8 hours; cumulative dose, 1.3 million units.

[§] The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high-power field.

If none of these criteria are present, testing for *N. gonorrhoeae* and *C. trachomatis* using NAATs might identify additional infections (248). If the results demonstrate infection with either of these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these criteria are present, empiric treatment of symptomatic males is recommended only for men at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated with drug regimens effective against gonorrhea and chlamydia. Partners of patients treated empirically should be evaluated and treated, if indicated.

Nongonococcal Urethritis

Diagnosis

All patients who have confirmed or suspected urethritis should be tested for gonorrhea and chlamydia. Testing for chlamydia is strongly recommended because of the increased utility and availability of highly sensitive and specific testing methods (e.g., NAATs) and because a specific diagnosis might enhance partner notification and improve compliance with treatment, especially in the exposed partner.

Treatment

Treatment should be initiated as soon as possible after diagnosis. Azithromycin and doxycycline are highly effective for chlamydial urethritis; however, infections with *M. genitalium* respond better to azithromycin (249,250). Single-dose regimens have the advantage of improved compliance and directly observed treatment. To maximize compliance with recommended therapies, medications should be dispensed on-site in the clinic, and the first dose should be directly observed.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

To minimize transmission, men treated for NGU should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen, provided their symptoms have resolved. To minimize the risk for reinfection, men should be instructed to abstain from sexual intercourse until all of their sex partners are treated.

Persons who have been diagnosed with a new STD should receive testing for other infections, including syphilis and HIV.

Follow-Up

Patients should be instructed to return for evaluation if symptoms persist or recur after completion of therapy. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for retreatment. Providers should be alert to the possibility of chronic prostatitis/chronic pelvic pain syndrome in male patients experiencing persistent pain (perineal, penile, or pelvic), discomfort, irritative voiding

symptoms, pain during or after ejaculation, or new-onset premature ejaculation lasting for >3 months.

Unless a patient's symptoms persist or therapeutic noncompliance or reinfection is suspected by the provider, a test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy) is not recommended for persons with documented chlamydia or gonococcal infections who have received treatment with recommended or alternative regimens. However, because men with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 months after treatment (251,252), repeat testing of all men diagnosed with chlamydia or gonorrhea is recommended 3–6 months after treatment, regardless of whether patients believe that their sex partners were treated (251).

Partner Referral

A specific diagnosis might facilitate partner referral. Therefore, testing for gonorrhea and chlamydia is encouraged. Because a substantial proportion of female partners of males with nonchlamydial NGU are infected with chlamydia, partner management is recommended for males with NGU regardless of whether a specific etiology is identified. All sex partners within the preceding 60 days should be referred for evaluation, testing, and empiric treatment with a drug regimen effective against chlamydia. Expedited partner treatment and patient referral are alternative approaches to treating partners (71).

Recurrent and Persistent Urethritis

Objective signs of urethritis should be present before the initiation of antimicrobial therapy. In persons who have persistent symptoms after treatment without objective signs of urethritis, the value of extending the duration of antimicrobials has not been demonstrated. Persons who have persistent or recurrent urethritis can be retreated with the initial regimen if they did not comply with the treatment regimen or if they were reexposed to an untreated sex partner. Persistent urethritis after doxycycline treatment might be caused by doxycycline-resistant *U. urealyticum* or *M. genitalium*. *T. vaginalis* is also known to cause urethritis in men; a urethral swab, first void urine, or semen for culture or a NAAT (PCR or TMA) on a urethral swab or urine can be

performed. If compliant with the initial regimen and re-exposure can be excluded, the following regimen is recommended while awaiting the results of the diagnostic tests.

Recommended Regimens

Metronidazole 2 g orally in a single dose

OR

Tinidazole 2 g orally in a single dose

PLUS

Azithromycin 1 g orally in a single dose (if not used for initial episode)

Studies involving a limited number of patients who experienced NGU treatment failures have demonstrated that Moxifloxacin 400 mg orally once daily for 7 days is highly effective against *M. genitalium* (253,254). Men with a low probability of *T. vaginalis* (e.g., MSM) are unlikely to benefit from the addition of metronidazole or tinidazole.

Urologic examinations usually do not reveal a specific etiology for urethritis. A four-glass Meares-Stamey lower-urinary-tract localization procedure (or four-glass test) might be helpful in localizing pathogens to the prostate (255). A substantial proportion of men with chronic nonbacterial prostatitis/chronic pelvic pain syndrome have evidence of urethral inflammation without any identifiable microbial pathogens. Estimates vary considerably depending on the source and sensitivity of the assay, but one study demonstrated that in 50% of men with this syndrome, ≥ 5 WBCs per high-power field were detected in expressed prostatic secretions (256). Referral to a urologist should be considered for men who experience pain for more than 3 months within a 6-month period.

If men require treatment with a new antibiotic regimen for persistent urethritis and a sexually transmitted agent is the suspected cause, all partners in the past 60 days before the initial diagnosis and any interim partners should be referred for evaluation and appropriate treatment.

Special Considerations

HIV Infection

Gonococcal urethritis, chlamydial urethritis, and nongonococcal, nonchlamydial urethritis might facilitate HIV transmission. Patients who have NGU and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

D. Gonococcal Infections

Gonococcal Infections in Adolescents and Adults

In the United States, an estimated 700,000 new *N. gonorrhoeae* infections occur each year (93,293). Gonorrhea is the second most commonly reported bacterial STD. The majority of urethral infections caused by *N. gonorrhoeae* among men produce symptoms that cause them to seek curative treatment soon enough to prevent serious sequelae, but treatment might not be soon enough to prevent transmission to others. Among women, gonococcal infections might not produce recognizable symptoms until complications (e.g., PID) have occurred. PID can result in tubal scarring that can lead to infertility or ectopic pregnancy.

The prevalence of gonorrhea varies widely among communities and populations; health-care providers should consider local gonorrhea epidemiology when making screening decisions. Although widespread screening is not recommended because gonococcal infections among women are frequently asymptomatic, targeted screening of young women (i.e., those aged <25 years) at increased risk for infection is a primary component of gonorrhea control in the United States. For sexually active women, including those who are pregnant, USPSTF (82) recommends that clinicians provide gonorrhea screening only to those at increased risk for infection (e.g., women with previous gonorrhea infection, other STDs, new or multiple sex partners, and inconsistent condom use; those who engage in commercial sex work and drug use; women in certain demographic groups; and those living in communities with a high prevalence of disease). USPSTF does not recommend screening for gonorrhea in men and women who are at low risk for infection (82).

Diagnostic Considerations

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* in symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection in asymptomatic men. In addition, Gram

stain of endocervical specimens, pharyngeal, or rectal specimens also are not sufficient to detect infection, and therefore are not recommended. Specific testing for *N. gonorrhoeae* is recommended because of the increased utility and availability of highly sensitive and specific testing methods and because a specific diagnosis might enhance partner notification.

Specific diagnosis of infection with *N. gonorrhoeae* can be performed by testing endocervical, vaginal, urethral (men only), or urine specimens. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of genitourinary infection with *N. gonorrhoeae* (197). Culture and nucleic acid hybridization tests require female endocervical or male urethral swab specimens. NAATs allow testing of the widest variety of specimen types including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women), and they are FDA-cleared for use. However, product inserts for each NAAT vendor must be carefully examined, because specimen types that are FDA-cleared for use vary by test. NAAT tests are not FDA-cleared for use in the rectum, pharynx, and conjunctiva; however, some public and private laboratories have established performance specifications for using NAAT with rectal and pharyngeal swab specimens, thereby allowing results to be used for clinical management. Laboratories that establish performance specifications for the use of NAATs with nongenital specimens must ensure that specificity is not compromised by cross-reaction with nongonococcal *Neisseria* species. The sensitivity of NAATs for the detection of *N. gonorrhoeae* in genital and nongenital anatomic sites is superior to culture but varies by NAAT type (197,278–281).

Because nonculture tests cannot provide antimicrobial susceptibility results, in cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing.

All persons found to have who have gonorrhea also should be tested for other STDs, including chlamydia, syphilis, and HIV.

Dual Therapy for Gonococcal and Chlamydial Infections

Patients infected with *N. gonorrhoeae* frequently are coinfecting with *C. trachomatis*; this finding has led to the recommendation that patients treated for gonococcal infection also be treated routinely with a regimen that is effective against uncomplicated genital *C. trachomatis* infection (294). Because most gonococci in the United States are susceptible to doxycycline and azithromycin, routine cotreatment might also hinder the development of antimicrobial-resistant *N. gonorrhoeae*. Limited data suggest that dual treatment with azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins (295,296).

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies (297). Quinolone-resistant *N. gonorrhoeae* strains are now widely disseminated throughout the United States and the world (298). As of April 2007, quinolones are no longer recommended in the United States for the treatment of gonorrhea and associated conditions, such as PID (299). Consequently, only one class of antimicrobials, the cephalosporins, is recommended and available for the treatment of gonorrhea in the United States. The CDC website (<http://www.cdc.gov/std/gisp>) and state health departments can provide the most current information.

The proportion of isolates in CDC's Gonococcal Isolate Surveillance Project (GISP) demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low over time; during 1987–2008, only four isolates were found to have decreased susceptibility to ceftriaxone, and 48 isolates had decreased susceptibility to cefixime. In 2008, no isolates demonstrated decreased susceptibility to ceftriaxone; cefixime was not part of test panel during that year (93). Although only two cases of suspected treatment failure with ceftriaxone have been reported (300), approximately 50 patients are thought to have failed oral cephalosporin treatment (301–304).

Most of the treatment failures resulting from use of oral cephalosporins have been reported from Asian countries, although one possible case was reported

in Hawaii in 2001 (305). To ensure appropriate antibiotic therapy, clinicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries.

Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (297). GISP, which samples approximately 3% of all U.S. men who have gonococcal infections, is a mainstay of surveillance. However, surveillance by clinicians also is critical. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should perform culture and susceptibility testing of relevant clinical specimens, consult a specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities. Health departments should prioritize partner notification and contact tracing of patients with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or associated with patients whose isolates demonstrate decreased susceptibility to cephalosporin.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose
OR, IF NOT AN OPTION
Cefixime 400 mg orally in a single dose
OR
Single-dose injectible cephalosporin regimens
PLUS
Azithromycin 1g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

To maximize compliance with recommended therapies, medications for gonococcal infections should be dispensed on site. Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in published clinical trials (306,307). A 250-mg dose of ceftriaxone is now recommended over a 125-mg dose given the 1) increasingly wide

geographic distribution of isolates demonstrating decreased susceptibility to cephalosporins in vitro, 2) reports of ceftriaxone treatment failures, 3) improved efficacy of ceftriaxone 250 mg in pharyngeal infection (which is often unrecognized), and 4) the utility of having a simple and consistent recommendation for treatment regardless of the anatomic site involved.

A 400-mg oral dose of cefixime does not provide as high, nor as sustained, a bactericidal level as that provided by the 250-mg dose of ceftriaxone. In published clinical trials, the 400-mg dose cured 97.5% of uncomplicated urogenital and anorectal (95% CI = 95.4%–99.8%) and 92.3% of pharyngeal gonococcal infections (95% CI = 74.9%–99.1%) (306,307). Although cefixime can be administered orally, this advantage is offset by the limited efficacy of cefixime (as well as other oral cephalosporins) for treating gonococcal infections of the pharynx. Providers should inquire about oral sexual exposure and if reported, treat these patients with ceftriaxone because of this drug's well documented efficacy in treating pharyngeal infection.

Single-dose injectible cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and highly effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime (500 mg, administered IM), cefoxitin (2 g, administered IM with probenecid 1 g orally), and cefotaxime (500 mg, administered IM). None of the injectible cephalosporins offer any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain (306,307).

Alternative Regimens

Several other antimicrobials are active against *N. gonorrhoeae*, but none have substantial advantages over the recommended regimens, and they should not be used if pharyngeal infection is suspected. Some evidence suggests that cefpodoxime 400-mg orally can be considered an alternative in the treatment of uncomplicated urogenital gonorrhea; this regimen meets the minimum efficacy criteria for alternative regimens for urogenital infection (demonstrated efficacy of $\geq 95\%$ in clinical trials with lower 95% CI of $>90\%$) (307). In one clinical trial, cefpodoxime 400 mg orally was found to have

a urogenital and rectal cure rate of 96.6% (95% CI = 93.9%), but the efficacy of cefpodoxime 400 mg orally at the pharyngeal site was poor (70.3%, 95% CI = 53.0%) (Hall, unpublished data, 2010). Gonococcal strains with decreased susceptibility to oral cephalosporins have been reported in the United States (308). With a cure rate of 96.5% (95% CI = 93.6%–98.3%) for urogenital and rectal infection, cefpodoxime proxetil 200 mg orally meets the criteria for an alternative regimen; however, its use is not advised because of concerns about the pharmacodynamics of cefpodoxime using this dose. Efficacy in treating pharyngeal infection with cefpodoxime 200 mg is unsatisfactory (78.9%; 95% CI = 54.5%–94%), as with cefpodoxime at the 400-mg dose.

Treatment with cefuroxime axetil 1 g orally meets the criteria for minimum efficacy as an alternative regimen for urogenital and rectal infection (95.9%; 95% CI = 94.3%–97.2%), but the pharmacodynamics of cefuroxime axetil 1 g orally are less favorable than those of cefpodoxime 400 mg, cefixime 400 mg, or ceftriaxone 125 mg (309). The efficacy of cefuroxime axetil 1 g orally in treating pharyngeal infection is poor (56.9%; 95% CI = 42.2%–70.7%).

Spectinomycin, which is useful in persons who cannot tolerate cephalosporins, is expensive, must be injected, and is not available in the United States (updates available at: www.cdc.gov/std/treatment) (310). However, it has been effective in published clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections. Spectinomycin has poor efficacy against pharyngeal infection (51.8%; 95% CI = 38.7%–64.9%) (306).

Azithromycin 2 g orally is effective against uncomplicated gonococcal infection (99.2%; 95% CI = 97.3%–99.9%), but concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides should restrict its use to limited circumstances. Although azithromycin 1 g meets alternative regimen criteria (97.6%; 95% CI = 95.7%–98.9%), it is not recommended because several studies have documented treatment failures, and concerns about possible rapid emergence of antimicrobial resistance with the 1-g dose of azithromycin are even greater than with the 2-g dose (311–313). *N. gonorrhoeae* in the United States is

not adequately susceptible to penicillins, tetracyclines, and older macrolides (e.g., erythromycin) for these antimicrobials to be recommended.

Uncomplicated Gonococcal Infections of the Pharynx

Most gonococcal infections of the pharynx are asymptomatic and can be relatively common in some populations (103,278,279,314). Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites (315). Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections (306,307). Providers should ask their patients about oral sexual exposure; if reported, patients should be treated with a regimen with acceptable efficacy against pharyngeal infection. Chlamydial coinfection of the pharynx is unusual; however, because coinfection at genital sites sometimes occurs, treatment for both gonorrhea and chlamydia is recommended.

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Follow-Up

Patients diagnosed with uncomplicated gonorrhea who are treated with any of the recommended or alternative regimens do not need a test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy). Patients who have symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by *C. trachomatis* or other organisms.

N. gonorrhoeae infection is prevalent among patients who have been diagnosed with and treated for gonorrhea in the preceding several months (64,251,252,267). Most infections result from reinfection rather than treatment failure, indicating a need for improved patient education and referral of sex partners. Clinicians should advise patients with

gonorrhea to be retested 3 months after treatment. If patients do not seek medical care for retesting in 3 months, providers are encouraged to test these patients whenever they next seek medical care within the following 12 months, regardless of whether the patients believe that their sex partners were treated. Retesting is distinct from test-of-cure to detect therapeutic failure, which is not recommended.

Management of Sex Partners

Effective clinical management of patients with treatable STDs requires treatment of the patients' recent sex partners to prevent reinfection and curtail further transmission. Patients should be instructed to refer their sex partners for evaluation and treatment. Sex partners of patients with *N. gonorrhoeae* infection whose last sexual contact with the patient was within 60 days before onset of symptoms or diagnosis of infection in the patient should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections. If a patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms.

For heterosexual patients with gonorrhea whose partners' treatment cannot be ensured or is unlikely, delivery of antibiotic therapy for gonorrhea (as well as for chlamydia) by the patients to their partners can be considered (see Partner Management). Use of this approach (68,71) should always be accompanied by efforts to educate partners about symptoms and to encourage partners to seek clinical evaluation. For male patients informing female partners, educational materials should include information about the importance of seeking medical evaluation for PID (especially if symptomatic). Possible undertreatment of PID in female partners and possible missed opportunities to diagnose other STDs are of concern and have not been evaluated in comparison with patient-delivered therapy and partner referral. This approach should not be considered a routine partner management strategy in MSM because of

the high risk for coexisting undiagnosed STDs or HIV infection.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Reactions to first generation cephalosporins occur in approximately 5%–10% of persons with a history of penicillin allergy and occur less frequently with third-generation cephalosporins (239). In those persons with a history of penicillin allergy, the use of cephalosporins should be contraindicated only in those with a history of a severe reaction to penicillin (e.g., anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis) (316).

Because data are limited regarding alternative regimens for treating gonorrhea among persons who have severe cephalosporin allergy, providers treating such patients should consult infectious disease specialists. Azithromycin 2 g orally is effective against uncomplicated gonococcal infection, but because of concerns over emerging antimicrobial resistance to macrolides, its use should be limited. Cephalosporin treatment following desensitization is impractical in most clinical settings.

Pregnancy

As with other patients, pregnant women infected with *N. gonorrhoeae* should be treated with a recommended or alternate cephalosporin. Because spectinomycin is not available in the United States, azithromycin 2 g orally can be considered for women who cannot tolerate a cephalosporin. Either azithromycin or amoxicillin is recommended for treatment of presumptive or diagnosed *C. trachomatis* infection during pregnancy (see Chlamydial Infections).

HIV Infection

Patients who have gonococcal infection and also are infected with HIV should receive the same treatment regimen as those who are HIV negative.

Suspected Cephalosporin Treatment Failure or Resistance

Suspected treatment failure has been reported among persons receiving oral and injectable cephalosporins (300–304). Therefore, clinicians of patients with suspected treatment failure or persons infected with a strain found to demonstrate in vitro resistance should consult an infectious disease specialist, conduct culture and susceptibility testing of relevant clinical specimens, retreat with at least 250 mg of ceftriaxone IM or IV, ensure partner treatment, and report the situation to CDC through state and local public health authorities.

Gonococcal Conjunctivitis

In the only published study of the treatment of gonococcal conjunctivitis among U.S. adults, all 12 study participants responded to a single 1-g IM injection of ceftriaxone (317).

Recommended Regimen

Ceftriaxone 1 g IM in a single dose

Consider lavage of the infected eye with saline solution once. Persons treated for gonococcal conjunctivitis should be treated presumptively for concurrent *C. trachomatis* infection.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infections, Management of Sex Partners).

Disseminated Gonococcal Infection (DGI)

DGI frequently results in petechial or pustular acral skin lesions, asymmetrical arthralgia, tenosynovitis, or septic arthritis. The infection is complicated occasionally by perihepatitis and rarely by endocarditis or meningitis. Some strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation. No recent studies have been published on the treatment of DGI.

Treatment

Hospitalization is recommended for initial therapy, especially for patients who might not comply with treatment, for those in whom diagnosis is uncertain, and for those who have purulent synovial effusions or other complications. Examination for clinical evidence of endocarditis and meningitis should be performed. Persons treated for DGI should be treated presumptively for concurrent *C. trachomatis* infection.

Recommended Regimen

Ceftriaxone 1 g IM or IV every 24 hours

Alternative Regimens

Cefotaxime 1 g IV every 8 hours

OR

Ceftizoxime 1 g IV every 8 hours

All of the preceding regimens should be continued for 24–48 hours after improvement begins, at which time therapy can be switched to cefixime 400 mg orally twice daily to complete at least 1 week of antimicrobial therapy. No treatment failures have been reported with the recommended regimens.

Management of Sex Partners

Gonococcal infection frequently is asymptomatic in sex partners of patients who have DGI. As with uncomplicated gonococcal infections, patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infection, Management of Sex Partners).

Gonococcal Meningitis and Endocarditis

Recommended Regimen

Ceftriaxone 1–2 g IV every 12 hours

Therapy for meningitis should be continued for 10–14 days; therapy for endocarditis should be continued for at least 4 weeks. Treatment of complicated DGI should be undertaken in consultation with an infectious disease specialist.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infection, Management of Sex Partners).

E. Epididymitis

Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts <6 weeks (402). Chronic epididymitis is characterized by a ≥ 6 week history of symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis. In most cases of acute epididymitis, the testis is also involved in the process — a condition referred to as epididymo-orchitis. Chronic epididymitis has been subcategorized into inflammatory chronic epididymitis, obstructive chronic epididymitis, and chronic epididymalgia (403).

Among sexually active men aged <35 years, acute epididymitis is most frequently caused by *C. trachomatis* or *N. gonorrhoeae*. Acute epididymitis caused by sexually transmitted enteric organisms (e.g., *Escherichia coli* and *Pseudomonas* spp.) also occurs among men who are the insertive partner during anal intercourse. Sexually transmitted acute epididymitis usually is accompanied by urethritis, which frequently is asymptomatic.

In men aged >35 years, sexually transmitted epididymitis is uncommon, whereas bacteriuria secondary to obstructive urinary disease (e.g., benign prostatic hyperplasia) is more common. In this older population, nonsexually transmitted epididymitis is associated with urinary tract instrumentation or surgery, systemic disease, and immunosuppression.

Chronic infectious epididymitis is most frequently seen in conditions associated with granulomatous reaction; *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis. Up to 25% of patients can have bilateral disease, with ultrasound demonstrating an enlarged hyperemic epididymis with multiple cysts and calcifications. Tuberculous epididymitis should be suspected in all patients with a known history of or recent exposure to TB or in patients whose clinical status worsens despite appropriate antibiotic treatment.

Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness; hydrocele and palpable swelling of the epididymis usually are present. Although the inflammation and swelling usually begin in the tail of the epididymis, they can spread to involve the rest of the epididymis and testicle. The spermatic cord is usually tender and swollen. Testicular torsion, a surgical emergency, should be considered in all cases, but it occurs more frequently among adolescents and in men without evidence of inflammation or infection. Emergency testing for torsion might be indicated when the onset of pain is sudden, pain is severe, or the test results available during the initial examination do not support a diagnosis of urethritis or urinary-tract infection. If the diagnosis is questionable, a urologist should be consulted immediately because testicular viability might be compromised. Radionuclide scanning of the scrotum is the most accurate radiologic method of diagnosis, but it is not routinely available. Although ultrasound is primarily used for ruling out torsion of the spermatic cord in cases of acute scrotum swelling, it will often demonstrate epididymal hyperemia and swelling in men with epididymitis. However, differentiation between testicular torsion and epididymitis must be made on the basis of clinical evaluation, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound. Ultrasound provides minimal utility for men with a clinical presentation consistent with epididymitis; a negative ultrasound does not alter physician management of clinical epididymitis. Ultrasound, therefore, should be reserved for patients with scrotal pain who cannot be diagnosed accurately by physical examination, history, and objective laboratory findings.

The evaluation of men for epididymitis should include one of the following:

- Gram stain of urethral secretions demonstrating ≥ 5 WBC per oil immersion field. Gram stain is the preferred rapid diagnostic test for evaluating urethritis because it is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing intracellular Gram-negative diplococci on urethral Gram stain.
- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high power field.

Culture, nucleic acid hybridization tests, and NAATs are available for the detection of both *N. gonorrhoeae* and *C. trachomatis*. Culture and nucleic acid hybridization tests require urethral swab specimens, whereas amplification tests can be performed on urine or urethral specimens. Because of their higher sensitivity, amplification tests are preferred for the detection of *C. trachomatis*. Depending on the risk, patients whose conditions are associated with acquiring an STD should receive testing for other STDs.

Treatment

Empiric therapy is indicated before laboratory test results are available. The goals of treatment of acute epididymitis caused by *C. trachomatis* or *N. gonorrhoeae* are 1) microbiologic cure of infection, 2) improvement of signs and symptoms, 3) prevention of transmission to others, and 4) a decrease in potential complications (e.g., infertility or chronic pain). As an adjunct to therapy, bed rest, scrotal elevation, and analgesics are recommended until fever and local inflammation have subsided. Because empiric therapy is often initiated before laboratory tests are available, all patients should receive ceftriaxone plus doxycycline for the initial therapy of epididymitis. Additional therapy can include a fluoroquinolone if acute epididymitis is not found to be caused by gonorrhea by NAAT or if the infection is most likely caused by enteric organisms. For men who are at risk for both sexually transmitted and enteric organisms

(e.g., MSM who report insertive anal intercourse), ceftriaxone with a fluoroquinolone are recommended.

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

PLUS

Doxycycline 100 mg orally twice a day for 10 days

For acute epididymitis most likely caused by enteric organisms

Levofloxacin 500 mg orally once daily for 10 days

OR

Ofloxacin 300 mg orally twice a day for 10 days

Although most patients can be treated on an outpatient basis, hospitalization should be considered when severe pain suggests other diagnoses (e.g., torsion, testicular infarction, or abscess) or when patients are unable or unlikely to comply with an antimicrobial regimen. Because high fever is uncommon and indicates a complicated infection, these patients should be admitted for further evaluation.

Follow-Up

Patients should be instructed to return to their health-care providers if their symptoms fail to improve within 48 hours of the initiation of treatment. Signs and symptoms of epididymitis that do not subside within 3 days requires re-evaluation of the diagnosis and therapy. Swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated comprehensively. Differential diagnoses include tumor, abscess, infarction, testicular cancer, TB, and fungal epididymitis.

Management of Sex Partners

Patients who have acute epididymitis that is confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sex partners for evaluation and treatment if their contact with the index patient was within the 60 days preceding onset of their own symptoms.

Patients should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., until therapy is completed and patient and partners no longer have symptoms).

Special Considerations

HIV Infection

Patients who have uncomplicated acute epididymitis and also are infected with HIV should receive the same treatment regimen as those who are HIV negative. Other etiologic agents have been implicated in acute epididymitis in HIV infection including CMV, salmonella, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium sp.*, *Mycoplasma sp.*, and *Mima polymorpha*. Fungi and mycobacteria are also more likely to cause acute epididymitis in immunosuppressed men than in immunocompetent men.

Human Papillomavirus (HPV) Infection

More than 100 types of HPV exist, more than 40 of which can infect the genital area. Most HPV infections are asymptomatic, unrecognized, or subclinical. Oncogenic, or high-risk HPV types (e.g., HPV types 16 and 18), are the cause of cervical cancers. These HPV types are also associated with other anogenital cancers in men and women, including penile, vulvar, vaginal, and anal cancer, as well as a subset of oropharyngeal cancers (404). Nononcogenic, or low-risk HPV types (e.g., HPV types 6 and 11), are the cause of genital warts and recurrent respiratory papillomatosis. Asymptomatic genital HPV infection is common and usually self-limited; it is estimated that more than 50% of sexually active persons become infected at least once in their lifetime (405). Persistent oncogenic HPV infection is the strongest risk factor for development of precancers and cancers.

HPV Tests

HPV tests are available for women aged >30 years undergoing cervical cancer screening. These tests should not be used for men, for women <20 years of age, or as a general test for STDs. These HPV tests detect viral nucleic acid (i.e., DNA or RNA) or capsid protein. Four tests have been approved by the FDA for use in the United States: the HC II High-Risk HPV test (Qiagen), HC II Low-Risk HPV test (Qiagen), Cervista HPV 16/18 test, and Cervista HPV High-Risk test (Hologic).

Treatment

Treatment is directed to the macroscopic (i.e., genital warts) or pathologic (i.e., precancerous) lesions caused by infection. Subclinical genital HPV infection typically clears spontaneously, and therefore specific antiviral therapy is not recommended to eradicate HPV infection. In the absence of lesions, treatment is not recommended for subclinical genital HPV infection whether it is diagnosed by colposcopy, acetic acid application, or by laboratory tests for HPV DNA. Treatment also is not recommended for cervical intraepithelial neoplasia 1 (CIN1).

Prevention

Two HPV vaccines are licensed in the United States: a bivalent vaccine (Cervarix) containing HPV types 16 and 18 and a quadrivalent vaccine (Gardasil) vaccine containing HPV types 6, 11, 16, and 18. Both vaccines offer protection against the HPV types that cause 70% of cervical cancers (i.e., types 16 and 18), and the quadrivalent HPV vaccine also protects against the types that cause 90% of genital warts (i.e., types 6 and 11). Either vaccine can be administered to girls aged 11–12 years and can be administered to those as young as 9 years of age (15,16); girls and women ages 13–26 years who have not started or completed the vaccine series also should receive the vaccine. HPV vaccine is indicated for girls in this age group, because benefit is greatest if it is administered before the onset of sexual activity. The quadrivalent (Gardasil) HPV vaccine can also be used in males aged 9–26 years to prevent genital warts (17). Administering the vaccine to boys before the onset of sexual activity is optimal. Both HPV vaccines are administered as a 3-dose series of IM injections over a 6-month period, with the second and third doses given 1–2 and then 6 months after the first dose. Ideally, the same vaccine product should be used for the entire 3-dose series. HPV vaccine is available for eligible children and adolescents aged <19 years through the Vaccines for Children (VFC) program (available by calling CDC INFO [800-232-4636]).

Women who have received HPV vaccine should continue routine cervical cancer screening because 30% of cervical cancers are caused by HPV types other than 16 or 18. In the United States, the vaccines are

not licensed or recommended for use in women >26 years of age. No published data are available on the effectiveness, programmatic requirements, or cost-effectiveness of administering the HPV vaccine in STD clinic settings.

F. Genital Warts

Of genital warts, 90% are caused by HPV 6 or 11. HPV types 6 or 11 are commonly found before, or at the time of, detection of genital warts (406). HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts (usually as coinfections with HPV 6 or 11) and can be associated with foci of high-grade intraepithelial neoplasia, particularly in persons who are infected with HIV infection. In addition to warts on genital areas, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

Genital warts are usually asymptomatic, but depending on the size and anatomic location, they can be painful or pruritic. Genital warts are usually flat, papular, or pedunculated growths on the genital mucosa. Genital warts occur commonly at certain anatomic sites, including around the introitus in women, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Genital warts can also occur at multiple sites in the anogenital epithelium or within the anogenital tract (e.g., cervix, vagina, urethra, perineum, perianal skin, and scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse, but they can also occur in men and women who do not have a history of anal sexual contact.

Diagnosis of genital warts is usually clinical, made by visual inspection. Genital warts can be confirmed by biopsy, which might be indicated if 1) the diagnosis is uncertain; 2) the lesions do not respond to standard therapy; 3) the disease worsens during therapy; 4) the lesion is atypical; 5) the patient has compromised immunity; or 6) the warts are pigmented, indurated, fixed, bleeding, or ulcerated. Genital warts are usually asymptomatic, but depending on the size and anatomic location, they might be painful or pruritic. The use of HPV DNA testing for genital wart diagnosis is not recommended, because test results would not alter clinical management of the condition.

The application of 3%–5% acetic acid, which causes skin color to turn white, has been used by some providers to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection. Therefore, the routine use of this

procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

Treatment

The primary reason for treating genital warts is the amelioration of symptoms (including relieving cosmetic concerns) and ultimately, removal of the warts. In most patients, treatment can induce wart-free periods. If left untreated, visible genital warts can resolve on their own, remain unchanged, or increase in size or number. Available therapies for genital warts likely reduce, but probably do not eradicate, HPV infectivity. Whether the reduction in HPV viral DNA resulting from treatment reduces future transmission remains unclear. No evidence indicates that the presence of genital warts or their treatment is associated with the development of cervical cancer.

Regimens

Treatment of genital warts should be guided by the preference of the patient, available resources, and the experience of the health-care provider. No definitive evidence suggests that any of the available treatments are superior to any other, and no single treatment is ideal for all patients or all warts. The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because of uncertainty regarding the effect of treatment on future transmission of HPV and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.

Factors that influence selection of treatment include wart size, wart number, anatomic site of the wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience. Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy, which can consist of either a single treatment or complete course of treatment. In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. Most genital warts respond within 3 months of ther-

apy. The response to treatment and any side effects should be evaluated throughout the course of therapy.

Complications occur rarely when treatment is administered properly. Patients should be warned that persistent hypopigmentation or hyperpigmentation occurs commonly with ablative modalities and has also been described with immune modulating therapies (imiquimod). Depressed or hypertrophic scars are uncommon but can occur, especially if the patient has had insufficient time to heal between treatments. Rarely, treatment can result in disabling chronic pain syndromes (e.g., vulvodynia and hyperesthesia of the treatment site) or, in the case of anal warts, painful defecation or fistulas. A limited number of case reports of severe systemic effects resulting from treatment with podophyllin resin and interferon have been documented.

Treatment regimens are classified into patient-applied and provider-applied modalities. Patient-applied modalities are preferred by some patients because they can be administered in the privacy of the patient's home. To ensure that patient-applied modalities are effective, patients must comply with the treatment regimen and must be capable of identifying and reaching all genital warts. Follow-up visits are not required for persons using patient-applied therapy. However, follow-up visits after several weeks of therapy enable providers to answer any questions patients might have about the use of the medication and any side effects they have experienced; follow-up visits also facilitate the assessment of a patient's response to treatment.

Recommended Regimens for External Genital Warts

Patient-Applied:

Podofilox 0.5% solution or gel

OR

Imiquimod 5% cream

OR

Sinecatechins 15% ointment

Provider-Administered:

Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks.

OR

Podophyllin resin 10%–25% in a compound tincture of benzoin

OR

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90%

OR

Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery.

Podofilox is an antimitotic drug that destroys warts, is relatively inexpensive, easy to use, safe, and self-applied. Podofilox solution should be applied with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm², and the total volume of podofilox should be limited to 0.5 mL per day. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. The safety of podofilox during pregnancy has not been established.

Imiquimod is a topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod cream should be applied once daily at bedtime, three times a week for up to 16 weeks (407). The treatment area should be washed with soap and water 6–10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulceration/erosions, and vesicles, are common with the use of imiquimod, and hypopigmentation has also been described (408). Imiquimod might weaken condoms and vaginal diaphragms. The safety of imiquimod during pregnancy has not been established.

Sinecatechin ointment, a green-tea extract with an active product (catechins), should be applied three times daily (0.5-cm strand of ointment to each wart) using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts. This product should not be continued for longer than 16 weeks (409–411). The medication should not be washed off after use. Sexual (i.e., genital, anal, or oral) contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins 15% are erythema, pruritis/burning, pain, ulceration, edema, induration, and vesicular rash. This medication may weaken condoms and diaphragms. No clinical data are available regarding the efficacy or safety of sinecatechins compared with other available anogenital wart treatment modalities. The medication is not recommended for HIV-infected persons, immunocompromised persons, or persons with clinical genital herpes because the safety and efficacy of therapy in these settings has

not been established. The safety of sinecatechins during pregnancy also is unknown.

Cryotherapy destroys warts by thermal-induced cytolysis. Health-care providers must be trained on the proper use of this therapy because over- and undertreatment can result in complications or low efficacy. Pain after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common. Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.

Podophyllin resin 10%–25% should be applied to each wart and allowed to air-dry before the treated area comes into contact with clothing; overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, two guidelines should be followed: 1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session and 2) the area to which treatment is administered should not contain any open lesions or wounds. The preparation should be thoroughly washed off 1–4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established. Podophyllin resin preparations differ in the concentration of active components and contaminants. The shelf life and stability of podophyllin preparations are unknown.

Both TCA and BCA are caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solutions have a low viscosity comparable with that of water and can spread rapidly if applied excessively; therefore, they can damage adjacent tissues. A small amount should be applied only to the warts and allowed to dry before the patient sits or stands, at which time a white frosting develops. If pain is intense, the acid can be neutralized with soap or sodium bicarbonate. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

Surgical therapy has the advantage of usually eliminating warts at a single visit. However, such therapy requires substantial clinical training, additional equipment, and a longer office visit. After local anesthesia is applied, the visible genital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care must be taken to control the depth of electrocautery to prevent scarring. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by laser, or by curettage. Because most warts are exophytic, this procedure can be accomplished with a resulting wound that only extends into the upper dermis. Hemostasis can be achieved with an electrocautery unit or a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in most cases if surgical removal is performed properly. Surgical therapy is most beneficial for patients who have a large number or area of genital warts. Both carbon dioxide laser and surgery might be useful in the management of extensive warts or intraurethral warts, particularly for those persons who have not responded to other treatments.

Because all available treatments have shortcomings, some clinics employ combination therapy (simultaneous use of two or more modalities on the same wart at the same time). Data are limited regarding the efficacy or risk of complications associated with use of such combinations.

Alternative Regimens

Alternative regimens include treatment options that might be associated with more side effects and/or less data on efficacy. Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.

Recommended Regimen for Cervical Warts

For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated. Management of exophytic cervical warts should include consultation with a specialist.

Recommended Regimens for Vaginal Warts

Cryotherapy with liquid nitrogen. The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

OR

TCA or BCA 80%–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

Recommended Regimens for Urethral Meatus Warts

Cryotherapy with liquid nitrogen

OR

Podophyllin 10%–25% in compound tincture of benzoin. The treatment area and adjacent normal skin must be dry before contact with podophyllin. This treatment can be repeated weekly, if necessary. The safety of podophyllin during pregnancy has not been established. Data are limited on the use of podofilox and imiquimod for treatment of distal meatal warts.

Recommended Regimens for Anal Warts

Cryotherapy with liquid nitrogen

OR

TCA or BCA 80%–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

OR

Surgical removal

Intra-anal warts should be managed in consultation with a specialist. Many persons with warts on the anal mucosa also have warts on the rectal mucosa, so persons with anal and/or intra-anal warts might benefit from an inspection of the rectal mucosa by digital examination, standard anoscopy, or high-resolution anoscopy.

Counseling

The following key counseling messages should be conveyed to all patients diagnosed with HPV infection:

- Genital HPV infection is very common. Many types of HPV are passed on through genital contact, most often during vaginal and anal sexual contact. HPV can also be spread by oral sexual contact.
- Most sexually active adults will get HPV at some point in their lives, though most will never know it because HPV infection usually has no signs or symptoms.

- In most cases, HPV infection clears spontaneously, without causing any health problems. Nevertheless, some infections do progress to genital warts, precancers, and cancers.
 - adolescent females; or
 - for health conditions other than cervical cancer.
 - The types of HPV that cause genital warts are different from the types that can cause anogenital cancers.
 - Within an ongoing sexual relationship, both partners are usually infected at the time one person is diagnosed with HPV infection, even though signs of infection might not be apparent.
 - A diagnosis of HPV in one sex partner is not indicative of sexual infidelity in the other partner.
 - Treatments are available for the conditions caused by HPV (e.g., genital warts), but not for the virus itself.
 - HPV does not affect a woman's fertility or ability to carry a pregnancy to term.
 - Correct and consistent male condom use might lower the chances of giving or getting genital HPV, but such use is not fully protective, because HPV can infect areas that are not covered by a condom.
 - Sexually active persons can lower their chances of getting HPV by limiting their number of partners. However, HPV is common and often goes unrecognized; persons with only one lifetime sex partner can have the infection. For this reason, the only definitive method to avoid giving and getting HPV infection and genital warts is to abstain from sexual activity.
 - Tests for HPV are now available to help providers screen for cervical cancer in certain women. These tests are not useful for screening adolescent females for cervical cancer, nor are they useful for screening for other HPV-related cancers or genital warts in men or women. HPV tests should not be used to screen:
 - men;
 - partners of women with HPV;
 - Two HPV vaccines are available, both of which offer protection against the HPV types that cause 70% of cervical cancers (i.e., types 16 and 18); the quadrivalent vaccine (Gardasil) also protects against the types that cause 90% of genital warts (i.e., types 6 and 11). These vaccines are most effective when all doses are administered before sexual contact. Either vaccine is recommended for 11- and 12-year-old girls and for females aged 13–26 years who did not receive or complete the vaccine series when they were younger. The quadrivalent HPV vaccine can be used in males aged 9–26 years to prevent genital warts.
- The following are specific counseling messages for those persons diagnosed with genital warts and their partners:
- Genital warts are not life threatening. If left untreated, genital warts might go away, stay the same, or grow in size or number. Except in very rare and unusual cases, genital warts will not turn into cancer.
 - It is difficult to determine how or when a person became infected with HPV; genital warts can be transmitted to others even when no visible signs of warts are present, even after warts are treated.
 - It is not known how long a person remains contagious after warts are treated. It is also unclear whether informing subsequent sex partners about a past diagnosis of genital warts is beneficial to the health of those partners.
 - Genital warts commonly recur after treatment, especially in the first 3 months.
 - Women should get regular Pap tests as recommended, regardless of vaccination or genital wart history. Women with genital warts do not need to get Pap tests more often than recommended.
 - HPV testing is unnecessary in sexual partners of persons with genital warts.