Health Advisory:

Increase in Syphilis Cases in the St. Louis Area

October 26, 2010

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Health Advisory
October 26, 2010

FROM: **MARGARET T. DONNELLY**
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SUBJECT: **Increase in Syphilis Cases in the St. Louis Area**

The Missouri Department of Health and Senior Services (DHSS) is alerting medical providers to **an increase in syphilis cases in the St. Louis area among men who have sex with men (MSM); more than half of these cases are co-infected with human immunodeficiency virus (HIV)**.

Based on provisional data, from January 1 through September 28, 2010, there were 70 primary and secondary (P&S) syphilis cases reported from the St. Louis area, all were male. Of these 70 P&S cases, 59 (84.3%) were self-identified MSM. In addition, 40 (57.1%) of the 70 cases were co-infected with HIV. By comparison, during the same time period in 2009, there were a total of 50 P&S syphilis cases reported from the St. Louis area; 45 (90.0%) of these cases were in males, and 23 (46.0%) of the 50 cases were co-infected with HIV.

Interviews conducted by Disease Intervention Specialists on the 2010 cases indicated that among the HIV-positive men reported with P&S syphilis in St. Louis City, 69% had at least one HIV-positive partner; and that among the HIV-positive men reported with P&S syphilis in St. Louis County, 46% had at least one HIV-positive partner.

Current DHSS recommendations for medical providers are the following:

1. **All HIV-infected MSM, regardless of their area of residence, should be screened for syphilis at least every 6 months.**
2. **In addition, in the St. Louis area, all HIV-negative and HIV-status unknown MSM whose sexual behaviors put them at higher risk for sexually transmitted diseases (STDs) should be screened for syphilis at least every 6 months**. Such behaviors include, but are not limited to, multiple sexual partners, a new sexual partner, trading sex for money and/or drugs, anonymous sex, having a history of a bacterial STD, or having a sexual partner who engages in high risk behaviors.

Public Health testing locations can be found at http://www.takethetest.info/.

Reporting

Missouri law requires health care providers to report all known or suspected syphilis cases to public health officials within 24 hours. Reporting should preferably be done immediately by telephone to 573/526-5271, or 800/392-0272 (24/7). Disease case reports (using a CD-1 form) can be faxed to (573) 751-6417.

Missouri law also requires laboratories to report all reactive syphilis test results within 24 hours.

Missouri's Communicable Disease Reporting Rule (19 CSR 20-20.020) can be found at: http://www.sos.mo.gov/adrules/csr/current/19csr/19c20-20.pdf .

Questions can be addressed to DHSS' Bureau of HIV, STD, and Hepatitis at (573) 751-6439.

Educational opportunity for medical providers: The St. Louis STD/HIV Prevention Training Center will provide a Syphilis Update course at Washington University Medical Center on November 2, 2010. For more information about this course and to register visit their website at http://std.wustl.edu.

STD Treatment Guidelines from the Centers for Disease Control and Prevention (CDC)

The following are selected sections of CDC's 2006 Sexually Transmitted Diseases Treatment Guidelines, available at http://www.cdc.gov/std/treatment/2006/rr5511.pdf. See the full document for additional information on treatment of syphilis, including guidance for managing children and pregnant women, persons with penicillin allergy, and infants with congenital syphilis. (Note that these guidelines are currently being updated. When the new version becomes available, it can be accessed at http://www.cdc.gov/std/treatment/default.htm.)

Syphilis

General Principles

Background

Syphilis is a systemic disease caused by *Treponema pallidum*. Patients who have syphilis might seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary infection (e.g., cardiac or ophthalmic manifestations, auditory abnormalities, or gummatous lesions). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis theoretically might require a longer duration of therapy because organisms are dividing more slowly; however, the validity of this concept has not been assessed.

Diagnostic Considerations and Use of Serologic Tests

Darkfield examinations and direct fluorescent antibody (DFA) tests of lesion exudate or tissue are the definitive methods for diagnosing early syphilis. A presumptive diagnosis is possible with the use of two types of serologic tests: 1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and 2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and *T. pallidum* particle agglutination [TP-PA]). The use of only one type of serologic test is insufficient for diagnosis because false-positive nontreponemal test results are sometimes associated with various medical conditions unrelated to syphilis.

Nontreponemal test antibody titers usually correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16–1:4 or from 1:8–1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed by using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Nontreponemal tests usually become nonreactive with time after treatment; however, in some patients, nontreponemal antibodies can persist at a low titer for a long period of time, sometimes for the life of the patient. This response is referred to as the serofast reaction.

The majority of patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15%–25% of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years. Treponemal test antibody titers do not correlate with disease activity and should not be used to assess treatment response.

Some clinical laboratories and blood banks have begun to screen samples using treponemal EIA tests. This strategy will identify both persons with previous treatment and persons with untreated or incompletely treated syphilis. False-positive results can occur, particularly among populations with a low prevalence of syphilis.

Persons with a positive treponemal screening test should have a standard nontreponemal test with titer to guide patient management decisions. If the nontreponemal test is negative, then a different treponemal test should be performed to confirm the results of the initial test. If a second trepomenal test is positive, treatment decisions should be discussed in consultation with a specialist. Some HIV-infected patients can have atypical serologic test results (i.e., unusually high, unusually low, or fluctuating titers). For such patients, when serologic tests do not correspond with clinical syndromes suggestive of early syphilis, use of other tests (e.g., biopsy and direct microscopy) should be considered. However, for the majority of HIV-infected patients, serologic tests are accurate and reliable for the diagnosis of syphilis and for following the response to treatment.

No single test can be used to diagnose neurosyphilis. The VDRL-cerebrospinal fluid (CSF) is highly specific, but it is insensitive. The majority of other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, or a reactive VDRL-CSF with or without clinical manifestations. The CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm^3) in patients with neurosyphilis; this count also is a sensitive measure of the effectiveness of therapy. The VDRL-CSF is the standard serologic test for CSF, and when reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. However, the VDRL-CSF

might be nonreactive even when neurosyphilis is present. Some specialists recommend performing an FTA-ABS test on CSF. The CSF FTA-ABS is less specific (i.e., yields more false-positive results) for neurosyphilis than the VDRL-CSF, but the test is highly sensitive. Therefore, some specialists believe that a negative CSF FTA-ABS test excludes neurosyphilis.

Management of Sex Partners

Sexual transmission of *T. pallidum* occurs only when mucocutaneous syphilitic lesions are present; such manifestations are uncommon after the first year of infection. However, 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. However, serologic titers should not be used to differentiate early from late latent syphilis for the purpose of determining 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.

For identification of at-risk sexual partners, the periods before treatment are 1) 3 months plus duration of symptoms for primary syphilis, 2) 6 months plus duration of symptoms for secondary syphilis, and 3) 1 year for early latent syphilis.

DHSS' STD Disease Intervention Specialists (DIS) will provide assistance in confidential partner elicitation, notification, and referral for appropriate evaluation and treatment. For more information about DIS, contact Larry Phelan at (314) 877-2835.

Primary and Secondary Syphilis

Treatment

Recommended Regimen for Adults*

Benzathine penicillin G 2.4 million units IM in a single dose

* Recommendations for treating HIV-infected persons and pregnant women for syphilis have been discussed in this report (see Syphilis, Special considerations and Syphilis in Pregnancy).

Other Management Considerations

All patients who have syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, patients 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) or ophthalmic disease (e.g., uveitis, iritis, neuroretinitis, or optic neuritis) should have an evaluation that includes CSF analysis and ocular slit-lamp examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by *T. pallidum* accompanied by CSF abnormalities is common among adults who have primary or secondary syphilis. However, neurosyphilis develops in only a limited number of patients 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, CSF analysis is not recommended for routine evaluation of patients 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. Nontreponemal test titers might decline more slowly for persons who previously had syphilis. Patients should be reexamined clinically and serologically 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. Clinical trial data have demonstrated that 15% of patients with early syphilis treated with the recommended therapy will not achieve a two dilution decline in nontreponemal titer used to define response at 1 year after treatment.

Failure of nontreponemal test titers to decline fourfold within 6 months after therapy for primary or secondary

syphilis might be indicative of probable treatment failure. Persons for whom titers remain serofast 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. HIV-infected patients should be evaluated more frequently (i.e., at 3-month intervals instead of 6-month intervals). If additional follow-up cannot be ensured, re-treatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, many specialists recommend CSF examination in such situations.

For retreatment, the majority of STD specialists recommend administering weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks, unless CSF examination indicates that neurosyphilis is present. In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. Additional therapy or repeated CSF examinations are not warranted in these circumstances.

Latent Syphilis

Treatment

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

Other Management Considerations

All persons who have latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis and gumma) and syphilitic ocular disease (e.g., iritis and uveitis). Patients who have syphilis and who demonstrate any of the following criteria should have a prompt CSF examination:

- neurologic or ophthalmic signs or symptoms,
- evidence of active tertiary syphilis (e.g., aortitis and gumma),
- treatment failure, or
- HIV infection with late latent syphilis or syphilis of unknown duration.

If dictated by circumstances and patient preferences, a CSF examination may be performed for patients who do not meet these criteria. Some specialists recommend performing a CSF examination on all patients who have latent syphilis and a nontreponemal serologic test of ≥1:32 or if the patient is HIV-infected with a serum CD4 count ≤350. However, the likelihood of neurosyphilis in this circumstance is unknown. If a CSF examination is performed and the results indicate abnormalities consistent with neurosyphilis, the patient should be treated for neurosyphilis.

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. Patients with a normal CSF examination should be re-treated for latent syphilis if 1) titers increase fourfold, 2) an initially high titer (≥1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might still not decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis. A patient who has clinical evidence of neurologic involvement with syphilis (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis) should have a CSF examination.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis; patients with these symptoms should be treated according to the recommendations for patients with neurosyphilis. A CSF examination should be performed for all such patients to identify those with abnormalities that require follow-up CSF examinations to assess treatment response.

Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the following regimen.

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

If compliance with therapy can be ensured, patients may be treated with the following alternative regimen.

Alternative Regimen

Procaine penicillin 2.4 million units IM once daily
PLUS
Probenecid 500 mg orally four times a day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than that of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, some specialists administer benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks 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 patients who have syphilis should be tested for HIV.
- Many specialists recommend treating patients who have evidence of auditory disease caused by syphilis in the same manner as patients who have neurosyphilis, regardless of CSF examination results. Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven 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 VDRL-CSF or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important. If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered. Recent data on HIV-infected persons with neurosyphilis suggest that CSF abnormalities might persist for extended periods in these persons, and close clinical follow-up is warranted.

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Unusual serologic responses have been observed among HIV-infected persons who have syphilis. The majority of 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. However, unusual serologic responses are uncommon, and the majority of specialists believe that both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for the majority of patients who are coinfected with *T. pallidum* and HIV.

When clinical findings are suggestive of syphilis but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, or DFA staining 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 and might have higher rates of treatment failure with currently recommended regimens. The magnitude of these risks is not defined precisely but is likely minimal. 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. Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment with benzathine penicillin G, 2.4 million units IM in a single dose is recommended. Some specialists recommend additional treatments (e.g., benzathine penicillin G administered at 1-week intervals for 3 weeks, as recommended for late syphilis) in addition to benzathine penicillin G 2.4 million units IM.

Other Management Considerations

Because CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in patients with early syphilis and in persons with HIV infection, the clinical and prognostic significance of such CSF abnormalities in HIV-infected persons with primary or secondary syphilis is unknown. Although the majority of HIV-infected persons respond appropriately to standard benzathine penicillin therapy, some specialists recommend intensified therapy when CNS syphilis is suspected in these persons. Therefore, some specialists recommend CSF examination before treatment of HIV-infected persons with early syphilis, with follow-up CSF examination conducted after treatment in persons with initial abnormalities.

Follow-Up. HIV-infected persons should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy. Although of unproven benefit, some specialists recommend a CSF examination 6 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 fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and re-treatment). CSF examination and re-treatment also

should be strongly considered for persons whose nontreponemal test titers do not decrease fourfold within 6–12 months of therapy. The majority of specialists would re-treat patients with benzathine penicillin G administered as 3 doses of 2.4 million units IM each at weekly intervals, if CSF examinations are normal.

Special Considerations

Penicillin Allergy. Penicillin-allergic patients who have primary or secondary syphilis and HIV infection should be managed according to the recommendations for penicillin-allergic, HIV-negative patients. The use of alternatives to penicillin has not been well studied in HIV-infected patients.

Latent Syphilis Among HIV-Infected Persons

Diagnostic Considerations

HIV-infected patients who have early latent syphilis should be managed and treated according to the recommendations for HIV-negative patients who have primary and secondary syphilis. HIV-infected patients who have either late latent syphilis or syphilis of unknown duration should have a CSF examination before treatment.

Treatment

Patients with late latent syphilis or syphilis of unknown duration and a normal CSF examination can be treated with benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks. Patients who have CSF consistent with neurosyphilis should be treated and managed as patients who have neurosyphilis.

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, the CSF examination should be repeated and treatment administered accordingly.

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. 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. However, optimal dose and duration of ceftriaxone therapy have not been defined.

Reference

Centers for Disease Control and Prevention, Division of Sexually Transmitted Disease Prevention. *2006 STD Treatment Guidelines*. http://www.cdc.gov/std/treatment/2006/rr5511.pdf